eman ta zabal zazu

Universidad del País Vasco

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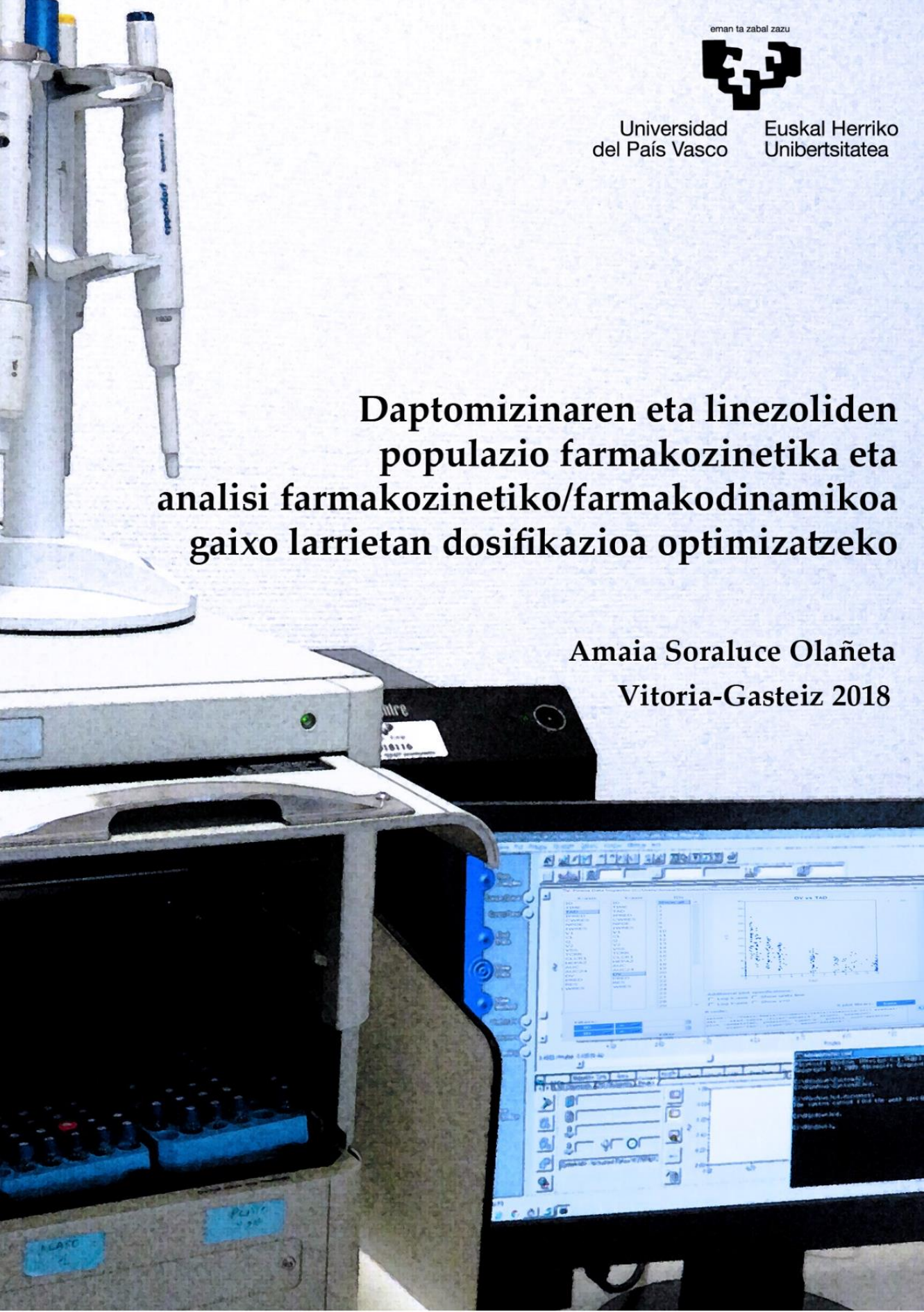


Daptomizinaren eta linezoliden populazio farmakozinetika eta analisi farmakozinetiko/farmakodinamikoa gaixo larrietan dosifikazioa optimizatzeko

Amaia Soraluce Olañeta

Vitoria-Gasteiz 2018

Daptomizinaren eta linezoliden populazio farmakozinetika eta analisi farmakozinetiko/ farmakodinamikoa gaixo larrietan dosifikazioa optimizatzeko

(Population pharmacokinetics and pharmacokinetic/ pharmacodynamic analysis of daptomycin and linezolid for dosing optimisation in critically ill patients)

PharmaNanoGene: Farmakozinetika, Nanoteknologia eta Terapia Genikoa taldea

Farmazia eta Elikagaien Zientziak saila

Universidad del País Vasco/Euskal Herriko Unibertsitatea

Han pasado casi seis años desde que decidí involucrarme en este proyecto. Desde entonces, no han sido pocas las vueltas que ha dado mi vida, y, por ello, probablemente esta no habrá sido la forma más convencional de realizar una tesis doctoral. Sin embargo, durante estos años tan caóticos he tenido la oportunidad de conocer a muchas personas (algunas de ellas maravillosas), y creo que, solo por eso, ha merecido la pena el esfuerzo realizado.

Por tanto, me gustaría daros las gracias a todos mis nuevos amigos, que, a pesar de no ser "los de siempre", lo seréis para siempre. También a los que habéis dedicado vuestro tiempo a enseñar a la novata, por la ilusión que ponéis en vuestro trabajo y por ser capaces de transmitir toda esa energía a los de alrededor. A aquellos que me sacáis de quicio con la forma que tenéis de ver el mundo, gracias. Ya que, siempre es enriquecedor escuchar cómo piensan los que, en principio, nada tienen que ver contigo.

A todos los que me habéis hecho reír, me habéis ayudado, divertido, enseñado, ilusionado, enloquecido y querido, ¡mil gracias de todo corazón!

Badira ia sei urte proiektu honetan sartzea erabaki nuenetik. Ordutik ugariak izan dira nire bizitzan eman diren aldaketak eta lan munduan eman ditudan bueltak. Beharbada ez dut doktoretza tesi bat egiteko modu konbentzionalena jarraitu, baina urte kaotiko hauek pertsona desberdin asko ezagutzeko aukera ere eman didate (benetako altxorrak batzuk) eta, horregatik bakarrik, esfortzuak pena merezi izan duela esan nezake.

Beraz, eskerrak eman nahi nizkizueke egindako lagun-min berriei, betikoak izan ez arren, betirako izango zaretenoi. Baita aprendizari irakasteko denbora hartu duzuen guztiei, zuen lanean ilusioa jarri eta albokori adorea emateko gai izan zaretenei. Mundua ikusteko duzuen erarekin nire onetik atera nauzuenoi ere, mila esker; aberasgarria baita, beti, bestelako ikuspuntuak entzutea.

Barre-arazi, lagundu, dibertitu, ilusionatu, irakatsi, zoratu eta maitatu nauzuen guztiei, bihotz-bihotzez, eskerrik asko!

Gracias a Arantxa y Alicia, por vuestros consejos y por permitirme realizar este trabajo en vuestro equipo.

Baina batez ere, mila esker beti hor egon zarienoi. Eskerrik asko Kuatrila, alkarrekin pasatako deskonexio ordu polit guztiengatik, ongien ezagutzen nauzuenak izateagatik. Mila esker Ander, tontoetan tontoena izateagatik, egun okerrenetan ere irribarre bat ataratzeko gai izateagatik. Eta nola ez, eskerrik asko Ama, Aita eta Jaione, nigan gehien sinetsi dozuenak izateagatik, etxeko txikia beti holako ederto zaintziagatik.

Pero se puede y vale la pena mejorar el mundo. No hay una salida apocalíptica, de un día para el otro, o que llegamos y tenemos un desfile o un arco del triunfo. Es una escalera interminable donde vamos subiendo escalones, aprendemos algo, dejamos algo, y otros siguen, y así sucesivamente. Es un camino sin fin. El día que creamos que hemos llegado, estamos fritos

-Pepe Mujica-

Badira bide batzuk derrigorrez ibili behar ditugunak, inora ez doazela jakiteko

-Joseba Sarrionaindia-

GLOSSARY// GLOSARIOA

AIC: Akaike information criteria// Akaike informazio kriterioa

AKI (en): Acute kidney injury

AME (eu): Antimikrobianoekiko erresistentzia

AMR (en): Antimicrobial resistance

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARC (en): Augmented renal clearance

AUC: Area under the curve// Kurba azpiko azalera

BMI (en): Body mass index

CFR: Cumulative fraction of response// Erantzunaren metatze frakzioa

CL: Total body clearance// Gorputzeko argitzapena

CL_{NR}: Non-renal clearance// Giltzurrun-kanpoko argitzapena

CL_{R}: Renal clearance// Giltzurrun-menpeko argitzapena

Clcr: Creatinine clearance// Kreatinina argitzapena

CL_{EC} : Extracorporeal clearance// Gorputz-kanpoko argitzapena

CLSI: Clinical and Laboratory Standard Institute

Cmax: Maximum plasma drug concentration// Farmakoaren plasma kontzentrazio maximoa

$Cmin_{ss}$: Minimum concentration in steady-state// Kontzentrazio minimoa oreka egonkorrean

CoNS: Coagulase negative *Staphylococcus*// Koagulasa negatiboko estafilokokoa

CPK: Creatinine phosphokinase// Kreatinina fosfokinasa

CRRT(en): Continuous renal replacement therapies

CV: Coefficient of variation// Aldakuntza-koefizientea

CVVHD: Continuous venovenous haemodialysis// Etengabeko hemodialisi beno-benosoa

CVVHDF: Continuous venovenous hemodiafiltration// Etengabeko hemodiafiltrazio beno-benosoa

CWRES: Conditional weighted residuals// Haztatutako baldintzapeko hondar-balioak

DV: Dependent variable. In pharmacokinetic modelling it normally refers to the concentration of the drug// Menpeko aldagaia. Analisi farmakozinetikoan orokorrean farmako kontzentrazioa da

EGOT (eu): Etengabeko giltzurrun - ordezkatze teknikak

EPA (eu): Efektu post-antibiotikoa

EUCAST: European Committee on Antimicrobial Susceptibility Testing

f: Unbound fraction of the drug// Farmakoaren frakzio askea

FOCE+I: First order conditioned estimation method with interaction// Baldintzazko lehen mailako estimazio metodoa interakzioarekin

GGA (eu): Giltzurrun-gutxiegitasun akutua

GMI (eu): Gorputz masaren indizea

GOF: Goodness-of-fit// Doikuntza-egokitasunaren ebaluazioa

HAI (en): Healthcare-associated infections

HPLC: High performance liquid chromatography// Bereizmen handiko kromatografia likidoa

ICU (en): Intensive care unit

IDSA: Infectious Diseases Society of America// Gaixotasun Infekziosoen Amerikako Elkartea

I + G (eu): Ikerketa eta garapena

IIV: Inter-individual variability// Aldakortasun interindibiduala

IOV: Inter-occasion variability// Aldi-desberdinetako aldakortasuna

IPRED: Individual predicted concentration// Norbanakoen aurreikusitako kontzentrazioak

IWRES: Individual weighted residuals// Norbanako bakoitzaren haztatutako hondar-balioak

LADME: Liberation, absorption, distribution, metabolism and excretion// Askapena, xurgapena, banaketa, metabolismoa eta iraizketa

LEBI (eu): Larruazal eta ehun bigunetako infekzio

MIC: Minimum inhibitory concentration// Kontzentrazio minimo inhibitzailea

MCS: Monte Carlo simulation// Monte Carlo simulazioa

MRSA: Methicillin-resistant *Staphylococcus aureus*// Metizilinarekiko erresistentea den *Staphylococcus aureus*

NBE (eu): Nazio Batuen Erakundea

NLME: Nonlinear mixed-effects// Efektu mistoetako modelizazio ez-lineala

OEI (eu): Osasun-asistentziarekin erlazionatutako infekzioa

OFV: Objective function value// Funtzio-objektiboaren balioa

PAE (en): Post-antibiotic effect

PD: Pharmacodynamic// Farmakodinamia

PDI: Pharmacokinetic/pharmaco-dynamic index// Indize farmakozinetiko/farmakodinamikoa

PDT: Pharmacodynamic target// Helburu farmakodinamikoa

PK: Pharmacokinetics// Farmakozinetika

PK/PD: Pharmacokinetics/ Pharmacodynamics// Farmakozinetiko/Farmakodinamiko

PRED: Predicted population concentrations// Aurreikusitako populazio kontzentrazioak

PTA: Probability of target attainment// Helburua lortzeko probabilitatea

pvc-VPC: Prediction-and-variability-corrected visual predictive check// Predikzioa eta aldakortasuna zuzenduta dituen azterketa bisual iragarlea

Q_{ef}: Effluent flow// Efluentearen fluxua

R&D (en): Research and development

RE: Residual error// Hondar-errorea

RSE: Relative standard error// Errore erlatibo estandarra

Sc: Sieving coefficient// Sieving koefizientea

TAD: Time after dose// Dosi osteko denbora

$T_{>MIC}$: Time above the MIC// MICaren gaineko denbora

UN (en): United Nations

V: Apparent volume of distribution// Banaketa-bolumena

V_1: Central compartment volume of distribution// Konpartimentu zentraleko banaketa-bolumena

V_2: Peripheral compartment volume of distribution// Konpartimentu periferikoko banaketa-bolumena

VPC: Visual predictive check// Azterketa bisual iragarlea

VRE: Vancomycin-resistant enterococci// Bankomizinarekiko erresistenteak diren enterokokoak

ZIU (eu): Zainketa intentsiboetako unitatea

AURKIBIDEA

SARRERA

1. Kapitulua

Analisi farmakozinetiko/farmakodinamikoa antimikrobianoen erabilera hobetzeko gaixo larrietan

A. Soraluce[1], A. Rodríguez-Gascón[1], A. Isla[1]

EKAIA. 2018;33:19-33

[1] Farmakozinetika, Nanoteknologia eta Terapia Genikoa taldea. Farmazia Fakultatea, Lascaray-ikergunea, Euskal Herriko Unibertsitatea UPV/EHU, Vitoria-Gasteiz.

LABURPENA: Azken urteotan infekzioen tratamendua mundu mailako osasun publikoko arazo bilakatu da, erresistentzien garapenaren ondorioz, bakterio multirresistenteen agerpena izugarri igo baita. Antibiotiko berrien gabeziak merkatuan daudenen dosifikazioen optimizazioaren premia areagotzen du. Zenbait pazientetan, gaixo larrietan esaterako, aipatutakoa egitea bereziki zaila suerta daiteke. Izan ere, beraien egoera fisiopatologikoa dela-eta, medikamentuen farmakozinetika eta farmakodinamia eraldatuta daukate. Analisi farmakozinetiko/farmakodinamikoak, Monte Carlo simulazioekin batera, dosifikazio-erregimenen optimizazioa ahalbidetzen du. Horrela, tratamenduaren arrakasta bermatu eta erresistentzien agerpena ekiditen da.

1. Sarrera

Gaur egun, infekzioen diagnostikoa eta tratamendua geroz eta konplexuagoa bilakatzen ari da medikuentzat. Alde batetik, osasun sistemarentzat gainkarga bat suposatzen duelako batez ere mendebaldeko herrialdeetan ematen ari den bizi itxaropenaren gorakadak. Izan ere, zenbait gaitzen intzidentzia altuagoa da pertsona nagusietan, gripea edota gaixotasun neumokozikoa kasu, eta, sarritan, epe luzerako zainketen beharra areagotzen dute. Bestalde, infekzioekiko bereziki sentikorrak diren immunokonprometituta dauden pazienteen gorakada eragin dutelako hainbat tratamenduk, besteak beste, minbiziaren aurkako kimioterapia zein organo transplanteak[1,2].

Badira ia 90 urte antibiotikoen aurkikuntzatik eta terapeutikan erabiltzeari ekin zitzaienetik. Ordutik, medikamentu hauek funtsezko papera eduki dute infekzioen tratamenduan. Haatik, azken hamarkadetan hainbat antimikrobianoekiko erresistentziak garatu dituzten patogenoen kopuruak gora egin du. Ondorioz, aurretik tratagarriak ziren zenbait infekziok ez diote behar bezain ondo erantzuten farmakoei. Erresistentzia mekanismoak mikroorganismoek garatzen dituzten fenomeno naturalak badira ere, antimikrobianoen erabilera ezegokia dela-eta, bizkortu eta areagotu daitezke[3]. Egun, antimikrobianoekiko erresistentziak (AME) direla-eta, estimatzen da urtean 700.000 hildako baino gehiago daudela. AMEn propagazioa murrizteko neurririk hartu ezean, zifra hori 2050. urtean 10 milioira igo daitekeela uste da[1]. Honek esan nahi du antimikrobianoekiko erresistentziak lehenengo hilkortasun kausa bilakatu

[1] Review on Antimicrobial Resistance. Tackling drug-resistant infections globally. Eskuragarri: *https://amr-review.org/Publications.html* [kontsulta: 2018ko maiatza].

[2] European Centre for Disease Prevention and Control. ECDC strategic multi-annual programme 2014–2020. Stockholm: ECDC; 2014.

[3] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277-83.

daitezkela, minbizia gailenduz, eta hiru segunduro pertsona bat hiltzea daukala bakterio erresistente batek eragindako infekzio batengatik.

Gauzak horrela, medikamentuekiko erresistenteak diren infekzioak medikuntzarentzat erronka izateaz gain, mundu mailako osasun-mehatxu bilakatu dira[4,5,6]. Honen harira, 2016. urteko irailean, munduko agintariak Nazio Batuen Erakundearen (NBE) Asanblada Orokorrean bildu ziren, antimikrobianoekiko erresistentzien aurka elkarrekin borrokatzeko konpromezua hartzeko[7]. Honakoa historiako laugarren aldia izan zen NBEn osasunarekin erlazionaturiko gai bat eztabaidatzen zela Asanblada Orokor batean. Aurretik landutako alorrak giza immunoeskasiaren birusa (GIB), gaixotasun ez kutsakorrak eta ebola izan ziren.

Egoera honetan, 2017. urte hasieran Osasunaren Munduko Erakundeak antibiotiko berrien premia duten bakterio erresistenteen zerrenda argitaratu zuen. Horrela, giza osasunarentzat arriskutsuenak kontsideratu zituzten 12 patogeno-familiak 3 talde desberdinetan banatu zituzten, lehentasun mailaren arabera: kritikoa, altua eta erdi mailakoa[8,9]. Kritikoen artean ospitale zein pertsona nagusien egoitzetan infekzio larriak eragiteagatik bereziki arriskutsuak diren bakterio multirresistenteak daude: *Acinetobacter baumannii, Pseudomonas aeruginosa* eta

[4] Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect. 2015;16;6:22-9.

[5] PLOS Medicine Editors. Antimicrobial Resistance: Is the World UNprepared? PLoS Med. 2016;13(9):e1002130.

[6] Hernández-Marrero P, Martins Pereira S, de Sá Brandão PJ, Araújo J, Carvalho AS. Toward a bioethical framework for antibiotic use, antimicrobial resistance and for empirically designing ethically robust strategies to protect human health: a research protocol. J Int Med Res. 2017;45(6):1787-93.

[7] General Assembly of the United Nations. High-level Meeting on Antimicrobial Resistance. Eskuragarri: *https://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/* [kontsulta: 2018eko maiatza].

[8] World Health Organization (WHO). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Eskuragarri: *http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/* [kontsulta: 2018ko maiatza].

[9] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-327.

zenbait enterobakterio. Lehentasun altua edo erdi mailakoa dutenen artean, aldiz, gaixotasun ohikoak eragin eta botikekiko geroz eta erresistenteago bilakatzen ari diren bakterioak daude, *Enterococcus faecium, Staphylococcus aureus* edota *Haemophilus influenzae*, esaterako. Zerrenda honen helburu nagusia antibiotikoen ikerketarako eta garapenerako (I+G) lehentasunak ezartzea da, eta mundu mailako koordinazioa bermatu.

Antimikrobiano berrien beharra bistakoa bada ere, ez da farmako hauetan asko inbertitzen. Horrela, 2003. eta 2013. urte-tartean industria farmazeutikoak I+Gra bideratutako kapitalaren %5 baino gutxiago gastatu zuen antimikrobianoak aztertzen[10]. Horren zergatietako bat da medikamentu hauen salmentek beraien garapenean inbertitutakoa ez dutela konpentsatzen[9,11]. Ondorioz, azken urteotan nabarmenki murriztu da antimikrobiano berrien garapena. Gainbehera horri aurre egiteko asmoz, hainbat ekimen martxan jarri dira. Hala nola, Gaixotasun Infekziosoen Amerikako Elkarteak (*Infectious Diseases Society of America*, IDSA) 2010. urtean abian jarritako 10 x 20' ekimena. Proiektu honek 2020 urtea baino lehen 10 antibiotiko sistemiko sortzeko konpromezu globala hartzea du helburu[12].

Botika berrien gabeziak egungo antibiotikoen efikazia babesteko premia areagotzen du. Erabilera egokirako, agente infekziosoek farmakoari dioten sentikortasunaz gain, medikamentuen, pazienteen eta mikroorganismoaren artean gertatzen diren elkarrekintza konplexuak ere kontuan hartu behar dira (**1. irudia**). Bada, hauen arteko aniztasunak dosi-erantzun erlazioan aldakortasun handia eragin dezake.

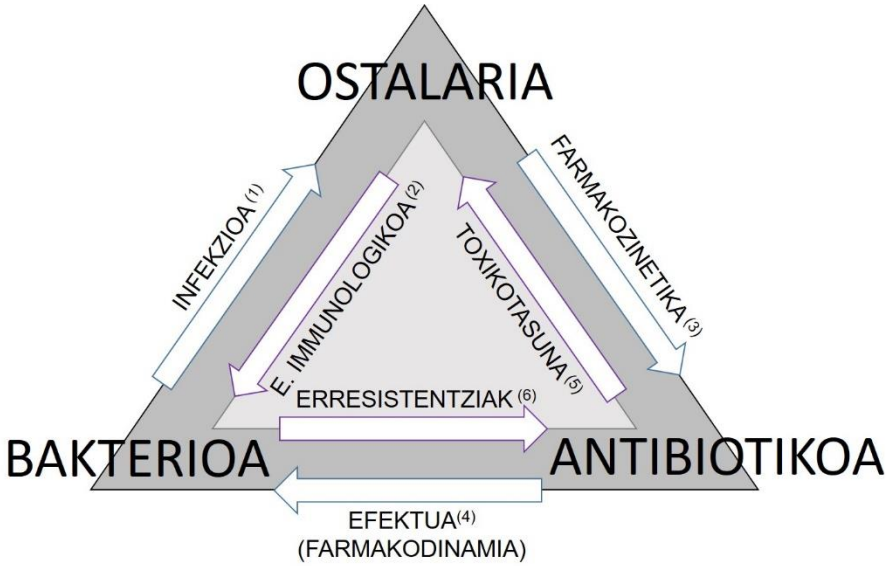
Beste botika batzuekin gertatzen ez den bezala (antihipertentsibo edota basopresoreak, esaterako), klinikan ezin daiteke antibiotikoen efektua zuzenean neurtu. Horregatik, zenbait paziente-taldetan bereziki zaila da hautatzea zein den

[10] Silver LL. Challenges of Antibacterial Discovery. Clin Microbiol Rev. 2011; 24(1): 71–109.

[11] Davies J. Where have All the Antibiotics Gone? Can J Infect Dis Med Microbiol. 2006;17(5):287-90.

[12] Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis. 2010;50(8):1081-3.

beraien tratamendurako antibiotiko eraginkorrena eta dosifikazio egokiena. Horren adibide dira gaixo pediatrikoak zein kritikoak.



1. Bakterioak infekzioa eragiten du.
2. Ostalariaren erantzun immunologikoa martxan jartzen da.
3. Ostalari eta antibiotikoak elkarri eragiten diote eta farmakozinetika zehaztu.
4. Antibiotikoak efektu bakteriostatiko edo bakterizida eragiten du.
5. Antibiotikoak pazientearen fisiologia eraldatu dezake eta toxikotasuna edota efektu sekundarioak eragin.
6. Bakterioak farmakoaren aurkako erresistentziak garatu ditzake.

1. irudia: Ostalariaren, mikroorganismoaren eta antibiotikoaren arteko elkarrekintzak.

2. Antibioterapia gaixo larrietan

Nahiz eta zerbitzuen zein pazienteen artean aldakortasun handia egon, infekzioek mundu osoko zainketa intentsiboetako unitateetan (ZIU) zehar presentzia nabarmena dute. Alde batetik, bertan ospitaleratzearen zergatietako bat infekzioak izan ohi direlako (hala nola, pneumonia, meningitisa edo sepsia).

Bestetik, gaitz desberdinengatik ingresaturiko pazienteak osasun-asistentziarekin erlazionatutako infekzioekin (OEI) kutsa daitezkeelako[13].

OEI terminoak pazientearen zainketarekin lotutako infekzio guztiak barne hartu arren, jakina da, orokorrean, ZIUetan tasa altuagoan gertatzen direla, gaixoen ahultasun orokorra dela-eta[14,15]. Bestalde, erabilitako teknika inbaditzaileek (intubazio endotrakealak zein nasogastrikoak edota maskuriko zundaketak, esaterako), infekzioak garatzeko arriskua handitzen lagundu dezakete[16]. Horrela, munduko 75 estatuk esku hartu zuten prebalentzia-ikerketa batean (EPIC II), 1.265 ZIU desberdinetako 14.414 parte-hartzaile egon ziren, eta gaixoen %51 infekzioren bat jasaten ari zirela konprobatu zuten. Horien artean nagusi ziren biriketako infekzioak (%63,5), infekzio intraabdominalak (%19,6) eta bakteriemiak (%15,1). Beste pazienteekin konparatuz, kutsatutakoen artean heriotza-tasa altuagoa izan zen, %11 eta %25, hurrenez hurren[17].

Beharbada horren ondorioz, nahiz eta ospitaleratzeen %10 baino gutxiago izan, gaixo kritikoek bestelako pazienteek baino hamar bat aldiz antibiotiko-kopuru handiagoa hartzen dute[18]. Kontsumo altu horren beste arrazoietako bat izan daiteke ZIUetako patogenoek antibiotikoei orokorrean baino sentikortasun baxuagoa diotela, medikamentu hauek maizago erabiltzeak erresistentziak

[13] Burke A. Cunha. Infectious Diseases in Critical Care Medicine (Third Edition). Informa Healthcare USA, Inc. 52 Vanderbilt Avenue New York, NY 10017. 2010.

[14] World Health Organization (WHO). Healthcare-associated infections: fact sheet;2014. Eskuragarri: *http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf.* [kontsulta: 2018ko maiatza].

[15] Bianco A, Capano MS, Mascaro V, Pileggi C, Pavia M. Prospective surveillance of healthcare-associated infections and patterns of antimicrobial resistance of pathogens in an Italian intensive care unit. Antimicrob Resist Infect Control. 2018;7:48.

[16] Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med. 2002;28(2):108-21.

[17] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323-9.

[18] Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med. 2015;36(1):136-53.

sorrarazteko presio selektiboa eragiten baitu[19,20]. Patogeno erresistenteen agerpenak antibiotikoen erabilera inplikatzen duen praktika klinikoa etengabe aldatu behar izatea eragiten du. Horren adibide dira, alternatiba gehiago ez edukitzeagatik, azken urteotan toxikotasun-arazoak direla-eta, administrazio-formula berriak garatzea eta aspaldi erabiltzeari utzi zitzaion antibiotikoak berriz ere ematen hasi izana (kolistina, adibidez)[21,22].

Medikamentuen dosi-erregimenen ezarpena boluntario osasuntsuekin burututako entsegu klinikoetan egin ohi da, eta ondoren, gaixo ez hain larrietan dosifikazioaren doikuntza gauzatu. Entsegu hauetan lortutako emaitzak gaixo kritikoetan erabiltzeko estrapolatzen dira sarritan. Dena den, estrapolazio horiek gehienetan ematen ez den baldintza bat onartzea dakartzate; alegia, gaixo kritikoetan eta gaixotasun moderatuak dituzten subjektuetan antibiotikoek antzeko farmakozinetika eta farmakodinamia daukatela baieztatzea. Izan ere, aipatu bezala, orokorrean patogeno erresistenteagoek eragin ohi dituzte infekzioak. Gainera, paziente kritikoetan aldaketa fisiopatologiko ugari ematen dira, beraien osasuna hobetzeko tratamendu desberdinak ezartzen zaizkie eta medikamentu konkomitanteak hartzen dituzte. Beraz, paziente hauetan protokolo estandarrekin dosifikazio erregimen egokiena aukeratzea ez da lan erraza izaten.

Laburbilduz, paziente kritikoetan farmakoen farmakozinetika eta farmakodinamia aldatuta egoten denez, askotan ez dira espero diren

[19] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

[20] Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Antimicrobial susceptibility pattern comparisons among intensive care unit and general ward Gram-negative isolates from the Meropenem Yearly Susceptibility Test Information Collection Program (USA). Diagn Microbiol Infect Dis. 2006;56(1):57-62.

[21] Cassir N, Rolain JM, Brouqui P. A new strategy to fight antimicrobial resistance: the revival of old antibiotics. Front Microbiol. 2014;5:551.

[22] Muller AE, Theuretzbacher U, Mouton JW. Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. Clin Microbiol Infect. 2015;21(10):881-5.

kontzentrazioak lortzen. Ondorioz, maiz gertatzen dira dosi baxuek eragindako porrot terapeutikoa, edo akumulazioak eragindako toxikotasuna[23,24].

3. Farmakozinetika (PK)

3.1. Kontzeptua

Behin farmako bat paziente bateri administratuta, LADME prozesuek (askapena, xurgapena, banaketa, metabolismoa eta iraizketa biltzen dituen ingeleseko terminoa) baldintzatuko dute botikaren kontzentrazio-denboraren profila. Farmakozinetikak farmakoen eta haien metabolitoen kontzentrazioen eboluzioa aztertzen du denboran zehar, pazienteen fluido desberdinetan. Hori dela-eta, "gorputzak medikamentuari egiten diona" aztertzen duela esaten da.

3.2. Aldaketa farmakozinetikoak gaixo larrietan

Antibiotikoei dagokienez, bereziki hiru dira gaixo larrietan aldaketa farmakozinetikoak eragin ditzaketen egoerak: banaketa-bolumena (V) handitzea, proteinekiko lotura modifikatzea eta gorputz-argitzapen totalean (CL) aldaketak gertatzea. Dena den, oso ohikoa da PK baldintzatu dezaketen egoera desberdinak

[23] del Mar Fernández de Gatta M, Martín-Suárez A, Lanao JM. Approaches for dosage individualisation in critically ill patients. Expert Opin Drug Metab Toxicol. 2013;9(11):1481-93.

[24] Olofsson SK, Cars O. Optimizing drug exposure to minimize selection of antibiotic resistance. Clin Infect Dis. 2007;45 Suppl 2:S129-36.

aldi berean gertatzea, eta honek kontzentrazioen iragarpen egokia gauzatzea zailtzen du[25,26,27].

3.2.1. Banaketa-bolumena handitzea

Edemak sortzean, sepsietan edota erredura handien fase postakutuetan, farmakoen Va handitu ohi da, bereziki likido interstiziala baldintzatuz. Bestalde, ZIUetan sarritan egiten diren bestelako interbentzioek ere (berpizte-fluidoek, bentilazio mekanikoak edota drainatze poskirurgikoek) Va handitu dezakete[25,28]. Banaketa-bolumenaren handipena bereziki garrantzitsua izango da antimikrobiano hidrofilikoetan, normalean ehunetan gutxi sakabanatu ohi baitira. Honen adibide dira, besteak beste, betalaktamikoak edota aminoglikosidoak[25]. Farmako hauek zelulaz kanpoko eremuetara mugatuak egoten direnez, antibiotiko diluzio nabarmena gertatuko da hodi barneko likidoak ehunetan zehar barreiatzen diren egoera patologikoetan. Antimikrobiano lipofiloek, aitzitik, sarritan zelula barnean sakabanatzen direnez, V handiagoak izaten dituzte. Hortaz, parametro farmakozinetiko hau normalean ez da horrenbeste aldatzen gaixo larrietan. Linezolid, makrolidoak edota rifanpizina antibiotiko lipofiloen adibide dira. Banaketa-bolumenaren handitzeak plasma kontzentrazio maximoaren (Cmax) gutxitzea ekar dezake, eta, honek, eraginkorrak ez diren kontzentrazioak izatea eta infra-dosifikazioa eragin.

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[25] Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient-concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3-11.

[26]Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. Chest. 2012;141(5):1327-1336.

[27] Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009-34.

[28] Álvarez-Lerma F, Grau S. Management of antimicrobial use in the intensive care unit. Drugs. 2012;72(4):447-70.

3.2.2. Proteinekiko lotura modifikatzea

Proteinekiko lotura farmakoen propietate garrantzitsua da; izan ere, soilik frakzio askeak dauka efektu farmakologikoa eragiteko gaitasuna. Proteinekiko loturaren arduradun nagusia albumina izan ohi denez, hipoalbuminemia ematen den kasuetan antimikrobianoen proteinekiko lotura gutxitu egiten da maiz. Gaixo kritikoetan oso ohikoa izaten da hipoalbuminemia. Horrela, ZIUetan onarturiko pazienteen %40-50ek 25 g/L baino albumina-kontzentrazio baxuagoak dituztela ikusi da[29]. Gainera, proteinetara lotzeko antibiotikoen eta beste medikamentu batzuen arteko lehia egon daiteke. Faktore hori proteinekiko lotura handia duten antibiotikoekin hartu beharko da aintzat batik bat[25], besteak beste, daptomizinarekin (%90)[30] eta ertapenemenekin (%95-92)[31].

Proteinen kontzentrazio baxuagoak izateak farmakoaren frakzio askearen proportzioa handitzea ekar dezake, eta horrek efektua eragiteko (alegia, bakterioak hiltzeko) probabilitatea handitzen du. Dena den, hipoalbuminemia Varen handipenarekin erlazionatuta egoten da normalean, proteinekiko lotura handia duten medikamentuetan bereziki. Izan ere, proteinekiko lotura gutxitzean, farmako molekula gehiagok odol-korrontea utzi dezakete eta ehunetan barrena banatu daitezke.

Gainera, kontuan hartuta soilik frakzio askeak jasan dezakela argitzapen hepatikoa edo giltzurrun bidezko eliminazioa, farmako askearen igoerak

[29] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99-110.

[30] Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin Pharmacokinetics and Safety following Administration of Escalating Doses Once Daily to Healthy Subjects. Antimicrob Agents Chemother. 2003;47(4):1318-23.

[31] Majumdar AK, Musson DG, Birk KL, Kitchen CJ, Holland S, McCrea J, et al. Pharmacokinetics of ertapenem in healthy young volunteers. Antimicrob Agents Chemother. 2002;46(11):3506-11.

argitzapen totalaren handipena eragin dezake. Horrela, jakina da hipoalbuminemiak farmakoaren eliminazio totala areagotzen duela[29,32].

3.2.3. Argitzapenean aldaketak

Farmako gehienak gibel-metabolismoz edo giltzurrun-iraizketaz eliminatzen dira. Gaixo larrietan organo hauen funtzionalitatea eraldatuta egon ohi denez, antimikrobianoen argitzapena baldintzatzen da. Kontuan hartu beharreko egoera nagusiak dira gibel-disfuntzioa, giltzurrun-gutxiegitasun akutua eta giltzurrun-funtzioa handitua izatea.

a) Gibel-disfuntzioa

Gaixo larrietan gibel-gutxiegitasuna infekzioekin loturiko kolestasiarekin eta min hepatozelularrarekin dago erlazionatuta gehien bat[33], nahiz eta farmako hepatotoxikoak administratzeagatik ere gerta daitekeen, adibidez[25,33]. Egoera honetan, medikamentuen metabolismo hepatikoa moteldu daiteke. Hala ere, botika baten argitzapen hepatikoa zehaztea ez da lan erraza izaten, ez baitago gibel-funtzioa espezifikoki neurtzea ahalbidetzen duen markatzailerik. Gutxiegitasun hepatikoa gibel-entzimen igoerarekin dago erlazionatuta, baita bilirrubinarenarekin eta amoniakoarenarekin ere. Bestalde, koagulazio-faktoreen eta albuminaren sintesiaren murrizpena ekar dezake[32] eta horrek, aipatu bezala, farmakoen Van eta proteinekiko loturan eragin dezake.

b) Giltzurrun-gutxiegitasun akutua (GGA)

Oliguria edo anuria eragiten duen gaitz honek giltzurrun-funtzioaren galtze partziala edo osoa dakar. Ondorioz, kreatinina-plasmatikoaren igoera gertatzen da. ZIUetako pazienteen erdiak baino gehiago gaitz hau pairatzen dutela ikusi

[32] Roberts JA, Joynt GM, Choi GY, Gomersall CD, Lipman J. How to optimise antimicrobial prescriptions in the Intensive Care Unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. Int J Antimicrob Agents. 2012;39(3):187-92.

[33] Chand N, Sanyal AJ. Sepsis-induced cholestasis. Hepatology. 2007;45(1):230-41.

da[34]. Proportzio desberdinetan bada ere, antibiotiko-kopuru handia giltzurrun bitartez eliminatzen denez, GGAk eragin nabarmena edukiko du farmako hauen PKn, eta sarritan dosifikazioa egokitzea beharrezkoa izango da.

GGAk bizi-arriskua eragiten duenean, giltzurrun-ordezkatze teknikak erabiltzen dira, eta horien artean, gehien bat, etengabekoak (EGOT). Teknika horiek antibiotikoen CLan parte hartzen dute, bereziki proteinekiko lotura txikia dutenetan. Horien bitartez eliminatzen den farmako-kantitatea teknika beraren, filtroaren materialaren eta azaleraren, eta odol fluxuaren menpe egongo da, besteak beste[35]. Hortaz, dosifikazio egokiena aukeratzerako orduan, teknika hauen bidez ematen den farmakoaren gorputz-kanpoko argitzapena (CL_{EC}) aintzat hartu beharko da[36,37].

c) Giltzurrun-funtzio handitua (GFH)

Paziente larrien %20-65k giltzurrun-funtzio handitua daukatela deskribatu da[38]. Gaixo hauetan gastu kardiakoa areagotu egiten da, eta, ondorioz, giltzurrunetako odol-fluxua handitzen da eta hiperfiltrazio glomerularra eragiten da. Egun, paziente batek GFH duela esango da baldin eta 130 mL/min/1,73m^2 baino altuagoa den filtrazio glomerularra badauka; ahal izanez gero, gernuan neurtutakoa izango dena. Gehienetan sepsia edota traumatismoren bat duten gizonezko gaixo gazteak izan ohi dira, larritasun maila baxuagoa dutenak. Giltzurrun-gutxiegitasunarekin gertatzen ez den

[34] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.

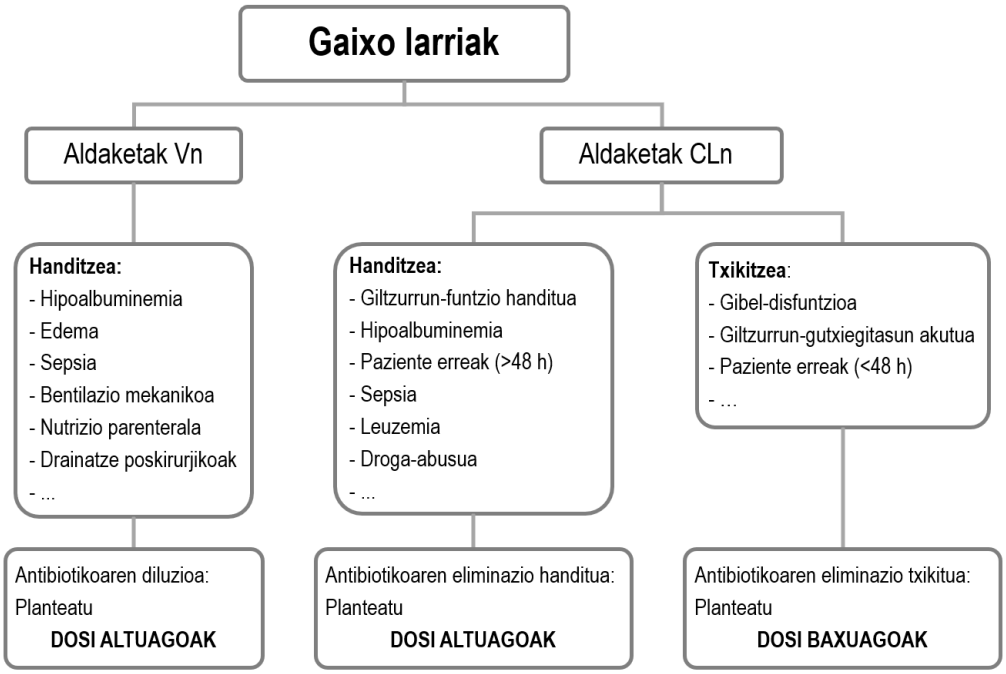
[35] Thongprayoon C, Cheungpasitporn W, Ahmed AH. Trends in the use of renal replacement therapy modality in intensive care unit: a 7 year study. Ren Fail. 2015;37(9):1444-7.

[36] Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L,et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med. 2012;40(5):1523-8.

[37] Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med. 2009; 37(7):2268-82.

[38] Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented Renal Clearance in Critically Ill Patients: A Systematic Review. Clin Pharmacokinet. 2018 Feb 13. doi: 10.1007/s40262-018-0636-7.

bezala, GFH ez da horren ondo ikertu, eta sarritan dosifikazio estandarrak administratzen zaizkie paziente hauei. Ondorioz, kontzentrazio sub-terapeutikoak eta emaitza kliniko okerragoak lortzeko probabilitate altuagoak dituzte[38,39].



2. irudia: Antibiotikoen distribuzioa eta eliminazioa baimentzen duten faktore fisiopatologiko eta iatrogenikoak eta kasu bakoitzean jarraitu beharreko gomendio orokorrak.

Laburbilduz, faktore fisiopatologiko ugarik eragin dezakete antibiotikoen propietate farmakozinetikoetan (**2.irudia**), ZIUetako pazienteen artean antzeman ohi den aldakortasun nabariaren eragile izanik. Bestalde, aldaketa hauek indibiduo berean ere gerta daitezke, gaixotasunaren larritasuna aldatzen den heinean. Horrela, paziente batentzat momentu batean dosi egokia dena ezegoki bilaka daiteke denbora gutxian.

[39] Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. Pharmacotherapy. 2015;35(11):1063-75.

Gaixo bakoitzari dosifikazio egokia administratzeko, farmakoaren portaera farmakozinetikoari erreparatzea ezinbestekoa bada ere, egunerokotasun klinikoan, ez da medikamentu hauen monitorizazioa egiten normalean[23,40]. Horrek paziente konkretuetan sarritan farmakoaren PK ezezaguna izatea eragiten du. Bestalde, zenbaitetan, paziente-talde berezi batentzat dosifikazio-gomendioak egin nahi izaten dira. Kasu horietan guztietan, informazioa aurretik egindako populazio-ikerketetatik lortu behar da.

3.3. Populazio-farmakozinetikaren ikuspuntua

Populazio batek farmako jakin baten klinikoki-egokiak diren dosiak jaso ostean, indibiduo desberdinen farmako kontzentrazioetan eragiten duten aldakortasunaren iturriak eta korrelazioak aztertzen ditu populazio-farmakozinetikak[41]. Dosi-kontzentrazio erlazioan aldaketak eragiten dituzten eta neurtu daitezkeen faktoreak bilatzea eta desberdintasun hauen magnitudea aztertzea da bere helburu nagusia. Hau bereziki baliagarria izango da populazio talde desberdinen artean farmakoaren farmakozinetika aldatu daitekeenaren susmoa dagoenean. Izan ere, dosia modu egokian pertsonalizatzea bermatzen du[42].

Tradizionalki, ikerketa farmakozinetikoak etapa biko metodoa erabiliaz burutu dira. Metodo honen lehenengo etapan, indibiduoen parametro farmakozinetikoak erregresio ez-linealaren bidez estimatzen dira. Horretarako, indibiduoen kontzentrazio-denboraren datu nahikoak beharko dira. Aurreneko etapa honetan estimatutako balioak bigarren fasean sarrera-datu moduan erabiliko dira, laginaren estatistika deskribatzaileak kalkulatzeko. Normalean estimatutako

[40] Minne L, Eslami S, Kuiper RA, Abu-Hanna A, Dongelmans DA. Five years of therapeutic drug monitoring in the intensive care did not change vancomycin prescription behaviour: perceived needs for decision support. Minerva Anestesiol. 2012;78(6):684-92.

[41] Aarons L. Population Pharmacokinetics: Theory and Practice. Br J Clin Pharmacol. 1991;32(6):669-70.

[42] Charles B. Population pharmacokinetics: an overview, Aust Prescr 2014;37:210-131.

parametroen batez bestekoa, bariantza eta kobariantza izan ohi dira. Metodo honen muga nagusia indibiduo bakoitzeko kontzentrazio-denbora datu nahiko behar direla da[43].

Etapa biko metodoa erabili ezin denean (datu sakabanatuak baino ez daudenean, adibidez), fase bakarreko metodoa erabili beharko da. Hau da, efektu mistoetako modelizazio ez-lineala (*non linear mixed-effects*, NLME). Metodo honen bidez indibiduoen arteko informazioa partekatu daitekeenez, datu sakabanatuak daudenean ez ezik, informazio aberatsa dagoenean edota azken bien konbinazio bat ematen denean ere erabili daiteke.

Efektu mistoetako modelizazio ez-lineala datuak erabiltzeko modu efizienteagoa da, farmakozinetikari buruz informazio integratua lortzeko aukera ematen baitu. Izan ere, metodo honek parametroen batez bestekoa eta aldakortasuna estimatzen ditu momentu berean, baina gai da aldakortasun-intra eta -interindibidualaren artean desberdintzeko. Beste modu batean esanda, ikertutako populazioaren batez besteko joera deskribatzen du; eta, aldi berean, subjektuen artean ikusitako profil desberdinen arduraduna den indibiduoen arteko aldakortasuna kuantifikatzen du.

Efektu mistoetako modelizazio ez-lineala inplementatua duten zenbait software badaude ere, azken hamarkadetan farmakometrian gehien erabili direnen artean NONMEM dago (NON-liner Mixed Effects Modelling)[44].

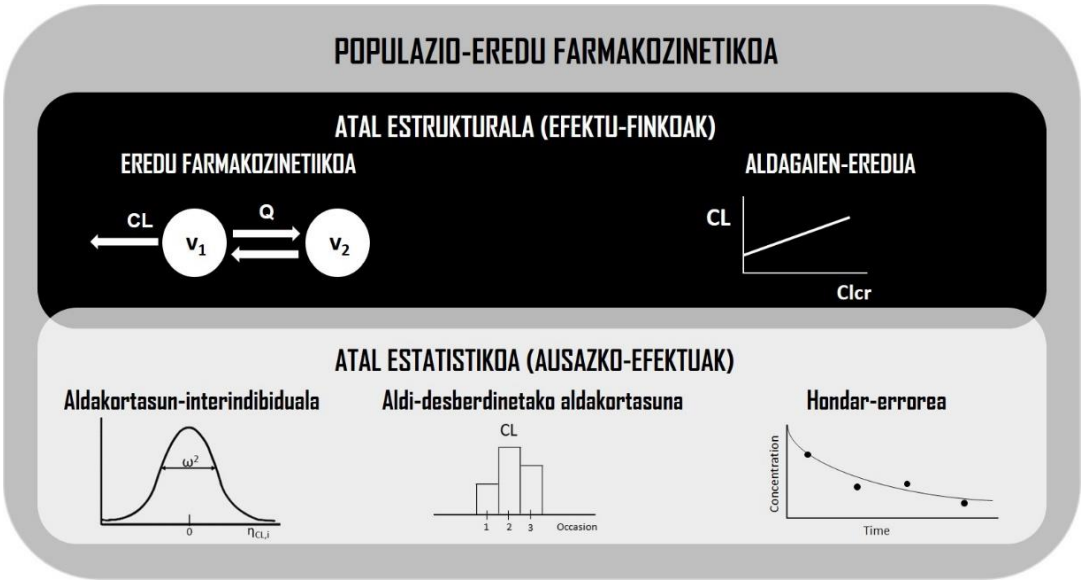
3. irudian populazio-farmakozinetika analisiaren oinarriak azaltzen dira. Farmako baten populazio-farmakozinetika aztertzean, eredu-estrukturalak parametro-tipikoak (efektu-finkoak) deskribatuko ditu. Hortaz, populazioaren kontzentrazio-denboraren profilaren arduraduna izango da. Ezaugarri demografiko edota fisiopatologikoek parametro horietan eragin dezakete; besteak

[43] U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Population Pharmacokinetics. Rockville; 1999.

[44] Bauer R. NONMEM users guide: introduction to NONMEM 7.4.1. ICON Plc. Gaithersburg, Maryland; 2017.

beste, sexuak, adinak edota kreatinina argitzapenak. Faktore horiei aldagai deritze. Aldagaiak eredu-estrukturalaren parte izango dira ere, eta indibiduoen arteko aldakortasuna azalduko dute.

Bestalde, eredu-estatistikoak ausazko-aldakortasuna kuantifikatzen du. Alegia, eredu-estrukturalaren bitartez populazioaren kontzentrazioetan azaldu ezin daitekeen aldakortasuna. Modu honetan, ausazko-efektuek honako aldakortasunak kontuan hartuko dituzte: aldakortasun-interindibiduala (*inter-individual variability*, IIV), aldi-desberdinetako aldakortasuna (*inter-occasion variability*; IOV) eta hondar-errorea (*residual error*, RE).



3**. irudia**. Analisi farmakozinetikoa populazio-ikuspuntua erabilita.

3.3.1. Aldakortasun-interindibiduala (IIV)

IIVk populazioaren parametro tipikoaren (θ) eta indibiduo bakoitzaren balioen arteko desberdintasunak definitzen ditu. Hobeto ulertu ahal izateko, argitzapena (CL) erabiliko da adibide moduan 1.ekuazioan (**Eq.1**):

$$CL_i = \theta_{CL} \times e^{\eta_{CL,i}} \quad \textbf{(Eq.1)}$$

Non *CLi i*-indibiduoaren argitzapena den; θ_{CL} populazioaren balio tipikoa eta $\eta_{CL,i}$ populazioaren eta indibiduoen arteko desberdintasuna. Era honetan, θ_{CL}-k balio bera edukiko du subjektu guztientzat eta η, aldiz, indibiduo bakoitzarentzat desberdina izango da. Populazio baten η balioen distribuzioa normaltzat hartuko da, 0 batez bestekoarekin eta estimatutako ω^2_{CL} bariantziarekin. Horrela, geroz eta bariantzia handiagoa izan, orduan eta CLrekin erlazionatutako IIV handiagoa izango da.

3.3.2. Aldi-desberdinetako aldakortasuna (IOV)

Subjektu berdinari farmako bat aldi desberdinetan administratuz gero, parametroetan ematen den aldakortasunari deritzo. Batzuetan aldakortasunaren jatorria identifikatzea dago; hala nola, pazientearen egoera aldatzea edota tratamenduari atxikimendu desegokia. IOVren parametroak horrela definitu daitezke (**Eq.2**):

$$\text{If (Occasion = 1) then IOV} = \eta_1$$

$$\text{If (Occasion = 2) then IOV} = \eta_2$$

$$\text{IIV} = \eta_3$$

$$CL_i = \theta_{CL} \times e^{IIV+IOV} \quad \textbf{(Eq.2)}$$

Populazio-ereduan IOV sartu ahal izateko, aldi bakoitzetik (okasio bakoitzetik) lagin bat baino gehiago behar izango da. Osterantzean, ezin izango da hondar-erroretik bereiztu.

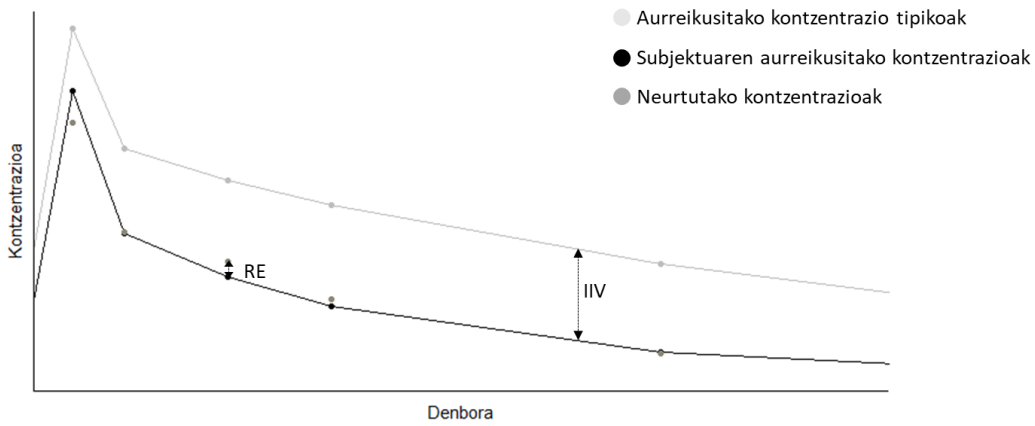
3.3.3. Hondar-errorea

Finkatutako parametroak subjektu baten, *i*, denbora jakin bateko, *j*, farmako-kontzentrazioak aurreikusteko erabiltzen dira. Dene den, neurtutako kontzentrazioak ($C_{obs,ij}$) eta aurreikusitakoak ($C_{pred,ij}$) ez dira berdinak izango. Desberdintasun hauek, ε_{ij}, hondar-erroreak hartuko ditu barne. Errore mota honek entseguarekin erlazionatutako erroreak, laginak hartzean eta dosifikazioan emandako akatsak edota ereduaren zehaztapen okerrak kontuan hartuko ditu (**Eq.3**):

$$C_{obs,ij} = C_{pred,ij} + \varepsilon_{ij} \qquad \textbf{(Eq.3)}$$

ε_{ij} balioek zero inguruan distribuzio normala daukatela eta beraien bariantza σ^2 dela onartuko da.

4. irudiak subjektu jakin batentzat neurtutako farmako kontzentrazioak, bere aurreikusiak eta populazioaren aurreikusiak (balio tipikoak) azaltzen dira. Gainera, aldakortasun desberdinak ere ikus daitezke.



4. irudia. Subjektu jakin batentzat neurtutako farmako kontzentrazioak eta aurreikusitakoak azaltzen dira, baita balio tipikoak ere. Bestalde, aldakortasun-interindibiduala (IIV) eta hondar-errorea (RE) ikus daitezke.

Populazio edota azpitalde jakin batentzat eredu farmakozinetiko bat sortzean aldakortasuna kuantifikatzea ezinbestekoa izango da. Gainera, eredu-estrukturalak egokia izan behar du, aldarapenik edota zehaztasun okerrik gabea, ondorio desegokiak ekiditeko. Hortaz, populazio-eredua garatzen ari den bitartean edota behin azken eredua lortu ostean, ezinbestekoa izango da ereduaren ebaluazioa egitea. Izan ere, ereduaren eta datuen arteko doikuntzaren egokitasuna aztertuz, egindako hurbilketen egokitasuna ezagutu ahal izango da.

3.4. Ereduaren ebaluazioa

Nahiz eta eredu farmakozinetikoak ebaluatzeko tresna ugari dauden, ez dago aurretik zehaztutako pausu idealik edo optimorik jarraitzeko. Ebaluazio-metodoak etengabe aldatzen ari dira eta diagnostiko tresna desberdinak erabiltzea

gomendagarria da[45]. Metodo hauek hiru talde desberdinetan banandu dira: zenbakizkoak, grafikoak eta simulazioetan oinarritutako diagnostikoak.

3.4.1. Zenbakizko diagnostikoa

Parametroak estimatzeko NONMEMek egiantza-maximoaren metodoa erabiltzen du. Hurbilketa honek karratu txiki zabalduen funtzio-objektiboa minimizatzen du. Azken hori, egiantza-logaritmoaren bikoitzarekiko proportzionala da ia (-2xlog egiantza). Normaltasun egoera batean, egiantza-maximoaren estimatuak funtzio-objektiboaren balio (OFV) minimoan lortzen dira. OFVren balio absolutua ez dauka esanahirik, eta bere beherakada da garrantzitsua izango dena. Horrela, habiratutako bi ereduren artean aukeratzeko OFV-ren diferentzia (ΔOFV, egiantza-ratioa) erabiliko da. Modu honetan, parametro extra bat ereduan gehitzean, ΔOFVren -3,84 eta -6,63 balioak <0,05 eta <0,01 esangura-mailekin bat etorriko dira, hurrez hurren[46]. Habiaratuta ez dauden ereduen artean ΔOFV eta esangura mailaren artean ezin daitekeenez erlaziorik zehaztu, konparaketak Akaike informazio-kriterioa (*Akaike information criteria*, AIC) erabiliz egin beharko dira.

Populazio-eredu bat eraikitzean ezinbestekoa izango da parametroak zein doitasunarekin estimatu diren jakitea. Horretarako, errore erlatibo estandarrak (*relative standard errors*, RSE) aintzat hartu behar dira, aldakuntza-koefiziente moduan adieraziko direnak (*coefficient of variation*, CV)[47]. Eredu-estrukturaleko parametroek ez dituzte %25 baino RSE balio handiagoak eduki behar eta eredu-estatistikoarenak %50 baino txikiagoak izan behar dira. Parametroen doitasunak

[45] Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol. 2017;6(2):87-109.

[46] Wählby U, Jonsson EN, Karlsson MO. Assessment of Actual Significance Levels for Covariate Effects in NONMEM. Pharmacokinet Pharmacodyn. 2001;28(3):231-52.

[47] Ette EI, Williams PJ. Population pharmacokinetics II: estimation methods. Ann Pharmacother. 2004;38(11):1907-15.

zenbait faktorek baldintzatuko dute, besteak beste, entseguaren diseinuak, datuen kalitateak edota ereduaren zehaztapen okerrek eta parametro gehiegi zehazteak.

Eredu farmakozinetikoak sendotasun nahikoa duen egiaztatzeko, bootstrap metodoak erabili daitezke. Horiek parametroen zehaztasuna estimatzeko erabiltzen diren ber-laginketa teknikak dira. Laburbilduz, bootstrap-ak datu basetik indibiduoak aleatorioki hartzen ditu eta base datu berriak erreplikatzen ditu. Hortaz, erreplika bakoitzean indibiduo bera behin baino gehiagotan hautatu daiteke edo behin ere ez. Behin erreplikazioak burutu ostean, parametro bakoitzeko mediana eta 5. eta 95. pertzentilak kalkulatzen dira eta hautatutako ereduarekin lortutako balioekin konparatu[48].

3.4.2. Grafikoen bidezko diagnostikoa

Ebaluazio metodo hauen abantaila nagusia zenbakizko-diagnostikoak baino errazago interpretatu daitezkela da. Nahiz eta grafiko mota asko egon, gehien erabiltzen direnak doikuntza-egokitasuna ebaluatzeko grafikoak (*goodness-of-fit*, GOF, *plots*) dira.

Ezagunenen artean honako GOF grafikoak daude:

a) Populazio- (*population predictions*, PRED) eta norbanakoen- (*individual predictions*, IPRED) aurreikusiak versus behatutakoak (*observations*, DV)

Grafiko hauek oso baliagarriak dira ereduaren errendimendu orokorra aztertzeko. Eredua egokia denean IPREDak DVetatik gertu egongo dira. Hortaz, datuak identitate-lerroaren ondoan sakabanatuta egongo dira. Bestalde, PREDen balioak eta neurtutakoen batez bestekoak antzekoak izango dira. Grafiko hauetan joerak antzemateak iradoki dezake aldaketak egin behar

[48] Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci. 1986;1: 54–77.

izatea eredu-estrukturalean edota hondar-erroreen ereduan zein aldakortasun-interindibidualean.

b) Haztatutako baldintzapeko hondar-balioak (CWRES) versus denbora edo versus PRED

Grafiko hauek eredu-estrukturala ebaluatzeko erabilgarriak dira. Datuak zero balioa duen lerro horizontalaren inguruan sakabanatuak egon behar dira, inolako joerarik aurkeztu gabe.

c) IPRED versus denbora edo norbanako bakoitzaren haztatutako hondar-balioak (*individual weighted residuals*, IWRES).

Grafiko hauek oso baliagarriak dira hondar-errorea modelizatzean egon daitezkeen akatsak hautemateko. IWRESi dagokionez, hautatutako eredua egokia denean, datuak zero balioa duen lerro horizontalaren inguruan sakabanatuak aurkituko dira, eta puntu gehienak -1,96 eta 1,96 balioen artean kokatuko dira.

Dena den, indibiduoen datuek parametro bateri edo gehiagori dagokionez informazio nahikoa ematen ez dutenean, IPREDak ez dira sinesgarriak izango. Izan ere, kasu hauetan, indibiduoen estimatutako parametroak populazioaren batez bestekoari hurbilduko zaizkio eta grafikoari so egitean eredua egokia dela ondoriozta daiteke; benetan ereduaren zehaztapen oker baten aurrean egon arren. Fenomeno hau kuantifikatzeko η-shrinkage-a eta ε-shrinkage-a erabiliko dira. Horrela, indibiduoen grafikoekin fidatu ahal izateko, desbiderapen estandar moduan kalkulatutako %20-30 arteko shrinkage balioak limite moduan finkatu dira[49].

[49] Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17-20.

3.4.3. Simulazioetan oinarritutako diagnostikoak

Populazio eredu farmakozinetiko bat ebaluatzeko gehien erabiltzen diren simulazioetan oinarritutako diagnostikoak azterketa bisual iragarleak dira (*visual predictive check*, VPC). Grafiko hauek aldagai-independentearen aurrean (gehienetan denbora) neurtutako balioen distribuzioa eta aurreikusitakoen distribuzioa konparatzen dituzte. Horrela, bisualki ebaluatu daiteke ea ereduaren zati estrukturala eta estatistikoa joera-zentrala eta neurtutako informazioaren aldakortasuna aurreikusteko gai diren. Horretarako, hautatutako eredua erabiltzen da jatorrizko informazioaren ezaugarri berdinak dituzten datu berriak simulatzeko (normalean 500 edo 1000). Simulatutako datu-multzo bakoitzeko 2,5., 50. eta 97,5. pertzentilak kalkulatzen dira denbora-puntu bakoitzeko. Ostean, horien %95ko konfiantza-tarteak datu experimentalen 2,5., 50. eta 97,5.pertzentilekin bat irudikatzen dira. Gainera VPCak desberdinketak eginda irudikatu daitezke, interesgarriak diren aldagaien arabera, pisua edota kreatinina argitzapena, esaterako. Modu honetan, ereduaren egokitasuna aldagai desberdinak aintzat hartuta ebaluatu daiteke. Dosifikazio erregimen desberdinak administratu direnean, edota aldagaien arteko erlazioan zein ikerketaren diseinuan desberdintasunak eman direnean, predikzioa zuzenduta duten VPCak erabili behar dira (*prediction-corrected VPC*, pc-VPC). Izan ere, neurtutako balioak eta PREDen oinarritutako simulatutako mendeko-aldagaia normalizatzen ditu eta diferentzia hauek maneiatzea bermatzen du.

Gaur egun, populazio-ereduak garatzeko eta ebaluatzeko tresna ugari dago. Ezagunenen artean honakoak topatu ditzakegu: Xpose (NONMEMekin

egindako populazio-ereduak lantzeko R-n oinarritutako laguntza-paketea)[50], PSN[51] edo Pirana[52].

4. Farmakodinamia (PD)

4.1. Kontzeptua

Medikamentuen posologia optimizatzeko, farmakozinetikaz gain, farmakodinamia ere kontuan hartu behar da. Farmakodinamiak medikamentu batek, bere ekintza mekanismoari esker, kontzentrazio zehatz batean, organismoan eragiten dituen efektu biokimiko eta fisiologikoak aztertzen ditu. Sinplifikatuz, "farmakoak gorputzari egiten diona" bezala definitu izan da. Terapia antimikrobianoan, farmakoaren esposizioa eta efektu mikrobiologikoa edo klinikoa erlazionatzen duen jakintzagaia da[53,54].

Antibiotiko baten efektua neurtzeko erabiltzen den adierazle nagusia kontzentrazio minimo inhibitzailea da (*minimum inhibitory concentration*, MIC). Alegia, bakterioen ageriko-hazkuntza ekiditeko beharrezkoa den kontzentrazio

[50] Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. 1999;58(1):51-64.

[51] Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)--a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 2004;75(2):85-94.

[52] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

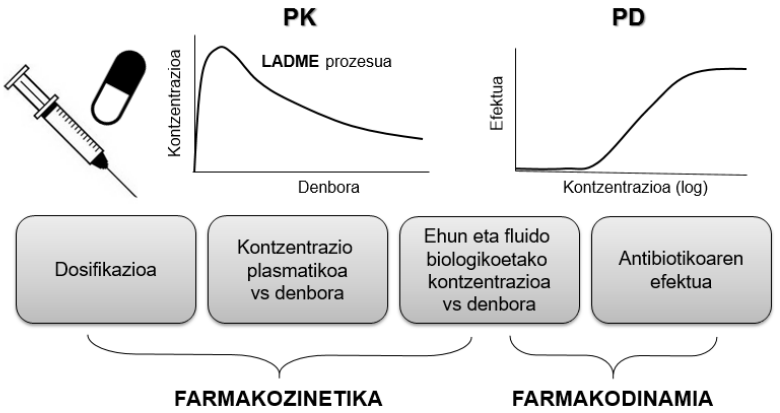
[53] Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004;2(4):289-300.

[54] Schmidt S, Schuck E, Kumar V, Burkhardt O, Derendorf H. Integration of pharmacokinetic/ pharmacodynamic modeling and simulation in the development of new anti-infective agents-minimum inhibitory concentration versus time-kill curves. Expert Opin Drug Discov. 2007;2(6):849-60.

minimoa. Adierazle hau kalkulatzeko metodologia desberdinak erabili izan dira[55]. MICak modu estatikoan, mikroorganismoen eta antibiotikoen arteko elkarrekintza baino ez du kontuan hartzen, ostalariarekin dituztenak aintzat hartu gabe. Ondorioz, antimikrobianoen efikazia ebaluatzeko soilik MIC balioak aintzat hartzea desegokia izan daiteke.

5. Analisi farmakozinetiko/farmakodinamikoa

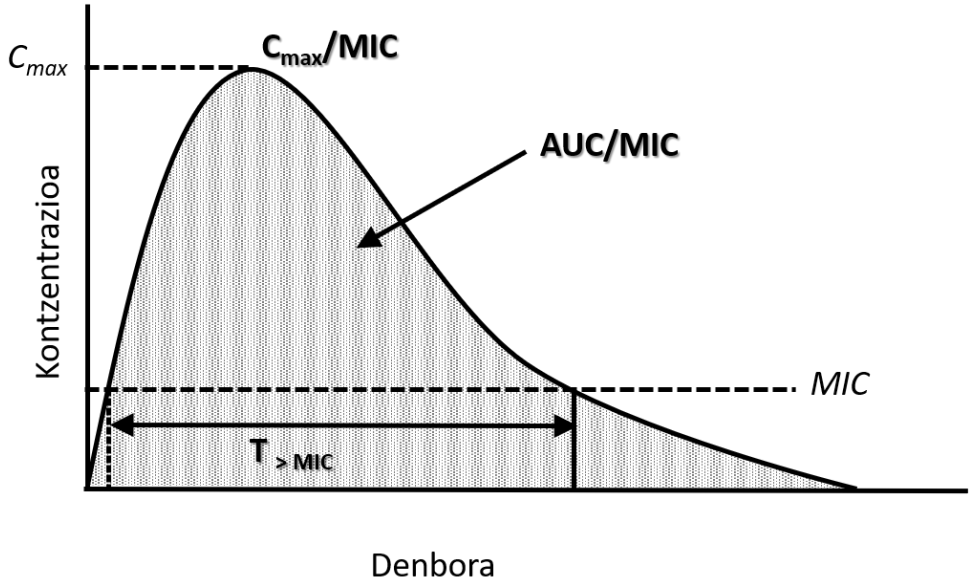
Farmakodinamia medikamentuaren kontzentrazioaren menpe dagoenez, eta kontzentrazioa farmakoaren farmakozinetikak baldintzatzen duela kontuan hartuz, PK eta PD estuki erlazionatuta daude (**5. irudia**). Analisi farmakozinetiko/farmakodinamikoak indibiduo desberdinentzat eta infekzio mota bakoitzarentzat antibiotikoen dosi egokiena aukeratzea ahalbidetzen du, eta efektu desiragaitzak edota erresistentziak agertzea saihesten du.



5. irudia. PKren eta PDren arteko erlazioa.

[55] Andrews JM. Determination of minimum inhibitory concentrations. J Antimicrob Chemother. 2001;48 Suppl 1:5-16.

Parametro farmakozinetikoen eta mikrobiologikoen arteko erlazio kuantitatiboari indize farmakozinetiko/farmakodinamiko (PDI) deritzo. Antibiotikoen efektua aurreikusteko hiru deskribatu dira (**6. irudia**). Alde batetik, oreka-egonkorreko egoeran kontzentrazio plasmatikoak MIC balioaren gainetik mantentzen diren denbora ($T_{>MIC}$); bestetik, antibiotikoaren kontzentrazio maximoaren eta MICaren arteko ratioa (Cmax/MIC), eta azkenik, oreka-egonkorrean farmakoaren kontzentrazio-denbora kurbaren azpian mugaturiko azalera (normalean 24 ordutan zehar) eta MICaren arteko erlazioa (AUC_{24h}/MIC). Antibiotiko bakoitzarentzat, indize horiek balio jakin bat lortu beharko dute eraginkortasuna bermatzeko[56,57].



6. irudia: Antibiotikoen efikaziarekin erlazionatuta dauden PDIak.

[56] Scaglione F. Pharmacokinetic/Pharmacodynamic (PK/PD) considerations in the management of Gram-positive bacteraemia. Int J Antimicrob Agents. 2010;36 Suppl 2:S33-9.

[57] Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the Intensive care unit. Crit Care Clin. 2011;27(1):1-18.

Antibiotikoek daukaten aktibitatearen arabera hiru patroi nagusi deskribatu dira, eta PDI egokiena farmakoaren araberakoa izango da:

a) Kontzentrazioaren menpeko eragina duten antimikrobianoak, efektu post-antibiotiko (EPA) luzearekin

EPA luzea dutenez, farmako kontzentrazioak MICaren azpitik daudenean ere inhibitua dago bakterioen hazkuntza. Beraien efikazia determinatzeko gehien erabiltzen diren indizeak Cmax/MIC eta AUC_{24h}/MIC dira. Horregatik, medikamentu-kontzentrazio altuak eta dosifikazio-tarte luzeak erabiltzen dira. Izan ere, bakterioen heriotza-tasa altuagoa eta efektu azkarragoa ikusi izan dira antibiotikoaren dosia handitzean. Talde honetan, besteak beste, aminoglikosidoak edota fluorokinolonak daude.

b) Denboraren menpeko efektua duten antibiotikoak, EPA motzarekin

Antibiotiko hauen efikaziarekin ongien korrelazionatu den indizea $T_{>MIC}$ da, eta normalean dosifikazio-tartearen ehuneko moduan adierazten da. Horrela, medikamentu baten erdibizitza geroz eta motzagoa izan, orduan eta maiztasun handiagoan administratu beharko da. Zenbait kasutan, bereziki behar den $T_{>MIC}$ altua denean, zain-barneko perfusioa beharrezkoa izan daiteke. Talde honen barruan antibiotiko betalaktamikoak daude[56,57].

c) Kontzentrazioarekiko independente den efektua duten antibiotikoak, EPA luzearekin

Lehenengo taldean gertatzen zen moduan, antibiotiko-kontzentrazio altuek heriotza bakterianoa handitzen dute arinki, baina mikroorganismoen hazkuntza inhibituko dute luzaroko, kontzentrazioak MICaren azpitik mantentzen direnean ere. Talde honetan erabiltzen diren indikadoreak AUC_{24h}/MIC edo Cmax/MIC dira eta bankomizina, tetraziklinak edota tigeziklina bezalako antibiotikoak hartzen ditu barne[56,57].

Esan bezala, analisi farmakozinetiko/farmakodinamiko egokia egiteko, PDI aproposa aukeratzeaz gain, antibiotiko bakoitzarekin arrakasta terapeutikoa lortzeko behar den indizearen balio zehatza ere determinatu behar da, alegia, helburu farmakodinamikoa zehaztu behar da (*pharmacodynamic target*, PDT)[58]. Antibiotiko baten dosifikazio bat eraginkortzat hartzeko, beraz, dagokion PDIarentzat helburu farmakodinamiko jakin batera heltzen den aztertu beharko da, aurretik egindako *in vivo*[59] zein *in vitro*[60,61] ikerketetan adostuko dena. Batzuetan, PDTa zehazteko, farmakoaren kontzentrazio totala kontuan hartu beharrean, frakzioa askea (*f*) hartzen da aintzat, hau baita efektu farmakologikoa eragiteko gai den bakarra. Adibide moduan, **1. taulan** zenbait antibiotikoren PDIak zein PDTak jaso dira.

[58] Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother. 2015;21(5):319-29.

[59] Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev. 2007;20(3):391-408.

[60] Andes D, Craig WA. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents. 2002;19(4):261-8.

[61] Zhao M, Lepak AJ, Andes DR. Animal models in the pharmacokinetic/pharmacodynamic evaluation of antimicrobial agents. Bioorg Med Chem. 2016;24(24):6390-400.

1. taula: Zenbait antibiotikoren aktibitate mota, PDIak eta PDTak.

Aktibitate mota	Antibiotikoa	Indize farmakozinetiko/ farmakodinamikoa	Helburu farmakodinamikoa
Kontzentrazio-menpekoa EPA luzearekin	Aminoglikosidoak	Cmax/MIC	10[62]
	Fluorokinolonak	AUC_{24h}/MIC	125[63,64]
	Daptomizina	AUC_{24h}/MIC	666[65]
Denbora-menpekoa EPA motzarekin	Betalaktamikoak:		
	Penizilinak	$fT_{>MIC}$	50-60[53]
	Zefalosporinak		60-70[53]
	Karbapenemak		40-50[53]
Kontzentrazio independentea EPA luzearekin	Linezolid	AUC_{24h}/MIC -- $T_{>MIC}$*	80 -- 85[66,67]*
	Bankomizina	AUC_{24h}/MIC	400[68]
	Tigeziklina	AUC_{24h}/MIC	17,9[69]

*Linezoliden kasuan, bai AUC_{24h}/MIC baita $T_{>MIC}$ ere kontuan har daitezke.

[62] Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother. 1999;43(3):623-9.

[63] Schentag JJ. Pharmacokinetic and pharmacodynamic surrogate markers: studies with fluoroquinolones in patients. Am J Health Syst Pharm. 1999;56(22 Suppl 3):S21-4.

[64] Aminimanizani A, Beringer P, Jelliffe R. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. Clin Pharmacokinet. 2001;40(3):169-87.

[65] Canut A, Isla A, Betriu C, Gascón AR. Pharmacokinetic-pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. Eur J Clin Microbiol Infect Dis. 2012;31(9):2227-35.

[66] Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012;67(8):2034-42.

[67] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003, 42:1411-23.

[68] Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet. 2004;43(13):925-42.

[69] Meagher AK, Passarell JA, Cirincione BB, Van Wart SA, Liolios K, Babinchak T, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. Antimicrob Agents Chemother. 2007;51(6):1939-45.

6. Monte Carlo simulazioa

Gaixo larrietan pertsonen arteko aldakortasuna nabaria izan ohi da eta ZIUetan egindako ikerketan parte hartzen duen gaixo-kopurua mugatua izaten da. Informazio murritz horrek dosifikazioen doikuntza ezegokia edota, helburu terapeutikoak lortzeari dagokionez, predikzio okerrak egitera eraman gaitzake. Hori gertatu ez dadin, indibiduoen arteko aldakortasuna aintzat hartu eta laginaren tamaina handiagotu edo maximizatu egiten duten estrategiak egin daitezke, Monte Carlo simulazioa (MCS) erabiliz. MCSak, aurretik eraikitako eredu farmakozinetikoaren ekuazioak aintzat hartzen ditu eta, indibiduo desberdinen artean lortutako parametroen distribuzioa kontuan hartuz (batez bestekoa eta desbiderapen estandarra, esaterako), milaka subjektu desberdin simulatzen ditu[70].

Simulazio horiek, beraz, baliagarriak izango dira terapia enpirikoan zein populazio berezietan (gaixo larriak, paziente obeso zein pertsona nagusiak, etab.) dosifikazio optimoak aurreikusteko. Dena den, emaitza fidagarriak lortzeko eta alborapenik egon ez dadin, nahitaezkoa izango da balioztatu den eredu farmakozinetiko bat edukitzea, barne hartzen dituen aldagaiak kontuan hartuz. Bestalde, ezinbestekoa izango da ere PKren eta PDren arteko erlazioa ondo definitzen duen eredu farmakodinamikoa izatea[71].

MCSa egitean, helburu farmakozinetiko/farmakodinamikoa lortzeko probabilitateen (PTA) kalkulua egiten da. PTAk, MIC balio zehatz batentzat, PDIak balio jakin bat lortzeko probabilitatea zehazten du, adibidez %30ko $T_{>MIC}$ edota 200eko AUC_{24h}/MIC. Hau da, simulatutako pazienteen zein ehunekok

[70] Bonate PL. A brief introduction to Monte Carlo simulation. Clin Pharmacokinet. 2001;40(1):15-22.

[71] Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. J Antimicrob Chemother. 2011;66(2):227-31.

lortzen duen PDIaren balio berdina edo handiagoa determinatzen du, MIC balio konkretu batentzat.

Hala ere, askotan, eguneroko praktika klinikoan ez da mikroorganismoen sentikortasuna ezagutzen. Kasu horietan, baliagarria izan daiteke erantzunaren metatze-frakzioa (CFR) erabiltzea. CFRak arrakasta izateko probabilitatea kalkulatzen du antibiotiko baten dosifikazio-erregimen zehatz batekin eta mikroorganismoen populazio jakin batentzat. Hortaz, populazio baten zein ehunekok lortuko duen helburu farmakodinamikora heltzea estimatzen du, Monte Carlo simulazioak burutu ostean eta mikroorganismo jakin baten distribuzioa ezagututa. CFRa horrela kalkulatuko da:

$$CFR = \sum_{i=1}^{n} PTA_i \times F_i \qquad \textbf{(Eq.4)}$$

Non *i* azpiindizeak mikroorganismo populazio batean dagoen MIC balio txikienetik handienerako balioak hartzen dituen; PTA*i* MIC balio bakoitzarentzat lortutako PTA den eta F*i* mikroorganismo populazioan MIC balio bakoitzak duen frakzioa den.

Hurbilketa hau patogenoen sentikortasuna oraindik ezaguna ez denetan baliagarria izan daiteke; baita ospitale konkretu batean antibiotiko baten dosifikazio-erregimen egokiena zein den determinatzeko ere. Hala ere, CFRaren estimazio egokia egiteko, ezinbestekoa izango da aurretik MICen distribuzioa leku eta denbora konkretu batentzat ondo zehaztua izatea. Izan ere, bakterioek antibiotikoekiko duten sentikortasun-patroiak alda daitezke denboran zehar, baita lurralde, ospitale zein zerbitzu artean ere. Hori dela eta, askotan literaturan argitaratutako MICen balioak ez dira momentu zehatz bateko errealitatearen adierazgarri.

7. Ondorioak

Analisi farmakozinetiko/farmakodinamikoak, populazioaren modelizazio farmakozinetikoarekin eta MCSekin batera, antibiotikoen dosifikazio-erregimenen optimizazioa egitea ahalbidetzen du. Hau bereziki erabilgarria izango da gaixo larrietan. Alde batetik, farmakoen PK modu nabarian eraldatuta izan ohi dutelako, eta bestetik, infekzioak antibiotikoekiko erresistenteagoak diren mikroorganismoek eragiten dizkietelako.

HELBURUAK

Helburuak

Azken urteotan, gaixotasun infekziosoen kudeaketa osasun publikoko arazo bilakatu da. Antimikrobianoekiko erresistentzien igoerak hainbat antibiotikoek infekzioen aurka egiteko zuten gaitasuna galarazi du, bakterioen aurkako tratamenduen efikazia gutxituz. Arazo honen larriagotzea ekiditeko, ezinbestekoa da hainbat ekintza desberdin aurrera eramatea, hala nola, antimikrobiano berrien garapena, infekzioen prebentzioa edota dosifikazioen optimizazioa bultzatzea.

Tratamenduaren optimizazioari dagokionez, premiazkoa da farmakoek pazienteetan jasaten dituzten prozesu farmakozinetikoak eta antibiotikoen farmakodinamia ezagutzea. Hau da, antibiotikoak eragiten duen efektuaren berri izatea infekzioa eragiten duen mikroorganismoan. Horrela, analisi farmakozinetiko/farmakodinamikoa eta Monte Carlo simulazioa erreminta erabilgarriak izan daitezke dosifikazio optimoa bermatzeko; arrakasta probabilitateak handituz eta erresistentziak zein eragin desiragaitzak azaltzea galaraziz. Horrek berebiziko garrantzia izango du farmakoen farmakozinetika zein farmakodinamia eraldatuak izan ohi dituzten pazienteetan, gaixo kritikoetan, esaterako.

Gauzak horrela, tesi honen helburu nagusia gaixo larrietan daptomizinarentzat eta linezolidentzat populazio-eredu farmakozinetikoak garatzea izango da; modu honetan, Gram-positiboen aurkakoak diren bi antibiotiko berrienetarako hauen dosifikazio-erregimenen eraginkortasuna ebaluatzeko, analisi farmakozinetiko/farmakodinamikoa eta Monte Carlo simulazioak erabiliz. Xede hau gauzatzeko asmoz, hurrengo helburu partzialak proposatu dira:

1) Daptomizinarentzat eta linezolidentzat populazio-eredu farmakozinetikoak garatzea, antimikrobiano hauen farmakozinetikan eragin esanguratsua duten faktore fisiologikoak eta patologikoak identifikatzeko, eta hortaz, pazienteek duten antibiotikoarekiko esposizioa aztertzeko asmoz. Aldakortasun farmakozinetikoaren zergatiak identifikatu eta kuantifikatuko dira; beharrezko kasuetan, etengabeko giltzurrun ordezkatze teknikak ere aintzat hartuta.

2) Tratamenduaren eraginkortasunarekin erlazionaturiko indize farmakozinetiko/farmakodinamikoak eta efektu desiragaitzekin lotutako kontzentrazioak kontuan hartuta, dosi estandarrarekin kontzentrazio eraginkorrak eta segurtasunarekin erlazionaturiko profilak lortzeko probabilitateak ebaluatzea.

3) Dosifikazio erregimen alternatiboen simulazioak egitea eta terapia antimikrobianoaren emaitza mesedegarriak lortzeko gomendioak proposatzea. Horretarako, tratamenduaren efikazia ez ezik, albo-eraginekin lotutako antibiotiko kontzentrazioak lortzeko probabilitateak ere kontuan hartu beharko dira.

ATAL-ESPERIMENTALA

2. kapitulua

Daptomizinaren populazio-farmakozinetika gaixo larrietan

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LABURPENA: Daptomizinak hainbat bakterio Gram-positiboren kontra aktibitatea erakutsi du. Haatik, gaixo kritikoetan onartutako dosiak sarritan ez dira nahikoak izaten. Ikerketa honen helburu nagusia izango da gaixo larrientzat daptomizinaren populazio-eredu farmakozinetiko bat garatzea eta baita analisi farmakozinetiko/farmakodinamikoa burutzea, terapiaren efikazia zein den estimatzeko asmoz. Zainketa intentsiboko unitateko hamasei pazientek parte hartu zuten ikerketan, eta horietatik lauk etengabeko giltzurrun-ordezkatze teknikak (EGOT) ezarriak zituzten. Behin daptomizina administratu ostean, plasma eta efluente laginak aurretik zehaztutako denbora-tarteetan jaso ziren. Datuak analizatzeko populazio-eredu bat garatu zen NONMEM 7.3 programa erabiliz. Dosifikazio-erregimen desberdinen egokitasuna zehazteko, Monte Carlo simulazioak egin ziren. Horrela, terapiaren arrakastarekin erlazionatutako balioak eta toxikotasunarekin lotutako kontzentrazioak lortzeko probabilitateak kalkulatu ziren; hau da, AUC_{24h}/MIC ≥ 666 eta $Cmin_{ss}$ ≥ 24.3 mg/L, hurrenez, hurren. Daptomizinaren plasma kontzentrazioak ongien deskribatu zituen eredua konpartimentu bakarrekoa izan zen. Kreatinina argitzapenaren (Clcr) eragina farmakoaren eliminazioan identifikatu zen, eta, EGOTak ezarriak zituzten pazienteetan, baita gorputz-kanpoko argitzapenarena ere. Analisi farmakozinetiko/farmakodinamikoaren bitartez, egiaztatu zen MIC balioak ≥ 1 mg/L direnean, 280 eta 420 mg/24h-ko dosiek ez dutela eraginkortasuna lortzeko probabilitatea altuak izango pazienteen Clcr > 60 mL/min denean, edo oraindik baxuagoa denean EGOTak ezarriak izatean. Horrela, paziente hauetan dosi altuagoak beharko lirateke (560-840 mg/24h). MIC balioa ≥ 4 mg/L duten bakterioek eragindako infekzioak tratatzeko, dosi altuena administratzea ere ez litzateke nahikoa izango.

1. Sarrera

Daptomizina bakterio Gram-positiboen aurkako jarduera duen antibiotiko lipopeptidikoa da. Besteak beste, eraginkortasuna frogatu du metizilinarekiko erresistenteak diren *Staphylococcus aureus* (MRSA) eta bankomizinarekiko sentikorrak diren enterokokoen aurka. Egun, bakterio Gram-positiboek sortutako larruazal eta atal biguinen infekzio konplexuak, eskuineko endokarditis infekziosoa eta *S. aureus*-ek sortutako bakteriemia tratatzeko indikazioetan baimendua dago[1,2,3].

Daptomizina zelulaz kanpoko fluidoetan zehar banatzen da gehienbat, eta odoleko proteinekiko lotura handia izan ohi du (%90 inguru). Batez ere giltzurrun bidez iraizten denez, giltzurrun-gutxiegitasuna duten pazienteetan dosia doitzea aholkatzen da. Egunean 4 mg/kg-tik 12 mg/kg-ra arteko dositan administratuz gero, antibiotiko honek farmakozinetika (PK) lineala duela egiaztatu da[3,4].

Antimikrobiano hau gaixo larrien terapia enpiriko moduan erabiltzen da maiz. Izan ere, zainketa intentsiboetako unitateetan (ZIU) oso ohikoak izan ohi dira bakterio Gram-positiboek eragindako infekzioak[5]. Pazienteen egoera fisiopatologikoa dela eta, antibiotikoen farmakozinetika eraldatuta egoten da sarritan, bereziki farmako hidrofilikoena. Horrela, farmakoen farmakozinetikan

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[1] Tally FP, DeBruin MF. Development of daptomycin for Gram-positive infections. J Antimicrob Chemother. 2000;46(4):523-6.

[2] Straus SK, Hancock RE. Mode of action of the new antibiotic for Gram-positive pathogens daptomycin: comparison with cationic antimicrobial peptides and lipopeptides. Biochim Biohys Acta. 2006;1758(9):1215-23.

[3]European Medicines Agency. Cubicin®: summary of product characteristics. Eskuragarri: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf [kontsulta: 2017ko maiatza].

[4] Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother. 2006;50(10):3245-9.

[5] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323–9.

ematen diren aldaketen artean daude, besteak beste, banaketa-bolumenaren handipena (V), proteinekiko loturaren aldaketa, giltzurrun-funtzioa handitua izatea edota giltzurrun-gutxiegitasuna zein gibel-disfuntzioa[6,7,8]. Gainera, zerbitzu hauetan osasuna bermatzeko erabiltzen diren zenbait bizi-euskarriko neurriek ere –etengabeko giltzurrun-ordezkatze teknikek (EGOT), esaterako– profil farmakozinetikoa eralda dezakete.

Hori dela eta, ZIUko pazienteen farmakozinetikan aldakortasun handia egon ohi da eta, ondorioz, antibiotikoen posologia egokiena aukeratzea erronka garrantzitsua da sarritan[8]. Gauzak horrela, populazio-eredu farmakozinetikoak eraikitzea lagungarri izan daiteke aldakortasun hori identifikatzeko eta kuantifikatzeko. Izan ere, eredu hauei esker, paziente bakoitzarentzat egokiena den dosifikazio optimoa zehazteko analisi farmakozinetiko/farmakodinamikoak (PK/PD) egin ahal izango dira. Hortaz, ikerketa-lan honen helburu nagusia izango da gaixo larrientzat daptomizinaren populazio-eredu farmakozinetiko bat garatzea eta baita analisi farmakozinetiko/farmakodinamikoa burutzea, efikazia-zein segurtasun-profilak aintzat hartuta, hain zuzen ere posologia egokiena zehazteko asmoz.

[6] Scaglione F. Can we transfer pharmacokinetics/pharmacodynamics of antimicrobials into clinical practice? Int J Antimicrob Agents. 2015;46(Suppl 1):S40–S42.

[7] Blot S, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient - concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3–11.

[8] Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care. 2015;21(5):412-20.

2. Pazienteak eta metodoak

2.1. Ikerketaren diseinua

Behaketa bidezko saiakuntza irekia, prospektiboa eta zentro-anitzekoa burutu zen Arabako Unibertsitate Ospitaleko (Vitoria-Gasteiz) eta Clinic Ospitaleko (Bartzelona) ZIUetan. Horretarako, aldez aurretik erakundeen Ikerketa Klinikoetarako Batzorde Etikoen oniritzia jaso zen. Bestalde, entsegu honetan parte hartu ahal izateko, paziente bakoitzaren edota gertuko senideen baimen informatua izatea premiazkoa zen. Parte hartzeko irizpideak honakoak izan ziren: i) ZIUko pazientea izatea; ii) bakterio Gram-positibo batek eragindako infekzioa pairatzeko susmoa izatea eta, ondorioz, daptomizinarekin tratatua izatea; iii) baimen informatua eman izana; eta iv) plasma-laginak eskuratzea posible izatea, baita efluente-laginak ere, pazienteek EGOTak ezarriak izatean. Baztertzeko irizpideak, berriz, honako hauek izan ziren: adin txikikoa izatea (<18 urte), haurdun egotea edota daptomizinarekiko zein eszipienteekiko hipersentikortasuna azaltzea.

1. taulan pazienteen datu demografikoak eta biokimikoak bildu dira, baita APACHE II puntuazioa ere (ingeleseko terminoa, *Acute Physiology and Chronic Health Evaluation II*). Kreatinina-argitzapena (Clcr) Cockcroft-Gault ekuazioa erabiliz kalkulatu zen. Horretarako, pazienteen benetako gorputz-pisua erabili zen gaixo ez obesoetan; aldiz, GMI ≥ 30 kg/m^2 zuten pazienteetan gorputz-pisu ideala erabili zen[9].

[9] Nguyen MT, Fong J, Ullah S, Lovell A, Thompson CH. Estimating glomerular filtration rate in obese subjects. Obes Res Clin Pract. 2015;9(2):152-7.

1. taula. Ikerketan parte hartu zuten 16 pazienteen datu demografikoak eta biokimikoak, APACHE II puntuazioa eta ingresatutako ospitalea. AUO: Arabako Unibertsitate Ospitalea; CO: Clinic Ospitalea; EGOT: etengabeko giltzurrun-ordezkatze teknikak; GMI: gorputz-masaren indizea; Clcr: kreatinina argitzapena; GOT: glutamato-oxalazetato transaminasa; GPT: glutamato-pirubato transaminasa; CPK: kreatinina-fosfokinasa; CL_{EC}: gorputz-kanpoko argitzapena.

Pazienteen ezaugarriak	N/N*	Mediana (Tartea)
Ospitalea		
AUO (EGOT gabe/EGOT)	12/2	
CO (EGOT gabe/EGOT)	0/2	
Datu demografikoak		
Adina (urteak)	-	67 (48-83)
Sexua (gizonezko/emakumezko)	7/9	-
Pisua (kg)	-	84 (52-100)
GMI (kg/m^2)	-	29,6 (20,3-42,2)
Datu biokimikoak		
Kreatinina (mg/dL)	-	0,95 (0,6-1,8)
Clcr (mL/min)	-	
EGOT gabe	-	66 (20-121)
EGOT	-	8 (0-54)
Glukosa (mg/dL)	-	197 (106-299)
Hemoglobina (g/dL)	-	9,1 (7,2-11,7)
Hematokritoa (%)	-	25,7 (21,0-33,2)
Albumina (g/dL)	-	2,7 (1,7-3,8)
Proteina totalak (g/dL)	-	5,3 (3,9-6,9)
Bilirrubina (mg/dL)	-	0,7 (0,3-2,6)
Leukozitoak (/mm^3)	-	13.100 (5.500-2.000)
GOT (UI/L)	-	25 (10-200)
GPT (UI/L)	-	38 (6-566)
CPK (U/L)	-	53 (7-520)
APACHE II	-	18 (7-30)
CL_{EC}[a] (L/h)		0,46 (0,32-0,48)

[a]Soilik EGOTak ezarriak zituzten pazienteentzat.

2.2. Farmakoaren administrazioa, lagin-bilketa eta analisia

350-850 mg bitarteko daptomizina-dosiak (Cubicin®) administratu zitzaizkien pazienteei, 24 edo 48 ordutik behin. Antibiotikoa zain-barneko infusio motz bidez eman zen kasu guztietan, 20-tik 60 minutura bitarteko iraupenarekin. Lagin-bilketarekin hasi baino lehen, paziente bakoitzari batez beste 4 daptomizina-

dosi eman zitzaizkion. Odol-laginak dosia eman baino lehen eta infusio amaieran jaso ziren. Bestalde, lagin bana hartu zen 4 eta 8 orduko tartean, 10 eta 14 orduko tartean eta 24 eta 48 ordu pasa ostean (azken hau bakarrik 48 orduro dosifikatu zenean). Lagin bakoitza berehala zentrifugatu zen, 10 minutuz 3.000 rpm-tan. Lortutako plasma-laginak -80º C-tan izoztu ziren analizatu arte. EGOTak ezarriak zituzten pazienteetan, odola ez ezik, efluente-laginak ere hartu ziren denbora tarte berdinetan, eta zuzenean -80º C-tan gorde ziren.

Plasma-laginetan zegoen antibiotiko-kontzentrazioa kuantifikatzeko, aldez aurretik balioztatutako detekzio ultramoredun bereizmen handiko kromatografia likidoa (*high performance liquid chromatography*, HPLC) erabili zen (**1. eranskina**). Lehenik eta behin, proteinak azetonitriloarekin prezipitatu ziren, eta horrek kuantifikaziorako erabiliko zen barne estandarra (propil-4-hidroxibenzoato) disolbatua zuen. Ostean, laginak 10 minutuz zentrifugatu ziren, 12.000 rpm-ko baldintzapean. Bertatik lortutako gainjalkinak, baita efluente-laginak ere, HPLC sisteman injektatu ziren. Banaketa Simmetry® C8 zutabe batekin burutu zen (4,6 mm x 150 mm x 5 μm). Linealtasuna plasman eta efluentean espero ziren kontzentrazio tarteetan frogatu zen; 2,5-150 μg/mL eta 0,1-20 μg/mL, hurrenez hurren. Intra eta inter-egun zehaztasuna eta doitasuna kuantifikazio-limiteekin eta linealtasun tarteko beste hiru kontzentraziorekin frogatu ziren. Alegia, plasma-laginen kasuan 2,5, 7, 40 eta 120 μg/mL-tako kontzentrazioekin, eta efluente-laginen kasuan 0,1, 0,3, 2 eta 16 μg/mL-rekin. Kalkulatutako kontzentrazioen desbiderapenak inoiz ez zuen balio teorikoaren %15 gainditu. Bestalde, intra- eta inter-saiakuntza doitasuna, aldakuntza-koefiziente moduan adierazia (*coefficient of variation*, CV), %15 balioaren azpitik mantendu zen beti. Daptomizina estandarra Novartis Pharma AGri esker lortu zen.

2.3. Populazio-eredu farmakozinetikoa

2.3.1. Oinarrizko eredua

Populazio-eredua sortzeko baldintzazko lehen mailako estimazio metodoa interakzioarekin (FOCE-I) erabili zen NONMEM 7.3 programa baliatuz[10]. Farmako totalaren kontzentrazioen disposizioa aztertzeko eredu konpartimentalak erabili ziren eta, hondar-balioen banaketa aztertu ostean, datuak logaritmoetara transformatzea erabaki zen. Ereduen ebaluaziorako, funtzio-objektiboaren balioaren beherakada (OFV = -2 x log-egiantza), parametroen kalkuluan emandako errore erlatibo estandarrak (*relative standard errors*, RSE) eta doikuntza-egokitasuna ebaluatzeko grafikoak (*goodness-of-fit*, GOF, *plots*) kontuan hartu ziren. Aldakortasun interindibiduala (*inter-individual variability*, IIV) adierazteko eredu esponentziala erabili zen, eta hondar-errorerako eredu aditiboa, eskala logaritmikoan. Bestalde, omega bariantza-kobariantza matrizearen diagonaletik kanpo geratzen diren elementuen esangura ikertu zen.

2.3.2. Aldagaien aukeraketa

Neurri batean IIV azaltzeko eta populazio eredua hobetzeko asmoz, pazienteen ezaugarri demografikoek eta biokimikoek (**1. taula**) daptomizinaren parametro farmakozinetikoetan izan dezaketen efektua behatu zen. Gainera, EGOTak ezarriak zituzten pazienteetan gorputz-kanpoko argitzapena (CL_{EC}) kontuan hartu zen. CL_{EC} efluentearen fluxua (Q_{ef}) eta sieving koefizientea (Sc) biderkatzean lortzen den parametroa da. Sc-a gorputz-ordezkatze tekniketan mintzaren bidez kanporatutako farmako-frakzioa da. Kasu honetan, denbora jakin bakoitzean harturiko efluente- eta plasma-laginen kontzentrazioen zatiduraren batez bestekoa eginez kalkulatu zen. Populazio-eredu farmakozinetikoan

[10] Beal S, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

aldagaiak gehitzean, paziente guztien medianarekin normalizatu ziren. Horien aukeraketa egiteko, mailakatutako prozesua burutu zen, PsN 4.7.0-ren SCM tresna erabiliz. Prozesua aurrerako barne-hartze prozesuan eta atzerako ezabatzean oinarritzen da. Horrela, ereduan gehitu eta bertan mantentzeko esangura-mailak 0,05-en eta 0,01-en finkatu ziren, hurrenez hurren. GOF grafikoak ere erabilgarriak izan ziren aldagaiak ereduan mantentzea edo ez mantentzea erabakitzerako orduan.

2.3.3. Ereduaren ebaluazioa

Ereduaren garapenean eta ebaluazioan parametroen egiantza eta zehaztasuna aintzat hartu ziren. Gainera, honako GOF grafikoak ere kontuan hartu ziren: mendeko-aldagaia (kuantifikaturiko daptomizina-kontzentrazioen logaritmoa) vs. populazioaren eta norbanakoen aurreikusiak (PRED eta IPRED), haztatutako baldintzapeko hondar-balioak (*conditional weighted residuals*, CWRES) vs. dosi osteko denbora (*time after dose*, TAD), eta norbanako bakoitzaren haztatutako hondar-balioak (*individual weighted residuals*, IWRES) vs. IPRED. Bestalde, predikzioa eta aldakortasuna zuzenduta dituen azterketa bisual iragarlea (*prediction-and-variability-corrected visual predictive check*, pvc-VPC) irudikatu zen ereduaren egokitasuna zehazteko. Horretarako, PsN 4.7.0-ko VPC tresnarekin mila paziente birtual simulatu ziren daptomizinaren populazio-eredu finala erabiliz eta baldintza berdinen mendean. Behaturiko datuak zein simulatutakoak 5 bin desberdinetan banatu ziren, dosi osteko denbora (h) kontuan harturik. Gainera, horien 2,5., 50. eta 97,5. pertzentilak kalkulatu eta konparatu ziren. Emaitzak grafiko batean irudikatu ziren, R 3.4.0 programaren Xpose4 paketea baliatuz[11]. Bestalde, parametroen zehaztasuna ebaluatzeko 2.000 datu multzoko bootstrap bat exekutatu zen (Bootstrap tresna PsN 4.7.0-n). Eredua sortu eta ebaluazio-

[11]Jonsson, EN, Karlsson, MO. Xpose--an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. Computer Methods and Programs in Biomedicine. 199;58(1):51-64.

prozesuan lortutako datu eta emaitzak antolatzeko Pirana v.2.9.5 softwarea erabili zen[12].

2.4. Monte Carlo simulazioa

2.4.1. Analisi farmakozinetiko/farmakodinamikoa (PK/PD)

Helburua lortzeko probabilitatearen (PTA) estimazioa

PTA (*probability of target attainment*) antibiotiko baten efikaziarekin erlazionaturiko indize farmakozinetiko/farmakodinamiko bat lortzeko probabilitatea da, patogeno-suszeptibilitate jakin batentzat (kontzentrazio minimo inhibitzailea edo *minimum inhibitory concentration*, MIC). PTAk kalkulatzeko, 5.000 subjektuko Monte Carlo simulazioak burutu ziren MIC desberdinentzat (0,25-tik 4-mg/L-rako tartean). Horretarako hainbat dosifikazio simulatu ziren: 280, 420, 560, 700 eta 840 mg/24 h. Hau da, 70 kg-ko pisua duen heldu estandar batentzat 4, 6, 8, 10 eta 12 mg/kg/24 h-ren baliokide izango liratekeen dosiak.

Daptomizinaren aktibitatea kontzentrazio-menpekoa denez gero, horren efikaziarekin ongien erlazionatuta dagoen parametro farmakozinetiko/farmakodinamikoa 24 h-tako kontzentrazio-denbora kurbaren azpian mugaturiko azalera eta mikroorganismoen kontzentrazio minimo inhibitzailearen arteko ratioa da (AUC_{24h}/MIC)[13,14]. Horrela, 666 baino altuagoak diren farmako-totalaren

[12] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

[13] Louie A, Kaw P, Liu W, Jumbe N, Miller MH, Drusano GL. Pharmacodynamics of daptomycin in a murine-thigh model of *Staphylococcus aureus* infection. Antimicrob Agents Chemother. 2001;45:845–51.

[14] Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother. 2004;48:63–68.

AUC_{24h}/MIC balioak terapiaren arrakastaren probabilitate altuekin erlazionatu dira[15].

EGOTak ezarriak ez zituzten pazienteentzat 10 eta 130 mL/min arteko Clcr-ak ebaluatu ziren. EGOTak ezarriak zituzten gaixoen kasuan, aldiz, 0tik 30 mL/min-ra arteko Clcr-ak aztertu ziren, eta, gainera, CL_{EC}-a ere aintzat hartu zen. Azken hori pazienteetan neurtutako Sc-a (0,2 ± 0,05) eta bi Q_{ef} desberdin kontuan izanda kalkulatu zen (1,5 eta 2,5 L/h, pazienteetan ezarritako fluxu baxuenetik eta altuenetik gertu zeuden balioak). Simulazioak R programaren 3.4.0 bertsioarekin burutu ziren, mlxR paketea erabiliz[16].

Erantzunaren metatze-frakzioaren (CFR) kalkulua

CFRak (*cumulative fraction of response*) antibiotiko baten dosifikazio-erregimen zehatzek arrakasta izateko duten probabilitatea kalkulatzen du; MICen balio espezifikorik ezagutu ez arren, populazio batean horien frekuentzia jakina denean. Horrela, MIC balio bakoitzarentzat lortutako PTA aintzat hartuz, eta populazio jakin bateko bakterioen MICen distribuzioa ezagututa, tratamenduaren emaitza onuragarriak lortzeko probabilitatea kalkula daiteke[17].

2013. eta 2015. urte bitartean Arabako Unibertsitate Ospitaleko ZIUetan lortutako suszeptibilitateen informazioa erabili zen CFRn balioak estimatzeko. Era horretan, tratamenduaren arrakasta lortzeko probabilitateak kalkulatu ziren honako bakterio hauentzat: *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus epidermidis*, *Staphylococcus aureus* eta koagulasa negatiboko

[15] Canut A, Isla A, Betriu C, Gascón AR. Pharmacokinetic-pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. Eur J Clin Microbiol Infect Dis. 2012;31(9):2227-35.

[16] Lavielle M. mlxR: Simulation of Longitudinal Data. R package version 3.2.0. 2016. Eskuragarri: *https://CRAN.R-project.org/package=mlxR*. [kontsulta: 2017ko abendua].

[17] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005;55(5):601-7.

estafilokokoak (**2. taula**). Mikrobiologiako departamentutik lortutako datuak Whonet programarekin kudeatu ziren[18] eta PTA-k estimatzeko erabilitako egoera berdinak ebaluatu ziren.

Bai PTA bai CFR balioentzat %90etik gorako emaitzak optimotzat hartu ziren. Arrakasta moderatuarekin erlazionatu ziren, aldiz, %90 eta %80 arteko datuak[19].

2. taula. 2013.eta 2015. urte bitartean Arabako Unibertsitate Ospitaleko ZIUetan lortutako MICen distribuzioa daptomizinarentzat, *E. faecium, E. faecalis, S. epidermidis, S. aureus* eta koagulasa negatiboko estafilokokoentzat (CoNS).

Mikroorganismoa	Suszeptibilitate mozte-puntu klinikoa MIC (mg/L)[a]	Isolatutako andui kopurua	MIC (mg/L) balio bakoitzarekin inhibitzen den anduien ehunekoa					
			0,5	1	2	4	8	16
Enterococcus faecium	4	18		17	38	39	6	
Enterococcus faecalis	4	52	21	60	15	2		2
Staphylococcus epidermidis	1	18		100				
Staphylococcus aureus	1	58	26	74				
CoNS	1	63	2	94	2		2	

[a] Clinical and Laboratory Standard Institute (CLSI) eta European Committee on Antimicrobial Susceptibility Testing (EUCAST) erakundeen arabera.

[18] WHONET 5.6. Eskuragarri: *http://www.who.int/medicines/areas/rational_use/AMR_WHONET_SOFTWARE/en/* [kontsulta: 2018ko maiatza].

[19] Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J. 2003;22(11):982-92.

2.4.2. Segurtasunaren ebaluazioa

Kontzentrazio minimoaren estimazioa oreka egonkorrean ($Cmin_{ss}$)

Simulatutako subjetuetatik toxikotzat hartzen diren antibiotiko-kontzentrazio plasmatikoak ($Cmin_{ss} \geq 24,3$ mg/L)[20] zer ehunekok lortzen zituzten behatu zen. Horretarako, R programaren mxlR paketea erabili zen[16].

3. Emaitzak

Guztira, adin nagusiko 16 gaixo larrik parte hartu zuten ikerketa honetan eta horietatik lauk EGOTak ezarriak zituzten (**1. taula**). Paziente bakoitzeko 5 plasma-lagin analizatu ziren (6 daptomizina 48 orduro administratzean). EGOTak ezarriak zituzten pazienteetan efluente-lagin kopuru bera bildu zen. Pazienteei diagnostikaturiko gaitzen artean, sepsia (n = 5), larruazal eta ehun bigunetako infekzioak (n = 3), infekzio abdominalak (n = 3), bakteriemia (n = 2) edota bestelako infekzioak (n = 3) zeuden.

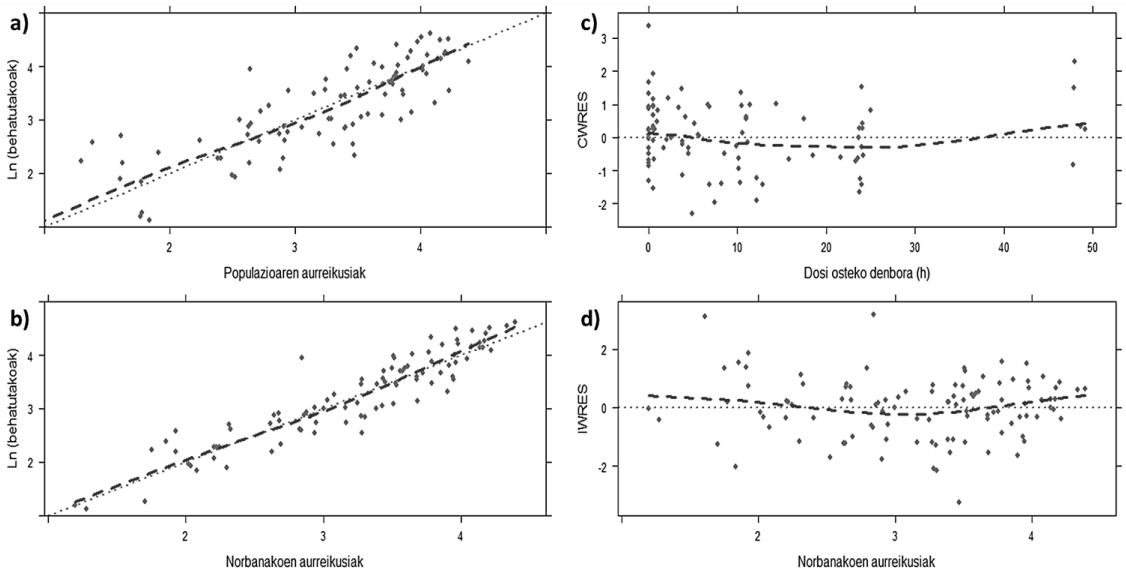
EGOTak ezarriak zituzten lau pazienteek etengabeko hemodiafiltrazio beno-benosoa egotzia zuten. Odol fluxua 150-180 mL/min artean mantendu zen eta efluentearena, aldiz, 1.600 eta 2.550 mL/h artean. Fluxua indikazio klinikoen arabera alda zitekeen. Ur-oreka negatiboa mantendu zen paziente orotan, 50 mL/h-tik 200 mL/h-ra.

[20] Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis. 2010;50(12):1568-74.

3.1. Populazio eredu farmakozinetikoa

3.1.1. Oinarrizko eredua

Daptomizinaren plasma kontzentrazioak (eskala logaritmikoan) ongien deskribatu zituen eredua konpartimentu bakarrekoa izan zen. Eredu horrekin gorputzeko argitzapena (CL) eta banaketa bolumena (V) kuantifikatu ziren. Doikuntza GOF grafikoekin egiztatu zen (**1. irudia**). IIV esponentzialki gehitu zitzaion CLri eta Vri eta ez zen korrelaziorik aurkitu bi parametroen artean.



1. irudia. Hautatutako ereduarekin lortutako GOF grafikoak: Populazioaren (PRED)[a] eta norbanakoen (IPRED)[b] aurreikusiak versus menpeko aldagaia (kuantifikatutako daptomizina plasma-kontzentrazioak, μg/mL, eskala logaritmikoan), haztatutako baldintzapeko hondar-balioak (CWRES) versus dosi osteko denbora (h)[c], eta norbanako bakoitzaren haztatutako hondar-balioak (IWRES) versus norbanakoen aurreikusitako balioak[d].

3.1.2. Aldagaien aukeraketa

Antibiotiko honen argitzapena, giltzurrun-kanpoko argitzapenaren (CL_{NR}) eta giltzurrun-menpeko argitzapenaren (CL_R) arteko batura moduan kalkulatu zen; eta azken hori Clcr-aren eraginpean zegoen. EGOTak egotziak zeuzkaten pazienteen kasuan, paziente bakoitzaren CL_{EC} propioa gehitu zitzaion argitzapenaren ekuazioari. Clcr ereduan sartzean argitzapenean azaldu gabeko IIVa erdira jaitsi zen (%75etik %37ra). SCMak emaitza hauek berretsi zituen. Ereduan barne hartzeko bestelako aldagai adierazgarririk ez zen aaurkitu.

3.1.3. Ereduaren ebaluazioa

GOF grafikoetan ez zen joera adierazgarririk sumatu, ez CWRES versus dosi osteko denboran ezta IWRES versus iragarritako balio indibidualetan ere (**1. irudia**). Gainera, neurtutako eta iragarritako populazioren zein norbanakoen balioek korrelazio egokia erakutsi zuten. Bestalde, RSE (%) eta bootstrap-aren emaitzek parametroen estimazioa zehaztasunarekin burutu zela erakutsi zuten (**3. taula**) eta pvc-VPCak (**2. irudia**) datu gordinen eta populazio-eredutik lortutako simulazioen arteko korrelazio ona irudikatu zuen.

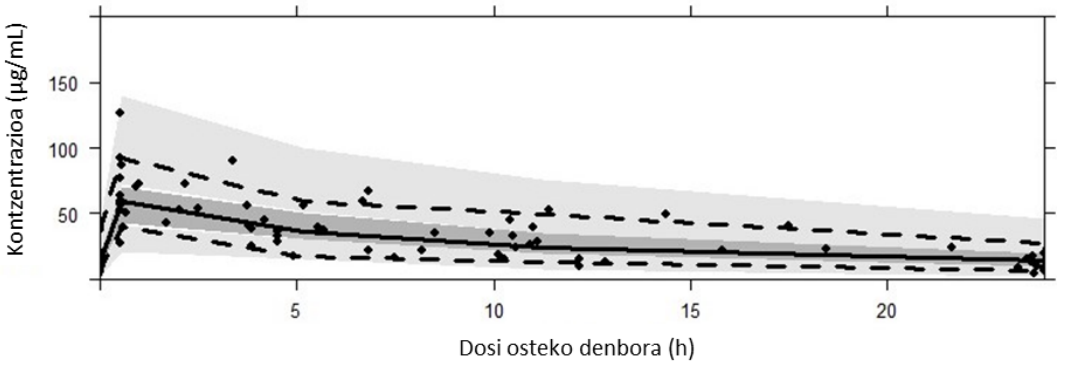
3.taula. Oinarrizko eredua eta hautatutako populazio-eredu farmakozinetikoa daptomizinaren zain-barneko infusio motzerako. Estimatutako parametroak, shrinkage[a] balioak eta bootstrap-aren emaitzak.

Parametroa	Oinarrizko eredua	Hautatutako eredua	Bootstrap, mediana (5. eta 95. pertzentilak)
	Estimatutako balioa, RSE (%)	Estimatutako balioa, RSE (%)	
CL (L/h) = CL_{NR} + CL_R+ CL_{EC}[b]	0,491 (21) +CL_{EC}		
CL_{NR}		0,16 (54)	0,160 (0,013-0,324)
CL_R = θ x (Clcr/49)		0,367 (20)	0,366 (0,239-0,527)
V(L)	12,50 (13)	12,30 (13)	12,31 (10,10-15,13)
IIV_$_{CL}$ (%)	74,6 (29)	36,7 (30)	32,5 (17,7-54,4)
IIV_$_{V}$ (%)	35,4 (25)	27,8 (30)	27,0 (11,9-42,8)
Hondar errorea_aditiboa (log-eskala)	0,110	0,123 (17)	0,114 (0,086-0,153)

[a]CLηsh= %30; Vηsh = %10; εsh = %11

[b] Soilik EGOTak ezarriak dituzten pazienteetan. Norbanakoen CL_{EC} balio aintzat hartu zen.

CL: argitzapena; CL_{NR}: giltzurrun-kanpoko argitzapena; CL_R: giltzurrun-menpeko argitzapena; Clcr: kreatinina-argitzapena; V: banaketa-bolumena; EGOT: etengabeko giltzurrun-ordezkatze teknikak; IIV: aldakortasun interindibiduala; RSE: errore erlatibo estandarra; ηsh: shrinkage balioa parametro batentzat; εsh: shrinkage balioa hondar-errorearentzat.



2. irudia. Dosi osteko denboran (0-tik 24 h-ra) lortutako pvc-VPCren emaitzak. Puntuak aurreikusitako kontzentrazioekin zuzendutako kuantifikatutako kontzentrazioak dira (µg/mL). Etengabeko marrak kuantifikatutako datuen batezbesteko balioa irudikatzen du eta bestelako marrek, 2,5. eta 97,5. pertzentilak. Itzal ilun eta argiek simulazioan lortutako %90eko konfiantza tartea erakusten dute, medianarentzat eta 2,5 eta 97,5. pertzentilentzat, hurrenez hurren.

3.2. Monte Carlo simulazioa

3.2.1. Analisi farmakozinetiko/farmakodinamikoa

Helburua lortzeko probabilitatea (PTA)

4. taulak eraginkortasunarekin erlazionaturiko helburu farmakodinamikoa (AUC_{24h}/MIC ≥ 666) lortzeko probabilitateak biltzen ditu simulatutako egoera guztientzat. Orokorrean, zenbat eta dosi altuagoak eta Clcr balio baxuagoak, orduan eta PTA handiagoak lortu ziren. Clcr balio berarentzat arrakasta-probabilitate baxuagoak estimatu ziren EGOT ezarriak zituzten pazienteetan. Kasu guztietan, badirudi 280 mg/24 h-ko dosia nahikoa litzatekela MIC ≤ 0,25 mg/L dituzten bakterioek eragindako infekzioak tratatzeko. MIC balioa 1 mg/L izanez gero, aldiz, tratamenduarekin arrakasta izateko probabilitate altuak (> %90) lortuko lirateke dosi altuenarekin (840 mg), 130 mL/min-ko Clcr-ak dituzten pazienteetan izan ezik. Bestalde, MIC ≥ 4 mg/L dituzten bakterioen infekzioak tratatzeko daptomizina ez litzateke eraginkorra izango.

Erantzunaren metatze-frakzioa (CFR)

5. taulan mikroorganismo desberdinentzat daptomizinarekin lortutako CFR balioak bildu dira. Ikus daitekeenez, *E. faecium*-entzat ez zen arrakasta terapeutikorako probabilitate alturik lortu, ezta dosi altuenarekin ere. *E. faecalis*-en kasuan, berriz, 560 mg-tako dosiekin, edo altuagoekin, CFR ≥ %90 balioak lortu ziren, betiere pazienteen Clcr ≤ 30 mL/min izanez gero eta EGOTak ezarriak ez bazituzten. Bestelako mikroorganismoei dagokienez, efikaziarekin erlazionatutako CFR balioak lortu ahal izatea dosiaren, Clcr-aren eta, EGOTak ezarriak egotean, CL_{EC}-aren menpe egongo litzateke.

4. taula. Daptomizinaren PTA balioak (%). Letra lodiz PTA ≥ %90 balioak eta letra etzanez PTA ≥ %80 balioak irudikatu dira.

Dosia/24h	**Clcr** (mL/min)	**EGOT gabe**					**EGOT**									
							Q_{ef} 1.5 L/h					**Q_{ef} 2.5** L/h				
280 mg	0						**100**	**100**	35	1	0	**100**	*89*	5	0	0
	10	**100**	**100**	**99**	38	5	**100**	**99**	18	0	0	**100**	73	3	0	0
	30	**100**	**100**	61	12	2	**100**	*84*	6	0	0	**100**	40	1	0	0
	60	**100**	*86*	21	4	1										
	90	**100**	52	10	2	1										
	130	**91**	25	5	2	1										
420 mg	0						**100**	**100**	**96**	8	0	**100**	**100**	40	1	0
	10	**100**	**100**	**100**	*83*	18	**100**	**100**	*80*	4	0	**100**	**100**	25	0	0
	30	**100**	**100**	**96**	32	6	**100**	**100**	38	1	0	**100**	**97**	10	0	0
	60	**100**	**100**	55	11	2										
	90	**100**	**93**	26	5	2										
	130	**100**	63	13	3	1										
560 mg	0						**100**	**100**	**100**	35	1	**100**	**100**	*89*	5	0
	10	**100**	**100**	**100**	**99**	38	**100**	**100**	**99**	18	0	**100**	**100**	73	3	0
	30	**100**	**100**	**100**	61	12	**100**	**100**	*84*	6	0	**100**	**100**	40	1	0
	60	**100**	**100**	86	21	4										
	90	**100**	**100**	52	10	2										
	130	**100**	**91**	25	5	2										
700 mg	0						**100**	**100**	**100**	75	3	**100**	**100**	**99**	17	0
	10	**100**	**100**	**100**	**100**	64	**100**	**100**	**100**	47	1	**100**	**100**	**97**	10	0
	30	**100**	**100**	**100**	85	20	**100**	**100**	**99**	18	1	**100**	**100**	*80*	3	0
	60	**100**	**100**	**98**	36	7										
	90	**100**	**100**	80	17	4										
	130	**100**	**99**	43	8	2										
840 mg	0						**100**	**100**	**100**	**96**	8	**100**	**100**	**100**	40	1
	10	**100**	**100**	**100**	**100**	*83*	**100**	**100**	**100**	*80*	4	**100**	**100**	**100**	25	0
	30	**100**	**100**	**100**	**96**	32	**100**	**100**	**100**	38	1	**100**	**100**	**97**	10	0
	60	**100**	**100**	**100**	55	11										
	90	**100**	**100**	**93**	26	5										
	130	**100**	**100**	63	13	3										
MIC (mg/L)		**0,25**	**0,5**	**1**	**2**	**4**	**0,25**	**0,5**	**1**	**2**	**4**	**0,25**	**0,5**	**1**	**2**	**4**

5. taula. Daptomizinaren CFR balioak bakteria desberdinentzat, kontuan hartuta 2013. eta 2015. urte bitartean Arabako Unibertsitate Ospitalean lortutako MICen distribuzioen frekuentzia. Letra lodiz CFR ≥ %90 balioak eta letra etzanez CFR ≥ %80 balioak irudikatu dira.

		Dosia (mg/24h) **EGOT gabe**					**Dosia** (mg/24h) **EGOT**									
							Q_{ef} 1.5 L/h					**Q_{ef} 2.5** L/h				
Bakterioa	**Clcr** (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
Enterococcus faecium	0						6	20	31	47	58	1	7	17	24	33
	10	34	57	71	*81*	*89*	3	15	24	36	50	0	4	14	20	27
	30	16	31	46	58	67	1	7	17	24	32	0	2	7	15	20
	60	6	14	25	34	43										
	90	3	7	14	21	28										
	130	2	4	7	11	17										
Enterococcus faecalis	0						42	*80*	*86*	**92**	**96**	22	45	75	*83*	*87*
	10	*86*	**94**	**97**	**97**	**98**	32	70	*83*	*88*	**93**	17	36	65	*81*	*85*
	30	60	*84*	**90**	**94**	**96**	21	44	72	*83*	*87*	9	26	45	69	*81*
	60	31	55	76	*85*	*89*										
	90	17	36	54	70	*81*										
	130	9	21	35	48	61										
Staphylococcus epidermidis	0						35	**96**	**100**	**100**	**100**	5	40	*89*	**99**	**100**
	10	**99**	**100**	**100**	**100**	**100**	18	*80*	**99**	**100**	**100**	3	25	73	**97**	**100**
	30	6	**96**	**100**	**100**	**100**	6	38	*84*	**99**	**100**	1	10	40	*80*	**97**
	60	21	55	*86*	**98**	**100**										
	90	10	26	52	*80*	**93**										
	130	5	13	25	43	63										
Staphylococcus aureus	0						52	**97**	**100**	**100**	**100**	27	56	**92**	**100**	**100**
	10	**99**	**100**	**100**	**100**	**100**	39	*85*	**100**	**100**	**100**	21	44	*80*	**98**	**100**
	30	71	**97**	**100**	**100**	**100**	26	54	*88*	**99**	**100**	11	33	55	*85*	**98**
	60	38	66	**90**	**98**	**100**										
	90	21	44	64	*83*	**95**										
	130	10	26	43	58	73										
Koagulasa negatiboko estafilokokoak	0						36	**93**	**98**	**98**	**99**	7	40	*86*	**97**	**98**
	10	**96**	**99**	**99**	**99**	**99**	19	78	**97**	**98**	**99**	4	26	72	**95**	**97**
	30	61	**94**	**98**	**99**	**99**	7	38	82	**96**	**98**	2	11	40	78	**94**
	60	22	54	*84*	**96**	**98**										
	90	11	27	52	76	**91**										
	130	5	13	26	43	63										

3.2.2. Segurtasunaren ebaluazioa

Kontzentrazio minimoa oreka egonkorrean ($Cmin_{ss}$)

6. taulan oreka egonkorrean daptomizina kontzentrazio minimoak 24,3 mg/L-tako balioak, edo altuagoak, lortzeko probabilitateak bildu dira; izan ere, toxikotasunarekin erlazionatu den kontzentrazioa da. Ikus daitekeenez, Clcr balio berdina izanda, toxikotasunarekin erlazionaturiko kontzentrazioak izateko probabilitate baxuagoak dituzte EGOTak ezarriak dituzten pazienteek. Horrela, EGOT gabeko pazienteetan, dosi baxuenarekin ere $Cmin_{ss} \geq 24,3$ mg/L lortzeko probabilitate altuak lortu ziren Clcr baxuentzat (Clcr ≤ 30 mL/min). EGOTak ezarriak dituzten pazienteei dagokienez, toxikotzat hartzen den kontzentrazioa lortzeko probabilitate altuagoak lortu ziren 1,5 L/h-ko efluente fluxuarekin.

6. taula. $Cmin_{ss} \geq 24,3$ mg/L balioak lortzeko probabilitatea (%).

	Dosia (mg/24h) **EGOT gabe**					**Dosia** (mg/24h) **EGOT**									
						Q_{ef} 1,5 L/h					**Q_{ef} 2,5** L/h				
Clcr (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
0						12	45	75	88	94	2	8	21	38	54
10	87	98	99	100	100	6	26	51	72	83	1	4	12	24	38
30	38	67	84	92	96	2	8	21	36	50	0	2	5	10	17
60	12	25	39	52	63										
90	6	11	18	25	33										
130	3	6	9	12	15										

4. Eztabaida

Lan honetan daptomizinarentzat populazio-eredu farmakozinetiko bat burutu da, gaixo larrietan. Eredu hau dosifikazio-erregimen desberdinen egokitasuna aurreikusteko erabili da, irizpide farmakozinetikoak eta farmakodinamikoak aintzat hartuta. Guk dakigula, EGOTak ezarriak dituzten eta ez dituzten gaixo larriak barne hartzen dituen lehenengo populazio-eredu farmakozinetikoa da honako hau. Horri esker, etengabeko teknikek farmakoaren farmakozinetikan duten eragina azter daiteke.

Daptomizinaren farmakozinetika eredu mono-[21,22,23] zein bi-konpartimentalen bidez[24,25,26] azaldu da. Lan honetan, plasma kontzentrazioa vs. denbora datuak ongien deskribatu zituen eredua mono-konpartimentala izan zen, hobekuntzarik ez baitzen sumatu eredu bi-konpartimentala aplikatzean. Aukeratutako ereduaren arabera, aztertutako antibiotikoaren argitzapena giltzurrun-menpeko (CL_R) eta giltzurrun-kanpoko argitzapenaren (CL_{NR}) arteko

[21] Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother. 2004;48(8):2799-807.

[22] Di Paolo A, Tascini C, Polillo M, Gemignani G, Nielsen EI, Bocci G, et al. Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. Int J Antimicrob Agents. 2013;42(3):250-5.

[23] Pai MP, Russo A, Novelli A, Venditti M, Falcone M. Simplified Equations Using Two Concentrations To Calculate Area under the Curve for Antimicrobials with Concentration-Dependent Pharmacodynamics: Daptomycin as a Motivating Example. Antimicrob Agents Chemother. 2014;58(6):3162-7.

[24] Aikawa N, Kusachi S, Mikamo H, Takesue Y, Watanabe S, Tanaka Y, et al. Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. J Infect Chemother. 2013;19(3):447-55.

[25] Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Ettorre G, et al. M. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother. 2013;19:732-9.

[26] Goutelle S, Roux S, Gagnieu MC, Valour F, Lustig S, Ader F, et al. Pharmacokinetic Variability of Daptomycin during Prolonged Therapy for Bone and Joint Infections. Antimicrob Agents Chemother. 2016;60(5):3148-51.

batura moduan kalkulatu zen. Gainera, giltzurrun-menpeko argitzapena Clcr-ren eraginpean dagoela ondorioztatu zen. Kreatinina-argitzapenak daptomizinaren ezabatzean duen eragina eta ereduarekin lorturiko pazienteen arteko aldakortasun handia ($IIV_{\_CL}$ = %37) bat datoz aurretik argitaratutako artikuluekin[22,27].

EGOTak ezarriak zituzten pazienteei dagokienez, haien CL_{EC} balioa argitzapenaren ekuazioari gehitu zitzaion; daptomizina teknika hauen bidez partzialki iraizten dela egiaztatu baita[28]. Ikerketa honetan parte hartu zuten pazienteen batez besteko CL_{EC} balioa (0,43 L/h) aurretik burututako bestelako ikerketen antzekoa izan zen[29,30], eta, aldi berean, boluntario osasuntsuetan deskribatutako argitzapenaren erdia (1 L/h inguru)[21]. Hortaz, daptomizinaren dosien optimizazioa egiteko, ezinbestekoa izango da teknika hauen bidez ezabatzen den farmako-frakzioa aintzat hartzea.

Gaixo larriek pertsona osasuntsuek baino farmakoen banaketa bolumen handiagoak izan ohi dituzte, edema, sepsia, proteinekiko loturen jaitsiera edota bolumen-gainkarga direla-eta, besteak beste. Gainera, paziente horien arteko heterogeneotasuna dela-eta, aldakortasun-interindibidual nabarmena antzematen da sarritan[7]. Horrela, ikerketa honetan lortutako banaketa-bolumena (12,3 L) boluntario osasuntsuena baino altuagoa izan zen. Aldiz, Di Paolo et al.-ek[22] eta Falcone et al.-ek[31] gaixo larrietan deskribatutako banaketa-bolumenek antzeko balioak izan zituzten (12,9 L eta 11,5 L, hurrenez hurren).

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[27] Chaves RL, Chakraborty A, Benziger D, Tannenbaum S. Clinical and pharmacokinetic considerations for the use of daptomycin in patients with *Staphylococcus aureus* bacteraemia and severe renal impairment. J Antimicrob Chemother. 2014;69(1):200-10.

[28] Churchwell MD, Pasko DA, Mueller BA. Daptomycin clearance during modeled continuous renal replacement therapy. Blood Purif. 2006;24:548-54.

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[30] Khadzhynov D, Slowinski T, Lieker I, Spies C, Puhlmann B, König T, et al. Plasma pharmacokinetics of daptomycin in critically ill patients with renal failure and undergoing CVVHD. Int J Clin Pharmacol Ther. 2011;49:656–65.

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Pisua aldagai moduan sartzeak ez zuen populazio-eredu farmakozinetikoa hobetu. Horren zergatietako bat ikerketa honetan parte hartutako kohortearen tamaina murritza litzake, lan honen muga nagusia izanik. Dena den, lortutako emaitzak beste azterlan batzuetan lortutako ondorioekin bat datoz; izan ere, ez zen loturarik ikusi pisua eta daptomizinaren CLaren zein Varen artean[22,31].

Analisi farmakozinetiko/farmakodinamikoa eta Monte Carlo simulazio integratua oso tresna baliagarriak izan daitezke antibiotikoen dosifikazio erregimenak optimizatzeko[32]. Ikerketa-lan honetan gauzatutako populazio-eredua eta analisi farmakozinetiko/farmakodinamikoa aintzat hartuta, daptomizinaren dosifikazio egokiena aukeratzeko bakterioen suszeptibilitatea ez ezik, profil farmakozinetikoa ere kontuan eduki beharko litzateke.

Ikerketa honetan burututako simulazioen arabera, gaur egun onarturiko dosiak (4 eta 6 mg/kg/24h, 70 kg-ko heldu batentzat 280 eta 420 mg/24h-ren baliokideak direnak) ez lirateke nahikoak izango 4 mg/L edo MIC altuagoak dituzten mikroorganismoek eragindako infekzioak tratatzeko. Aitzitik, MIC balio hau da, CLSI (Clinical and Laboratory Standards Institute)[33] eta EUCAST (European Committee on Antimicrobial Susceptibility Testing)[34] erakundeen arabera, enterokokoen suszeptibilitate mozte-puntu klinikoa daptomizinarentzat. Bestalde, 1 mg/L-tako MIC balioak dituzten bakterioei aurre egiteko (suszeptibilitate mozte-puntu klinikoa estreptokokoentzat eta estafilokokoentzat) daptomizinaren dosi estandarrak Clcr baxua duten pazienteentzat soilik eraginkorrak izango liratekela ondoriozta daiteke. Alegia, Clcr ≤ 30 mL/min denean eta EGOTak ezarriak ez daudenean. Emaitza horiek bat datoz aurretik

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[33] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 26th Edition. M100-S26. CLSI, Wayne, PA, USA, 2016.

[34] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, 2017. Eskuragarri: *http://www.eucast.org* [kontsulta: 2017ko abendua].

argitaratutako beste artikulu batzuekin, baimendutako daptomizina-dosiak gaixo kritikoak tratatzeko eskasak direla ondorioztatu baitute[22,25,35].

Ildo berdinean, 2011. urtean IDSAren (*Infectious Diseases Society of America*) jarraibideek MRSAk eragindako endokarditisetan edota bakteriemia kasuetan 8-10 mg/kg daptomizina erabiltzeko gomendatu zuten. Bestalde, bankomizinarekin porrot egindako tratamenduetan, edota bakteriemia iraunkorretan, 10 mg/kg administratzea aholkatzen zuten, bestelako antibiotikoekin konbinatuta[36]. Gauza bera ondorioztatu zuten ere García de la María et al.-ek untxietan egindako metizilinarekiko erresistentea den *Staphylococcus epidermidis*-ek eragindako endokarditis ereduan[37].

Entsegu honetan daptomizina tratamendu enpiriko moduan administratu zen oro har eta, paziente gehienetan, ez zen antibiotikoarekiko mikroorganismo sentikorrik topatu. Hortaz, 2013 eta 2015 urteetan zehar Arabako Unibertsitate Ospitaleko ZIUetan lortutako suszeptibilitateen informazioa erabili zen CFRen balioak kalkulatzeko (**5. taula**). Lortutako emaitzen arabera, daptomizina ez litzateke eraginkorra izango *E. faecium*-ek sortutako infekzioak tratatzeko. Beste mikroorganismoen kasuan, aldiz, tratamenduaren arrakasta probabilitate altuak lortzea pazientearen Clcr-ren eta EGOTak ezarriak izatearen menpe egongo da. Zentzu honetan, garrantzitsua da aintzat hartzea suszeptibilitate datu hauek denboran zehar alda daitezkela, baita lurralde, zonalde zein osasun zentroetan barrena ere[31].

Antibiotiko baten dosifikazio-erregimen optimoa ezartzean, efektua maximizatzeaz gain, toxikotasuna edota eragin desiragaitzak murriztea ere

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[35] Senneville E, Caillon J, Calvet B, Jehl F. Towards a definition of daptomycin optimal dose: Lessons learned from experimental and clinical data. Int J Antimicrob Agents. 2016;47(1):12-9.

[36] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55.

[37] García-de-la-María C, Marco M, Armero Y, Soy D, Moreno A, Del Río A, et al. Daptomycin is effective for treatment of experimental endocarditis due to methicillin-resistant and glycopeptide-Intermediate *Staphylococcus epidermidis*. Antimicrob Agents Chemother 2010;54(7):2781-6.

ezinbestekoa da. Daptomizinaren kasuan, 24,3 mg/L-tik gorako $Cmin_{ss}$ balioak kreatinina-foskokinasa (CPK) maila areagotzearekin erlazionatu dira, antimikrobianoekin erlazionaturiko muskulu-toxikotasunaren aurrekaria izan daitekeena[20]. Hortaz, kontuan hartu behar da antibiotiko honen dosia handitzeak, efikazia areagotzeaz gain, toxikotasunarekin loturiko kontzentrazio-plasmatikoetara iristeko probabilitatea ere igo dezakeela. Dena den, dosia ez da segurtasuna arriskuan jartzen duen faktore bakarra; haatik, farmakoaren farmakozinetika baldintzatu dezaketen faktore desberdinak ere kontuan hartu behar dira. Adibide moduan, eta **6. taulan** ikus daitekeen bezala, $Cmin_{ss} \geq 24,3$ mg/L lortzeko probabilitate altuagoa dute 280 mg/24h jasotzen dituzten gaixoek euren Clcr 10 mL/min (%87) eta 30 mL/min (%38) denean, 130 mL/min-ko giltzurrun argitzapena izanda 840 mg/24h administratzen zaienean baino (%15). Emaitza horiek aintzat hartuta, simulazio berriak gauzatu ziren, daptomizina 48 orduro administratuta. Kasu horretan, EGOTik ez eta Clcr baxuak zituzten pazienteetan (≤ 30 mL/min) soilik lortu ziren PTA altuak (> %90) 1 mg/L-tako MIC balioentzat (ez dira datuak aurkeztu). Horrela, 560 mg/48h (10mL/min Clcr balioentzat) edo 840 mg/48h administratzean (30 mL/min Clcr baliontzat) 24,3 mg/L baino kontzentrazio minimo altuagoak lortzeko probabilitateak %65 eta %39 izan ziren, hurrenez hurren. Ehuneko horiek 280 edota 420 mg/24h-rekin lortutakoak baino baxuagoak izan arren, segurtasuna arriskuan jartzen jarraitzen zuten.

CPK balioa efektu muskulu-eskeletiko desiragaitzen markatzaile sentikorra izan arren, zenbait ikerketek zalantzan jarri dute daptomizinaren dosi altuak CPKren igoerarekin erlazionatuta egotea, ez baita desberdintasun esanguratsurik topatu dosi estandar eta altuagoen artean[35]. Bestalde, beste ikerketa batek 12 mg/kg daptomizina 14 egunetan zehar administratu ostean ondo toleratua zela ondorioztatu zuen; izan ere, ez zen ondorio kaltegarririk dokumentatu[4]. Nahiz eta lan honetan 3 pazientek 24,3 mg/L baino $Cmin_{ss}$ balio altuagoak izan, ez hauek, ezta beste 13 gaixoek ere, ez zuten CPK maila alturik izan (**1. taula**).

Ikerketa-lan honetan lortutako emaitzen arabera, eta kontuan izanda isolatutako bakterioen gehiengoaren MIC balioak ≥ 1 mg/L izan zirela, daptomizina-dosi estandarrak ez lirateke egokiak izango 60 mL/min edo altuagoak diren Clcr balioak dituzten pazienteak tratatzeko. Horrela, 60 eta 90 mL/min bitarteko Clcr balioak dituzten pazienteek 700 mg/24h beharko lukete. Giltzurrun argitzapen altuagoak dituzten pazienteei, aldiz, 840 mg/24h administratu beharko litzaieke. Nahiz eta Clcr ≤ 30 mL/min dituzten pazienteetan arrakasta probabilitate altuenak lortu, kontzentrazio toxikoak izateko aukerak ere nabariak dira subjektu horietan. Beraz, terapiaren onura-arrisku balantza aztertu beharko litzateke horrelakoetan. EGOTak ezarriak dituzten pazienteetan, gutxienez 560 mg/24h-ko dosia beharko litzateke. Dena den, CL_{EC}-k dosi bat edo beste erabiltzea baldintzatuko du, eta hori, aipatu bezala, Sc eta Q_{ef}-ren menpe egongo da.

Hala ere, bakterioen MIC balioa jakina denean edo ospitalearen edo lurraldearen suszeptibilitate-distribuzioa ezaguna bada, dosifikazio-erregimenen gomendioa informazio hori aintzat hartuta egin beharko da.

5. Ondorioak

Lan honetan daptomizinaren populazio-eredu farmakozinetiko bat eraiki da gaixo larrientzat. Datuak logaritmoetara transformatu ostean, eredu mono-konpartimentala izan zen ongien egokitu zena. Antibiotiko honen argitzapena kreatinina-argitzapenaren menpekoa izan zen eta, etengabeko giltzurrun-ordezkatze teknikak ezarriak zituzten pazienteen kasuan, gorputz-kanpoko argitzapenaren eragina gehitu zen ekuazioan. Gaixoen ezaugarriek profil farmakozinetikoan sortutako aldaketen ondorioz, arrakasta- eta toxikotasun-

probabilitate desberdinak lortu ziren. Beraz, gaixo kritikoetan daptomizinaren indibidualizazioa egitea gomendagarria litzake terapiaren arrakasta bermatzeko eta toxikotasuna ekiditeko. Toxikotzat hartzen den kontzentrazio minimoetara iristea dosiaren menpekoa izateaz gain, pazienteen argitzapenaren menpe ere dagoela ondorioztatu zen.

3. kapitulua

Linezoliden populazio-farmakozinetika gaixo larrietan

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Argitaratzeko prestatzen

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LABURPENA: Linezolid espektro zabaleko aktibitatea dauka mikobakterio eta bakterio Gram-positiboen aurka, eta Zainketa Intentsiboetako Unitateetan oso erabilia da. Lan honen helburu nagusia gaixo larrientzat linezoliden populazio eredu farmakozinetiko bat garatzea eta PK/PD analisia burutzea izan zen, terapiaren egokitasuna aztertzeko asmoz. Guztira 41 gaixo larriren datuak erabili ziren populazio-eredu farmakozinetikoan, eta hauetatik 23k EGOTak egotziak zituzten. Behin linezoliden dosi estandarra administratu ostean (600 mg/12h), plasma eta efluente laginak aurretik zehaztutako denbora-tarteetan jaso ziren. NONMEM 7.3 programa erabiliz, populazio-eredu farmakozinetikoa garatu zen. Linezoliden plasma kontzentrazioak ongien deskribatu zituen eredua konpartimentu bikoa izan zen. Kreatinina argitzapenaren (Clcr) eragina farmakoaren eliminazioan identifikatu zen, eta, EGOTak ezarriak zituzten pazienteetan, baita gorputz-kanpoko argitzapena ere. Dosi estandarraren eta 600 mg/8h-ren egokitasuna zehazteko, Monte Carlo simulazioak egin ziren. Horrela, terapiaren arrakastarekin erlazionatutako balioak (AUC_{24h}/MIC > 80) eta toxikotasunarekin lotutako kontzentrazioak lortzeko probabilitateak ($Cmin_{ss}$ > 10 mg/L eta AUC_{24h} > 400 mg*h/L) kalkulatu ziren. Linezoliden dosi estandarra ez litzateke egokia izango 2 mg/L-tako MIC balioak, edo altuagoak, dituzten patogenoek eragindako infekzioak tratatzeko. Dosia 600 mg/8h-ra handitzean, ez lirateke arrakasta probabilitate altuagoak lortuko; ordea, toxikotzat hartzen diren kontzentrazioak izateko aukerak handituko lirateke. Gaixo larrietan etengabeko perfusioa erabiltzea aukera egokia izan daiteke, bereziki giltzurrun gutxiegitasuna pairatzen ez dutenetan (Clcr ≥ 60 mL/min).

1. Sarrera

Linezolid oxazolidinonen deribatua den antibiotikoa da. Espektro zabaleko aktibitatea dauka mikobakterio eta bakterio Gram-positiboen aurka; hala nola, estafilokokoak, estreptokokoak eta enterokokoak. Horrela, patogeno hauen aurka eraginkorra dela ikusi da: metizilinarekiko erresistentea den *Staphylococcus aureus* (*methicillin-resistant Staphylococcus aureus*, MRSA) eta bankomizinarekiko erresistenteak diren enterokokoak (*vancomycin-resistant enterococci*, VRE)[1,2]. Zainketa intentsiboetako unitateetan (ZIU) ematen diren infekzioen %50 inguru bakterio Gram-positiboek eragiten dituztenez, ospitale-erabilera duen antibiotiko hau sarritan erabiltzen da zerbitzu hauetan pneumonia, larruazal eta atal biguinen infekzioak edota bakteriemia tratatzeko. Gaitz hauek, askotan, bakterio multi-erresistenteek eragiten dituzte, MRSA edota VRE, esaterako[3,4].

Paziente kritikoen infekzioak tratatzean posologia optimoa aukeratzea erronka garrantzitsua izan ohi da. Alde batetik, gaixoek interbentzio mediko erasotzaileak jasaten dituztelako, bentilazio mekanikoa edota giltzurrun-ordezkatze teknikak, esaterako. Bestetik, sarritan gertatzen diren aldaketa fisiopatologikoek (adibidez, giltzurrun-gutxiegitasun akutuak edo hipoalbuminemiak) antibiotikoen banaketa-bolumena (V) edota argitzapena (CL) eraldatu dezaketelako. Gainera, paziente hauek aldakortasun farmakozinetiko (PK) handiagoa izaten dute normalean, eta, hortaz, dosifikazio egokiena hautatzea

[1] Ager S, Gould K. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. Infect Drug Resist. 2012; 5:87-102.

[2] Ryvak MJ, Akins RL. Emergence of methicillin-resistant *Staphylococcus aureus* with intermediate glycopeptide resistance: clinical significance and treatment options. Drugs. 2001; 61:1-7.

[3] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

[4] Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence. 2016;7(3):267-79.

zailagoa suertatzen da. Honek guztiak, zenbait kasutan pazienteetan emaitza sub-optimoak lortzea dakar[5,6].

Giltzurrun-gutxiegitasun akutua (GGA) gaixo kritikoetan gehien ematen den patologia da, paziente ospitaleratuen %30-60 inguruk jasaten baitute. Gaitz hau tratatzeko etengabeko giltzurrun-ordezkatze teknikak (EGOT) erabiltzen dira maiz, eta estimatzen da ZIUetako pazienteen %5 inguruk ezarriak dituztela[7,8,9]. EGOTak konposatu endogenoen argitzapenean parte hartzeaz gain, pazienteei administraturiko farmakoen kanporatze prozesuan ere laguntzen dute. Era honetan, antibiotiko asko teknika hauen bidez eliminatzen dira nabarmenki. Hortaz, kontuan hartu beharko dira infra-dosifikazioa minimizatzeko, eta, horrela, porrot terapeutikoa eta erresistentzien agerpena ekiditeko.

Gorputz-kanpoko eliminazioa (*extracorporeal clearance*, CL_{EC}) baldintzatu dezaketen faktore ugari dago; hala nola, farmakoaren banaketa-bolumena edo proteinekiko lotura, mintzaren iragazkortasuna, efluentearen fluxua edo EGOT modalitatea bera, besteak beste[10]. Alderdi hauek guztiek, EGOTak ezarriak dituzten gaixo larrietan antzematen den aldakuntza nabarian eragina dute[11]. Nahiz eta giltzurrun bidez aldatu gabeko linezoliden %30 inguru soilik eliminatzen den,

[5] Varghese JM, Roberts JA, Lipman J. Pharmacokinetics and pharmacodynamics in critically ill patients. Curr Opin Anaesthesiol 2010; 23:472-8.

[6] Roberts JA, Joynt GM, Choi GY, Gomersall CD, Lipman J. How to optimise antimicrobial prescriptions in the Intensive Care Unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. Int J Antimicrob Agents. 2012; 39(3):187-92.

[7] Thongprayoon C, Cheungpasitporn W, Ahmed AH. Trends in the use of renal replacement therapy modality in intensive care unit: a 7 year study. Ren Fail. 2015;37(9):1444-7.

[8] Rahman TM, Treacher D. Management of acute renal failure on the intensive care unit. Clin Med. 2002; 2:108-13.

[9] Herrera-Gutiérrez ME, Seller-Pérez G, Maynar-Moliner J, Sánchez-Izquierdo-Riera JA; Grupo de trabajo "Estado actual del fracaso renal agudo y de las técnicas de reemplazo renal en UCI. Estudio FRAMI". Epidemiology of acute kidney failure in Spanish ICU. Multi center prospective study FRAMI. Med Intensiva 2006; 30:260-7.

[10] Meyer MM. Renal Replacement therapies. Crit Care Clin. 2000;16(1):29-58.

[11] Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med. 2012; 40(5):1523-8.

antibiotikoak proteinekiko lotura txikia (≈ % 30 subjektu osasuntsuetan) eta pisu molekular baxua (337,45 g/mol) dauka. Ondorioz, teknika hauen bidez kanporatu daiteke, bereziki fluxu altuko mintzak erabiltzen direnean[12].

Antibiotikoen optimizaziorako analisi farmakozinetiko/farmakodinamikoa (PK/PD) erabiltzean sendatze klinikoa eta biziraupena hobetzen direla ikusi da[13,14]. Hori dela eta, ikerketa lan honen helburu nagusia gaixo kritikoentzat linezoliden populazio eredu farmakozinetiko bat garatzea izan zen; farmakozinetikan aldakortasuna eragiten duten zergatiak identifikatzeko eta kuanfikatzeko asmoz. Gainera, aldakortasun horretan EGOTek duten eragina ere aztertu zen. Bigarren helburua analisi farmakozinetiko/farmakodinamikoa burutzea izan zen; era honetan, Monte Carlo simulazioak erabiliz, ebaluatzeko zein zen bai linezoliden dosi estandarrarekin (600 mg/12 h) eraginkorrak kontsideratzen diren kontzentrazioak eskuratzeko probabilitatea, bai eta segurtasunarekin erlazionatutako balioak lortzeko probabilitatea. Modu honetan, eta behar izanez gero, dosifikazio erregimen berriak proposatu ahal izateko.

[12] Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, et al. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother. 2003; 47(9):2775-80.

[13] Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care. 2015; 21(5):412-20.

[14] Tängdén T, Ramos Martín V, Felton TW, Nielsen EI, Marchand S, Brüggemann RJ, et al. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. Intensive Care Med. 2017;43(7):1021-32

2. Pazienteak eta metodoak

2.1. Ikerketaren diseinua

Behaketa bidezko saiakuntza irekia, prospektiboa eta zentro-anitzekoa burutu zen hiru ospitale desberdinetako ZIUetan: Arabako Unibertsitate Ospitalea (Vitoria-Gasteiz), Doce de Octubre Unibertsitate Ospitalea (Madril) eta Joan XXIII Unibertsitate Ospitalea (Tarragona). Protokoloa Euskadiko Medikamentuen gaineko Ikerkuntza Batzorde Etikoak (EPA2014025) eta Medikamentuen eta Osasun Produktuen Espainiako Agentziak (FJM-LIN-2012-01) onartu zuten. Bestalde, entsegu honetan parte hartu ahal izateko, paziente bakoitzaren, edota gertuko senideen, baimen informatua izatea premiazkoa zen. Parte hartzeko irizpideak honakoak ziren: i) ZIUko pazientea izatea; ii) bakterio Gram-positibo batek eragindako infekzioa pairatzeko susmoa izatea eta, ondorioz, linezolidekin tratatzea; iii) baimen informatua ematea; eta iv) plasma laginak eskuratzea posible izatea, baita efluente laginak ere, pazienteek EGOTak ezarriak izatean. Baztertze-irizpideak, aldiz, honako hauek izan ziren: adin txikikoa izatea (< 18 urte), haurdun egotea, linezolidekiko zein eszipienteekiko hipersentikortasuna azaltzea edota A edo B monoamino-oxidasak inhibitzen dituen medikamenturen bat hartzea.

1. taulan pazienteen datu demografikoak eta biokimikoak bildu dira, baita APACHE II puntuazioa ere (ingeleseko terminoa, *Acute Physiology and Chronic Health Evaluation II*). Paziente bakoitzaren kreatinina argitzapena (Clcr) honako ekuazioa erabiliz kalkulatu zen**:** Clcr (mL/min) = (Cr_u x V_u)/ (Cr_p x 600 min), non Cr_p plasmako kreatinina kontzentrazioa (mg/dL) den, Cr_u gernuko kreatinina kontzentrazioa (mg/dL) eta V_u 10 ordutan zehar bildutako gernu bolumena (mL).

Ordezkatze tekniken bidez eliminatutako farmako frakzioari sieving koefizientea (Sc) deritzo. Dosifikazio-tarte batean zehar lortutako efluentearen eta plasmaren kontzentrazio-denbora kurben azpian mugatutako azaleren arteko zatidura eginda kalkulatu zen (AUC_{ef}/ AUC_p). Linezoliden gorputz-kanpoko argitzapena (CL_{EC}), efluentearen fluxua (Q_{ef}) eta Sc biderkatuz lortu zen.

1. taula. 41 pazienteen datu demografikoak eta biokimikoak, APACHE II puntuazioa eta ingresatutako ospitalea. AUO: Arabako Unibertsitate Ospitalea; DOUO: Doce de Octubre Unibertsitate Ospitalea; JUO: Joan XXIII Unibertsitate Ospitalea; EGOT: etengabeko giltzurrun-ordezkatze teknikak; GMI: gorputz-masaren indizea; Clcr: kreatinina argitzapena; GOT: glutamato-oxalazetato transaminasa; GPT: glutamato-pirubato transaminasa; CL_{EC}: gorputz-kanpoko argitzapena; CVVHDF: etengabeko hemodiafiltrazio beno-benosoa; CVVHD: etengabeko hemodialisi beno-benosoa.

	EGOT gabe		EGOT	
Pazienteen ezaugarriak	**n**	**Mediana (Tartea)**	**n**	**Mediana (Tartea)**
Ospitalea				
AUO	18		9	
DOUO	0		13	
JUO	0		1	
Datu demografikoak				
Adina (urteak)		72 (22-85)		68 (37-79)
Sexua (gizonezko/emakumezko)	14/4		16/7	
Pisua (kg)		71 (60-95)		74 (55-110)
Altuera (m)		1,70 (1,60-1,85)		1,69 (1,53-1,85)
GMI (kg/m^2)		24,5 (20,8-31,3)		25,9 (21,2-33,1)
Datu biokimikoak				
Clcr (mL/min)		71,2 (11,0-179,5)		6,0 (0,0-45,6)
Kreatinina (mg/dL)		0,80 (0,40-2,10)		1,15 (0,56-2,60)
Glukosa (mg/dL)		144 (73-187)		140 (69-210)
Hemoglobina (g/dL)		9,85 (7,00-15,50)		8,50 (6,70-11,40)
Hematokritoa (%)		30,5 (20,0-46,0)		26,4 (18,7-34,7)
Albumina (g/dL)		2,8 (1,9-4,0)		2,2 (1,7-3,6)
Proteina totalak (g/dL)		5,8 (4,2-7,4)		5,2 (2,7-7,3)
Bilirrubina (mg/dL)		0,65 (0,20-1,30)		0,80 (0,12-2,60)
GPT (U/L)		25 (6-340)		50 (5-570)
GOT (U/L)		33 (16-330)		43 (8-675)
APACHE II		16 (11-36)		22 (16-34)
CL_{EC} (L/h)			23	2,51 (0,79-3,09)
CVVHDF			18	2,61 (0,79-3,09)
CVVHD			5	1,06 (1,00-2,73)

2.2. Farmakoaren administrazioa eta lagin bilketa

Paziente bakoitzari 600 mg linezolid (Zyvoxid®) administratu zitzaion, 12 orduro. Antibiotikoa 30 minutuko iraupena zuen zain-barneko infusio bidez eman zen kasu guztietan, batean izan ezik, 60 minuturako iraupena izan zuena. Lagin bilketarekin hasi baino lehen, paziente bakoitzari bataz beste 8 linezolid dosi eman zitzaizkion, oreka egonkorra bermatuz. Odol-laginak dosia eman baino lehen eta infusio amaieran (0,5 h) jaso ziren. Bestalde, lagin bana hartu zen 1, 2, 3, 6, 8tik 10ra eta 12 ordu pasa ostean. Laginak heparina sodikoa zuten Vacutainer™ saiodietan bildu eta berehala zentrifugatu ziren, 10 minututan zehar 3.000 rpm-tan. Lortutako plasma laginak -80º C-tan izoztu ziren analizatu arte. EGOTak ezarriak zituzten pazienteetan, odola ez ezik, efluente laginak ere hartu ziren denbora-tarte berdinetan, eta zuzenean -80º C-tan gorde.

2.3. Metodo analitikoa

Plasma-laginetan zegoen antibiotiko-kontzentrazioa kuantifikatzeko, aldez aurretik balioztatutako detekzio ultramoredun bereizmen handiko kromatografia likidoa (*high performance liquid chromatography,* HPLC) erabili zen (**1. eranskina**). Lehenik eta behin, proteinak azetonitriloarekin prezipitatu ziren, eta horrek kuantifikaziorako erabiliko zen barne estandarra (propil-4-hidroxibenzoato) disolbatua zuen. Ostean, laginak 10 minutuz zentrifugatu ziren, 15.000 rpm-ko baldintzapean. Bertatik lortutako gainjalkinak, baita efluente-laginak ere, HPLC sisteman injektatu ziren. Banaketa Simmetry® C8 zutabe batekin burutu zen (4,6 mm x 150 mm x 5 μm). Linealtasuna espero ziren plasma eta efluente kontzentrazio tartean frogatu zen, 0,5-50 μg/mL eta 0,2-30 μg/mL, hurrenez hurren. Linezoliden estandarra Pfizer Pharmaceuticals enpresari esker lortu zen.

Intra eta inter-egun zehaztasuna eta doitasuna kuantifikazio limiteekin eta linealtasun tarteko beste hiru kontzentraziorekin demostratu ziren. Alegia, plasma

laginen kasuan 0,5, 1,5, 10 eta 40 μg/mL-tako kontzentrazioekin eta efluente laginen kasuan 0,2, 0,6, 5 and 24 μg/mL-rekin. Kalkulatutako kontzentrazioen desbiderapenak inoiz ez zuen balio teorikoaren %15 gainditu. Bestalde, intra- eta inter-saiakuntza doitasuna, aldakuntza-koefiziente moduan adierazia (*coefficient of variation*, CV), %15 azpitik mantendu zen beti.

2.4. Populazio eredu farmakozinetikoa

2.4.1. Oinarrizko eredua

Populazio eredua sortzeko baldintzazko lehen mailako estimazio metodoa interakzioarekin (FOCE-I) erabili zen NONMEM 7.3 programa baliatuz[15]. Farmako totalaren kontzentrazioen disposizioa eredu konpartimentalak erabiliz aztertu zen, eta datuak logaritmoetara transformatzeko aukera aintzat hartu zen. Ereduen ebaluaziorako funtzio-objektiboaren balioaren (OFV) beherakada, parametroen kalkuluan emandako errore erlatibo estandarrak (RSE) eta doikuntza-egokitasuna ebaluatzeko (*goodness-of-fit*, GOF) grafikoak kontuan hartu ziren. Hondar-errorea ebaluatu zen eta aldakortasun-interindibidualak (IIV) zein kobariantza posible bat ikertu ziren.

2.4.2. Aldagaien aukeraketa

Behin oinarrizko eredua aukeratu ostean, eta IIV azaltzeko asmoz, **1. taulan** bildu diren faktore guztiak aztertu ziren aldagai potentzial moduan. Bost pazientek edo gutxiagok aldagai baten informazioa faltan zutenean, beste pazienteen mediana esleitu zitzaien. Clcr aldagai jarraitu bezala aztertu zen.

[15] Beal S, Sheiner, LB, Boeckmann, A, Bauer R.J. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

Gainera, pazienteak bost talde desberdinetan kategorizatu ziren, beraien Clcr aintzat hartuta: < 10 mL/min, ≥ 10 baina < 30 mL/min, ≥ 30 baina < 60 mL/min, ≥ 60 baina < 130 mL/min eta Clcr ≥ 130 mL/min. Bestalde, hiru aldagai dikotomiko sortu ziren, pazienteek ondorengo hiru parametro biokimiko desberdinetatik bat, bi edo hiru normaltasunetik at zituzten edo ez kontuan hartuta: bilirrubina (tarte normala: 0,3-0,9 mg/dL), GOT (tarte normala: 8-30 UI/L gizonezkoentzat eta 6-25 UI/L emakumezkoentzat) eta GPT (tarte normala: 8-35 UI/L gizonezkoen kasuan eta 6-25 UI/L emakumezkoentzat).

Aldagaiak aukeratzeko mailakatutako prozesua burutu zen (PsN 4.7.0-ren SCM tresna). Prozesu hau aurrerako barne-hartze prozesuan eta atzerako ezabatzean oinarritua dago. Horrela, ereduan gehitu eta bertan mantentzeko esangura-mailak 0,05 eta 0,01-n finkatu ziren, hurrenez hurren. GOF grafikoak ere erabili ziren eredu desberdinen egokitasuna aztertzeko.

2.4.3. Ereduaren ebaluazioa

Hautatutako ereduaren egokitasuna aztertzeko GOF grafikak analizatu ziren. Erabilitako GOF grafikak honakoak izan ziren: populazio- eta norbanakoen-aurreikusiak (PRED eta IPRED) vs. neurtutako kontzentrazioak (DV, μg/mL-tan), haztatutako baldintzapeko hondar-balioak (*conditional weighted residuals*, CWRES) vs. dosi osteko denbora (*time after dose*, TAD) eta norbanako bakoitzaren haztatutako hondar-balioak (*individual weighted residuals*, IWRES) vs. IPRED.

Bestalde, VPC bat irudikatu zen ereduaren zuzentasuna determinatzeko (PsN 4.7.0-ren VPC tresna). Horrela, neurtutako kontzentrazioen 2,5., 50. eta 97,5. pertzentilak irudikatu ziren. Ostean, mila paziente birtual simulatu ziren populazio eredu finalean lortutako parametroen balioak erabiliz, eta baldintza berdinen mendean. Simulatutako 2,5., 50. eta 97,5. pertzentilen %95eko konfiantza-

tarteak ere grafikan gehitu ziren, R 3.4.0 programaren xpose4 paketea erabiliz[16]. Azkenik, parametroen zehaztasuna ebaluatzeko 2.000 datu-multzoko bootstrap bat exekutatu zen (Bootstrap tresna, PsN 4.7.0). Eredua sortzeko eta ebaluazio prozesuan lortutako datuak eta emaitzak antolatzeko Pirana v.2.9.5 softwarea erabili zen[17].

2.4.4. Kanpo-balidazioa

Guztira 44 plasma lagin erabili ziren kanpo-balidazioa egiteko, 11 gaixo larri desberdinetatik lortu zirenak. Laginak Arabako Unibertsitate Ospitalean egindako ikerketa prospektibo batetik lortu ziren. **2. taulan** pazienteen datu demografikoak eta biokimikoak bildu dira, baita APACHE II puntuazioa ere. Faktore hauek populazio-eredu farmakozinetikoa garatzeko parte hartu zuten 41 pazienteen datuekin konparatu ziren eta bi taldeen artean estatistikoki esanguratsuak diren desberdintasunak zeuden ala ez aztertu zen. Horretarako IBM SPSS statistic® programa (21. bertsioa)[18] erabili zen. Aldagai jarraien azterketarako t-testa edo Mann–Whitney-ren U testa aplikatu ziren, distribuzio normala zuten ala ez aintzat hartuta, hurrenez hurren. Aldagai kategorikoei dagokionez, Pearson-en khi-karratuaren testa (χ^2) erabili zen.

Kanpo-balidazioko pazienteei etengabeko zain-barneko perfusioaren bidez 1.200 mg administratu zitzaien 24 orduro, 30 minututan zehar 600 mg-tako karga-dosi bat eman ostean. Aurretik aipatutako irizpideez gain, soilik EGOTak ezarriak ez zituzten eta Clcr > 40 mL/min zuten pazienteak onartu ziren. Lau egun jarraietan zehar plasma lagin bana hartu zitzaien gaixoei. Linezoliden

[16] Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. 1999;58(1):51-64.

[17] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

[18] IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

kontzentrazioak aurretik deskribatu den HPLC teknika berdina erabiliz kuantifikatu ziren (**1. eranskina**).

2. taula. Etengabeko perfusioan parte hartu zuten pazienteen datu demografikoak eta biokimikoak, eta APACHE II. GMI: gorputz-masaren indizea; Clcr: kreatinina argitzapena; GOT: glutamato-oxalazetato transaminasa; GPT: glutamato-pirubato transaminasa.

	Etengabeko perfusioa	
Pazienteen ezaugarriak	**n**	**Mediana (Tartea)**
Datu demografikoak		
Adina (urteak)		60 (24-84)
Sexua (gizonezko/emakumezko)	4/7*	
Pisua (kg)		80 (70-115)
Altuera (m)		1,67 (1,65-1,80)
GMI (kg/m^2)		28,5 (24,2-35,5)
Datu biokimikoak		
Clcr (mL/min)		111 (45-240)*
Kreatinina (mg/dL)		0,70 (0,50-1,10)*
Glukosa (mg/dL)		136 (114-217)
Hemoglobina (g/dL)		10,3 (8,2-11,7)
Albumina (g/dL)		3,0 (2,5-3,6)*
Proteina totalak (g/dL)		5,4 (5,3-7,4)*
Bilirrubina (mg/dL)		0,70 (0,50-2,10)
GPT (U/L)		37 (18-220)
GOT (U/L)		25 (16-74)
APACHE II		16 (6-25)*

*Estatistikoki esanguratsuak diren desberdintasunak ($p < 0,05$) etengabeko perfusioa (n=11) eta perfusio-motza (n=41) (**1.taula**) administratutako pazienteen artean.

Garatutako eredu farmakozinetikoa erabiliz, paziente hauetan linezoliden kontzentrazioak aurreikusi ziren. Horretarako, 5.000 subjektu simulatu ziren honako Clcr balioentzat: 40, 80, 120, 160, 200 eta 240 mL/min; izan ere, balio hauen artean zeuden aztertutako pazienteen Clcr-ak. Simulatutako datuen 2,5., 50. eta 97,5. pertzentilak kalkulatu ziren, eta neurtutako balioekin konparatu.

2.5. Monte Carlo simulazioa

2.5.1. Analisi farmakozinetiko/farmakodinamikoa

Helburua lortzeko probabilitatearen (PTA) estimazioa

PTA (*probability of target attainment*) MIC zehatz batentzat gutxienez helburu farmakozinetiko/farmakodinamikoaren balioa (adibidez, AUC/MIC = 80) lortzeko probabilitateari deritzo[19].

Linezolidek kontzentrazio-independentea den aktibitate patroia dauka. Bere efikaziarekin ongien erlazionatutako indizeak bi dira. Lehenengoa, oreka egonkorrean linezolid totalaren kontzentrazio-denbora kurbaren azpian mugatutako azalera (24 ordu) eta MICaren arteko ratioa (AUC_{24h}/MIC) da. Bigarrena, plasma kontzentrazioak MICaren gainetik dauden denboraren ehunekoa ($T_{>MIC}$) da. Era honetan, tratamenduaren arrakasta altuak ikusi dira AUC_{24h}/MIC > 80 tik 120ra denean edota $T_{>MIC}$ > % 85 lortzean[20].

Linezoliden dosi estandarra aintzat hartuta, alegia, 600 mg 12 orduro perfusio motz baten bidez, 5.000 subjektuko simulazioak egin ziren, EGOTak ere kontuan hartuta. Horrela, egoera desberdinak simulatu ziren, Clcr balio desberdinentzat: 0, 10 eta 30 mL/min EGOTak zituzten pazienteetan eta 10, 30, 60, 90 eta 130 mL/min gainerakoetan. Efluente fluxuak CL_{EC}-n eragin nabarmena duenez ($CL_{EC} = Q_{ef} \times Sc$), Q_{ef} desberdinak kontsideratu ziren, PTAn zuten influentzia aztertzeko. Bestalde, gorputz-kanpoko argitzapena kalkulatzeko erabilitako Sc balioa, ikertutako pazienteen batez bestekoa izan zen (0,8). Amaitzeko, aipatu berri diren paziente talde guztientzat, 600 mg/8h-tako linezolid perfusio motzak (30 min) simulatu ziren ere. Helburua lortzeko probabilitateak

[19] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/ pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005;55(5):601-7.

[20] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003, 42:1411-23.

MIC desberdinentzat kalkulatu ziren, 0,25-tik 4 mg/L-rako tartean. Simulazioak NONMEM 7.3 programa erabiliz gauzatu ziren.

Erantzunaren metatze-frakzioaren (CFR) kalkulua

CFRak (*cumulative fraction of response*) antibiotiko baten dosifikazio-erregimen zehatz batentzat eta bakterio populazio jakin batentzat, populazioaren PTA kalkulatzen du. Hau da, MICen distribuzioa ezagututa, populazio batean zein proportziok PK/PD balio jakin bat lortuko duen kalkulatzen du, Monte Carlo simulazioen bidez. Hurrengo formula erabiliz kalkulatzen da:

$$CFR = \sum_{i=1}^{n} PTA_i \times F_i \qquad \textbf{(Eq. 1)}$$

Non *i* azpiindizeak mikroorganismo populazio batean dagoen MIC balio txikienetik handienerako balioak hartzen dituen; PTA_i MIC balio bakoitzarentzat lortutako PTA den eta F_i mikroorganismo populazioan MIC balio bakoitzak suposatzen duen frakzioa den. CFR balioak dosi estandarrentzat (600 mg/12h) eta 600 mg/8h-ko dosi altuagoarentzat kalkulatu ziren.

CFRn balioak estimatzeko, 2013. eta 2015. urte artean Arabako Unibertsitate Ospitaleko ZIUetan lortutako suszeptibilitateen informazioa erabili zen. Era horretan, tratamenduaren arrakasta lortzeko probabilitateak kalkulatu ziren honako bakterio hauentzat: *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus epidermidis*, *Staphylococcus aureus* eta koagulasa negatiboko estafilokokoak (**3. taula**). Mikrobiologiako departamentutik lortutako datuak Whonet programarekin kudeatu ziren[21].

[21] WHONET 5.6. Eskuragarri: *http://www.who.int/medicines/areas/rational_use/AMR_WHONET_SOFTWARE/en/* [kontsulta: 2018ko maiatza].

3. taula. 2013. eta 2015. urte bitartean Arabako Unibertsitate Ospitaleko ZIUetan lortutako MICen distribuzioa *E. faecium, E. faecalis, S. epidermidis, S. aureus* eta koagulasa negatiboko estafilokokoentzat (CoNS).

Mikroorganismoa	Suszeptibilitate mozte-puntu klinikoa MIC (mg/L)[a]	Isolatutako andui kopurua	MIC (mg/L) balio bakoitzarekin inhibitzen den anduien ehunekoa			
			1	2	4	8
E. faecium	2/4	18	22	78		
E. faecalis	2/4	53	26	72		2
S. epidermidis	4	34		82	3	15
S. aureus	4	60		92	8	
CoNS	4	70		88	3	9

[a] Clinical and Laboratory Standard Institute (CLSI) eta the European Committee on Antimicrobial Susceptibility Testing (EUCAST) erakundeen arabera.

Bai PTA bai CFR balioentzat %90tik gorako emaitzak optimotzat hartu ziren. Arrakasta moderatuarekin, aldiz, %90 eta %80 arteko datuak erlazionatu ziren[22,23].

2.5.2. Segurtasunaren ebaluazioa

Linezoliden segurtasun profila ebaluatzeko, simulatutako subjektuetatik toxikotzat hartzen diren antibiotiko-kontzentrazio plasmatikoak (AUC_{24h} > 400

[22] Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J. 2003;22(11):982-92.

[23] Drusano GL, Preston SL, Hardalo C, Hare R, Banfield C, Andes D, et al. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob Agents Chemother. 2001;45(1):13-22.

mg*h/L eta $Cmin_{ss}$ > 10 mg/L)[24,25] zein ehunekok lortzen zituzten behatu zen. Simulazio hauek ere NONMEM 7.3 programarekin egin ziren.

3. Emaitzak

Populazio-eredu farmakozinetikoa eraikitzeko 41 gaixo larriren datuak aintzat hartu ziren. Paziente bakoitzeko 8 plasma lagin bildu ziren, eta guztira 331 kontzentrazioren datuak gehitu ziren eredua eraikitzeko base-datuan. Pazienteei diagnostikatutako gaitzen artean biriketako infekzioak (n = 15), infekzio abdominalak (n = 10), neurologikoak (n = 9), behazun-xixkukoak (n = 2) eta bestelako infekzioak (n = 5) zeuden.

Gainera, EGOTak zituzten 23 pazienteetan beste zortzi efluente lagin bildu ziren denbora berdinetan. Hemezortzi pazientek etengabeko hemodiafiltrazio beno-benosoa (c*ontinuous venovenous hemodiafiltration*, CVVHDF) ezarria zuten eta beste bostek etengabeko hemodialisi beno-benosoa (c*ontinuous venovenous haemodialysis*, CVVHD). Efluentearen fluxua 1,1 eta 3,3 L/h artean mantendu zen. Fluidoen balantzea egoera klinikoaren arabera ezarri zen. Behar izanez gero pazienteak antikoagulatu ziren, 0,1 eta 5 UI/kg/h bitarteko zatikatu gabeko heparina dosiekin. Iragazkien mintzak polisulfonakoak (Aquamax HF 12;

[24] Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012; 67:2034-42.

[25] Cattaneo D, Orlando G, Cozzi V, Cordier L, Baldelli S, Merli S, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with Gram-positive infections. Int J Antimicrob Agents. 2013; 41:586-89.

Fresenius, Alemania) edo AN69 mintzak (Nephral ST400, Hospal, Bolonia, Italia) izan ziren eta beraien azalerak 1,80 eta 1,65 m^2-takoak ziren, hurrenez hurren.

3.1. Populazio-eredu farmakozinetikoa

3.1.1. Oinarrizko eredua

Linezoliden plasma kontzentrazioak ongien deskribatu zituen eredua bi konpartimentukoa izan zen. Aldakortasun-interindibiduala (IIV) gehitu zitzaion argitzapenari (CL) eta konpartimentu zentraleko banaketa-bolumenari (V_1). Ez zen korrelaziorik aurkitu bi parametro horien artean. IIV-a esponentzialki modelizatu zen eta hondar-errore konbinatua erabili zen.

3.1.2. Aldagaien aukeraketa

Linezoliden argitzapena, giltzurrun-kanpoko argitzapenaren (CL_{NR}) eta giltzurrun-menpeko argitzapenaren (CL_R) arteko batura moduan kalkulatu zen; eta azken hori Clcr-aren eraginpean zegoen. Clcr ereduan gehitzean, argitzapenaren IIVa %98,7tik %61,5ra murriztu zen. EGOTak egotziak zituzten pazienteen kasuan, gorputz-kanpoko argitzapenak ere bere ekarpena izan zuen argitzapenean. Esplorazio-analisian pisua eta adina V_1-arekin erlazionatuta zeudela susmatu arren, aldagaien aukeraketa prozesuan ez zuten esangura estatistikorik lortu ($p > 0,05$). Bilirrubina, GOT eta GPT taldekatu eta aldagai potentzial moduan aztertu ziren, baina ez zuten ereduaren hobekuntzarik eragin. Nahiz eta SCMan 130 mL/min baino Clcr altuagoak zituzten pazienteek konpartimentu periferikoko banaketa-bolumen (V_2) handiagoak izan, Clcr kategorikoa ez zen gehitu aldagai moduan eredu farmakozinetikoan. Izan ere, ez zen hobekuntza nabarmenik antzeman aurreikusitako kontzentrazioetan, eta

estimatutako hondar-erroreak gora egiten zuen. Bestelako aldagaiek ez zuen OFVaren jaitsiera esanguratsurik lortu.

3.1.3. Ereduaren ebaluazioa

4. taulan populazio-eredu farmakozinetikoan linezolidentzat estimatutako parametroen balioak azaltzen dira, baita RSEak (%) ere. Gainera, bootstrap-aren emaitzak bildu dira eta parametroen estimazioa zehaztasunarekin burutu zela erakusten dute. GOF grafikoetan (**1. irudia**) ez zen joera adierazgarririk sumatu, ez CWRES versus dosi osteko denboran ezta IWRES versus iragarritako balio indibidualetan ere. Bestalde, neurtutako eta aurreikusitako populazio zein norbanakoen balioek korrelazio egokia erakutsi zuten. VPCak (**2. irudia**) datu gordinen eta populazio-eredutik lortutako simulazioen pertzentilen arteko korrelazio ona irudikatu zuen.

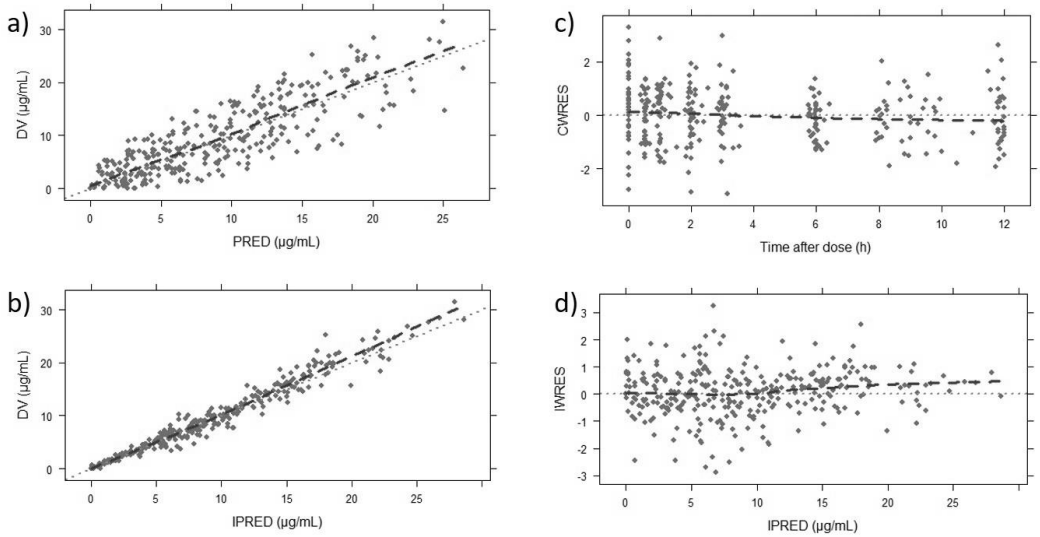
4. taula. Oinarrizko eredua eta hautatutako populazio-eredu farmakozinetikoa linezoliden zain-barneko infusio motzerako. Estimatutako parametroak, shrinkage[a] balioak eta bootstrap-aren emaitzak.

Parametroa	Oinarrizko eredua Estimatutako balioa, RSE (%)	Hautatutako eredua Estimatutako balioa, RSE (%)	Bootstrap, mediana (5^{th}-95^{th} pertzentilak)
CL (L/h) = CL_{NR} + CL_R+ CL_{EC}[b]	5,59 (13) + CL_{EC}		
CL_{NR}		2,62 (18)	2,65 (2,02 – 3,65)
CL_R = θ x (Clcr/44)		4,35 (19)	4,33 (2,99 – 5,84)
V_1 (L)	16,1 (20)	16,2 (14)	16,6 (11,7 – 24,4)
Q (L/h)	72,3 (18)	71,7 (14)	69,5 (40,4 – 92,0)
V_2 (L)	29,1 (8)	29,0 (7)	28,6 (23,0 – 32,6)
IIV_{CL} (%)	98,7 (10)	61,5 (9)	59,3 (48,9 – 69,4)
IIV_{V1} (%)	66,6 (20)	65,9 (17)	62,4 (37,7 – 91,6)
Residual error_additive (mg/L)	0,260 (24)	0,266 (24)	0,267 (0,156 – 0,464)
Residual error_propor.(%)	0,160 (9)	0,159 (19)	0,157 (0,122– 0,183)

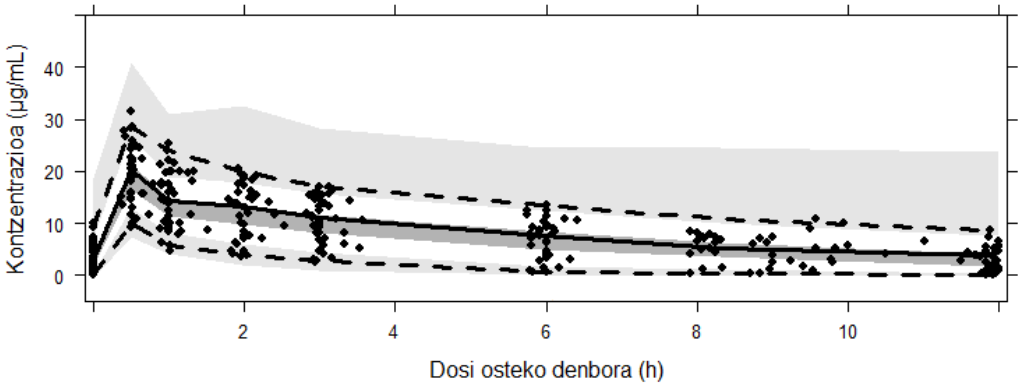
[a] CLηsh = %1; V_1ηsh = %18; εsh = %11

[b] Soilik EGOTak ezarriak zituzten pazienteetan. Norbanakoen CL_{EC} balio aintzat hartu zen.

CL: argitzapena; CL_{NR}: giltzurrun-kanpoko argitzapena; CL_R: giltzurrun-menpeko argitzapena; CL_{EC}: gorputz-kanpoko argitzapena; Clcr: kreatinina-argitzapena; V_1: konpartimentu zentraleko banaketa-bolumena; V_2: Konpartimentu periferikoko banaketa-bolumena; IIV: aldakortasun-interindibiduala; RSE: errore erlatibo estandarra; ηsh: shrinkage balioa parametro batentzat; εsh: shrinkage balioa hondar-errorearentzat.



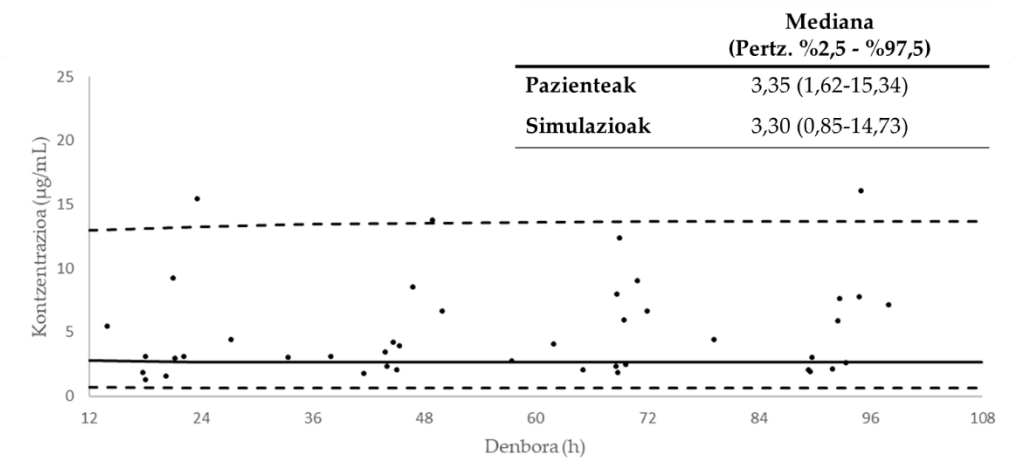
1. Irudia. Hautatutako ereduarekin lortutako GOF grafikoak: Populazioaren (PRED)[a] eta norbanakoen (IPRED)[b] aurreikusiak versus kuantifikatutako linezolid plasma-kontzentrazioak, (µg/mL), haztatutako baldintzapeko hondar-balioak (CWRES) versus dosi osteko denbora (h)[c], eta norbanako bakoitzaren haztatutako hondar-balioak (IWRES) versus norbanakoen aurreikusiak[d].



2. irudia. Dosi osteko denboran (0-tik 12 h-ra) lortutako VPCren emaitzak. Puntuak kuantifikatutako kontzentrazioak dira (µg/mL). Etengabeko marrak kuantifikaturiko datuen batezbesteko balioa irudikatzen du eta bestelako marrek, 2,5. eta 97,5. pertzentilak. Itzal ilun eta argiek simulazioan lortutako %95eko konfiantza-tarteak erakusten dute, medianarentzat eta 2,5. eta 97,5. pertzentilentzat, hurrenez hurren.

3.1.4. Kanpo-balidazioa

3. irudian linezolid etengabeko perfusio bidez administratu zitzaien 11 pazienteetan neurtutako kontzentrazioak eta simulazio bidez iragarritako mediana eta %2,5 eta %97,5 pertzentilak konparatu dira. Ikus daitekeen moduan, hautatuko eredua gai izan zen modu egokian pazienteen kontzentrazioak aurreikusteko.



3. irudia. Etengabeko perfusioan neurtutako kontzentrazioak eta populazio-eredua erabilita simulazio bidez lortutako mediana eta %2,5 eta %97,5 pertzentilak.

3.2. Monte Carlo simulazioa

3.2.1. Analisi farmakozinetiko/farmakodinamikoa

Helburua lortzeko probabilitatea (PTA)

5. taulak zenbait egoera desberdinetan AUC_{24h}/MIC > 80 lortzeko probabilitateak biltzen ditu. Orokorrean, zenbat eta dosi altuagoa eta Clcr baxuagoa, orduan eta PTA altuagoak lortuko dira. EGOTak ezarriak ez dituzten pazienteetan, eta Clcr ≤ 60 mL/min baldintzapean, 600 mg/12h-ko dosia nahikoa izango litzake 1 mg/L edo baxuagoak diren MIC balioak dituzten bakterioek

eragindako infekzioak tratatzeko. Haatik, 2 mg/L-ko MIC balioentzat dosi hau ez litzateke nahikoa izango orokorrean, soilik eraginkortasun probabilitate altuak lortuz 10 mL/min edo gutxiagoko kreatinina argitzapena izatean. Dosia handitzean, 600 mg/8h-ra, 30 mL/min-ko Clcr balioak dituzten subjektuentzat PTA %68tik %88ra igo zen 2 mg/L-ko MICentzat. Dena den, beste kasu guztietan ez zen arrakasta lortzeko probabilitatea modu nabarmenean handitu.

EGOTak ezarriak dituzten pazienteetan, 1 mg/L edo baxuagoak diren MICentzat arrakasta izateko probabilitate altuak lortuko lirateke. Dena den, 2 mg/L-ko MIC balioa duten bakterioei aurre egiteko, 600 mg/8h-ko dosia beharko litzateke Q_{ef} altua edota 30 mL/min balioak dituzten pazienteetan.

Erantzunaren metatze-frakzioa (CFR)

6. taulan ikerketa-lan honetan lortutako CFR balioak bildu dira. Simulatutako dosifikazio erregimenek ez dute arrakasta probabilitate altuak lortzen (≥ %90) *S. epidermidis*-ek eragindako infekzioak tratatzeko. Dosi estandarrarekin, eta EGOTik gabeko pazienteetan, beste mikroorganismoek eragindako infekzioak tratatzeko arrakasta probabilitate altuak lortuko lirateke soilik giltzurrun gutxiegitasun larria (Clcr ≤ 10 mL/min) duten pazienteetan. Orokorrean, 600 mg/8h-ko dosia onuragarria izango litzateke 10 eta 30 mL/min bitarteko Clcr balioak dituzten pazienteentzat. Izan ere, kasu hauetan arrakasta lortzeko probabilitateek gora egiten dute.

EGOTak ezarriak dituzten pazienteei dagokionez, infekzioa eragiten duen mikroorganismoa *E. faecium, E. faecalis, S. aureus* edo CoNS denean, arrakasta lortzeko probabilitateak desberdinak izango dira Clcr-aren eta CL_{EC}-aren arabera. Hala ere, ikus daiteke 30 mL/min edo handiagoa den kreatinina argitzapena duten pazienteetan 600 mg/8h-ko dosia ere ez litzatekela orokorrean nahikoa izango mikroorganismo hauek eragindako infekzioak tratatzeko.

5. taula. Linezoliden PTA balioak (%) AUC_{24h}/MIC > 80 helburu farmakodinamikoa aintzat hartuta. Letra lodiz PTA ≥ %90 balioak eta letra etzanez PTA ≥ %80 balioak irudikatu dira.

Dosia	**Clcr** (mL/min)	**EGOT gabe**					**EGOT**														
							Q_{ef} 1,5 L/h					**Q_{ef} 2,5** L/h					**Q_{ef} 3** L/h				
600 mg/12h	0						**100**	**100**	**100**	**93**	48	**100**	**100**	**100**	**90**	23	**100**	**100**	**100**	*87*	12
	10	**100**	**100**	**99**	**90**	54	**100**	**100**	**99**	*85*	27	**100**	**100**	**99**	78	11	**100**	**100**	**98**	74	4
	30	**100**	**100**	**96**	68	24	**100**	**100**	**95**	58	9	**100**	**100**	**93**	49	2	**100**	**98**	**92**	43	1
	60	**100**	**99**	*85*	40	7															
	90	**100**	**95**	*67*	23	2															
	130	**100**	*88*	47	10	1															
600 mg/8h	0						**100**	**100**	**100**	**99**	*81*	**100**	**100**	**100**	**99**	70	**100**	**100**	**100**	**98**	63
	10	**100**	**100**	**100**	**98**	79	**100**	**100**	**100**	**97**	65	**100**	**100**	**100**	**96**	50	**100**	**100**	**100**	**95**	42
	30	**100**	**100**	**99**	*88*	50	**100**	**100**	**99**	*85*	34	**100**	**100**	**99**	*81*	23	**100**	**100**	**99**	79	16
	60	**100**	**100**	**96**	70	23															
	90	**100**	**99**	*88*	47	11															
	130	**100**	**97**	75	29	4															
MIC (mg/L)		**0,25**	**0,5**	**1**	**2**	**4**	**0,25**	**0,5**	**1**	**2**	**4**	**0,25**	**0,5**	**1**	**2**	**4**	**0,25**	**0,5**	**1**	**2**	**4**

6. taula. Linezoliden CFR balioak bakterio desberdinentzat, kontuan hartuta 2013. eta 2015. urte bitartean Arabako Unibertsitate Ospitalean lortutako MICen distribuzioen frekuentzia. Letra lodiz CFR ≥ %90 balioak eta letra etzanez CFR ≥ %80 balioak irudikatu dira.

		Dosia EGOT gabe		**Dosia EGOT**					
				Q_{ef} 1.5 L/h		**Q_{ef} 2.5** L/h		**Q_{ef} 3** L/h	
Bakter.	**Clcr** (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
Enterococcus faecium	0			**95**	**99**	**92**	**99**	**90**	**99**
	10	**92**	**98**	*88*	**97**	*82*	**96**	*80*	**96**
	30	74	**91**	66	*88*	59	*85*	54	*83*
	60	50	75						
	90	33	56						
	130	18	39						
Enterococcus faecalis	0			**93**	**98**	**91**	**97**	89	**97**
	10	**91**	**97**	*87*	**96**	*82*	**95**	79	**94**
	30	74	*89*	*67*	*87*	60	*84*	55	*82*
	60	51	75						
	90	34	57						
	130	19	40						
Staphylococcus epidermidis	0			78	*87*	74	*83*	72	*82*
	10	77	*85*	70	*82*	64	*80*	61	79
	30	57	75	48	71	40	*67*	35	65
	60	33	58						
	90	19	39						
	130	8	24						
Staphylococcus aureus	0			**90**	**98**	*85*	**96**	*81*	**95**
	10	*87*	**96**	*80*	**94**	72	**92**	69	**90**
	30	65	*85*	54	*81*	45	76	39	74
	60	38	66						
	90	21	44						
	130	9	27						
CoNS	0			*85*	**92**	*81*	**90**	78	*89*
	10	*83*	**91**	76	*89*	69	*87*	66	*85*
	30	62	*80*	52	77	44	73	38	70
	60	36	63						
	90	20	42						
	130	9	26						

3.2.2. Segurtasunaren ebaluazioa

7. eta **8. taulek** $Cmin_{ss}$ > 10 mg/L eta AUC_{24h} > 400 mg*h/L lortzeko probabilitateak biltzen dituzte, hurrenez hurren. Bi balio horiek linezolidek eragindako toxikotasunarekin lotu dira. Dosi estandarra erabiltzean (600 mg/12h) toxikotasunarekin erlazionatutako kontzentrazioak lortzeko probabilitateak baxuak dira, salbuespen batzuetan izan ezik; alegia, EGOT gabeko Clcr ≤ 10 mL/min balioak dituzten pazienteetan edota fluxu baxuko EGOTak ezarriak dituzten paziente anurikoetan. Dosi altuago bat erabiltzeak (600 mg/8h) modu nabarmenean baldintzatuko luke segurtasun profila. Horrela, bereziki sentikorrak izango lirateke Clcr balio baxuak dituzten pazienteak (≤ 60 mL/min), edota fluxu baxuko EGOTak ezarriak dituztenak.

7. taula. Linezoliden $Cmin_{ss}$ > 10 mg/L lortzeko probabilitateak.

	EGOT gabe		**Q_{ef} 1.5** L/h		**Q_{ef} 2** L/h		**Q_{ef} 3** L/h	
Clcr (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
0			32	92	9	87	3	83
10	43	88	15	81	3	73	1	68
30	16	65	4	53	1	43	0	36
60	4	36						
90	1	19						
130	0	8						

8. taula. Linezoliden AUC_{24h} > 400 mg*h/L lortzeko probabilitateak.

	EGOT gabe		**Q_{ef} 1.5** L/h		**Q_{ef} 2** L/h		**Q_{ef} 3** L/h	
Clcr (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
0			26	65	5	45	1	34
10	38	66	11	44	1	27	0	17
30	13	35	2	18	0	8	0	4
60	3	12						
90	1	5						
130	0	1						

4. Eztabaida

Lan honetan, linezoliden populazio-eredu farmakozinetiko bat garatu da gaixo larrientzat. Datuak ongien deskribatu zituen eredua konpartimentu bikoa izan zen, aurretik argitaratutako beste ikerketekin bat datorrena[26,27,28,29]. Estimatutako banaketa-bolumena (V_{ss} = 45,2 L) gorputz osoko ur kantitatearen antzekoa izan zen eta zenbait lanetan gaixo larrietan lortutako balioekin bat zetorren (adibidez, Taubert et al.[27]: 41,55 L). Gainera, ez zen desberdintasunik antzeman EGOTak ezarriak zituzten eta ez zituztenen artean. Bestalde, Slatter et al.-ek[30] edota MacGowan et al.-ek[31] boluntario osasuntsuetan deskribatutako banaketa-bolumenaren antzekoa izan zen ere (30-50 L). Banaketa-bolumenean ikusitako desberdintasun eza linezoliden izaera lipofiliko moderatuarekin erlazionatu daiteke. Izan ere, farmako hauen Van ez ohi da aldaketa esanguratsurik ematen gaixo larrien eta osasuntsuen artean. Farmako hidrofilikoekin ostera, aldaketa nabarmenak ematen dira sarritan, gertatu ohi den kanpoko fluidoen handipenak Va baldintzatzen baitute gaixo larrietan.

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Linezoliden eliminazioari dagokionez, giltzurrun-kanpoko (CL_{NR}) eta giltzurrun-menpeko (CL_R) argitzapena gehitu ziren ereduan. Gainera, CL_R pazienteen kreatinina argitzapenaren menpe zegoela ondorioztatu zen. Aldagai honen inklusioa linezoliden eredu farmakozinetikoan eztabaidagarria izan da. Izan ere, zenbait egilek Clcr-aren eta argitzapenaren arteko erlazioa deskribatu badute ere[28,32,33], beste hainbatek ezin izan dute bien arteko harreman sendorik demostratu[27,34]. Desberdintasun hauek azaldu ditzakeen zergatietako bat kreatinina argitzapena kalkulatzeko *Cockcroft-Gault*-en ekuazioa erabiltzea izan daiteke; frogatu baita gaixo larrietan ez dela behar bezain zehatza izaten[35,36]. Lan honetan, kreatinina argitzapena ereduan aldagai moduan gehitzeak CL-ren IIVa %97,8tik %61,5ra murriztu zuen.

Linezolid EGOT bidez partzialki kanporatzen denez gero, teknika hauek ezarriak zituzten pazienteetan CL_{EC}-a argitzapen totalaren ekuazioari gehitu zitzaion[37]. EGOTak dituzten pazienteetan argitzapenaren estimazioa egitea lan konplexua bilakatu daiteke. Izan ere, antibiotikoarekin erlazionatutako faktoreek zein teknikarekin lotutakoek baldintzatuko dute eliminazioa; hala nola, azalera, mintzaren konposaketa edota poroaren diametroa, erabilitako efluente fluxua edota teknika modalitatea[38]. Ikerketa-lan honetan batez besteko sieving

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[37] Villa G, Di Maggio P, De Gaudio AR, Novelli A, Antoniotti R, Fiaccadori E, et al. Effects of continuous renal replacement therapy on linezolid pharmacokinetic/pharmacodynamics: a systematic review. Crit Care. 2016;20(1):374.

[38] Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis. 2005;41(8):1159-66.

koefizientea 0,8 ingurukoa izan zen, gaixo kritikoetan aztertutako farmako frakzio askearekin bat datorrena[33]. Ez zen Sc-an diferentzia esanguratsurik antzeman teknika desberdinen artean edota erabilitako mintzaren arabera bereizketa egitean. Sc balioen arteko antzekotasun hau aurretik deskribatu izan da, eta farmakoaren pisu molekular baxuarekin erlazionatu da[37]. Dena den, teknika-modalitate desberdinen artean erabilitako efluente fluxuek CL_{EC}-an antzeman daitezkeen desberdintasunak azaldu ditzakete. Hori dela eta, gorputz-kanpoko argitzapen balio baxuagoak lortuko dira etengabeko hemofiltrazioa (CVVH) edo CVVHD[39,40] erabiltzean CVVHDF[41] hautatzean baino, azken honetan fluxu altuagoak erabiltzen baitira. Nahiz eta aldakortasun nabarmena egon, lan honetan kalkulatutako CL_{EC}-ak (**1. taula**) aipatu berri diren ikerketetan deskribatutako balioen antzekoak izan ziren[39,40,41].

Jakina da, boluntario osasuntsuetan behintzat, linezoliden argitzapena giltzurrun bidezkoa zein mekanismo hepatikoen bitartekoa dela, %30 eta %65, hurrenez hurren. Gibeleko metabolismoa eraztun morfolinikoaren oxidazioaren bidez geratzen da, P450 zitokromoaren esku-hartzerik gabe[30]. Hori kontuan hartuta, gibel funtzioarekin erlazionatutako aldagaiak aztertu ziren. Bilirrubinaren eta transaminasen balioak izan arren, eta nahiz eta horiek erabilita hiru aldagai dikotomiko sortu, beraien inklusioak ez zuen eredu farmakozinetikoa hobetu. Gibel-funtzioarekin erlazionaturiko aldagairik ereduan ez sartzearen arrazoia

[39] Pea F, Viale P, Lugano M, Pavan F, Scudeller L, Della Rocca G, et al. Linezolid disposition after standard dosages in critically ill patients undergoing continuous venovenous hemofiltration: a report of 2 cases. Am J Kidney Dis. 2004;44(6):1097-102.

[40] Meyer B, Kornek GV, Nikfardjam M, Karth GD, Heinz G, Locker GJ, et al. Multiple-dose pharmacokinetics of linezolid during continuous venovenous haemofiltration. J Antimicrob Chemother 2005; 56: 172-9.

[41] Roger C, Muller L, Wallis SC, Louart B, Saissi G, Lipman J, et al. Population pharmacokinetics of linezolid in critically ill patients on renal replacement therapy: comparison of equal doses in continuous venovenous haemofiltration and continuous venovenous haemodiafiltration. J Antimicrob Chemother. 2016;71(2):464-70.

gaur egun honen adierazle den parametro fidagarri, ekomoniko eta praktikoaren falta litzake[42,43].

Denbora-kontzentrazio profilak aztertzean, pazienteen heren batean linezoliden erpin bat antzeman zen dosia eman eta 2-4 ordutara. Kontzentrazioen bat-bateko handitze hori esplikaezina da bi-konpartimentuko eredua erabiliz. Hainbat argitalpenek linezoliden behazun-xixku bidezko iraizketa deskribatu dutenez, zenbait pazientetan behatutako erpina azalduko lukeen zirkulazio enterohepatikoa zuen eredua ebaluatu zen[44,45]. Zoritxarrez, gure datuak ez ziren gai izan eredu horri aurre egiteko.

Gaixoen artean behatutako aldakortasun-interindibidual handiak (IIV_{CL} = %61,5 eta IIV_{V1} = %65.9) bat dator paziente larrietan burututako beste ikerketetan deskribatutakoarekin. Taubert et al.-ek[27], esaterako, %58 eta %37-ko IIVa (aldakuntza koefiziente moduan adierazia) deskribatu zuten CLarentzat eta V_1-rentzat hurrenez, hurren. Hori dela eta, zenbait egilek farmakoaren monitorizazio terapeutikoa gomendatu dute[25,32,46]. Haatik, Galar et al.-ek[47] argitaratu berri duten ikerketan, ez zen korrelazio argirik aurkitu emaitza kliniko eta linezoliden ezohiko kontzentrazio minimoen artean, eta, beraz, beraien esanetan, monitorizazioa ez litzateke aholkatuta egongo. Desadostasun hauetaz gain, sarritan farmakoen monitorizazioa gauzatzea ez da posible izaten. Izan ere, askotan, osasun-langileek

[42] Watkins PB, Merz M, Avigan MI, Kaplowitz N, Regev A, Senior JR. The clinical liver safety assessment best practices workshop: rationale, goals, accomplishments and the future. Drug Saf. 2014;37 Suppl 1:S1-7.

[43] Wicha SG, Frey OR, Roehr AC, Pratschke J, Stockmann M, Alraish R, et al. Linezolid in liver failure: exploring the value of the maximal liver function capacity (LiMAx) test in a pharmacokinetic pilot study. Int J Antimicrob Agents. 2017;50(4):557-63.

[44] Pea F, Viale P, Lugano M, Baccarani U, Pavan F, Tavio M, et al. Biliary penetration and pharmacodynamic exposure of linezolid in liver transplant patients. J Antimicrob Chemother. 2009; 63(1):167-9.

[45] Cremaschi E, Maggiore U, Maccari C, Cademartiri C, Andreoli R, Fiaccadori E. Linezolid levels in a patient with biliary tract sepsis, severe hepatic failure and acute kidney injury on sustained low-efficiency dialysis (SLED). Minerva Anestesiol. 2010; 76(11):961-4.

[46] Pea F, Furlanut M, Cojutti P, Cristini F, Zamparini E, Franceschi L, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother. 2010;54(11):4605-10.

[47] Galar A, Valerio M, Muñoz P, Alcalá L, García-González X, Burillo et al. Systematic Therapeutic Drug Monitoring for Linezolid: Variability and Clinical Impact. Antimicrob Agents Chemother. 2017;61(10).

ezin diote aurre egin honetarako beharrezkoak diren denbora eta baliabideei. Hori dela eta, analisi farmakozinetiko/ farmakodinamiakoa, Monte Carlo simulazioekin batera, oso tresna baliagarria bilakatu daiteke posologia zehatz baten arrakasta probabilitateak aurresateko; baita tratamenduaren emaitza hobeak lortzeko gomendioak emateko ere[48]. Adibide moduan, ikerketa-lan honetan frogatu da sortutako eredu farmakozinetikoa gai dela pazienteei etengabeko perfusioa administratzean linezoliden kontzentrazio plasmatikoak aurreikusteko. Nahiz eta perfusio motza edo etengabekoa administratu zitzaien pazienteek estatistikoki esanguratsuak diren desberdintasunak izan zenbait faktore demografikoetan eta biokimikoetan, hauek ez ziren traba izan linezoliden kontzentrazioak doitasunarekin aurreikusteko.

Lan honetan burututako simulazioak aintzat hartuz gero, dosi estandarra erabilita (600 mg/ 12h), AUC_{24h}/MIC > 80 lortzeko probabilitateak onargarriak izango lirateke 1 mg/L-ko MIC balioa duten bakterioek eragindako infekzioak tratatzeko, baldin eta pazienteen Clcr ≤ 60 mL/min den. Bestalde, Clcr ≤ 10 mL/min duten pazienteetan edota EGOTak ezarriak dituzten paziente anurikoetan izan ezik, dosi hori ez litzateke nahikoa izango 2 mg/L-ko MIC balioa duten mikroorganismoen gaixotasunak tratatzeko. Clinical and Laboratory Standard Institute (CLSI) erakundearen arabera[49], enterokokoentzat mozte-puntu klinikoa 2 mg/L-tako MICa da. Halaber, simulatutako egoera desberdin guztietan 600 mg/ 12h-tako linezolid dosia ez litzateke nahikoa izango 4 mg/mL MIC balioak dituzten bakterioen infekzioak tratatzeko. Azken hau, estafilokoko eta enterokokoentzat mozte-puntu klinikoa da European Committee on Antimicrobial Susceptibility Testing (EUCAST) erakundearen esanetan[50].

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[48] Asín-Prieto E, Rodriguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother. 2015;21(5):319-29

[49] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 28th Edition. M100-S28. CLSI. Wayne, PA, USA, 2018.

[50] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018. Eskuragarri: *http://www.eucast.org* [kontsulta: 2018ko martxoa].

Entsegu honetan linezolid tratamendu enpiriko moduan administratu zen eta, paziente gehienetan, ez zen antibiotikoarekiko mikroorganismo sentikorrik isolatu. Horrek korrelazio farmakodinamiko zuzena egitea saihestu zuen. Beraz, 2013. eta 2015. urte bitartean Arabako Unibertsitate Ospitaleko ZIUetan lortutako suszeptibilitateen informazioa erabili zen CFRen balioak kalkulatzeko (**5. taula**). Isolatutako andui gehienen MIC balioa 2 mg/L edo altuagoa zenez (**3. taula**), erantzunaren metatze-frakzioa baxuak lortu ziren gauzatutako simulazioetan.

Tratamenduaren arrakasta izateko probabilitateak handituko ote ziren jakiteko intentzioarekin, linezoliden dosi altuago bat simulatu zen, alegia, 600 mg 8 orduro. **5. taulan** ikus daitekeen moduan, posologia horrek, oro har, ez lituzke modu esanguratsuan igoko arrakasta lortzeko probabilitateak. Aitzitik, gainesposizioa pairatzeko, eta ondorioz, efektu desiragaitzak jasateko, probabilitateak handituko lituzke (**7. eta 8.taulak**).

Linezoliden efektu desiragaitz nagusia mielosupresio itzulgarria da, bereziki tronbozitopenia[32,51]. Prozesu honekin erlazionatutako arrisku faktoreak gibel-disfuntzio kronikoa[52], linezoliden terapia luzea (> 14 egun), pisu baxua edota giltzurrun gutxiegitasuna dira[53,54], esaterako. Ikerketa-lan honetako pazienteek ez zuten $Cmin_{ss}$ > 10 mg/L edota AUC_{24h} > 400 mg*h/L baliorik lortu, eta ez zen dokumentatu linezolidekin erlazionaturiko efektu desiragaitzik. Nahiz eta paziente askok giltzurrun gutxiegitasuna pairatu, gehienak EGOTak ezarriak zituzten, soilik batek gainditu zuen 14 eguneko tratamendua eta erdiak baino gehiagok gainpisua zuten edo obesoak ziren (GMI > 25 kg/m^2).

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[51] Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. Hematologic Effects of Linezolid: Summary of Clinical Experience. Antimicrob Agents Chemother. 2002; 46(8): 2723-26.

[52] Ikuta S, Tanimura K, Yasui C, Aihara T, Yoshie H, Iida H, et al. Chronic liver disease increases the risk of linezolid-related thrombocytopenia in methicillin-resistant *Staphylococcus aureus*-infected patients after digestive surgery. J Infect Chemother. 2011; 17(3):388-91.

[53] Echeverría-Esnal D, Retamero A, Pardos SL, Grau S. Severe thrombocytopenia caused by linezolid poisoning in an underweight critically ill patient with renal impairment treated with the recommended doses. Enferm Infecc Microbiol Clin. 2016;34(3):213-4.

[54] Natsumoto B, Yokota K, Omata F, Furukawa K. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014; 42(6):1007-12.

Linezoliden etengabeko perfusioak dosi altuagoek eragin dezaketen toxikotasuna saihestu lezake. Hori dela eta, zenbait egilek posologia hau aurrera eramatea proposatu dute, gure ondorioekin ere bat datorrena[27,55]. Kanpo-balidazioa burutzeko erabilitako paziente guztien plasma kontzentrazioak 1 mg/L baino altuagoa izan ziren. Gainera, neurtutako kontzentrazioen %86 2 mg/L-tik gorako kontzentrazioak zituzten. Hortaz, arrakasta terapeutikoa izateko probabilitate altuak esperoko lirateke 2 mg/L-tako MIC balioak dituzten infekzioak tratatzean, giltzurrun-funtzio handitua duten pazienteetan ere. Bestalde, bi pazientek gutxienez 10 mg/L baino altuagoa den kontzentrazio bat izan zuten; hasiera batean, toxikotasuna pariatzeko arriskuarekin erlazionatu daitekeena. Dena den, kontuan hartu behar da limite hori perfusio motzentzat ezarria dagoela, non kontzentrazio altuagoak egongo diren dosifikazio tarte osoan zehar. Hortaz, ez litzateke egokia izango 10 mg/L-ko kontzentrazio konstanteekin konparatzea eta ikerketa gehiago egin beharko lirateke dosifikazio-erregimen honentzat, toxikotasunarekin erlazionatutako kontzentrazioa zein den zehazteko.

5. Ondorioak

Lan honetan linezoliden populazio-eredu farmakozinetiko bat eraiki da, gaixo larrientzat. Plasma kontzentrazio datuak ongien deskribatu zituen eredua konpartimentu-bikoa izan zen. Argitzapena giltzurrun-kanpoko argitzapenaren eta giltzurrun menpeko argitzapenaren arteko batura moduan kalkulatu zen; eta azken hori Clcr-aren eraginpean zegoen. Gainera, EGOTak ezarriak zituzten pazienteetan, gorputz-kanpoko argitzapena ere gehitu zitzaion ekuazioari.

[55] Richards GA, Brink AJ. Therapeutic drug monitoring: linezolid too? Critical Care. 2014; 18:525.

Garatutako eredua erabilgarria izan daiteke arrakasta lortzeko probabilitatea kalkulatzeko, irizpide farmakozinetiko/farmakodinamikoei jarraiki. Hauen arabera, linezoliden dosi estandarra (600 mg/12h) ez litzateke egokia izango 2 mg/L-tako MIC balioak dituzten patogenoek eragindako infekzioak tratatzeko. Dosia 600 mg/8h-ra handitzean, ez lirateke arrakasta probabilitate altuagoak lortuko; ordea, toxikotzat hartzen diren kontzentrazioak izateko aukerak handituko lirateke. Gaixo larrietan etengabeko perfusioa erabiltzea aukera egokia izan daiteke, bereziki giltzurrun-gutxiegitasuna pairatzen ez dutenetan (Clcr≥ 60 mL/min).

EZTABAIDA OROKORRA

Eztabaida orokorra

Gaixotasun infekziosoen kudeaketaren gaur egungo konplexutasunak eta antibiotikoekiko erresistentzien gorakadak ezinbestekoa egin dute antimikrobianoen erabilera optimizatzea. Aditzera eman denez, ospitaleetan antibiotikoen erabileraren % 50 hobetu egin daiteke eta gaixoen % 30-40ak jasotzen duten zainketa ez dago zientzia-ebidentzietan oinarrituta[1].

Antibiotikoak agintzea erabakitzeko prozesuak barnean hartu beharko luke informazio klinikoa, epidemiologikoa, mikrobiologikoa eta farmakologikoa; izan ere, gaixotasun infekziosoek ez baitute soilik arriskuan jartzen banakoen osasuna, baita osasun publikoaren ongizatea ere. Gainera, ongizate publikoa mantentzea eta banakoen askatasuna babestea elkarren arteko lehian egon daitezke hainbat egoeratan[2]. Diziplina anitzeko ikuspegia benetan onuragarria izan daiteke konplexutasun handiko zainketa zerbitzuetan, batik bat zainketa intentsiboen unitateetan.

Kontuan hartuta tratamendu enpirikoa ospitaleetan agintzen diren antimikrobianoen bi herenen atzean dagoela, gaixotasun espezifikoetarako aukerako erregimen enpirikoak ezarri beharko lirateke, tokiko eta estatuko jarraibideak eta tokiko mikrobioen aurkako sentikortasunak aintzat hartuta[3,4]. Protokoloak diseinatzeak eta optimizatzeak emaitza klinikoak hobetuko lituzke, tratamendu antibiotiko enpiriko egokiak goiz ematen direnean heriotza-tasak

[1] Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. Lancet Infect Dis. 2010; 10(3):167-75.

[2] Hernández-Marrero P, Martins Pereira S, de Sá Brandão PJ, Araújo J, Carvalho AS. Toward a bioethical framework for antibiotic use, antimicrobial resistance and for empirically designing ethically robust strategies to protect human health: a research protocol. J Int Med Res. 2017;45(6):1787-93.

[3] Centre of Disease Control. CDC Core Elements of Hospital Antibiotic Stewardship Programs. US Dep Heal Hum Serv CDC. Eskuragarri: *https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html*. [kontsulta: 2018ko maiatza].

[4] Campion M, Scully GJ. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. Intensive Care Med. 2018 Jan 1:885066618762747. doi:10.1177/0885066618762747.

behera egiten baitu[5,6,7,8]. Hori lortzeko, ezinbestekoa da antibiotikoekiko erresistentzia behatzeko sistema bat garatzea, metodoetarako, datuak partekatzeko eta koordinatzeko arau bateratuekin, tokiko, estatuko eta nazioarteko mailan[9]. Hala ere, estaldura enpiriko egokia ziurtatzeak ez luke tratamenduaren helburu bakarra izan beharko. Diagnosi mikrobiologikoak lagungarriak izan daitezke terapia antibiotiko egokiena ziurtatzeko eta infekzioaren tratamendu espezifiko eta eraginkorragoa emateko, mikroorganismoei buruzko informazioa emateaz gain, gehien erabiltzen diren antibiotikoekiko sentikortasuna zehazten dutelako. Hortaz, identifikazio goiztiarra baliagarria izan daiteke emaitza klinikoa hobetzeko eta albo-ondorioak murrizteko[4,6].

Oro har, mikroorganismo Gram-negatiboek eragindako infekzioak goian jarri dira ikerketarako lehentasunen zerrendan, intzidentzia handia dutelako eta antibiotikoekiko erresistentzia asko garatzen ari direlako[10]. Dena den, bakterio Gram-positiboek eragindako infekzioak ez dira gutxietsi behar. Izan ere, gaixo larrien bakteriemien heren bat edo erdi bitarte bakterio Gram-positibo batek eragindakoa omen dela adierazi da, ZIUetako espezie nagusien artean

[5] Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596.

[6] Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence. 2016;7(3):267-79.

[7] Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, Kelesidis T, Weisenberg SA, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect Dis. 2014;14(12):1220-7.

[8] Garnacho-Montero J, Arenzana-Seisdedos A, De Waele J, Kollef MH. To which extent can we decrease antibiotic duration in critically ill patients? Expert Rev Clin Pharmacol. 2017;10(11):1215-23.

[9] World Health Organization (WHO). Global Antimicrobial Resistance Surveillance System. Manual for Early Implementation. Eskuragarri:
http://apps.who.int/iris/bitstream/handle/10665/188783/9789241549400_eng.pdf;jsessionid=47A822CD2C92661EB7483A4E36842BD9?sequence=1 [kontsulta: 2018ko maiatza]

[10] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-27.

kokatuz[6,11,12,13]. Bakterio horiek eragiten dituzten gaixotasun ohikoenen artean dago osasun-zainketarekin lotutako pneumonia, zehazki haizagailuekin lotutako pneumonia (askotan MRSA bakterioak eragindakoa), eta gailu inbaditzaile aurreratuekin lotutako bakteriemia, hala nola bentrikuluko gailu lagungarriek edo zain barneko kateterrek eragindakoa[13].

Bankomizina da gaixo larrietan bakterio Gram-positiboek eragindako infekzioen tratamendurako gehien erabili den antibiotikoa; besteak beste, metizilinarekiko erresistenteak diren *Staphylococcus aureus* edo *Enterococcus spp* bakterioen aurka. Nolanahi ere, antibiotiko horren erabilerak erresistentzien gorakada eragin du eta, kasu batzuetan, bankomizinaren kontzentrazio minimo inhibitzailea handitzea ekarri du ("MIC-lerradura" bezala ezagutu izan dena)[14,15,16]. Ondorioz, bankomizinarekiko erresistenteak diren enterokokoek (VRE) eta *S. aureus* (VRSA) mikroorganismoek eragindako infekzio nosokomialak gero eta ugariagoak dira, eta tratamendu-hutsegiteak eragin ditzakete maiz. Gauzak horrela, antimikrobiano horren ordezkoak bilatzea ezinbestekoa bilakatu da. Azken urteotan, bakterio Gram-positiboen aurkako antibiotiko berriak oso garrantzitsuak izan dira infekzioen kudeaketan (adibidez, zeftarolina, tigeziklina, daptomizina eta linezolid).

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[11] Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012;38(12):1930-45.

[12] Vázquez-Guillamet C, Kollef HM. Treatment of gram - positive infections in critically ill patients. BMC Infect Dis. 2014; 14: 92.

[13] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

[14] Rengaraj R, Mariappan S, Sekar U, Kamalanadhan A. Detection of Vancomycin Resistance among *Enterococcus faecalis* and *Staphylococcus aureus*. J Clin Diagn Res. 2016;10(2):DC04-6.

[15] Sancak B, Yagci S, Mirza HC, Hasçelik G. Evaluation of vancomycin and daptomycin MIC trends for methicillin-resistant *Staphylococcus aureus* blood isolates over an 11 year period. J Antimicrob Chemother. 2013;68(11):2689-91.

[16] Díaz R, Ramalheira E, Afreixo V, Gago B. Evaluation of vancomycin MIC creep in *Staphylococcus aureus*. J Glob Antimicrob Resist. 2017;10:281-4.

Antibiotikoekiko erresistentziak garatzeko arriskua eta aukera terapeutiko erabilgarri murritza kontuan hartuta, antibiotikoen dosifikazio egokia ezinbestekoa da gaixo larrien kudeaketa egokirako. Hortaz, gaixoen faktore espezifikoak kontuan hartzen dituzten antimikrobianoen dosifikazio-erregimenak hobetzea ezinbestekoa izango da. Helburu horrekin, populazioaren ikuspegi farmakozinetikoa probetxugarria izango da gaixo larrien populazio-parametroak deskribatzeko eta profil farmakozinetikoarekin lotutako aldakortasunaren eta gaixoen ezaugarri psikopatologikoen arteko loturak identifikatzeko.

Analisi farmakozinetiko/farmakodinamikoak (PK/PD) barnean hartzen ditu informazio farmakozinetikoa eta mikroorganismoek antimikrobiano espezifiko batekiko duten sentikortasunari buruzko informazioa (MIC balioak). Analisi horren bitartez, gaixo eta infekzio-prozesu bakoitzarentzat antibiotikorik eta dosifikazio-erregimenik egokiena aukera daiteke, antibiotikoaren eragin egokia ziurtatzeko eta albo-ondorioak agertzea eta erresistentziak garatzea minimizatzeko.

Analisi PK/PDak aplikatzean, muga nagusia da MIC balioak antibiotiko kontzentrazio estatikoak daudenean bakterioak inkubatu ondoren kalkulatzen direla. Beraz, antibiotiko kontzentrazioak aldatzen diren bitartean bakterioen garapenak pairatzen duen bilakaerari buruzko informaziorik ez da ematen, eta horrek lotura hobea dauka giza gorputzeko fluidoen benetako egoerarekin. *In vitro* denbora-hilkortasuneko zinetika-azterketetan oinarritutako eredu farmakodinamikoek gaixoekin gertatzen denaren inguruko ikuspegi hurbilago bat eman dezaketen arren, normalean ez dira erabiltzen, denbora asko behar izaten dutelako eta garestiak izan ohi direlako[17,18].

[17] Nielsen EI, Cars O, Friberg LE. Predicting in vitro antibacterial efficacy across experimental designs with a semimechanistic pharmacokinetic-pharmacodynamic model. Antimicrob Agents Chemother. 2011;55(4):1571-9.

[18] Sy SKB, Derendorf, H. in: Schmidt S, Derendorf H (Eds.) Pharmacometrics in bacterial infections. Springer, New York; 2014: 229–58.

Parametro farmakozinetikoen eta mikrobiologikoen arteko harreman kuantitatiboari indize PK/PD esaten zaio. Hiru indize PK/PD daude antibiotikoen eraginarekin lotuta: antimikrobianoaren kontzentrazioa MIC balioaren gainetik dagoen denbora ($T_{>MIC}$), kontzentrazio pikoa eta MIC ratioa (Cmax/MIC), eta kontzentrazio denbora kurbaren azpiko tartea (normalean 24 orduko denbora tartean) MIC balioarekin zatituta lortzen den ratioa (AUC_{24h}/MIC). Bestalde, indize PK/PD egokia hautatzeaz gain, eraginkortasun antimikrobianoarekin lotuta dagoen indizearen magnitudea ere zehaztu behar da; hau da, helburu farmakodinamikoa (PDT) ezarri behar da.

Eredu farmakozinetiko bat garatu ondoren, eta parametro farmakozinetikoen eta farmakodinamikoen arteko erlazioa aztertu ostean, terapiaren emaitzaren gaineko aurreikuspenak eta bestelako dosifikazioek arrakasta izateko probabilitatearen balioespenak egin daitezke, Monte Carlo simulazioaren bitartez. Horrenbestez, simulazio horien bitartez mozte-puntu farmakozinetiko/farmakodinamiko fidagarriak lortzeko, derrigorrezkoa izango da populazio-eredu farmakozinetiko balioztatu bat erabiltzea aztertutako gaixoentzat, baita eraginkortasunarekin lotutako PDT zehatz bat ere. Bestela, lortutako emaitzek alborapenak izango dituzte eta alferrikakoak izango dira.

Adierazitakoaren ildotik, lan honetan populazio-eredu farmakozinetikoak diseinatu eta ebaluatu dira bakterio Gram-positiboen aurka gaixo larrietan erabilitako bi botika antimikrobianorentzat: daptomizina eta linezolid. Gainera, dosifikazio-erregimenen doitasuna aztertu da, analisi farmakozinetiko/ farmakodinamikoa eta Monte Carlo simulazioa aplikatuz, eta eraginkortasun eta segurtasun profilak kontuan hartuta.

Modu honetan, bigarren kapituluan, daptomizinaren populazio-eredu farmakozinetiko bat garatu zen. Konpartimentu bakarreko eredua izan zen informazioa ongien deskribatu zuena, eta batez beste 12,3 L-ko banaketa-bolumena estimatu zen. Antibiotikoaren eliminatzea giltzurrun-kanpoko argitzapenaren (0,16 L/h) eta giltzurrun-menpeko argitzapenaren menpe egon zen

(batez beste 0,37 L/h), bigarrena kreatinina argitzapenaren menpe egonik. Gainera, EGOTak ezarriak zituzten subjektuetan, gorputz-kanpoko argitzapena (CL_{EC}) ere argitzapen-ekuazioan sartu zen, CL osoaren %39tik 80ra bitarteren erantzule izanik. Aintzat hartuta guztizko argitzapenean %25etik gorako CL_{EC}-ren ekarpena esanguratsutzat jotzen dela[19], teknika horien bitartez antibiotikoa nabarmen ezabatzen dela ondoriozta daiteke. Daptomizinak boluntario osasuntsuetan %90eko proteina-lotura erakutsi duen arren, askotan adierazi da gaixo larrietan antibiotikoen proteinekiko lotura normalean baxuagoa dela (hipoalbuminemiaren eraginez, beste hainbat arrazoien artean)[20]. Hortaz, aztertutako gaixoetan ikusitako sieving koefizientea (batez besteko balioa: 0,2) bat etor daiteke odoleko daptomizinaren frakzio askearekin.

Daptomizina gaixoaren pisuaren arabera dosifikatzea gomendatzen bada ere, ereduan parametro hau aldagai moduan sartzeak ez zuen hobekuntzarik eragin. Baliteke azterketan bildutako gaixoen kohortearen tamaina txikia (n = 16) izatea horren arrazoia, bai eta gaixo gehienek (%75) obesitatea edo gehiegizko pisua zutela ere. Beste azterketa batzuekin bat etorriz pisua kontuan hartu ez bazen ere[21,22], kontuz ibili behar da populazio-eredua askoz gorputz-pisu gutxiagoko gaixoentzako dosi egokiak edo kontzentrazioak aurresateko erabiltzean.

Daptomizina 4 mg/kg-ko dosian dago onartuta larruazal eta ehun bigunetako infekzio (LEBI) zailen tratamendurako, eta 6 mg/kg-ko dosian, *S. aureus*-ek eragindako bakteriemietarako, eskuineko endokarditisaren tratamendua

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[22] Falcone M, Russo A, Venditti M, Novelli A, Pai MP. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2013;57(11):1568-76.

ere barnean hartuta[23]. Bestalde, indikaziotik kanpo erabili izan da bakterio Gram-positiboek eragindako nerbio-sistema zentraleko infekzioak edo VRE-ek eragindako bakteriemia tratatzeko[24,25]. Era berean, daptomizinak oso ondo jarduten du biofilmen aurka, eta, beraz, abantailatsua izan daiteke infekzioaren eragileak kateterrak edo bestelako gailuak direnean[26]. Bestalde, deskribatu izan da *S. aureus*-ek eragindako infekzio baten susmoa dagoenean, daptomizina-dosi handi batekin (8-10 mg/kg/egunean) egindako tratamendu enpirikoa eraginkorragoa dela glukopeptidoen edo betalaktamikoen erregimen enpiriko bat baino, bereziki MRSAren prebalentzia altua dagoenetan[27].

Hala ere, oraindik ez dago adostasunik daptomizina dosi egokienari dagokionez. Ikerketa honetan egindako analisi farmakozinetiko /farmakodinamikoek eta Monte Carlo simulazioek erakutsi dutenez, daptomizina-dosi estandarrek ez lukete estaliko 4 mg/L-ko MIC balioek eragindako infekzioak, eta hori da, hain zuzen ere, CLSIk (Clinical and Laboratory Standard Institute)[28] eta EUCAST erakundeek (European Committee on Antimicrobial Susceptibility Testing)[29] markatutako mozte-puntu klinikoa enterokokoentzat. Dosi-maila horiek 1 mg/L-ko MIC balioak (estreptokoko eta estafilokokoentzako mozte-puntu

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[23] European Medicines Agency. Cubicin®: summary of product characteristics. Eskuragarri: *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf* [Kontsulta: 2017ko maiatza].

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[29] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018. Eskuragarri: *http://www.eucast.org* [kontsulta 2018ko martxoa].

klinikoa) dituzten mikroorganismoek eragindako infekzioak estaliko lituzkete gaixoek giltzurrun-gutxiegitasuna izatean (≤ 30 mL/min) eta EGOTak ezarriak ez dituztenean bakarrik. Emaitza horiek bat datoz IDSAren (*Infectious Diseases Society of America*) jarraibideekin eta aurretiazko ikerketekin; izan ere, dosi altuak lehenetsi dituzte ere (8-12 mg/kg/egunean edo 560-840 mg/egunean) [21,22,30,31].

3. kapituluan, populazio-eredu farmakozinetiko bat garatu zen linezolidentzat. ZIUko 41 gaixoren antibiotikoen plasma-mailak neurtu ziren eta kontzentrazio-denbora kurba ongien deskribatu zuen eredua bi-konpartimentukoa izan zen. Aldakortasun interindibiduala (IIV) gehitu zitzaion argitzapenari (CL) eta konpartimentu zentraleko banaketa-bolumenari (V_1), eta gaixoen arteko aldakortasun handiak ikusi ziren, %61,5 eta %65,9, hurrenez hurren.

Estimatutako banaketa-bolumena (V_{ss} = 45,2 L) gorputzaren guztizko urari hurbildu zitzaion eta gaixo larriekin aurretik egindako beste ikerketa batzuetan lortutakoaren antzekoa izan zen (adibidez, Taubert et al.[32]: 41,55 L). Antibiotikoaren izaera lipofiloa dela eta, balio hori ez zen aldendu, ezta ere, boluntario osasuntsuentzat kalkulatutako balioetatik[33,34]. Linezoliden eliminatzeari dagokionez, giltzurrun-kanpoko nahiz giltzurrun-menpeko argitzapenak gehitu ziren ereduan, bigarrena gaixoen Clcr-ren eraginpean izanik. Aldatu gabeko linezoliden %30 soilik giltzurrunen bidez ezabatzen denez gero,

[30] Senneville E, Caillon J, Calvet B, Jehl F. Towards a definition of daptomycin optimal dose: Lessons learned from experimental and clinical data. Int J Antimicrob Agents. 2016;47(1):12-9.

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kreatinina-argitzapenak guztizko argitzapenean duen eragina eztabaidagarria izan da. Nolanahi ere, Clcr-ren eta CL-ren arteko harreman estua atzeman zen, eta aldagaia gehitzeak argitzapenaren aldakortasun-interindibiduala jaitsi zuen %97,8tik %61,5era.

Linezolid EGOTen bidez partzialki eliminatzen denez gero, CLEC balioa gehitu zitzaion gorputzaren guztizko argitzapenaren ekuazioari[35]. CLEC balioak CLri egindako ekarpena % 5etik % 67rako tartean mugitu zen, eta kreatinina-argitzapenak baldintzatu zuen nagusiki. Hortaz, EGOTen bidez antibiotiko proportzio handiagoak eliminatu ziren gaixo anurikoetan edo giltzurrun-funtzio mugatua zutenetan. Ikerketa honetan kalkulatutako batez besteko sieving koefizientearen balioa (0,8) gaixo larrietan proteinei lotu gabeko frakzioaren antzekoa izan zen[36].

Linezoliden erabilera baimenduta dago pneumoniaren eta larruazal eta ehun biguinetako infekzioen tratamendurako. Hala ere, indikaziotik kanpo erabili izan da MRSAk eragindako bigarren mailako bakteriemia edota meningitis tuberkulosoa tratatzeko, besteak beste[37,38,39]. ZIUetako infekziorik ohikoenak arnas-bideetako infekzioak (bereziki pneumonia) direla aintzat hartuta, eta

[35] Villa G, Di Maggio P, De Gaudio AR, Novelli A, Antoniotti R, Fiaccadori E, et al. Effects of continuous renal replacement therapy on linezolid pharmacokinetic/pharmacodynamics: a systematic review. Crit Care. 2016;20(1):374.

[36] Tsuji Y, Holford NHG, Kasai H, Ogami C, Heo YA, Higashi Y, et al. Population pharmacokinetics and pharmacodynamics of linezolid-induced thrombocytopenia in hospitalized patients. Br J Clin Pharmacol. 2017;83(8):1758-72.

[37] Park HJ, Kim SH, Kim MJ, Lee YM, Park SY, Moon SM, et al. Efficacy of linezolid-based salvage therapy compared with glycopeptide-based therapy in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteremia. J Infect. 2012;65(6):505-12.

[38] Pereira NM, Shah I, Ohri A, Shah F. Methicillin resistant *Staphylococcus aureus* meningitis. Oxf Med Case Reports. 2015;19;2015(11):364-6.

[39] Sun F, Ruan Q, Wang J, Chen S, Jin J, Shao L, et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother. 2014;58(10):6297-301.

heriotza-tasarik altuenak dituztenak direla jakinda, linezolid oso antibiotiko baliagarria bihurtzen da gaixo larrien infekzioak tratatzeko[40].

CLSI[28] eta EUCAST[29] erakundeen arabera, mozte-puntu klinikoa enterokokoen kasuan 2-4 mg/L-koa da eta estafilokokoen kasuan 4 mg/L-koa. Lan honetan gauzatutako analisi farmakozinetiko/farmakodinamikoa aintzat hartuta, linezoliden dosi estandarra (600 mg/12h) ez litzateke sarritan nahikoa izango gaixo larrietan helburua lortzeko probabilitate altuak izateko. Haatik, soilik Clcr ≤ 10 mL/min balioak dituzten pazienteek edota EGOTak ezarriak izatean paziente anuriakoek, lortuko lituzkete soilik PTA balio altuak 2 mg/L-tako MIC balioa duten mikroorganismoek eragindako infekzioak tratatzeko. Dosia 600 mg/8h-ra igotzeak ez luke nabarmen handituko eraginkortasuna lortzeko probabilitatea, baina pazienteen segurtasuna arriskuan jarriko luke. Dosi altuekin lotutako toxikotasun-arazo potentzialak saiheste aldera, ikerketa honetan lortutako emaitzek argi uzten dute dosifikazio-estrategia berriak bilatu behar direla, etengabeko perfusioa barnean hartuta. Estrategia hori bereziki betalaktamikoekin erabiltzea iradoki bada ere[41,42], hainbat ikertzailek linezolidekin erabiltzeko ere proposatu dute[32,43]. Etengabeko perfusioa bereziki onuragarria izan daiteke giltzurrun-funtzioa handitua duten gaixoentzat; izan ere, kasu horietan, infusio motz bidez emanez gero, tratamenduak arrakasta izateko oso probabilitate baxuak dituelako. Etengabeko perfusioaren kasuan, lan honetan lortutako emaitzak baikorrak diren arren, ikerketa gehiago egin behar dira arlo horretan.

Ikerketa honetako hainbat muga kontuan hartzekoak dira. Alde batetik, arestian adierazi den moduan, analisi farmakozinetiko/farmakodinamikoak MIC

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[40] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198-208.

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[42] Van Herendael B, Jeurissen A, Tulkens PM, Vlieghe E, Verbrugghe W, Jorens PG. Continuous infusion of antibiotics in the critically ill: The new holy grail for beta-lactams and vancomycin? Ann Intensive Care. 2012;2(1):22.

[43] Richards GA, Brink AJ. Therapeutic drug monitoring: linezolid too? Critical Care. 2014; 18:525.

balioetan oinarritutako ereduetan egin dira, eta, beraz, balio estatikoak izan dira kontuan bakarrik. Beste aldetik, infekzioaren eremua ez da aintzat hartu dosifikazio-gomendioak zehazteko, eta plasma-kontzentrazioak erabili dira bakarrik. Gainera, erresistentzien garapenaren ondorioak ez dira aztertu, nahiz eta oso baliagarriak izan daitezkeen, bereziki antibiotiko horien gaineko erresistentzien agerpena dagoeneko atzeman dela kontuan hartuz gero. Ildo horretatik, linezolidekiko eta daptomizinarekiko erresistenteak diren *Staphylococcus aureus* bakterioak aurkitu dira[44,45], baita linezolidekiko erresistenteak diren *Staphylococcus epidermidis*[46] bakterioak ere, besteak beste.

[44] Karavasilis V, Zarkotou O, Panopoulou M, Kachrimanidou M, Themeli-Digalaki K, Stylianakis A, et al. Wide dissemination of linezolid-resistant *Staphylococcus epidermidis* in Greece is associated with a linezolid-dependent ST22 clone. J Antimicrob Chemother. 2015;70(6):1625-9.

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ONDORIOAK

Ondorioak

1. Daptomizinaren populazio-eredu farmakozinetiko bat garatu egin da gaixo larrientzat. Kontzentrazio-denbora datuak ongien deskribatu zituen eredua konpartimentu bakarrekoa izan zen. Antibiotikoaren argitzapena, giltzurrun-kanpoko argitzapenaren (CL_{NR}) eta giltzurrun-menpeko argitzapenaren (CL_R) arteko batura moduan kalkulatu zen; eta azken hori Clcr-aren eraginpean zegoen. Gainera, EGOTak egotziak zeuzkaten pazienteen kasuan, gorputz-kanpoko argitzapena gehitu zitzaion ekuazioari.

2. Daptomizinaren dosi estandarrak sarritan ez dira nahikoak izango gaixo larriak tratatzeko. Horrela, giltzurrun-gutxiegitasunik gabeko subjektuak eta etengabeko gorputz-ordezkatze teknikak ezarriak dituzten pazienteak izango lirateke bereziki infradosifikazio arrisku handiena dutenak. Izan ere, tratamenduaren arrakasta izateko probabilitate baxuak lortuko lirateke 1 mg/L-tako zein 4 mg/L-tako MIC balioentzat; alegia, estreptokoko eta estafilokokoentzat zein enterokokoentzat ezarri diren mozte-puntu klinikoentzat, hurrenez hurren.

3. Gauzatutako analisi farmakozinetiko/farmakodinamikoaren arabera, daptomizinaren tratamenduaren arrakasta ziurtatzeko, 60 mL/min eta 90 mL/min arteko kreatinina argitzapena duten gaixoek 700 mg/24h-ko dosia beharko lukete. Clcr balio altuagoak dituzten pazienteetan, aldiz, 840 mg/24h-ko dosia administratu beharko litzateke. Nahiz eta arrakasta terapeutikoa izateko probabilitate altuagoak izan 30 mL/min edo Clcr balio baxuagoak dituzten pazienteetan, toxikotasunarekin erlazionatutako kontzentrazioak lortzeko arriskua ere handitzen da. Hortaz, terapiaren onura-arrisku balantza aztertu beharko litzake horrelakoetan. EGOTak ezarriak dituzten pazienteetan, gutxienez 560 mg/24h beharko litzateke. Dena den, azken hau CL_{EC}-ren menpe egongo da.

4. Linezoliden populazio-eredu farmakozinetiko bat garatu da gaixo larrientzat. Antibiotikoaren farmakozinetika bi konpartimentutako eredu batekin deskribatu zen ongien. Kreatinina argitzapenak argitzapen totala baldintzatu zuen. Gainera, EGOTak ezarriak zituzten pazienteetan, CLa gorputz kanpoko argitzapenaren menpe egon zen ere.

5. Infekzioa 2 edo 4 mg/L-ko MICa duen mikroorganismo batek eragiten duenean, linezoliden dosi estandarrak (600 mg/12h) ez ditu bermatuko arrakasta izateko probabilitate altuak. Balio hauek enterokoko eta estafilokokoen mozte-puntu klinikoak dira CLSI eta EUCAST erakundeen arabera.

6. Linezoliden dosia 600 mg/8h-ra handitzeak ez ditu arrakasta izateko probabilitateak handitzen, baina toxikotasuna pairatzeko aukerak areagotzen ditu. Hortaz, dosifikazio-erregimen alternatiboak aztertu beharko dira, besteak beste, etengabeko perfusioa.

1. ERANSKINA

I. ERANSKINA. HPLC bidezko daptomizinaren eta linezoliden kuantifikazioa gaixo kritikoen plasma eta efluente laginetan

1. Produktu kimikoak eta erreaktiboak

Daptomizina eta linezolid estandarrak Novartis Pharma AG-ri eta Pfizer Pharmaceuticals-i esker lortu ziren, hurrenez hurren. Propil-4-hiroxibenzoatoa (PHB4) eta amonio fosfatoa Sigma Aldrich-i (Bartzelona) eskatu zitzaizkion eta azetonitriloa, aldiz, Merck-i (Darmstadt, Alemania). Ur-ultrapurua Milli-Q® aparatua erabiliz lortu zen (Millipore). Azkenik, giza-plasma Gasteizko Transfusio eta Giza Ehunen Euskal Zentroari esker eskuratu zen.

2. Laginen prozesamendua eta analisia

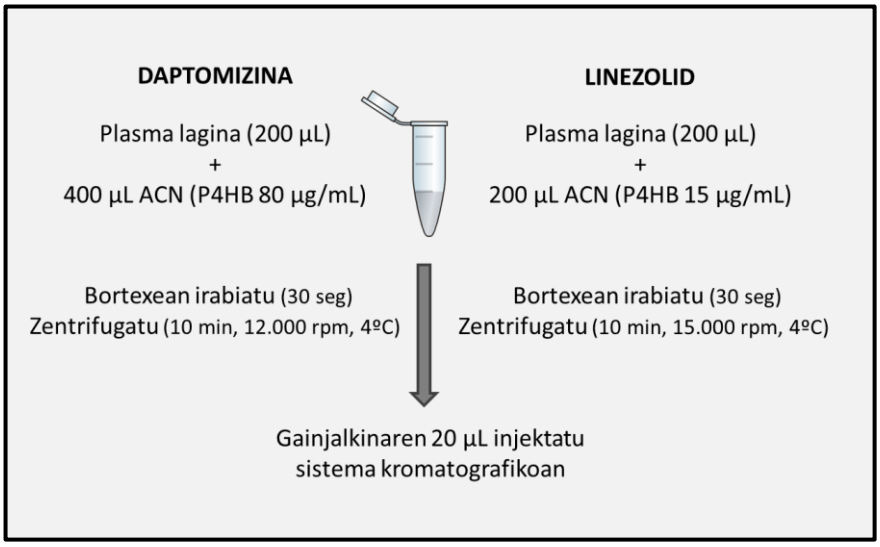
Plasma eta efluente laginen antibiotiko kuantifikazioa bereizmen handiko kromatografia likido bidez (HPLC) egin zen, detekzio ultrabioleta zuen teknika erabiliz (UV). **1. taulan** daptomizinaren eta linezoliden kuantifikaziorako erabilitako baldintzak bildu dira.

1. taula. Aztertutako antibiotikoen kuantifikaziorako erabilitako baldintza kromatografikoak.

	Baldintza kromatografikoak	
	Daptomizina	**Linezolid**
Zutabea	Symmetry® C8 4,6 mm x 150 mm x 5μm	Symmetry® C8 4,6 mm x 150mm x 5 μm
Uhin-luzera (nm)	224	254
Tenperatura (ºC)	30	30
Injekzio-bolumena (μL)	20	20
Fluxua (mL/min)	1,2	1
Fase-mobila	Amonio fosfatoa (%0,5): Azetonitriloa (62:38, v: v)	Amonio fosfatoa (%0,5): Azetonitriloa (66:34; v: v)

Plasma laginen prozesamendua proteinen prezipitazioa eginez hasi zen. Horretarako, azetonitriloa gehitu zitzaien laginei, non barne estandarra (propil 4-hidroxibenzoatoa) disolbatua zegoen aurretik. Ondoren laginak bortexean irabiatu ziren (30 segundo) eta 10 minututan zehar zentrifugatu, 4ºC-tan. Lortutako gainjalkinen 20 μL sistema kromatografikoan injektatu ziren. **1. irudian** bi antibiotikoentzat jarraitutako prozesamenduak irudikatu dira.

Efluente laginei dagokionez, ez zitzaien inolako prozesamendurik aplikatu. Beraz, behin laginak desizoztu ostean, zuzenean mikro-bialetan sartu eta sistema kromatografikoan injektatu ziren.



1. irudia. Daptomizinaren eta linezoliden plasma laginen kuantifikaziorako jarraitutako prozesua. ACN: azetonitriloa; P4HB: propil 4-hidroxibenzoatoa.

3. Metodo analitikoaren balidazioa

Metodo analitikoek analito baten kontzentrazioa kuantifikatzen dute matrize biologiko batean, besteak beste, odolean, plasman edota gernuan. Lortutako balioen fidagarritasuna bermatzeko, ezinbestekoa da aurretik metodo horren balidazioa burutzea.

Lan honetan plasma eta efluente laginetan daptomizinaren eta linezoliden kuantifikazioa egin ahal izateko, aurretik erabilitako metodo analitikoaren balidazioa burutu zen, EMAren jarraibideak aintzat hartuta (*Guideline on*

bioanalytical method validation)[1]. Protokolak adierazten duen moduan, emaitza analitikoen eraginkortasunaren onesgarritasuna eta fidagarritasuna bermatzeko ezinbestekoak izango dira honako ezaugarriak: selektibitatea, linealtasuna, doitasuna, zehaztasuna eta egonkortasuna.

3.1. Selektibitatea

Metodo analitikoa gai izan behar da analitoa(k) eta barne estandarra (*internal standard*, IS) matrizean dauden osagai endogeno zein laginean dauden bestelako osagarriengandik bereizteko. Selektibitatea aztertzeko, gutxienez 6 indibiduoren matrize "zuriak" beharrezkoak dira, banaka analizatu eta interferentziak dauden ala ez ebaluatzeko. Horrela, interferentziarik ez dagoela onartuko da erantzuna analitoaren beheko kuantifikazio-limitearen %20 baino gutxiago denean eta barne estandarraren %5 baino baxuagoa denean.

Selektibitate entsegua gauzatzeko, 6 emaile desberdinen giza-plasma erabili zen. Analitoaren erretentzio denboran barne-estandarraren interferentzia erpinak agertzen ziren edo ez ikertu zen, eta alderantziz. Horretarako, plasma bakoitzeko, honako laginak prestatu ziren: plasma-zuria, barne estandarra zuen plasma lagina, eta azken lagin bat non antibiotikoa ere gehitu zen, linealtasun-tarteko kontzentrazio minimoan.

3.2. Linealtasuna

Kontzentrazio tarte batean, metodo analitikoak analitoaren kontzentrazioei proportzionalki linealak diren erantzunak lortzeko duen gaitasunari deritzo linealtasuna. Tarte hau beheko eta goiko kuantifikazio-limiteek

[1] European Medicines Agency. Guideline on bioanalytical method validation. Committee for Medical Products for Human Use (CHMP), 2011. Eskuragarri: *www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf* [kontsulta: 2018ko martxoa].

zehaztuko dute, alegia LLOQ (*lower limit of quantification*) eta ULOQ (*upper limit of quantification*).

Metodoaren linealtasuna neurtzeko, plasma eta efluentean LLOQ eta ULOQ zituzten antibiotiko disoluzioak prestatu ziren; baita gutxienez linealtasun-tarte barruan zeuden beste 6 antibiotiko kontzentrazio disoluzio ere. Laginak hiru aldiz prestatu ziren, hiru egun desberdinetan, eta antibiotiko kontzentrazioaren eta antimikrobianoaren eta P4BH-ren (IS) azaleren ratioaren arteko linealtasuna aztertu zen.

Kasu bakoitzean errore erlatiboaren ehunekoa kalkulatzeko (%E), ondoko ekuazioa erabili zen:

$$\%E = \frac{Kontzentrazio\ teorikoa - Kalkulatutako\ Kontzentrazioa}{Kontzentrazioa\ teorikoa} \times 100 \qquad \textbf{(Eq.1)}$$

Teknika analitikoak linealtasun irizpideak betetzen dituela ondorioztatzeko, kalibrazio estandar bakoitzarentzat errore erlatiboa %15 baino baxuagoa izan behar da, beheko kuantifikazio-limitearen kasuan izan ezik, non %20 baino baxuagoak diren erroreak onartzen diren.

3.3. Doitasuna eta zehaztasuna

Kuantifikatutako analito kontzentrazioa balio teorikoari zenbat gerturatzen zaion deskribatzen du doitasunak (%E moduan adierazia). Doitasuna LLOQan eta kalitate kontroletan (*quality controls*, QC) ebaluatu behar da. Azken horiek, linealtasun tartearen barruan dauden balioak izango dituzte: hiru aldiz LLOQ (QC baxua), kalibrazio kurbaren tartearen %30-50 bitartean dagoen

kontzentrazioa (erdiko QC) eta gutxienez goiko kuantifikazio-limitearen %75 den balioa (QC altua). Kalitate kontrol hauek kalibrazio kurba aintzat hartuta analizatuko dira, eta kuantifikatutako kontzentrazioak balio teorikoarekin konparatu. Doitasunaren ebaluaketa saiakuntza berean eta saiakuntza desberdinen artean gauzatu beharko da (intra eta inter-saiakuntza doitasuna, hurrenez hurren).

Teknika baten zehaztasunak errepikatutako analitoaren neurketa indibidualen arteko gertutasuna neurtzen du eta aldakuntza-koefiziente bezala adierazten da (*coefficient of variation*, CV, %). Doitasunarekin gertatzen den bezala, zehaztasuna LLOQ eta QC laginetan ebaluatu behar da, saiakuntza berean eta saiakuntza desberdinen artean. Horrela, kuantifikazio-limitea doitasun eta zehaztasunarekin neurtu daitekeen kalibrazio kurbako kontzentrazio baxuena izango da.

3.4. Egonkortasuna

Normalean lagin biologikoen analisia ez da bildu bezain laster egiten. Hori dela eta, ezinbestekoa izango da laginak egonkor mantentzen diren biltegiratze eta kontserbatze baldintzak zehaztea. Egonkortasuna analitoaren ezaugarri bat da, denboran zehar, eta manipulazio prozesuen ostean, aldatu gabe mantentzea baimentzen diona. Behe eta goi kalitate kontrolak erabiliz ebaluatzen da. Horrela, QCak prestatu eta zuzenean analizatzen dira, baita ebaluatu behar diren biltegiratze baldintzak aplikatu ondoren ere. Lagin hauek kalibrazio-kurba erabiliz analizatuko dira, momentuan prestaturiko kalibrazio estandarrek osatuko dutena. Lortutako kontzentrazioak balio nominalarekin alderatuko dira. Kalibrazio kontrol bakoitzaren batezbestekoak kontzentrazio nominalaren ±%15 barne egon behar du.

Laginen egonkortasuna baieztatzeko, honakoak aztertu ziren:

3.4.1. Analitoaren egonkortasuna matrize biologikoan biltegiratze denboran zehar

Plasma laginen egonkortasuna biltegiratze baldintza desberdinetan (-80ºC eta -20ºC) aztertu zen denbora tarte desberdinetan. Horretarako goi eta behe kalitate kontrol bakoitzeko 3 lagin erabili ziren.

3.4.2. Analitoaren egonkortasuna matrizean izozte-desizozte prozesuetan, izozte baldintzetatik giro tenperaturara

Goi eta behe QCen 3 lagin gorde ziren -80ºCtan. Lagin hauei 3 izozte-desizozte ziklo ezarri zitzaizkien. Zikloen artean, laginak gutxienez 12 orduz mantendu ziren izozkailuan. Ondoren, alikuotak analizatu ziren eta beraien egonkortasuna kalkulatu.

3.4.3. Egonkortasuna sistema kromatografikoan

Alikuotak analizatu eta kromatografia bialetan mantendu ziren 24 orduz. Behin denbora hau pasatuta, berriz ere analizatu ziren, neurketen artean desberdintasunik zeuden ala ez aztertzeko.

3.4.4. Analito eta barne estandar disoluzio-amen egonkortasuna

Antibiotikoen ama-disoluzioak prestatu ziren, baita barne estandarrarenak ere. Kontzentrazio bakoitzeko 3 lagin prestatu ziren. Disoluzio-amen erantzun kromatografikoak (azalera) zero denboran eta 24 ordutara neurtu ziren, eta beraien artean konparatu.

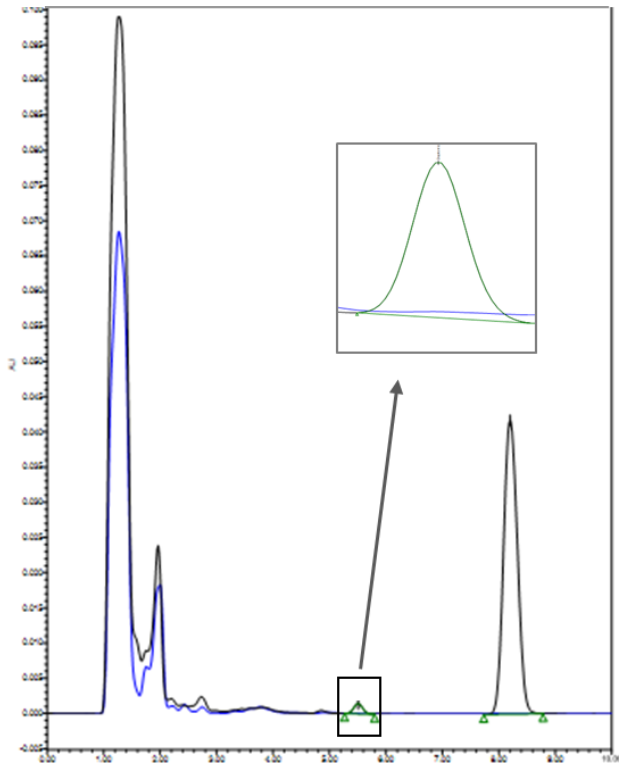
Nahiz eta balidazioa plasma zein efluente laginentzat burutu, gehiegi ez luzatzeko asmoz, eranskin honetan soilik plasma laginentzat lortutako emaitzak gehitu dira; izan ere, hauen prozesamendua konplexuagoa da.

4. Daptomizina: balidazioaren emaitzak

4.1. Selektibitatea

Analizatutako lagin guztietan interferentziazko erpinen erantzuna, alegia, azalera kromatografikoa, kuantifikazio limitearen %20 baino baxuagoa izan zen daptomizinaren erretentzio-denboran. Bestalde, barne estandarraren erretentzio-denboran agerturiko interferentzien erantzuna analisian erabilitako barne estandarraren kontzentrazioaren (80 μg/mL) %5 baino baxuagoa izan zen beti.

Adibide moduan, **2.irudian** analizatutako sei paziente horietako baten kromatograma azaltzen da:



2. irudia. Zuriaren eta daptomizina gehi P4HB zuen laginaren kromatogramak. Erretentzio denbora 5,5 minutu daptomizinarentzat eta 8,2 minutu P4HBrentzat izan zen.

4.2. Linealtasuna

2. taulan lortutako emaitzak eta errore erlatiboa (%E) bildu dira. Bestalde, **3. taulan** gehitu egin dira kalibrazio kurba bakoitzeko kalkulatutako malda (a), oinarrizko jatorria (b), korrelazio-koefizientea (r) eta determinazio-koefizientea (r^2).

Emaitzei erreparatuz gero, teknika analitikoak linealtasun irizpideak betetzen dituela esan daiteke, estandar guztietan errore erlatiboa %15 baino txikiagoa izan baitzen (%20 kuantifikazio-limitearen kasuan).

2. taula. Linealtasun-azterketaren emaitzak.

Kontzentrazio teorikoa (µg/mL)	Kalkulatutako kontzentrazioa (µg/mL)			% Errore erlatiboa (%E)		
	1.zuzena	2.zuzena	3.zuzena	1.zuzena	2.zuzena	3.zuzena
2,5	2,44	2,63	2,38	2,44	-5,11	5,02
5	4,95	5,02	5,12	1,08	-0,34	-2,36
10	9,16	9,41	9,57	8,40	5,94	4,32
25	25,73	24,83	25,74	-2,93	0,70	-2,95
50	56,43	50,92	54,94	-12,86	-1,84	-9,87
100	100,78	98,62	92,92	-0,78	1,38	7,08
150	143,01	151,08	151,84	4,66	-0,72	-1,23

3. taula. Plasma kalibrazio-kurba bakoitzarentzat kalkulatutako malda (a), oinarrizko jatorria (b), korrelazio-koefizientea (r) eta determinazio-koefizientea (r^2).

Parametroa	1. zuzena	2. zuzena	3. zuzena
a	0,012	0,012	0,011
b	0,004	0,007	-0,001
r	0,998	0,999	0,998
r^2	0,996	0,999	0,996

4.3. Doitasuna eta zehaztasuna

4. taulan plasmarentzat lortutako doitasun eta zehaztasun entseguen emaitzak bildu dira.

4. taula. Doitasun eta zehaztasun emaitzak plasman.

	Kontzentrazio teorikoa (μg/mL)	Kalkulatutako kontzentrazioa Batez bestekoa ± SD (μg/mL)	Intra-saiakuntza (n = 6) CV (%)	Intra-saiakuntza E (%)
1. eguna	2,5	2,41 ± 0,16	6,51	3,59
	7	6,7 ± 0,27	4,00	4,10
	40	44,39 ± 1,08	2,44	-0,97
	120	133,39 ± 4,35	3,27	-11,16
2. eguna	2,5	2,67 ± 0,18	6,74	-6,72
	7	6,93 ± 0,02	1,93	0,95
	40	37,22 ± 1,31	3,51	6,99
	120	114,83 ± 7,18	6,25	4,31
2. eguna	2,5	2,25 ± 0,14	6,06	10,43
	7	6,65 ± 0,32	4,87	5,03
	40	41,66 ± 0,94	2,26	-4,15
	120	132,34 ± 5,33	4,03	-10,28
	Kontzentrazio teorikoa (μg/mL))	Kalkulatutako kontzentrazioa Batez bestekoa ± SD (μg/mL)	Inter-saiakuntza (n = 18) CV (%)	Inter-saiakuntza E (%)
	2,5	2,44 ± 0,23	9,51	2,32
	7	6,77 ± 0,27	3,99	3,32
	40	41,09 ± 3,22	7,84	-2,72
	120	126,85 ± 10,28	8,11	-5,71

*SD: desbiderapen estandarra; CV: aldakuntza-koefizientea; E: errore erlatiboa.

Ikus daitekeen moduan, kalitate kontrolen aldakuntza koefizientea eta errore erlatiboa ez zen inoiz %15 baino altuagoa izan. Bestalde, 2,5 μg/mL-ko daptomizina kontrolarentzat intra zein inter-saiakuntzen errore erlatiboak eta

aldakuntza koefizienteak %20 azpitik egon zirela baiezta daiteke. Hortaz, demostratua geratzen da metodo analitiko honek beharrezko doitasun eta zehaztasuna dituela 2,5 μg/mL-ko daptomizina kontzentrazioak kuantifikatzeko, eta, beraz, kuantifikazio-limitetzat har daiteke.

4.4. Egonkortasuna

4.4.1. Analitoaren egonkortasuna matrize biologikoan biltegiratze denboran zehar

5. taulan biltegiratze kondizioetan laginen egonkortasunaren emaitzak azaltzen dira. Ikus daitekeen moduan, desbiderapena %15 baino baxuagoa izan zen beti. Hortaz, gutxienez hilabete batez, plasma laginetan daptomizina egonkorra dela esan daiteke , -20 eta -80ºC-tan.

4.4.2. Analitoaren egonkortasuna matrizean izozte-desizozte prozesuetan, izozte baldintzetatik giro tenperaturara

5. taulan 3 izozte-desizozte ziklo jasan ostean laginen egonkortasunaren emaitzak bildu dira. Lagin bakoitzaren errorea %15 baino baxuagoa izan zen beti. Horrek esan nahi du prozesu honetan zehar laginak egonkor mantendu zirela.

4.4.3. Egonkortasuna sistema kromatografikoan

Hurrengo taulan ikus daitekeen moduan, gutxienez 24 orduz, laginak egonkor mantendu ziren sistema kromatografikoan, errorea beti %15 azpitik egon baitzen.

5. taula. Egonkortasun entseguan lortutako emaitzak.

Kontzentrazio teorikoa (µg/mL)	7		120	
	Kalkulatutako kontz. Batez bestekoa ± SD	E (%)	Kalkulatutako kontz. Batez bestekoa ± SD	E (%)
Egonkortasuna biltegiratze-denboran zehar				
1 hilabete (-20ºC)	7,48 ± 0,32	-1,04	113,33 ± 0,80	9,64
1 hilabete (-80ºC)	6,88 ± 0,04	7,03	115,29 ± 1,29	8,08
Egonkortasuna matrizean izozte-desizozte prozesuetan	7,14 ± 0,38	3,51	116,04 ± 1,51	7,48
Egonkortasuna sistema kromatografikoan (24h)	7,37 ± 0,39	0,40	118,37 ± 1,336	5,62

*SD: desbiderapen estandarra; E: errore erlatiboa; Kalkulatutako kontz.: kalkulatutako kontzentrazioa

4.4.4. Analito eta barne estandar disoluzio-amen egonkortasuna

6. taulan daptomizina eta barne estandar disoluzio-amen batezbestekoa eta desbiderapena (SD) bildu dira, 0 denboran eta handik 24 ordutara. Aztertutako disoluzion azalera 0 eta 24 ordu pasa ostean %95-105 artean mantendu zen beti; hau da, errore erlatiboa %5 azpitik egon zen beti.

6.taula. Disoluzio-amen egonkortasuna 24 ordutan.

Disoluzio-amak (µg/mL)	Azalera ± SD		E (%) (versus t= 0 h)
	t = 0 h	t = 24 h	
Daptomizina			
50	1.506.860 ± 84.485	1.518.243 ± 20.492	0,76
500	15.094.098 ± 134.168	15.076.133 ± 197.449	-0,12
Barne estandarra			
80	98.4168 ± 20.603	1.006.699 ± 1.860	2,29

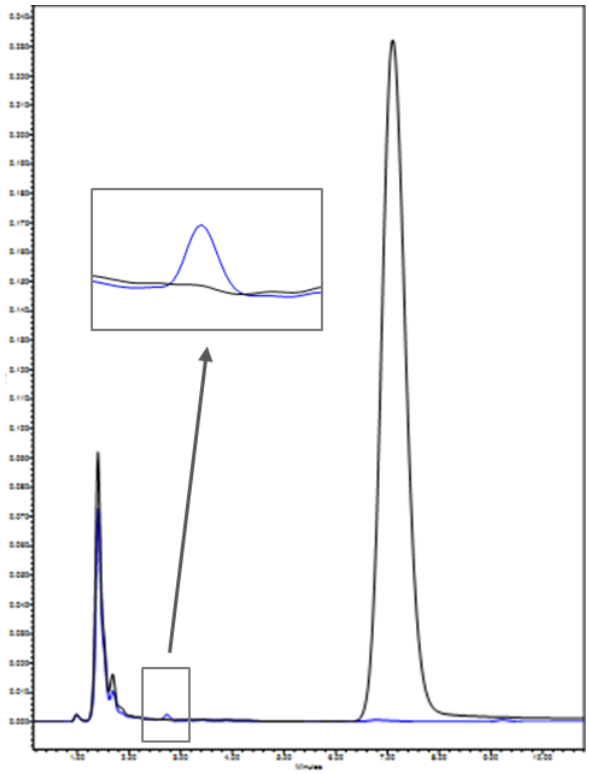
*SD: desbiderapen estandarra; E: errore erlatiboa.

5. Linezolid: balidazioaren emaitzak

5.1. Selektibitatea

Analizatutako lagin guztietan interferentziazko erpinen erantzuna, alegia, azalera kromatografikoa, kuantifikazio limitearen %20 baino baxuagoa izan zen linezoliden erretentzio-denboran. Bestalde, barne estandarraren erretentzio-denboran agerturiko interferentzien erantzuna, analisian erabilitako barne estandarraren kontzentrazioaren (15 μg/mL) %5 baino baxuagoa izan zen beti.

Adibide moduan, **3. irudian** analizatutako sei paziente horietako baten kromatograma azaltzen da:



3. irudia. Zuriaren eta linezolid gehi P4HB zuen laginaren kromatogramak.
Erretentzio denbora 2,8 minutu linezolidentzat eta 7,2 minutu P4HBrentzat izan zen.

5.2. Linealtasuna

7. taulan lortutako emaitzak eta errore erlatiboak (%E) bildu dira. Bestalde, **8. taulan** gehitu dira kalibrazio kurba bakoitzeko kalkulatutako malda (a), oinarrizko jatorria (b), korrelazio-koefizientea (r) eta determinazio-koefizientea (r^2).

Emaitzei erreparatuz gero, teknika analitikoak linealtasun irizpideak betetzen dituela esan daiteke, estandar guztietan errore erlatiboa %15 baino txikiagoa izan baitzen (%20 kuantifikazio-limitearen kasuan).

7. taula. Linealtasun-azterketaren emaitzak.

Kontzentrazio teorikoa (μg/mL)	Kalkulatutako kontzentrazioa (μg/mL)			Errore erlatiboa (%E)		
	1.zuzena	2.zuzena	3.zuzena	1.zuzena	2.zuzena	3.zuzena
0,5	0,46	0,45	0,41	8,91	8,94	18,70
2	2,10	1,96	2,25	-5,00	2,22	-12,58
5	5,11	5,51	5,31	-2,27	-0,24	-6,09
20	20,28	20,23	19,73	-1,37	-1,12	1,36
30	30,86	30,82	31,33	-2,87	-2,73	-4,44
50	48,70	48,53	48,48	2,61	2,93	3,04

8. taula. Plasma kalibrazio-kurba bakoitzarentzat kalkulaturiko malda (a), oinarrizko jatorria (b), korrelazio-koefizientea (r) eta determinazio-koefizientea (r^2).

Parametroa	1.zuzena	2.zuzena	3.zuzena
a	0,003	0,007	0,014
b	0,035	0,040	0,036
r	1,000	0,999	0,999
r^2	0,999	0,999	0,998

5.3. Doitasuna eta zehaztasuna

9. taulan plasmarentzat lortutako doitasun eta zehaztasun entseguen emaitzak bildu dira.

9. taula. Doitasun eta zehaztasun emaitzak plasman.

	Kontzentrazio teorikoa (μg/mL)	Kalkulatutako kontzentrazioa Batez bestekoa ± SD (μg/mL)	Intra-saiakuntza (n = 5) CV (%)	Intra-saiakuntza E (%)
1. eguna	0,5	0,48 ± 0,04	9,19	3,52
	1,5	1,49 ± 0,05	3,54	0,35
	10	10,94 ± 0,30	2,77	-9,44
	40	40,11 ± 1,26	3,15	-0,29
2. eguna	0,5	0,47 ± 0,08	17,50	7,00
	1,5	1,54 ± 0,06	4,17	-2,41
	10	9,36 ± 0,13	1,39	6,36
	40	40,56 ± 3,63	8,94	-1,41
3. eguna	0,5	0,43 ± 0,03	7,67	14,48
	1,5	1,50 ± 0,09	6,35	0,33
	10	11,26 ± 0,30	2,63	-12,61
	40	44,14 ± 1,64	3,71	-10,34
	Kontzentrazio teorikoa (μg/mL)	Kalkulatutako kontzentrazioa Batez bestekoa ± SD (μg/mL)	Inter-saiakuntza (n = 15) CV (%)	Inter-saiakuntza E (%)
	0,5	0,46 ± 0,02	5,22	8,33
	1,5	1,51 ± 0,07	4,66	-0,58
	10	10,52 ± 0,89	8,46	-5,23
	40	41,60 ± 2,91	6,99	-4,01

*SD: desbiderapen estandarra; CV: aldakuntza-koefizientea; E: errore erlatiboa.

Ikus daitekeen moduan, kalitate kontrolen aldakuntza koefizientea eta errore erlatiboa ez zen inoiz %15 baino altuagoa izan. Bestalde, 0,5 μg/mL-ko linezolid kontrolarentzat intra zein inter-saiakuntzen errore erlatiboak eta

aldakuntza koefizienteak %20 azpitik egon zirela baiezta daiteke. Hortaz, demostratua geratzen da metodo analitiko honek beharrezko doitasun eta zehaztasuna dituela 0,5 μg/mL-ko linezolid kontzentrazioak kuantifikatzeko, eta, beraz, kuantifikazio-limitetzat har daiteke.

5.4. Egonkortasuna

5.4.1. Analitoaren egonkortasuna matrize biologikoan biltegiratze denboran zehar

10. taulan biltegiratze kondizioetan laginen egonkortasunaren emaitzak azaltzen dira. Ikus daitekeen moduan, desbiderapena %15 baino baxuagoa izan zen beti. Hortaz, gutxienez hilabete batez, plasma laginetan linezolid egonkorra dela esan daiteke , -20 eta -80ºC-tan

5.4.2. Analitoaren egonkortasuna matrizean izozte-desizozte prozesuetan, izozte baldintzetatik giro tenperaturara

10. taulan 3 izozte-desizozte ziklo jasan ostean laginen egonkortasun emaitzak bildu dira. Lagin bakoitzaren errorea %15 baino baxuagoa izan zen beti. Horrek esan nahi du prozesuan zehar laginak egonkor mantendu zirela.

5.4.3. Egonkortasuna sistema kromatografikoan

Hurrengo taulan ikus daitekeen moduan, gutxienez 24 orduz, laginak egonkor mantendu ziren sistema kromatografikoan, , errorea beti %15 azpitik egon baitzen.

10. taula. Egonkortasun entseguan lortutako emaitzak.

Kontzentrazio teorikoa (µg/mL)	1,5		40	
	Kalkulatutako kontz, Batez bestekoa ±SD	E (%)	Kalkulatutako kontz, Batez bestekoa ±SD	E (%)
Egonkortasuna biltegiratze denboran zehar				
1 hilabete (-20ºC)	1,56 ± 0,02	-4,00	37,11 ± 1,03	7,22
1 hilabete (-80ºC)	1,56 ± 0,02	-4,00	43,49 ± 1,96	-8,73
Egonkortasuna matrizean izozte-desizozte prozesuetan	1,49 ± 0,02	0,67	41,67 ± 1,03	-4,19
Egonkortasuna sistema kromatografikoan (24 h)	1,72 ± 0,10	-14,67	44,78 ± 1,23	-11,96

*SD: desbiderapen estandarra; E: errore erlatiboa; Kalkulaturiko kontz.: kalkulatutako kontzentrazioa.

5.4.4. Analito eta barne estandar disoluzio-amen egonkortasuna

11. taulan linezolid eta barne estandar disoluzio-amen batezbestekoa eta desbiderapena (SD) bildu dira, 0 denboran eta handik 24 ordutara. Aztertutako disoluzion azalera 0 eta 24 ordu pasa ostean %95-105 artean mantendu zen beti; hau da, errore erlatiboa %5 azpitik egon zen kasu guztietan.

11. taula. Disoluzio-amen egonkortasuna 24 ordutan.

Disoluzio-amak (µg/mL)	Azalera ± SD		E (%) (versus t=0 h)
	t =0 h	t = 24 h	
Linezolid			
10	541.053 ± 2.953	556.340 ± 3.880	2,82
100	4.910.858 ± 24.212	5.029.011 ± 28.178	2,4
Barne estandarra			
15	1.445.212 ± 5.370	1.466.392 ± 25.763	1,46

*SD: desbiderapen estandarra; E: errore erlatiboa.

eman ta zabal zazu

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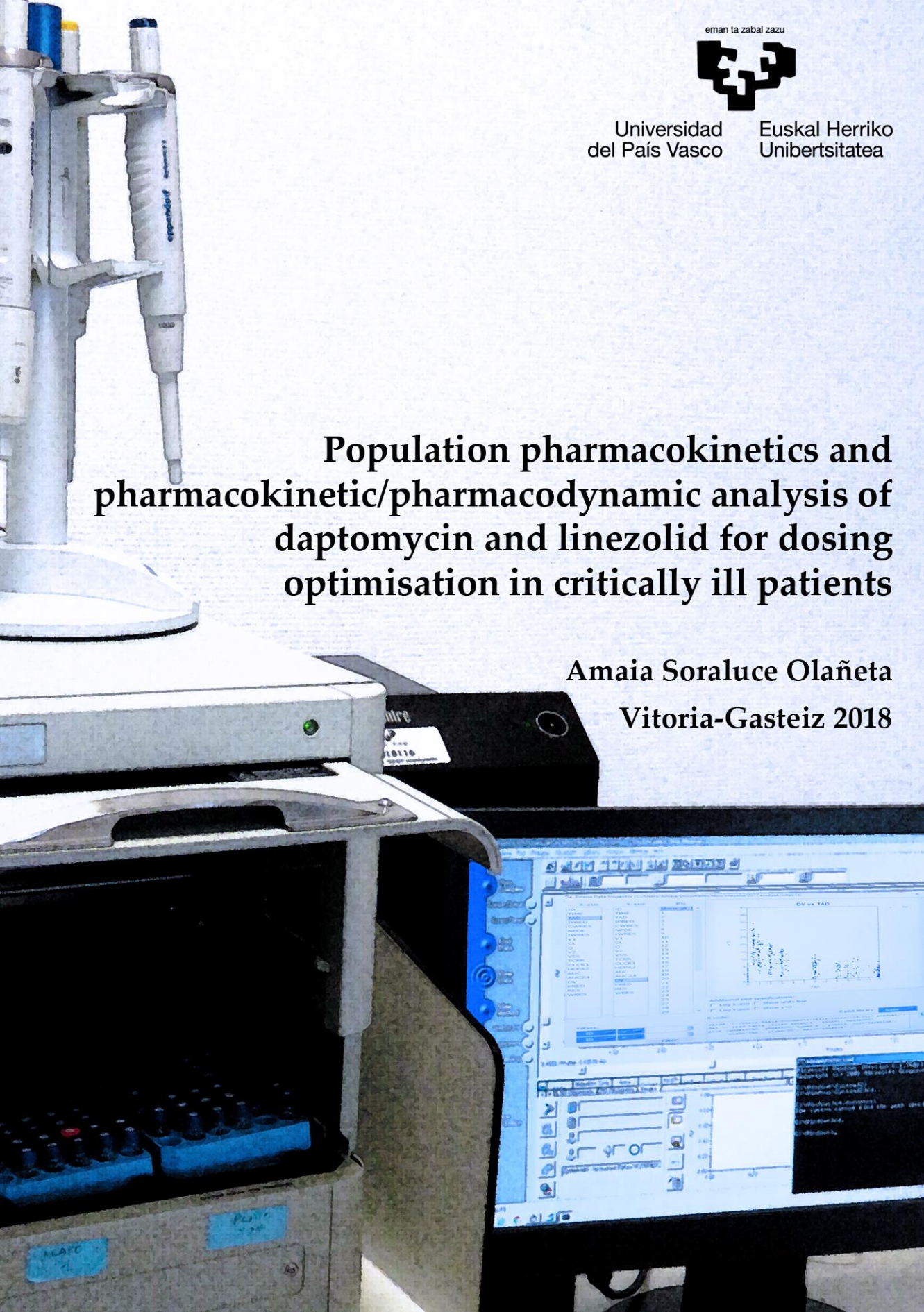

Population pharmacokinetics and pharmacokinetic/pharmacodynamic analysis of daptomycin and linezolid for dosing optimisation in critically ill patients

Amaia Soraluce Olañeta

Vitoria-Gasteiz 2018

CONTENTS

INTRODUCTION

Chapter 1

Pharmacokinetic/pharmacodynamic modelling to optimise antimicrobial agents' dosage in critically ill patients

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EKAIA. 2018;33:19-33

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ABSTRACT: Nowadays, the treatment of infectious diseases has become a global health issue, due to multi-drug resistant bacteria. The lack of new antibiotics enhances urgent need for current antimicrobials' dosing regimens optimisation. This could become an extremely challenging duty when treating some kind of patients, such as the critically ill; as due to their physiophatological situation, both pharmacokinetics and pharmacodynamics might be altered. PK/PD analysis, together with Monte Carlo Simulation, might be a useful tool to optimise dosing regimens of antibiotic agents and, therefore, improve clinical outcome and diminish emergence of resistances.

1. Introduction

Nowadays, diagnosis and treatment of infectious diseases is becoming an increasingly complicated duty for physicians. On the one hand, increasing life expectancy, mainly in western countries, implies a burden on health systems because of the high rate of infections affecting old people, such as influenza or pneumococcal disease, which usually increases the need for long-term care. Moreover, some medical treatments (e.g. cancer chemotherapy or organ transplantation) have led to an increase in the number of immunocompromised individuals, who are highly vulnerable to infections[1,2].

Since their discovery and introduction in therapeutics, almost 90 years ago, antimicrobial agents have played a crucial role in treating infections. However, over the last few decades there has been a relevant increase in the number of pathogens resistant to multiple antimicrobial agents, meaning that some infections that were previously treatable no longer respond properly to medication. Despite the fact that developing resistance is a natural evolutionary phenomenon for microorganisms, it is clear that this has been accelerated by antimicrobial abuse and misuse[3]. It is estimated that, today, antimicrobial resistance (AMR) causes more than 700,000 deaths per year worldwide; which could rise to 10 million deaths in 2050, if no measures are taken to stop the resistance from spreading[1]. This means that AMR could become the first cause of death, beating cancer and resulting in one person dying every three seconds due to infections caused by resistant bacteria.

[1] Review on Antimicrobial Resistance. Tackling drug-resistant infections globally. Available at: *https://amr-review.org/Publications.html* [Accessed May 2018].

[2] European Centre for Disease Prevention and Control. ECDC strategic multi-annual programme 2014–2020. Stockholm: ECDC; 2014.

[3] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277-83.

Thus, drug-resistant infections have not only become a modern medicine issue, but also a global health threat[4,5,6]. Proof thereof is the fact that in September 2016, global leaders met at the United Nations (UN) General Assembly to commit to fighting antimicrobial resistance together[7]. This was the fourth time in the history of the UN that a health topic had been discussed at the General Assembly, previously focussing on the human immunodeficiency virus (HIV), noncommunicable diseases and ebola.

In 2017 the World Health Organization developed a global priority pathogens list of antibiotic-resistant bacteria. Experts agreed on grouping what they considered to be the 12 most dangerous pathogens into three priority tiers: critical, high and medium[8,9]. The most critical group of all includes multidrug resistant bacteria that pose a particular threat in hospitals or nursing homes, including *Acinetobacter baumannii, Pseudomonas aeruginosa* and various Enterobacteriaceae. The high and medium priority categories contain other increasingly drug-resistant bacteria that cause more common diseases, namely, *Enterococcus faecium, Staphylococcus aureus* or *Haemophilus influenzae*. The main goal of this list is to help prioritize the research and development (R&D) of new and effective antibiotic treatments, ensuring global coordination.

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[4] Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect. 2015;16;6:22-9.

[5] PLOS Medicine Editors. Antimicrobial Resistance: Is the World UNprepared? PLoS Med. 2016;13(9):e1002130.

[6] Hernández-Marrero P, Martins Pereira S, de Sá Brandão PJ, Araújo J, Carvalho AS. Toward a bioethical framework for antibiotic use, antimicrobial resistance and for empirically designing ethically robust strategies to protect human health: a research protocol. J Int Med Res. 2017;45(6):1787-93.

[7] General Assembly of the United Nations. High-level Meeting on Antimicrobial Resistance. Available at: *https://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/* [Accessed May 2018].

[8] World Health Organization (WHO). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Available at: *http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/* [Accessed May 2018].

[9] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-327.

Regardless of evident medical needs, the investment made by the pharmaceutical industry in antimicrobials is far from ideal. Proof of this is that, between 2003 and 2013, less than 5% of capital investment in pharmaceutical R&D targeted this kind of drugs[10]. The main reason for the lack of interest is that commercial sales of antibiotics are not high enough to justify further investigation[9,11]. As a result, over the last few years the development of antimicrobials has decreased considerably. To counteract this decline, different initiatives have been implemented, such as the 10 x '20 Initiative, started in 2010 by the Infectious Diseases Society of America (IDSA). This initiative seeks a global commitment to produce 10 new systemic antibiotics by the year 2020[12].

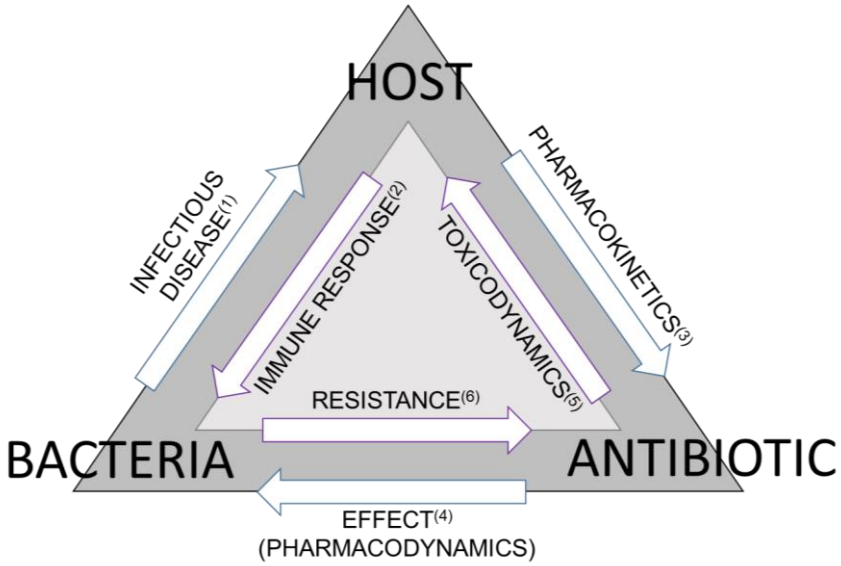
The lack of new antibiotics in the coming years, means that current antimicrobials should be protected urgently. To do so, not only the susceptibility of the pathogen against the antibiotic should be taken into consideration, but also the complex interactions among host, microorganism and drug (**Figure 1**), since variability among these interactions could be the source of a great variability in dose-effect relationship.

Unlike with other drugs, such as antihypertensives or vasopressors, it is not easy to measure the effect of antibiotics in clinical practice. Thus, in some groups of patients (e.g. the critically ill or paediatric patients), selecting the most suitable antibiotic and the optimal dosage becomes particularly challenging.

[10] Silver LL. Challenges of Antibacterial Discovery. Clin Microbiol Rev. 2011; 24(1): 71–109.

[11] Davies J. Where have All the Antibiotics Gone? Can J Infect Dis Med Microbiol. 2006;17(5):287-90.

[12] Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis. 2010;50(8):1081-3.



1. The bacteria cause the infection in the host.
2. The hot's immune response is activated.
3. The host and the antibiotic interact and determine the pharmacokinetics.
4. The antibiotic induces bacteriostatic or bactericidal effect.
5. The antibiotic may alter the physiology of the patient, provoking toxicity or side-effects.
6. The bacteria could develop resistances against the drug.

Figure 1. Interactions between the host, bacteria and antibiotic.

2. Antibiotic therapy in critically ill patients

Despite the great variability found among different services and between patients, infectious diseases maintain a remarkable presence in intensive care units (ICU) worldwide. On the one hand, many ICU admissions are due to infections (such as pneumonia, meningitis or sepsis). Moreover, a high rate of patients

admitted into these services for non-infectious disorders get infected during their stay, that is, they develop healthcare-associated infections (HAI)[13].

Although HAI involve all infectious diseases associated with patient care (especially in hospitals and long-term care facilities), it is well known that HAI usually occur at a greater rate in the ICU than in general wards[14,15]. This is due to the general weakness of the patients. Furthermore, the invasive techniques used, such as endotracheal or nasogastric intubation and urinary catheterization, could contribute to the development of infections[16]. In this context, in a point prevalence research work carried out in 75 European countries (EPIC II), 51% of the 14,414 patients from 1,265 different ICUs were considered to be infected. Moreover, higher mortality was observed in the group of infected patients when compared to the non-infected group (25% vs. 11%, respectively). The most prevalent diseases were pulmonary (63.5%) and intra-abdominal (19.6%) infections, and bacteraemia (15.1%)[17].

Even though critically ill subjects represent less than 10% of hospitalized individuals, they are administered ten times more antibiotics than any other patients[18]. Apart from the greater number of infections observed in the critically ill, another reason for this high use of antimicrobials is that pathogens found in ICUs are usually less susceptible, since the higher rate of antibiotic use puts selective

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[13] Burke A. Cunha. Infectious Diseases in Critical Care Medicine (Third Edition). Informa Healthcare USA, Inc. 52 Vanderbilt Avenue New York, NY 10017. 2010.

[14] World Health Organization (WHO). Healthcare-associated infections: fact sheet;2014. Available at: *http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf.* [Accessed: May 2018]

[15] Bianco A, Capano MS, Mascaro V, Pileggi C, Pavia M. Prospective surveillance of healthcare-associated infections and patterns of antimicrobial resistance of pathogens in an Italian intensive care unit. Antimicrob Resist Infect Control. 2018;7:48.

[16] Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med. 2002;28(2):108-21.

[17] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323-9.

[18] Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med. 2015;36(1):136-53.

pressure on producing resistance[19,20]. The emergence of resistant pathogens forces clinical practice to constantly adapt. In this context, over the last few years, the lack of alternatives made researchers develop new pharmaceutical forms, while physicians started to administrate old antibiotics which had fallen into disuse due to their toxicity profile, such as colistin[21,22].

An antibiotic dosage regimen is generally established through results obtained from clinical trials conducted among healthy volunteers after which, dose-adjustment is performed in mildly to moderately ill patients. Results from these trials are usually extrapolated for use among critically ill patients. However, such extrapolations assume similar drug pharmacokinetics and pharmacodynamics in critically ill patients compared to subjects with mild illnesses, which is hardly presumable. On the one hand, and as mentioned above, because the microorganisms that cause infections are often more resistant. On the other hand, due to several pathophysiological changes observed during illness, concomitant treatment used to improve their health outcomes and other drug administration. Therefore, selecting the most suitable dosage regimen for critically ill patients using standard protocols usually becomes a hard task.

In brief, as the pharmacokinetics and pharmacodynamics of plenty of drugs are usually altered in critically ill patients, expected drug concentrations are

[19] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

[20] Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Antimicrobial susceptibility pattern comparisons among intensive care unit and general ward Gram-negative isolates from the Meropenem Yearly Susceptibility Test Information Collection Program (USA). Diagn Microbiol Infect Dis. 2006;56(1):57-62.

[21] Cassir N, Rolain JM, Brouqui P. A new strategy to fight antimicrobial resistance: the revival of old antibiotics. Front Microbiol. 2014;5:551.

[22] Muller AE, Theuretzbacher U, Mouton JW. Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. Clin Microbiol Infect. 2015;21(10):881-5.

not always achieved. Therefore, therapeutic failure (due to low dosages) or toxicity (associated with drug accumulation) may often occur[23,24].

3. Pharmacokinetics (PK)

3.1. Concept

Once a drug is administered to a patient, it undergoes LADME processes (liberation, absorption, distribution, metabolism and excretion), that condition the drug's concentration over time. The evolution of drug concentrations in the different organs and fluids is studied by pharmacokinetics (PK), which has been described as "what the body does to the drug".

3.2. Pharmacokinetic alterations in critically ill patients

In critically ill patients, some PK parameters concerning antibiotics may be altered in comparison to healthy subjects: volume of distribution (V), protein binding, and total body clearance (CL). Moreover, it is quite common that changes

[23] del Mar Fernández de Gatta M, Martín-Suárez A, Lanao JM. Approaches for dosage individualisation in critically ill patients. Expert Opin Drug Metab Toxicol. 2013;9(11):1481-93.

[24] Olofsson SK, Cars O. Optimizing drug exposure to minimize selection of antibiotic resistance. Clin Infect Dis. 2007;45 Suppl 2:S129-36.

in more than one of these parameters occur at the same time, which make it more complicated to predict drug concentrations properly[25,26,27].

3.2.1. Increased volume of distribution

Oedema, sepsis or post-acute phases after severe burns are some examples of disease entities influencing V, where interstitial fluid is principally affected. Moreover, other interventions employed in ICUs, such as life-sustaining devices, mechanical ventilation or post-surgical drainage, also induce the increase of V[25,28]. The augmentation of V would be especially relevant for hydrophilic antimicrobials, which usually have a limited tissue distribution (e.g. beta-lactams or aminoglycosides)[25]. Since these agents are normally restricted to the extracellular space, relevant antibiotic dilution might occur whenever intravascular fluid escapes into tissue. On the contrary, lipophilic antimicrobials usually have greater V, as they are also usually distributed within cells, and are less affected in critically ill patients. Some examples of lipophilic drugs are linezolid, macrolides or rifampicin. Increases in the V are likely to decrease the maximum plasma drug concentration (Cmax), which can lead to potential underdosing and sub-therapeutic concentrations.

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[25] Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient-concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3-11.

[26] Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. Chest. 2012;141(5):1327-1336.

[27] Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009-34.

[28] Álvarez-Lerma F, Grau S. Management of antimicrobial use in the intensive care unit. Drugs. 2012;72(4):447-70.

3.2.2. Altered protein binding

The ability of antibiotics to bind serum proteins is an influential property of drugs, as only the free fraction is able to exert pharmacological effect. Since albumin is responsible for most of drug-protein binding, decreased protein binding of antimicrobials is likely to occur in the presence of hypalbuminaemia. In this regard, hypalbuminaemia is a typical condition in critically ill patients; actually, it has been reported that almost half of ICU patients (around 40-50%) have albumin values below 25 g/L[29]. Furthermore, co-administration of an antibiotic with other drugs could induce competition among them to bind to serum proteins. The protein binding competition is especially relevant for antibiotics with high protein binding[25], such as daptomycin (90%)[30] or ertapenem (95-92%)[31].

Lower protein levels in blood may lead to higher antibiotic free fraction in blood, which might result in higher probabilities of achieving the expected effect, namely, killing bacteria. However, particularly with high protein binding hydrophilic drugs, hypoalbuminemia is usually associated with an increased V; since due to a lower protein binding, a larger number of unbound drug molecules are able to get out of the bloodstream and spread further into tissues.

Moreover, and given the fact that only unbound molecules can be cleared by the kidneys and liver, higher concentrations of unbound drug may lead to an increased drug elimination. In fact, it is well known that hypalbuminaemia may enhance total drug clearance[29,32].

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[29] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99-110.

[30] Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin Pharmacokinetics and Safety following Administration of Escalating Doses Once Daily to Healthy Subjects. Antimicrob Agents Chemother. 2003;47(4):1318-23.

[31] Majumdar AK, Musson DG, Birk KL, Kitchen CJ, Holland S, McCrea J, et al. Pharmacokinetics of ertapenem in healthy young volunteers. Antimicrob Agents Chemother. 2002;46(11):3506-11.

[32] Roberts JA, Joynt GM, Choi GY, Gomersall CD, Lipman J. How to optimise antimicrobial prescriptions in the Intensive Care Unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. Int J Antimicrob Agents. 2012;39(3):187-92.

3.2.3. Altered clearance

The vast majority of the drugs are eliminated by liver metabolism or kidney clearance. In critically ill patients, the functionality of these organs is usually impaired, conditioning the clearance of antibiotics. The main situations that may alter clearance are liver dysfunction, acute kidney injury and augmented renal clearance.

a) Hepatic dysfunction

In critically ill patients, hepatic impairment, which leads to diminished liver clearance, is mainly associated with hepatocellular damage and cholestasis[33]. All the same, it may be also related to other causes, such as direct injury from hepatotoxic drugs[25,33]. In any case, it is not easy to determine the hepatic clearance of drugs, since there is no simple endogenous marker that specifically predicts liver function. Alternately, hepatic dysfunction is reflected by elevated liver enzymes, bilirubin, ammonia, or reduced synthesis of coagulant factors or albumin[32]. The latter, as previously mentioned, may influence drugs' V and protein binding.

b) Acute kidney injury (AKI)

Due to partial or total loss of kidney functionality, AKI may be the origin of oliguria or anuria in ICU patients, with an increase of plasma creatinine. It has been described that more than half of ICU patients suffer from this pathological condition[34]. Since many antibiotics are eliminated renally, AKI has an important influence on antimicrobial PK and dosage adjustments are usually needed.

When AKI compromises a patients' life, renal replacement procedures are often used, mainly continuous renal replacement therapies (CRRT). These

[33] Chand N, Sanyal AJ. Sepsis-induced cholestasis. Hepatology. 2007;45(1):230-41.

[34]Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.

processes help eliminate antibiotics, especially if protein binding is low. The amount of drug that will be eliminated may vary according to the mode of renal replacement therapies, filter material and surface area or blood flow, to name a few[35]. Hence, when selecting the most appropriate dosage, the influence of these techniques in total drug elimination, known as extracorporeal clearance (CL_{EC}), should be taken into consideration[36,37].

c) Augmented renal clearance (ARC)

It has been stated that augmented renal clearance is present in 20-65% of critically ill patients[38]. In these subjects, cardiac output is increased and renal blood flow enhanced, leading to glomerular hyperfiltration. Today, a patient is considered to suffer from ARC if their glomerular filtration values are greater than 130 mL/min/1,73m^2 (preferable measured in urine). They are usually young males with sepsis or traumatic injuries and lower severity illness. Unlike renal dysfunction, ARC is not such a well-studied phenomenon and standard dosage guidelines have often been followed with these patients, leading to subtherapeutic concentrations and poorer clinical outcomes[38,39].

In summary, there are many physiophatological factors that may influence the pharmacokinetics of antibiotics (**Figure 2**), explaining the high variability observed among ICU patients. Moreover, differences within individuals over time might also occur, due to several factors that can be modified during illness. In this

[35] Thongprayoon C, Cheungpasitporn W, Ahmed AH. Trends in the use of renal replacement therapy modality in intensive care unit: a 7 year study. Ren Fail. 2015;37(9):1444-7.

[36] Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L,et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med. 2012;40(5):1523-8.

[37] Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med. 2009;37(7):2268-82.

[38] Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented Renal Clearance in Critically Ill Patients: A Systematic Review. Clin Pharmacokinet. 2018 Feb 13. doi: 10.1007/s40262-018-0636-7.

[39] Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. Pharmacotherapy. 2015;35(11):1063-75.

way, a dosage that may be appropriate for a certain patient, at certain time, may quickly become inadequate.

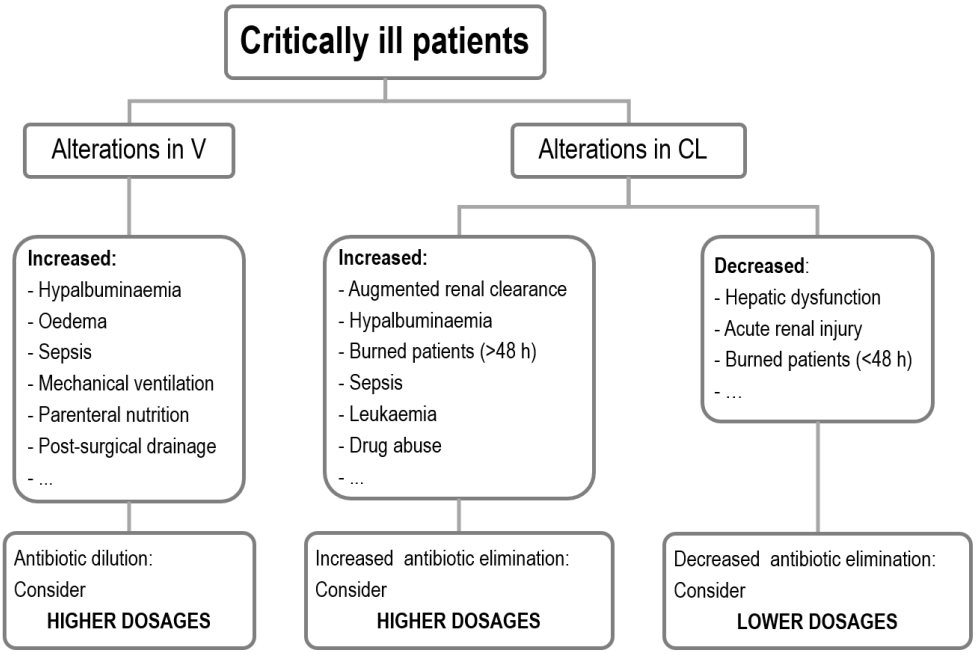

Figure 2. Physiopathological and iatrogenic factors that affect both the distribution and elimination of antibiotics, and general clinical recommendations for each case.

Even though it is essential to know the pharmacokinetics of a drug to select the correct dosing, drug monitoring is not common in clinical practice[23,40]. Thus, it is not frequent to know the PK behaviour of an antibiotic in a certain patient. In addition, it is sometimes interesting to make dosage recommendations for specific groups of patients. In all these cases, the information has to be compiled from prior population studies.

[40] Minne L, Eslami S, Kuiper RA, Abu-Hanna A, Dongelmans DA. Five years of therapeutic drug monitoring in the intensive care did not change vancomycin prescription behaviour: perceived needs for decision support. Minerva Anestesiol. 2012;78(6):684-92.

3.3. Pharmacokinetic population approach

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest[41]. It seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the magnitude of these variations. It is particularly useful when it is suspected that the pharmacokinetics of the drug will vary between population subgroups, since it makes it possible to conveniently customise dosage[42].

Traditionally, PK studies have been carried out by the so-called two-stage approach. The first step of this method estimates the individual PK parameters through nonlinear regression using an individual's dense concentration-time data. Individual parameter estimates obtained during the first stage serve as input data for the second-stage, where descriptive summary statistics on the sample are computed, typically mean parameter estimates, variance and covariance of the individual parameter estimates. The main limitation of this method is that it requires an individual's dense concentration-time data, or data-rich situation[43].

When the two-stage approach is not applicable, such as in sparse data situations, a single-stage method, namely, nonlinear mixed-effects modelling (NLME), should be used. Since information can be shared among individuals in this approach, it becomes suitable not only for sparse data, but also for rich-data or for a combination of both of them.

Nonlinear mixed-effects modelling is a more efficient way of utilising the data, as it offers the possibility of gaining integrated information on PK. Thus, this approach estimates mean and variability parameters at the same time but it is able

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[41] Aarons L. Population Pharmacokinetics: Theory and Practice. Br J Clin Pharmacol. 1991;32(6):669-70.

[42] Charles B. Population pharmacokinetics: an overview, Aust Prescr 2014;37:210-131.

[43] U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Population Pharmacokinetics. Rockville; 1999.

to differentiate between inter-individual and intra-individual variability. In other words, it describes the median tendency of the studied population and quantifies the variability found among individuals, responsible for the different profiles among subjects.

Several pieces of software that implement the nonlinear mixed-effects modelling have been developed over the last few decades. NONMEM (NON-liner Mixed Effects Modelling) is one of the most extensively-used programs among pharmacometricians[44].

Figure 3 shows the components of the population PK approach analysis. When studying the population pharmacokinetics of a drug, the structural model describes the typical parameters (fixed effects) responsible for the concentration-time course within the population. These parameters may be influenced by demographic and/or pathophysiological characteristics of the patients such as sex, age or creatinine clearance, among others. These factors, which are also part of the structural model, are called covariates and identify and explain variability among subjects.

On the other hand, the statistical model quantifies the unexplainable (random) variability in concentration within population that could not be explained by the structural model. Thus, random-effects account for the inter-individual variability (IIV), the inter-occasion variability (IOV) and the residual error (RE).

[44] Bauer R. NONMEM users guide: introduction to NONMEM 7.4.1. ICON Plc. Gaithersburg, Maryland; 2017.

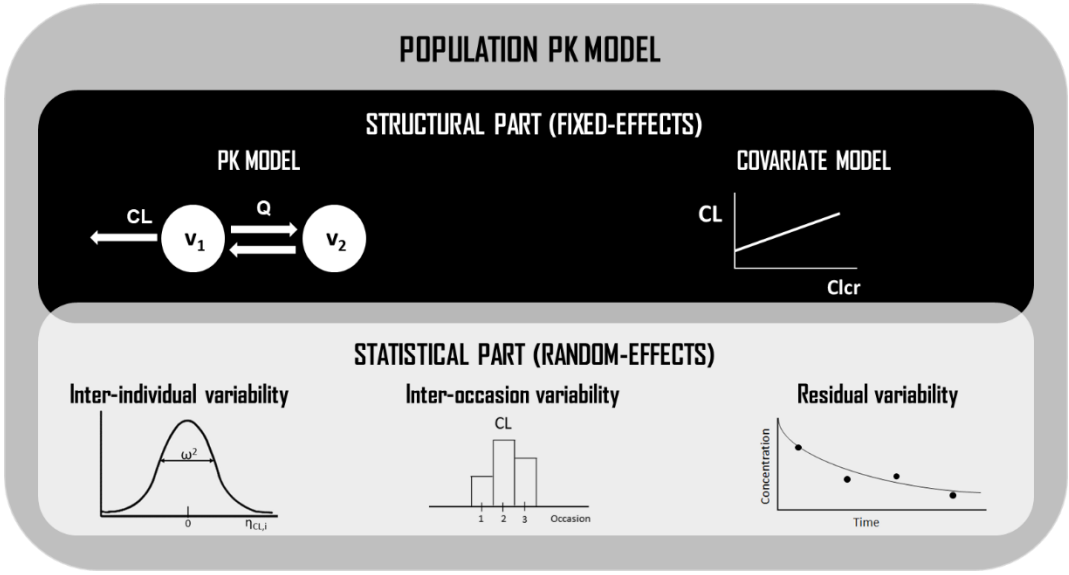

Figure 3. Components of the population pharmacokinetic approach.

3.3.1. Inter-individual variability (IIV)

The IIV defines the discrepancies between the population's typical value for a parameter (θ) and the individual values. For a better understanding of IIV, in equation 1 (**Eq.1**), clearance (CL) parameter would be used as an example:

$$CL_i = \theta_{CL} \times e^{\eta_{CL,i}} \qquad \textbf{(Eq.1)}$$

Where CL_i corresponds to the clearance value of i^{th} individual, θ_{CL} to the typical value of the population and $\eta_{CL,i}$ to the difference between the population and the individual value. Therefore, while θ_{CL} remains equal for every subject, η would be different for each individual. η values within a population are assumed to be normally distributed, with a mean of 0 and an estimated variance of ω^2_{CL}. Thus, the greater the variance, the higher the IIV associated with the CL will be.

3.3.2. *Inter-occasion variability (IOV)*

When a drug is administered on two or more occasions to the same subject, individual pharmacokinetic parameters may change (IOV). The source of variability can sometimes be identified, such as changing patient status or compliance. IOV parameters can be set as follows (**Eq.2**):

If (Occasion = 1) then IOV = η_1

If (Occasion = 2) then IOV = η_2

IIV = η_3

$$CL_i = \theta_{CL} \times e^{IIV+IOV} \qquad \textbf{(Eq.2)}$$

In order to include IOV in the population model more than one sample or measurement per occasion is required, otherwise it would be indistinguishable from residual error.

3.3.3. *Residual error*

Although the parameters for each subject are established, and these are used to predict the drug concentration in each individual at a certain time-point, *j*, the measured or observed concentration ($C_{obs,ij}$) would differ from the predicted ($C_{pred,ij}$). This discrepancy, ε_{ij}, is referred to as residual error. It might be associated with an assay error, errors in dosing or sampling time or model misspecification, among others (**Eq.3**):

$$C_{obs,ij} = C_{pred,ij} + \varepsilon_{ij} \qquad \textbf{(Eq.3)}$$

The ε_{ij} values are assumed to be normally distributed around the zero value and estimated variance of σ^2.

Figure 4. displays the observed concentrations for an individual, together with individual and population predictions (typical predictions) and different types of variability.

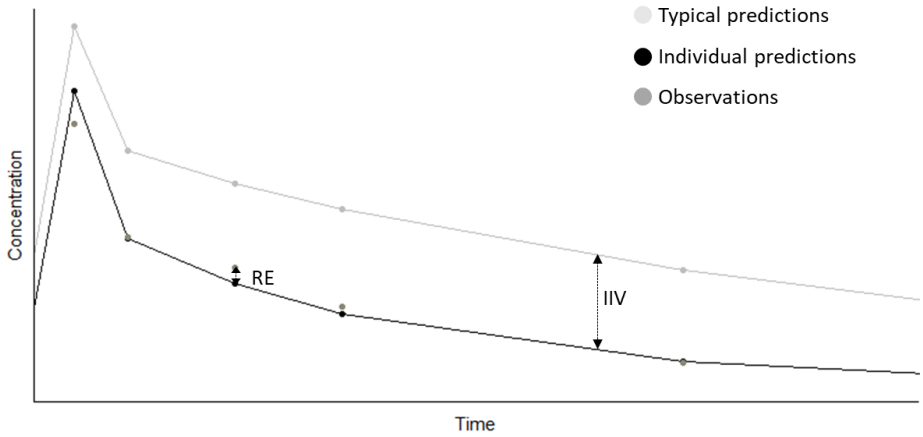

Figure 4. Observed drug concentrations for a specific individual and the typical and individual predictions. Inter-individual variability (IIV) and residual error (RE) are also shown.

The development of a PK model for a population or subgroup requires the quantification of the variability. Moreover, the structural model must be appropriate, without bias or misspecifications, to avoid coming to erroneous conclusions. Hence, during the model development process and once the final model has been built, it is vital to assess the goodness-of fit between the model and the dataset, to determine whether the underlying model assumptions seem appropriate; in other words, model evaluation must be performed.

3.4. Model evaluation

Although many tools used to evaluate a PK model have been described, there are no predetermined ideal or optimum steps to follow. Methods for model evaluation are continuously evolving, and a combination of different diagnostic

tools should be employed[45]. These methods have been divided into three main groups: numerical, graphical and simulation-based diagnostics.

3.4.1. Numerical diagnostics

NONMEM estimates parameters using the maximum likelihood method. This approach minimizes the extended least squares objective function, which is nearly proportional to two times the logarithm of the likelihood (-2xlog likelihood) of the data. Under the assumption of normality, maximum likelihood estimates are obtained at the minimum objective function value (OFV). The absolute OFV is meaningless and only its reduction remains important. The difference in OFV (ΔOFV, likelihood ratio) is used to discriminate between two nested models. Thus, by adding one extra parameter ΔOFVs of -3.84 and -6.63 would correspond to significance levels of <0.05 and <0.01, respectively[46]. Since level of significance could not be assigned to differences in OFV among non-nested models, in these cases comparison should be performed using Akaike information criteria (AIC).

When building a population model, it is also important to determine the precision with which the parameters have been estimated. To do so, the value of the relative standard errors (expressed as coefficient of variation, CV) should be taken into consideration[47]. It is stated that RSE for structural model parameters should be no greater than 25%, while for random effects parameters, they must not exceed 50%. Parameter precision might be affected by several factors, such as, experimental design, quality of data and/or model misspecification or over-parametrization.

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[45] Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol. 2017;6(2):87-109.

[46] Wählby U, Jonsson EN, Karlsson MO. Assessment of Actual Significance Levels for Covariate Effects in NONMEM. J Pharmacokinet Pharmacodyn. 2001;28(3):231-52.

[47] Ette EI, Williams PJ. Population pharmacokinetics II: estimation methods. Ann Pharmacother. 2004;38(11):1907-15.

In order to verify whether a PK model is robust enough, bootstrap methods could be used. These are resampling techniques used to estimate the accuracy of the parameters. In brief, bootstrapping involves generating replicate data-sets where individuals are randomly drawn for the original data-base. Thus, in each replicate, they can be drawn multiple times, or might not be selected at all. Once the replicates have been performed, the median value and 5th and 95th percentiles calculated for each parameter can be compared with values obtained in the final model[48].

3.4.2. Graphical diagnostics

The main advantage of graphical methods over numeric diagnostics is that they are, overall, easier to understand. Even though different types of graphical representations are available to assess model performance, the most widely used are the Goodness-of-fit (GOF) plots.

The most popular GOF plots include the following graphs[45]:

a) Observations (DV) versus population or individual predictions (PRED or IPRED)

These plots might be very useful to check the general performance of the model. If the model is appropriate, IPRED will be approximate to the DVs, so data points will be scattered evenly around the identity line. On the other hand, the PRED will be similar to the mean of the observations. Trends in these plots may suggest a modification of structural model, residual error model or inter-individual variability model.

[48] Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci. 1986;1: 54–77

b) Conditional weighted residuals (CWRES) versus time or versus PRED

These GOF plots are useful to evaluate the structural part of the model. In this case, data points should be scattered around the horizontal zero-line, without showing any apparent tendency.

c) IPRED versus time or individual weighted residuals (IWRES)

These graphics are very useful to find misspecification at the residual error level. In the case of IWRES, when the selected model is appropriate, data points will be scattered evenly around the horizontal zero-line, and most of the points should lie between -1.96 to 1.96 values.

However, IPRED will not be reliable if the individual data are not sufficiently informative with respect to one or more parameters; since individual parameter estimates would shrink close to the population mean under these conditions, providing favourable agreement when there is actually a model misspecification. This phenomenon can be quantified by the η-shrinkage and the ε-shrinkage. In order to be able to rely on individual plots, shrinkage values of 20-30% (if calculated from standard deviation) have been suggested as a threshold[49].

3.4.3. Simulation-based diagnostics

In order to evaluate a population PK model, Visual Predictive Checks (VPCs) are some of the most used simulation-based tools. These plots compare the distribution of observations and the distribution of predictions versus an independent variable (commonly time). Thus, they make it possible to visually assess whether the structural and statistical parts of the model are capable of predicting the central trend and the variability among the observed information. To do so, the final model is used to simulate new data sets (usually 500 or 1,000)

[49] Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17-20.

with the same characteristics as the original data. From each simulated dataset the 2.5th, 50th and 97.5th percentiles are calculated for each time point and their 95% confidence intervals are superimposed on to the same 2.5th, 50th and 97.5th percentiles of the raw data. VPC plots stratified by other relevant covariates (such as weight or creatinine clearance) or dose could also be constructed to evaluate model performance in these subsets. In the case of a different dosage regimen, covariate relationship or study design, prediction-corrected VPC (pc-VPC) should be used. Given the fact that they normalize the observed and simulated dependent variable based on the PRED, they are able to handle these discrepancies.

Nowadays, there are many instruments that can cope with population pharmacokinetic model building and evaluation process. Some of the best-known are Xpose (an R-based model building aid for population analysis using NONMEM)[50], PSN[51] or Pirana[52].

[50] Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. 1999;58(1):51-64.

[51] Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)--a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 2004;75(2):85-94.

[52] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

4. Pharmacodynamics (PD)

4.1. Concept

In order to optimise drug dosage, it is crucial to take into consideration not only a drug's pharmacokinetics, but also its pharmacodynamic behaviour. Pharmacodynamics is the study of the biochemical and physiologic effects of a drug, in a certain concentration, caused by its action mechanism. In brief, it has been described as "what the drug does to the body". In antimicrobial therapy, it is the discipline that relates exposure to the drug and the microbiological or clinical effect[53,54].

The main indicator to measure the effect of an antibiotic is the MIC or minimum inhibitory concentration. That is, the lowest concentration of a drug which prevents visible growth of a bacterium. In order to estimate this indicator, different laboratory methodologies have been employed[55]. Consequently, MICs are static values that only take into account the interactions between the antibiotic and microorganisms, regardless of the host. Thus, the use of MIC values as the unique indicator of the efficacy of an antimicrobial agent could be inaccurate.

[53] Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004;2(4):289-300.

[54] Schmidt S, Schuck E, Kumar V, Burkhardt O, Derendorf H. Integration of pharmacokinetic/ pharmacodynamic modeling and simulation in the development of new anti-infective agents-minimum inhibitory concentration versus time-kill curves. Expert Opin Drug Discov. 2007;2(6):849-60.

[55] Andrews JM. Determination of minimum inhibitory concentrations. J Antimicrob Chemother. 2001;48 Suppl 1:5-16.

5. Pharmacokinetic/pharmacodynamic analysis

Since pharmacodynamics depends on drug concentration, and the latter is conditioned by pharmacokinetics, it is easy to deduce that PK and PD are closely related to each other (**Figure 5**). PK/PD analysis is used to determine the optimum dose for different individuals and type of infection, avoiding the appearance of adverse effects or resistance.

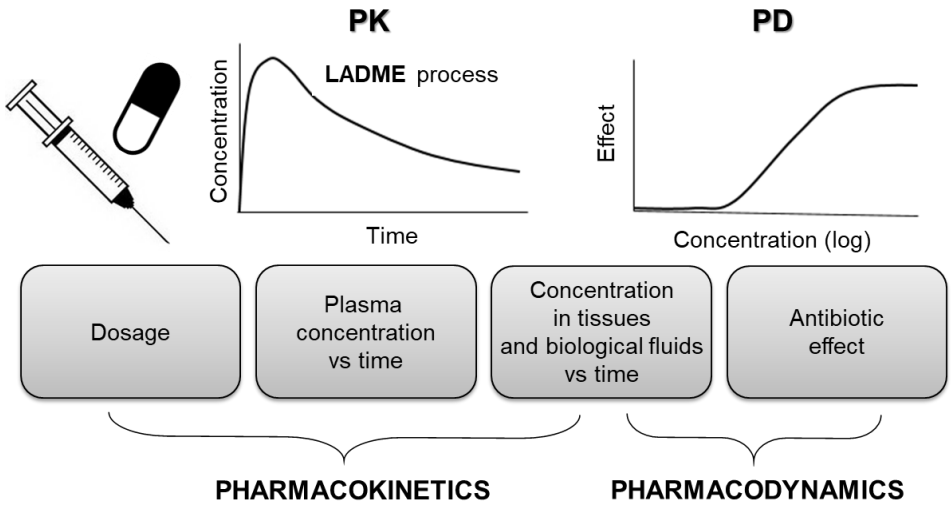

Figure 5. Relationship between PK and PD.

The quantitative relationship between a pharmacokinetic parameter and a microbiological parameter is labelled as a PK/PD index (PDI). There are three main PK/PD indices related to the effect of antibiotics (**Figure 6**): the cumulative percentage of a period of time that the drug concentration exceeds the MIC in steady-state pharmacokinetic conditions ($T_{>MIC}$), the peak level divided by the MIC (Cmax/MIC), and the area under the concentration-time curve (commonly over 24

h) in steady-state divided by the MIC (AUC_{24h}/MIC). For each antibiotic, these indices should achieve a certain value in order to ensure efficacy[56,57].

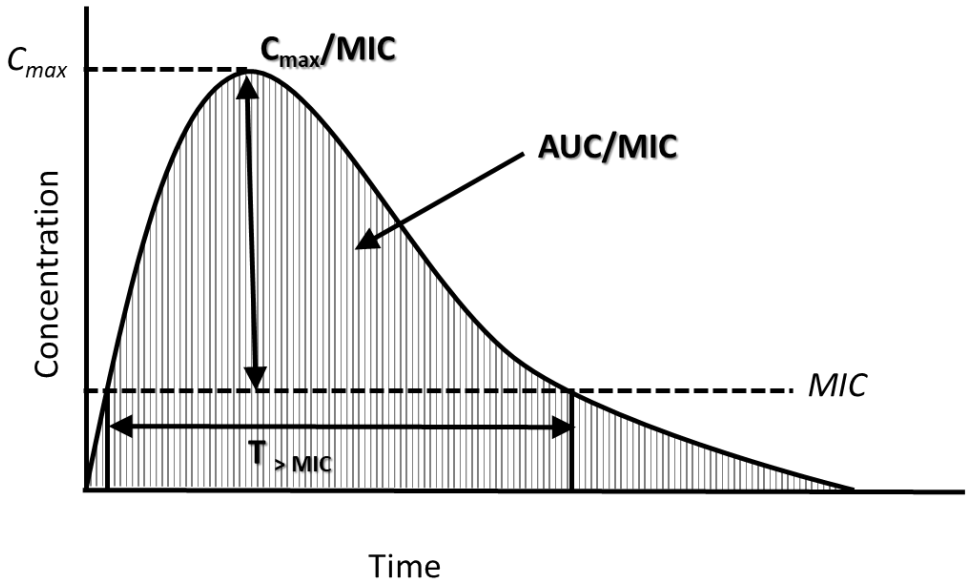

Figure 6. PK/PD indices related to antibiotic efficacy.

Three major patterns of antimicrobial activity have been described, and the best PK/PD index varies for each of them:

a) Antimicrobials with concentration-dependent killing along with prolonged post-antibiotic effect (PAE)

   Due to their prolonged PAE, bacterial regrowth is inhibited even when active drug concentration is below the MIC. The indices that are most currently used to determine the efficacy of these antibiotics are Cmax/MIC and AUC_{24h}/MIC. For these antibiotics, high doses and large dosing intervals are used, since a greater bacterial rate of killing

[56] Scaglione F. Pharmacokinetic/Pharmacodynamic (PK/PD) considerations in the management of Gram-positive bacteraemia. Int J Antimicrob Agents. 2010;36 Suppl 2:S33-9.

[57] Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the Intensive care unit. Crit Care Clin. 2011;27(1):1-18.

and a quicker effect is observed with increasing concentrations of the antibiotic. This antibiotic group includes aminoglycosides and fluoroquinolones, among others[56,57].

b) Antimicrobials with time-dependent killing and no or very short PAE

The best PK/PD index correlated with efficacy for antibiotics that belong to this group (e.g. beta-lactams) is $T_{>MIC}$, which is usually expressed as the percentage of the dosing interval. The lower the half-life of a drug, the greater the frequency with which it should be administered. In some cases, especially when high $T_{>MIC}$ is needed, intravenous administration by continuous perfusion may be required[56,57].

c) Antimicrobials with concentration-independent killing and prolonged PAE

As in the case of the first antimicrobial group, high antibiotic concentrations provoke rapid bacteria killing, but they also protect against regrowth when active drug concentration falls below the MIC. Thus, the best PK/PD indices for these drugs are Cmax/MIC or the AUC_{24h}/MIC. Some antibiotics, such as vancomycin, tetracyclines and tigecycline, among others, follow this pattern[56,57].

As previously mentioned, performing a successful PK/PD analysis should take into consideration not only the right PDI, but also the exact value that this index should reach, namely, pharmacodynamic target (PDT)[58]. Therefore, to consider an antibiotic dosage to be effective, it would be necessary to know whether a specific PDT is reached or not. In order to establish which PK/PD index

[58] Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother. 2015;21(5):319-29.

or pharmacodynamic target (PDT) should be achieved, both *in vivo*[59] and *in vitro*[60,61] studies are used. Since only the fraction unbound of the drug (*f*) is able to produce pharmacological effect, in some cases the PK/PD indices are specified for the unbound fraction. **Table 1** also shows the magnitude of PK/PD indices related to treatment success for some antibiotics.

[59] Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev. 2007;20(3):391-408.

[60] Andes D, Craig WA. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents. 2002;19(4):261-8.

[61] Zhao M, Lepak AJ, Andes DR. Animal models in the pharmacokinetic/pharmacodynamic evaluation of antimicrobial agents. Bioorg Med Chem. 2016;24(24):6390-400.

Table 1. Activity patterns of different antibiotics, PK/PD indices and PDTs.

Activity pattern	Antibiotic	PK/PD index	PDT
Concentration-dependent killing with prolonged PAE	Aminoglycosides	Cmax/MIC	10[62]
	Fluoroquinolones	AUC_{24h}/MIC	125[63,64]
	Daptomycin	AUC_{24h}/MIC	666[65]
Time-dependent killing with no or very short PAE	Beta-lactams:		
	Penicillins	$fT_{>MIC}$	50-60[53]
	Cephalosporins		60-70[53]
	Carbapenems		40-50[53]
Concentration-independent killing with prolonged PAE	Linezolid	AUC_{24h}/MIC -- $T_{>MIC}$*	80 -- 85[66,67*]
	Vancomycin	AUC_{24h}/MIC	400[68]
	Tigecycline	AUC_{24h}/MIC	17.9[69]

* In the case of linezolid, both AUC_{24h}/MIC and $T_{>MIC}$ are taken into consideration.

[62] Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother. 1999;43(3):623-9.

[63] Schentag JJ. Pharmacokinetic and pharmacodynamic surrogate markers: studies with fluoroquinolones in patients. Am J Health Syst Pharm. 1999;56(22 Suppl 3):S21-4.

[64] Aminimanizani A, Beringer P, Jelliffe R. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. Clin Pharmacokinet. 2001;40(3):169-87.

[65] Canut A, Isla A, Betriu C, Gascón AR. Pharmacokinetic-pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. Eur J Clin Microbiol Infect Dis. 2012;31(9):2227-35.

[66] Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012;67(8):2034-42.

[67] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003, 42:1411-23.

[68] Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet. 2004;43(13):925-42.

[69] Meagher AK, Passarell JA, Cirincione BB, Van Wart SA, Liolios K, Babinchak T, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. Antimicrob Agents Chemother. 2007;51(6):1939-45.

6. Monte Carlo simulation

Inter-individual variability among critically ill patients is usually high, while the number of patients included in clinical trials carried out in the ICUs is often small. This lack of information could result in poor adjustment of the dosage or making incorrect predictions in terms of achieving the therapeutic targets. In order to avoid these situations, strategies to enhance or maximise the sample size might be carried out, using Monte Carlo simulation (MCS). This method simulates thousands of different subjects, considering the equations of a previously developed pharmacokinetic model, and taking into account the variability between patients in different parameters, using the mean value or the standard deviation, among others[70].

Monte Carlo simulation might be a useful tool to predict the optimal dosage in empirical treatment or specific populations, such as the critically ill, elderly subjects or obese patients. Nevertheless, in order to obtain reliable results and avoid biases, it is essential to have a validated population PK model including the structural model, a variability model and a covariate model. Moreover, a PD model where the interrelationship of the PK and PD parameters has been studied would also be required[71].

When performing MCS, the probability of target attainment (PTA) is calculated. PTA is the probability that at least a specific value of a pharmacodynamic index (e.g. 30% $T_{>MIC}$; AUC_{24h}/MIC of 200) is achieved at a

[70] Bonate PL. A brief introduction to Monte Carlo simulation. Clin Pharmacokinet. 2001;40(1):15-22.

[71] Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. J Antimicrob Chemother. 2011;66(2):227-31.

certain minimum inhibitory concentration (MIC)[72]. In other words, the percentage of simulated patients that would reach the PDT for a specific MIC is determined.

However, in clinical practice, the susceptibility of microorganisms is often unknown. Therefore, the estimation of the cumulative fraction of response (CFR) could be useful. CFR is the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms[72]. It is an estimate of the proportion of population achieving a certain PDI value, given the Monte Carlo simulation and the MIC distribution of the target microorganisms. It is calculated as:

$$CFR = \sum_{i=1}^{n} PTA_i \times F_i \qquad \textbf{(Eq.4)}$$

Where the subscript *i* indicates the MIC category ranked from lowest to highest MIC value of a population of microorganisms, PTA_i is the PTA of each MIC category and F_i is the fraction of the population of microorganisms at each MIC category.

This approximation might be helpful when the susceptibility of the pathogen is still unknown and also to determine the most suitable dosage regimen of an antibiotic for a given hospital. Thus, to estimate the CFR appropriately, it would be essential to identify the MIC distribution of a certain place in a given period of time; since the patterns of bacteria susceptibility to an antibiotic vary depending on time, region, hospital or even different services. Therefore, MIC values published in the literature often do not properly describe the real situation at a particular time.

[72] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/ pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005;55(5):601-7.

7. Conclusions

PK/PD analysis, together with population PK modelling and Monte Carlo simulation, allows us to optimise the dosing regimen of antibiotics. This would be especially useful in critically ill patients since the PK of drugs is usually altered in these patients and infections are often caused by more resistant bacteria.

OBJECTIVES

Objectives

The management of infectious diseases has become a global health issue in the last years. The increase of antimicrobial resistances has hindered the ability of several antibiotics to fight against infections, which has decreased the effectiveness of antibacterial treatments. Different kind of actions are essential to avoid the exacerbation of this problem, such as the development of new antimicrobial agents, the prevention of the infection in the first-place or the optimisation of the dosages, to name a few.

Regarding the optimisation of the therapy, it becomes essential to understand the pharmacokinetic processes in the patients and the pharmacodynamics of the drug; that is, the effect of the antibiotics on the microorganism responsible for the infection. Hence, the application of pharmacokinetic/pharmacodynamic (PK/PD) analysis and Monte Carlo simulation appears to be a useful tool to perform dose optimisation. This would help increase the probabilities of success and reduce the emergence of resistances and the incidence of side effects, which would be especially beneficial in subjects where pharmacokinetics and pharmacodynamics are altered (e.g. critically ill patients).

That said, the main goal of this thesis is to develop population pharmacokinetic models for two of the newest antimicrobial drugs used in critically ill patients against Gram-positive bacteria, daptomycin and linezolid, and to evaluate the adequacy of the dosage regimens by applying PK/PD analysis and Monte Carlo simulation. To fulfil this goal, the following partial objectives have been planned:

1) Development of population pharmacokinetic models for daptomycin and linezolid with the aim of identifying the physiological and pathological

factors that significantly influence drug pharmacokinetics and, therefore, antibiotic exposure in these patients. In this regard, causes of pharmacokinetic variability will be identified and quantified, including those related to techniques of continuous renal replacement therapies, when applied to the patients.

2) Evaluation of the probability of achieving efficient concentrations and safety-related profiles with the standard dosages, considering PK/PD indices associated with treatment success and concentrations linked to toxic events.

3) Simulating alternative dosing regimens and proposing recommendations to assess favourable outcomes of the antimicrobial therapy, considering the characteristics of the patients and taking into consideration not only effectiveness of the treatment, but also the probability of reaching antibiotic concentrations associated with adverse events.

EXPERIMENTAL-DESIGN

Chapter 2

Population pharmacokinetics of daptomycin in critically ill patients

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ABSTRACT: Daptomycin has shown activity against a wide range of Gram-positive bacteria, however, the approved dosages usually seem insufficient for critically ill patients. The aim of this study was to develop a population pharmacokinetic model for daptomycin in critically ill patients and to estimate the success of the therapy by applying pharmacokinetic/pharmacodynamic (PK/PD) criteria. Sixteen intensive care unit patients were included, four of whom underwent continuous renal replacement therapies (CRRT). Blood and, when necessary, effluent samples were drawn after daptomycin administration at previously defined time points. A population approach using NONMEM 7.3 was performed to analyse data. Monte Carlo simulations were executed to evaluate the suitability of different dosage regimens. The probabilities of achieving the PK/PD target value associated with treatment success (AUC_{24h}/MIC ≥ 666) and to reach daptomycin concentrations linked to toxicity ($Cmin_{ss}$ ≥ 24.3 mg/L) were calculated. The pharmacokinetics of daptomycin was best described by a one-compartment model. Elimination was conditioned by the creatinine clearance (Clcr) and also by the extra-corporeal clearance when patients were subjected to CRRT. The PK/PD analysis confirmed that 280 and 420 mg/qd dosages would not be enough to achieve high probabilities of target attainment for MIC values ≥ 1 mg/L in patients with Clcr > 60 mL/min or in subjects with lower Clcrs but receiving CRRT. In these patients, higher dosages (560-840 mg/qd) should be needed. When treating infections due to MIC values ≥ 4 mg/L, even the highest dose would be insufficient.

1. Introduction

Daptomycin is a lipopeptide antibiotic with activity against a wide range of Gram-positive microorganisms, including methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible enterococci. It is currently approved for the treatment of complicated skin and soft tissue infections (SSTI), right-sided infective endocarditis and *S. aureus* bacteraemia[1,2,3].

Daptomycin is mostly distributed to extracellular fluid and is highly bound to serum proteins (around 90%). Since it is mainly eliminated by the kidneys, dosage adjustment is recommended in patients with renal failure. Additionally, it has demonstrated a linear pharmacokinetic (PK) profile in the dose range of 4-12 mg/kg/qd (*quaque die*, per day)[3,4].

This antibiotic is commonly used for empirical therapy in the critically ill, as Gram-positive infections are frequent in patients in the intensive care unit (ICU)[5]. The pharmacokinetics of antibiotics, especially hydrophilic ones, is usually altered in these subjects. Some of the changes include increased volume of distribution (V), altered protein binding, augmented renal clearance, impaired renal clearance and hepatic dysfunction. The alteration of the PK behaviour might

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[1] Tally FP, DeBruin MF. Development of daptomycin for Gram-positive infections. J Antimicrob Chemother. 2000;46(4):523-6.

[2] Straus SK, Hancock RE. Mode of action of the new antibiotic for Gram-positive pathogens daptomycin: comparison with cationic antimicrobial peptides and lipopeptides. Biochim Biohys Acta. 2006;1758(9):1215-23.

[3] European Medicines Agency. Cubicin®: summary of product characteristics. Available at: *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf* [Accessed: May 2017].

[4] Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother. 2006;50(10):3245-9.

[5] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323–9.

be due to several pathophysiological changes present during illness[6,7,8]. Moreover, concomitant treatment used to improve medical outcomes, such as life sustaining devices (e.g. continuous renal replacement therapies, CRRT), may also alter the PK profile.

Therefore, ICU patients often have a high PK variability and selecting the most suitable antimicrobial dosage usually becomes a challenge[8]. In this scenario, building a population PK model is a useful tool to identify and quantify causes of variability and to then determine the optimal posology for each patient by applying pharmacokinetic and pharmacodynamic (PK/PD) analysis. Consequently, the main goal of this research study was to develop a PK model for daptomycin in critically ill patients and to carry out a PK/PD analysis to establish optimal dosages for each subject, in order to explain the efficacy and safety profiles.

2. Patients and methods

2.1. Study design and settings

An observational multi-centre open-label prospective study was carried out in the ICU at Araba University Hospital (Vitoria-Gasteiz, Spain) and Hospital Clínic (Barcelona, Spain). The Ethics Committees of both institutions approved the study. Written informed consent prior to enrolment was required from all patients,

[6] Scaglione F. Can we transfer pharmacokinetics/pharmacodynamics of antimicrobials into clinical practice? Int J Antimicrob Agents. 2015;46(Suppl 1):S40–S42.

[7] Blot S, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient - concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3–11.

[8] Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care. 2015;21(5):412-20.

or their legal representatives. Patients were eligible for inclusion if they i) were admitted to the ICU; ii) had an infection probably caused by Gram-positive microorganisms and subsequent treatment with daptomycin; iii) gave informed consent; and iv) if it was possible to obtain plasma samples and also effluent samples from the extracorporeal circuit when undergoing CRRT. The exclusion criteria were age < 18 years, pregnancy and hypersensitivity to daptomycin or any of the excipients.

Table 1 shows both demographic and biochemical data of the patient population, together with the APACHE II health score (Acute Physiology and Chronic Health Evaluation II). Creatinine clearance (Clcr) was estimated for each subject using the Cockcroft-Gault equation. For the estimation of the Clcr the actual body weight was used in non-obese patients, whereas the ideal body weight was used in those with BMI values of 30 kg/m^2 or higher[9].

[9] Nguyen MT, Fong J, Ullah S, Lovell A, Thompson CH. Estimating glomerular filtration rate in obese subjects. Obes Res Clin Pract. 2015;9(2):152-7.

Table 1. Hospital, demographic and biochemical data of the 16 patients included in the study and their APACHE II health score. AUH: Araba University Hospital; HC: Hospital Clinic; CRRT: Continuous renal replacement therapies; BMI: Body mass index; Clcr: creatinine clearance; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; CPK: creatinine-phosphokinase; CL_{EC}: extracorporeal clearance.

Patient characteristic	N/N*	Median (Range)
Hospital		
AUH (No CRRT/CRRT)	12/2	
HC (No CRRT/CRRT)	0/2	
Demographic data		
Age (years)	-	67 (48-83)
Sex (male/female)	7/9	-
Body weight (kg)	-	84 (52-100)
BMI (kg/m^2)	-	29.6 (20.3-42.2)
Biochemical data		
Creatinine (mg/dL)	-	0.95 (0.6-1.8)
Clcr (mL/min)	-	
No CRRT	-	66 (20-121)
CRRT	-	8 (0-54)
Glucose (mg/dL)	-	197 (106-299)
Haemoglobin (g/dL)	-	9.1 (7.2-11.7)
Haematocrit (%)	-	25.7 (21.0-33.2)
Albumin (g/dL)	-	2.7 (1.7-3.8)
Total proteins (g/dL)	-	5.3 (3.9-6.9)
Bilirubin (mg/dL)	-	0.7 (0.3-2.6)
Leukocytes ($/mm^3$)	-	13,100 (5,500-21,000)
GOT (UI/L)	-	25 (10-200)
GPT (UI/L)	-	38 (6-566)
CPK (U/L)	-	53 (7-520)
APACHE II	-	18 (7-30)
CL_{EC}[a](L/h)		0.46 (0.32-0.48)

[a] Only for patients undergoing CRRT.

2.2. Drug administration, sampling procedure and analysis

Daptomycin (Cubicin®) was administered via short intravenous infusion (from 20 to 60 min) at a dose ranging from 350 to 850 mg every 24 or 48 hours. Before starting sample collection, a mean of 4 previous doses was administered. Blood samples were drawn at pre-dose and the end of the infusion. Moreover, one sample was taken within the interval of 4 to 8 h, a second at 10 to 14 h, and another

at 24 h and 48 h (when dosed every 48 h). Each sample was immediately centrifuged at 3,000 rpm for 10 min to collect the plasma, which was frozen at -80ºC until analysis. Effluent samples were taken at the same time points and directly stored at -80ºC.

Daptomycin in samples was quantified by a formerly validated High Performance Liquid Chromatography (HPLC) technique with ultraviolet detection (**appendix 1**). Plasma sample preparation consisted of a protein precipitation step with acetonitrile, where internal standard (propyl 4-hydroxybenzoate) was previously diluted. Afterwards, they were centrifuged (10 min at 12,000 rpm) and the supernatants were injected into the HPLC system. Separation was performed with a Symmetry® C8 column (4.6 mm x 150 mm x 5 μm). Linearity in plasma samples was settled over the expected concentration range (2.5-150 μg/mL), whilst for effluent samples, linearity ranged from 0.1 to 20 μg/mL. Intra and inter-day accuracy and precision assays were set at the limits of quantification, as well as at three concentrations in the established range (7, 40 and 120 μg/mL for plasma and 0.3, 2 and 16 μg/mL for the effluent). The calculated concentration never deviated more than 15% from the nominal concentration. The intra-day and inter-day precision, expressed as CV, was always below 15%. The daptomycin standard was kindly provided by Novartis Pharma AG.

2.3. Population pharmacokinetic model

2.3.1. Base model

A population pharmacokinetic model was built using the first-order conditional estimation method with interaction (FOCE-I) utilizing NONMEM 7.3[10]. The disposition of the total drug plasma concentration was studied using

[10] Beal S, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

compartmental models. Based on the distribution of the residuals, the data was logarithmically transformed. To evaluate the model, the decrease in objective function value (OFV =-2 log-likelihood), the relative standard errors (RSE) for the parameters and the goodness-of-fit (GOF) plots were considered. The inter-individual variability (IIV) was modelled exponentially and the residual error with an additive model on a logarithmic scale. Moreover, the significance of the off-diagonal elements of the omega variance-covariance matrix was explored.

2.3.2. Covariate selection

The effect of patient characteristics on the pharmacokinetic parameters was studied, in order to minimise the IIV and support a better fit. Thus, demographic and biochemical data was evaluated for inclusion in the model (**table 1**). Moreover, the extracorporeal clearance (CL_{EC}), set as effluent flow (Q_{ef}) multiplied by the sieving coefficient (Sc), was also taken into account. The Sc is defined as the fraction of drug eliminated across the membrane during CRRT, and was estimated as the mean ratio of the daptomycin effluent to plasma concentrations at each time-point. The inclusion of covariates in the model was normalized by the median value of the population studied. The selection of covariates was carried out using stepwise covariate model building procedure (SCM tool in PsN 4.7.0). This is based on a forward inclusion approach followed by a backward deletion. The significance levels used to incorporate the model and to keep a covariate in the model were set to 0.05 and 0.01 in the forward inclusion and backward deletion approaches, respectively. GOF plots were useful to support the covariate selection.

2.3.3. Model evaluation

The model development and evaluation was guided on the basis of plausibility and parameter estimate precision, as well as the following GOF plots: the dependent variable (logarithmic transformation of the observations) against

population and individual predictions, conditional weighted residuals (CWRES) vs. time after dose (TAD) and the individual weighted residuals (IWRES) vs. individual predictions. Furthermore, a prediction-and-variability-corrected VPC (pvc-VPC) was plotted in order to determine the suitability of the selected model, using Xpose4 package in R 3.4.0[11]. Thereby, using the VPC tool in PsN 4.7.0, data from 1,000 virtual patients was simulated for the daptomycin concentration, based on the final model and the same study design. Both observed and simulated data was divided into 5 bins by ranges of TAD (h) and their 2.5th, 50th and 97.5th percentiles were calculated and compared. Moreover, the parameter precision was evaluated by running a 2,000-data set bootstrap (Bootstrap tool in PsN 4.7.0). Pirana v. 2.9.5 software was used to organise the model building and evaluation process[12].

2.4. Monte Carlo simulation

2.4.1. Pharmacokinetic/pharmacodynamic analysis

Probability of target attainment (PTA) estimation

PTA is understood as the probability of achieving a specific PK/PD index related to the efficacy of an antibiotic treatment at a certain pathogen susceptibility (minimum inhibitory concentration, MIC). In order to estimate the PTA, 5,000 subject simulations were performed over a range of doubling MICs between 0.25 and 4 mg/L and for different dosage regimens: 280, 420, 560, 700 and 840 mg/qd.

[11] Jonsson, EN, Karlsson, MO. Xpose--an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. Computer Methods and Programs in Biomedicine. 199;58(1):51-64.

[12] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

These doses would be the equivalent to 4, 6, 8, 10 and 12 mg/kg/qd, respectively, for a standard adult body weight of 70 kg.

As daptomycin shows concentration-dependent activity, the best indicator of its efficacy is the ratio of the area under the plasma concentration-time curve over 24 hours divided by the MIC (AUC_{24h}/MIC)[13,14]. High probabilities of success are achieved when total-drug $AUC_{24h}/MIC \geq 666$[15].

In patients without CRRT, different Clcr values (ranging from 10 to 130 mL/min) were evaluated for the calculation of the PTAs. In patients receiving CRRT, Clcr values from 0 to 30 were included and CL_{EC} was also contemplated. The latter was estimated from the Sc measured in patients (0.2 ± 0.05) and considering 2 different Q_{ef} values (1.5 and 2.5 L/h, close to the lower and upper flows applied to these patients). Simulations were performed using the mlxR package on R 3.4.0[16].

Calculation of the cumulative fraction of response (CFR)

CFR is defined as the expected population PTA for a specific drug dose and a specific population of microorganisms[17]. It allows us to determine the probability of a favourable outcome for a treatment taking into account the PTA for each MIC

[13] Louie A, Kaw P, Liu W, Jumbe N, Miller MH, Drusano GL. Pharmacodynamics of daptomycin in a murine-thigh model of *Staphylococcus aureus* infection. Antimicrob Agents Chemother. 2001;45:845–51.

[14] Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother. 2004;48:63–68.

[15] Canut A, Isla A, Betriu C, Gascón AR. Pharmacokinetic-pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. Eur J Clin Microbiol Infect Dis. 2012;31(9):2227-35.

[16] Lavielle M. mlxR: Simulation of Longitudinal Data. R package version 3.2.0. 2016. Available at: *https://CRAN.R-project.org/package=mlxR*. [Accessed: Dec 2017].

[17] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/ pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005;55(5):601-7.

value and the MIC distribution of the bacterial population, when the susceptibility of a clinical pathogen is unknown.

Susceptibility data of all isolates from ICU inpatients at Araba University Hospital from January 2013 to December 2015 was used to calculate CFR values for *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus epidermidis*, *Staphylococcus aureus* and Coagulase negative staphylococci (**table 2**). The susceptibility data was managed with Whonet[18] and the same scenarios as for estimating the PTA were evaluated.

For both PTA and CFR, values greater than or equal to 90% were considered optimal, while values lower than 90% but higher than 80% were linked to moderate probabilities of success[19].

Table 2. MIC distributions for daptomycin for *E. faecium*, *E. faecalis*, *S. epidermidis*, *S. aureus* and coagulase-negative staphylococci (CoNS) at Araba University Hospital from January 2013 to December 2015.

Microorganism	Clinical break point MIC (mg/L) [a]	no. of isolates	% of strains inhibited at a MIC (mg/L) of					
			0.5	1	2	4	8	16
Enterococcus faecium	4	18		17	38	39	6	
Enterococcus faecalis	4	52	21	60	15	2		2
Staphylococcus epidermidis	1	18		100				
Staphylococcus aureus	1	58	26	74				
CoNS	1	63	2	94	2		2	

[a] According to the Clinical and Laboratory Standard Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

[18] WHONET 5.6. Available at: *http://www.who.int/medicines/areas/rational_use/AMR_WHONET_SOFTWARE/en/* [Accessed: May 2018].

[19] Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J. 2003;22(11):982-92.

2.4.2. Safety evaluation

Estimation of minimum concentration at steady-state ($Cmin_{ss}$)

The percentage of simulated patients that would reach plasma concentrations considered toxic ($Cmin_{ss}$ ≥ 24.3 mg/L)[20] was calculated to analyse safety profile by mxlR package in R[16].

3. Results

Sixteen critically ill patients, described in **table 1**, were included in the study (four of them underwent CRRT). Five plasma samples per patient were analysed, six when administering daptomycin every 48 hours. In patients undergoing CRRT, the same amount of effluent samples were collected. The patients suffered from sepsis (n = 5), SSTI (n = 3), abdominal infections (n = 3), bacteraemia (n = 2) or other infections (n= 3).

The four patients subjected to CRRT underwent continuous venovenous hemodiafiltration. The blood flow rate was maintained between 150 and 180 mL/min and the effluent flow between 1,600 and 2,550 mL/h and replaced as clinically indicated. A negative water balance was maintained, from 50 to 200 mL/h.

[20] Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis. 2010;50(12):1568-74.

3.1. Population pharmacokinetic model

3.1.1. Base model

Plasma concentrations (in log scale) were best described by a one-compartment model, characterized by drug total body clearance (CL) and apparent volume of distribution (V). The fit was verified by GOF plots (**Figure 1**). IIV was included exponentially for total CL and V, and no correlation was detected between them.

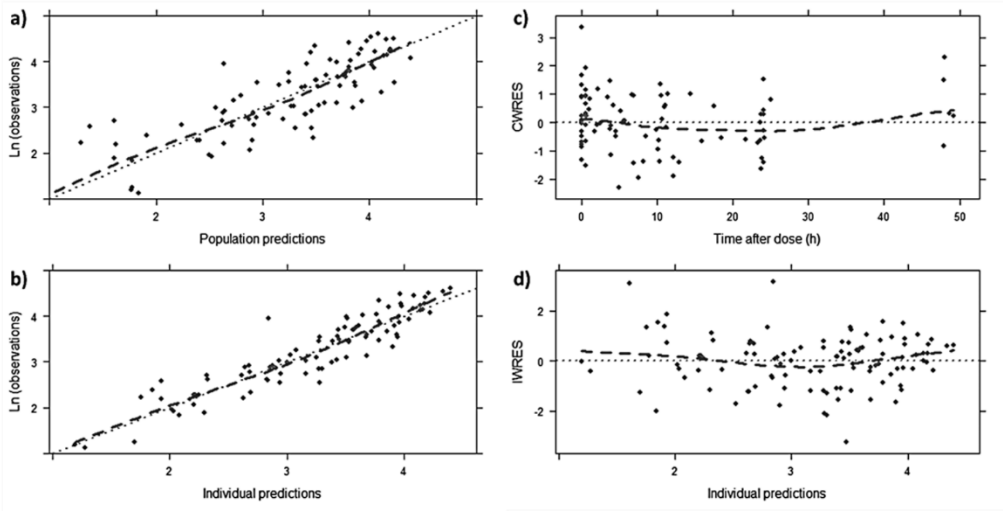

Figure 1. GOF plots obtained for the final model: Population predictions (PRED)[(a)] and individual predictions (IPRED)[(b)] against dependent variable (logarithmic transformation of observed daptomycin plasma concentrations, DV, μg/mL); conditional weighted residuals (CWRES) versus time after dose (h)[(c)] and the individual weighted residuals (IWRES) versus individual predictions[(d)].

3.1.2. Covariate selection

The CL of daptomycin resulted in the sum of a non-renal (CL_{NR}) and a renal clearance (CL_R), dependent on Clcr. In subjects undergoing CRRT, their own CL_{EC}

was included in the total CL. The inclusion of Clcr in the CL halved the unexplained IIV in CL (from 75% to 37%). SCM results confirmed these findings. No other covariate turned out to be relevant for inclusion in the model.

3.1.3. Model evaluation

GOF plots (**Figure 1**) showed no relevant trend in CWRES along TAD or IWRES along individual predictions. Likewise, they displayed a good correlation between population or individual prediction against the dependent variable. Moreover, RSE (%) and bootstrap results showed that parameters were accurately estimated (**table 3**). In addition, pvcVPC (**Figure 2**) also demonstrated a good correlation between raw data and data obtained by simulation with the final model.

Table 3. Base and final population pharmacokinetic models estimates, shrinkage[a] values and bootstrap results for daptomycin after short-term intravenous infusion.

Parameter	Base model	Final model	Bootstrap
	Estimate, RSE (%)	Estimate, RSE (%)	median (5^{th}-95^{th} percentile)
CL (L/h) = CL_{NR} + CL_R+CL_{EC}[b]	0.491 (21) +CL_{EC}		
CL_{NR}		0.16 (54)	0.160 (0.013-0.324)
CL_R = θ x (Clcr/49)		0.367 (20)	0.366 (0.239-0.527)
V(L)	12.50 (13)	12.30 (13)	12.31 (10.10-15.13)
IIV_{CL} (%)	74.6 (29)	36.7 (30)	32.5 (17.7-54.4)
IIV_{V} (%)	35.4 (25)	27.8 (30)	27.0 (11.9-42.8)
Residual error_additive (log-scale)	0.110	0.123 (17)	0.114 (0.086-0.153)

[a] $CL\eta sh$ = 30%; $V\eta sh$ = 10%; εsh = 11%

[b] Only for patients undergoing CRRT. The individual value of CL_{EC} was considered.

CL: clearance; CL_{NR}: no-renal clearance; CL_R: renal clearance; CL_{EC}: extra-corporeal clearance; Clcr: creatinine clearance; V: volume of distribution; CRRT: continuous renal replacement therapies; IIV: inter-individual variability. RSE: relative standard error; ηsh: shrinkage value for a parameter; εsh: shrinkage value for the residual error.

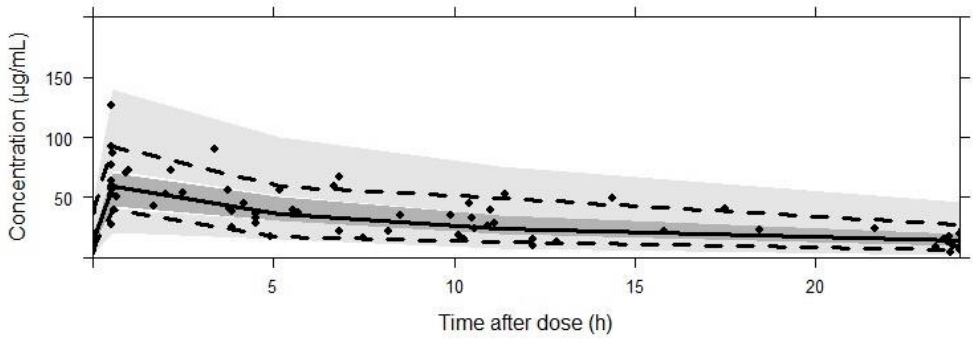

Figure 2. Results from the pvc-VPC from 0 to 24 h after dose. Dots correspond to the prediction-corrected observed concentrations (µg/mL). The continuous line represents the median, while the dashed lines correspond to the 2.5th and 97.5th observed percentiles. Simulation-based 90% CIs for the median and both 2.5th and 97.5th percentiles are displayed by dark and light grey shading, respectively.

3.2. Monte Carlo simulation

3.2.1. Pharmacokinetic/pharmacodynamic analysis

Probability of target attainment (PTA)

Table 4 shows the probability of achieving the target value for the PK/PD index (AUC_{24h}/MIC ≥ 666) for the simulated scenarios. Overall, the higher the dose and the lower the Clcr, the higher the PTA. For the same Clcr, lower probabilities of success were obtained in patients undergoing CRRT. In all simulated patients, the 280 mg/qd dose appears to be enough to cover infections caused by microorganisms with MICs ≤ 0.25 mg/L. For MICs of 1 mg/L, PTA values greater than 90% were obtained with the highest dose (840 mg/qd), except for patients with Clcrs of 130 mL/min. Infections caused by microorganisms with MICs ≥ 4 mg/L would be never covered by daptomycin.

Table 4. PTA values (%) of daptomycin. Bold values represent PTA ≥ 90%. Italics correspond to PTA ≥ 80%.

Dose/day	Clcr (mL/min)	No CRRT					CRRT									
							Q_{ef} **1.5** L/h					Q_{ef} **2.5** L/h				
280 mg	0						**100**	**100**	35	1	0	**100**	*89*	5	0	0
	10	**100**	**100**	**99**	38	5	**100**	**99**	18	0	0	**100**	73	3	0	0
	30	**100**	**100**	61	12	2	**100**	*84*	6	0	0	**100**	40	1	0	0
	60	**100**	*86*	21	4	1										
	90	**100**	52	10	2	1										
	130	**91**	25	5	2	1										
420 mg	0						**100**	**100**	**96**	8	0	**100**	**100**	40	1	0
	10	**100**	**100**	**100**	*83*	18	**100**	**100**	*80*	4	0	**100**	**100**	25	0	0
	30	**100**	**100**	**96**	32	6	**100**	**100**	38	1	0	**100**	**97**	10	0	0
	60	**100**	**100**	55	11	2										
	90	**100**	**93**	26	5	2										
	130	**100**	63	13	3	1										
560 mg	0						**100**	**100**	**100**	35	1	**100**	**100**	*89*	5	0
	10	**100**	**100**	**100**	**99**	38	**100**	**100**	**99**	18	0	**100**	**100**	73	3	0
	30	**100**	**100**	**100**	61	12	**100**	**100**	*84*	6	0	**100**	**100**	40	1	0
	60	**100**	**100**	86	21	4										
	90	**100**	**100**	52	10	2										
	130	**100**	**91**	25	5	2										
700 mg	0						**100**	**100**	**100**	75	3	**100**	**100**	**99**	17	0
	10	**100**	**100**	**100**	**100**	64	**100**	**100**	**100**	47	1	**100**	**100**	**97**	10	0
	30	**100**	**100**	**100**	85	20	**100**	**100**	**99**	18	1	**100**	**100**	*80*	3	0
	60	**100**	**100**	**98**	36	7										
	90	**100**	**100**	80	17	4										
	130	**100**	**99**	43	8	2										
840 mg	0						**100**	**100**	**100**	**96**	8	**100**	**100**	**100**	40	1
	10	**100**	**100**	**100**	**100**	*83*	**100**	**100**	**100**	*80*	4	**100**	**100**	**100**	25	0
	30	**100**	**100**	**100**	**96**	32	**100**	**100**	**100**	38	1	**100**	**100**	**97**	10	0
	60	**100**	**100**	**100**	55	11										
	90	**100**	**100**	**93**	26	5										
	130	**100**	**100**	63	13	3										
MIC (mg/L)		**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**

Cumulative fraction of response (CFR)

Table 5 features calculated CFR values. None of the dosing regimens provided high probabilities of success for infections caused by *E. faecium*. In the case of *E. faecalis*, doses ≥ 560 mg may provide CFR values ≥ 90%, as far as patients show Clcr values ≤ 30 mL/min and they do not undergo CRRT. For the rest of microorganisms, CFRs would only reach values related to efficacy in some situations, which would depend on the dose, Clcr and, when CRRT are applied, on CL_{EC}.

3.2.2. Safety evaluation

Minimum concentration at steady-state ($Cmin_{ss}$)

Table 6 shows the probability of achieving daptomycin $Cmin_{ss} \geq 24.3$ mg/L, associated with toxicity. For the same Clcr value, the probability of reaching concentrations related to toxic events is much lower in patients undergoing CRRT. It is remarkable that in patients without CRRT and Clcr ≤ 30 mL/min, high probabilities of reaching $Cmin_{ss}$ greater than 24.3 mg/L were obtained even with the lowest dose. In patients undergoing CRRT, the probability of reaching concentrations related to toxicity is considerably higher in subjects with an effluent flow of 1.5 L/h.

Table 5. CFR values (%) of daptomycin for different bacteria taking into consideration frequency distributions of MICs in Araba University Hospital, from January 2013 to December 2015. Bold values represent CFR ≥ 90%. Italics correspond to CFR ≥ 80%.

		Dose (mg/day) **No CRRT**					**Dose** (mg/day) **CRRT**									
							Q_{ef} 1.5 L/h					**Q_{ef} 2.5** L/h				
Bacteria	**Clcr** (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
Enterococcus faecium	0						6	20	31	47	58	1	7	17	24	33
	10	34	57	71	*81*	*89*	3	15	24	36	50	0	4	14	20	27
	30	16	31	46	58	67	1	7	17	24	32	0	2	7	15	20
	60	6	14	25	34	43										
	90	3	7	14	21	28										
	130	2	4	7	11	17										
Enterococcus faecalis	0						42	*80*	*86*	**92**	**96**	22	45	75	*83*	*87*
	10	*86*	**94**	**97**	**97**	**98**	32	70	*83*	*88*	**93**	17	36	65	*81*	*85*
	30	60	*84*	**90**	**94**	**96**	21	44	72	*83*	*87*	9	26	45	69	*81*
	60	31	55	76	*85*	*89*										
	90	17	36	54	70	*81*										
	130	9	21	35	48	61										
Staphylococcus epidermidis	0						35	**96**	**100**	**100**	**100**	5	40	*89*	**99**	**100**
	10	**99**	**100**	**100**	**100**	**100**	18	*80*	**99**	**100**	**100**	3	25	73	**97**	**100**
	30	6	**96**	**100**	**100**	**100**	6	38	*84*	**99**	**100**	1	10	40	*80*	**97**
	60	21	55	*86*	**98**	**100**										
	90	10	26	52	*80*	**93**										
	130	5	13	25	43	63										
Staphylococcus aureus	0						52	**97**	**100**	**100**	**100**	27	56	**92**	**100**	**100**
	10	**99**	**100**	**100**	**100**	**100**	39	*85*	**100**	**100**	**100**	21	44	*80*	**98**	**100**
	30	71	**97**	**100**	**100**	**100**	26	54	*88*	**99**	**100**	11	33	55	*85*	**98**
	60	38	66	**90**	**98**	**100**										
	90	21	44	64	*83*	**95**										
	130	10	26	43	58	73										
Coagulase negative staphylococci	0						36	**93**	**98**	**98**	**99**	7	40	*86*	**97**	**98**
	10	**96**	**99**	**99**	**99**	**99**	19	78	**97**	**98**	**99**	4	26	72	**95**	**97**
	30	61	**94**	**98**	**99**	**99**	7	38	82	**96**	**98**	2	11	40	78	**94**
	60	22	54	*84*	**96**	**98**										
	90	11	27	52	76	**91**										
	130	5	13	26	43	63										

Table 6. Probability of attaining $Cmin_{ss}$ values ≥ 24.3 mg/L (%).

	Dose (mg/day) **No CRRT**					**Dose** (mg/day) **CRRT**									
						Q_{ef} 1.5 L/h					**Q_{ef} 2.5** L/h				
Clcr (mL/min)	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**	**280**	**420**	**560**	**700**	**840**
0						12	45	75	88	94	2	8	21	38	54
10	87	98	99	100	100	6	26	51	72	83	1	4	12	24	38
30	38	67	84	92	96	2	8	21	36	50	0	2	5	10	17
60	12	25	39	52	63										
90	6	11	18	25	33										
130	3	6	9	12	15										

4. Discussion

In this study we have developed a population PK model of daptomycin for critically ill patients. This model has been applied to estimate the adequacy of different dosing regimens considering PK and PD criteria. To the best of our knowledge, this is the first population PK model that includes critically ill patients with and without CRRT, allowing for the observation of the effect of these continuous renal therapies on drug PK behaviour.

The PK of daptomycin has been previously described by both one[21,22,23] and two-compartment models[24,25,26]. In our study, plasma concentrations vs. time data was entered into a one-compartment model, as no improvement was found when applying a two-compartment model. The daptomycin elimination included both non-renal and renal clearance, the latter being conditioned by patients' Clcr. The influence of Clcr in daptomycin clearance has been widely documented before, and the high intrinsic inter-individual variability obtained in the final model developed for this parameter (IIV_{CL} = 37%) was consistent with studies published previously on critically ill patients[22,27].

Regarding patients undergoing CRRT, their own CL_{EC} value was included in the total body clearance equation, as daptomycin is partially eliminated by CRRT[28]. Mean CL_{EC} observed in the present study (0.43 L/h) was similar to that

[21] Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother. 2004;48(8):2799-807.

[22] Di Paolo A, Tascini C, Polillo M, Gemignani G, Nielsen EI, Bocci G, et al. Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. Int J Antimicrob Agents. 2013;42(3):250-5.

[23] Pai MP, Russo A, Novelli A, Venditti M, Falcone M. Simplified Equations Using Two Concentrations To Calculate Area under the Curve for Antimicrobials with Concentration-Dependent Pharmacodynamics: Daptomycin as a Motivating Example. Antimicrob Agents Chemother. 2014;58(6):3162-7.

[24] Aikawa N, Kusachi S, Mikamo H, Takesue Y, Watanabe S, Tanaka Y, et al. Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. J Infect Chemother. 2013;19(3):447-55.

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obtained in previous studies[29,30], which was nearly half of the mean daptomycin total CL shown in healthy volunteers (around 1 L/h)[21]. Therefore, the proportion of drug eliminated by extracorporeal techniques should be considered for dosing optimisation.

It is well known that in critically ill patients drug distribution volumes are usually higher than in healthy volunteers, as a consequence of oedema, sepsis, decreased protein binding or liquid overload, to name a few. Moreover, due to the great heterogeneity observed among these patients, high inter-individual variability is detected[7]. In this regard, the distribution volume obtained in this study (12.3 L) is slightly higher than that observed in healthy volunteers and consistent with the distribution volume of daptomycin in critically ill patients reported by Di Paolo et al.[22] and Falcone et al.[31] (12.9 L and 11.5 L, respectively).

The inclusion of patients' weight as a covariate did not improve the population PK model. This could be due to the small cohort size of the evaluated population, which might be the main limitation of this research paper. However, our findings are in accordance with other studies, where no relationship was found between weight and daptomycin CL or V[22,31].

Integrated PK/PD analysis and Monte Carlo simulation is a very useful tool that allows us to optimise regimen dosing of antibiotics[32]. Considering the population model and the PK/PD analysis performed in this study, the selection of the most suitable daptomycin dose should be based not only on the susceptibility

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of the bacteria responsible for the infection, but also on the pharmacokinetic profile.

According to the simulations performed in this study, the approved dosage regimens of daptomycin (4 and 6 mg/kg/qd, which would be equivalent to 280 and 420 mg/qd for a standard adult body weight of 70 kg) would be insufficient to treat infections caused by microorganisms with MICs ≥ 4 mg/L, the clinical breakpoint determined for enterococci by the Clinical and Laboratory Standard Institute (CLSI)[33] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[34]. Moreover, these dose levels would cover infections caused by microorganism with MICs of 1 mg/L (the clinical breakpoint for streptococci and staphylococci) when patients' Clcr is ≤ 30 mL/min and are not subjected to CRRT. These results are consistent with previous studies, which conclude that authorized daptomycin dosages usually seem to be insufficient for critically ill patients[22,25,35]. In fact, in 2011, the Infectious Diseases Society of America (IDSA) guidelines recommended daily doses of daptomycin of 8-10 mg/kg in cases of endocarditis due to MRSA or complicated bacteraemia, and 10 mg/kg/qd, in combination with other antimicrobials, for persisting bacteraemia during treatment and/or failing vancomycin treatment[36]. This has been also observed by García de la Maria et al. in an experimental rabbit model for methicillin-resistant *Staphylococcus epidermidis* (MRSE) endocarditis[37].

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[35] Senneville E, Caillon J, Calvet B, Jehl F. Towards a definition of daptomycin optimal dose: Lessons learned from experimental and clinical data. Int J Antimicrob Agents. 2016;47(1):12-9.

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[37] García-de-la-María C, Marco M, Armero Y, Soy D, Moreno A, Del Río A, et al. Daptomycin is effective for treatment of experimental endocarditis due to methicillin-resistant and glycopeptide-Intermediate *Staphylococcus epidermidis*. Antimicrob Agents Chemother 2010;54(7):2781-6.

In this study, daptomycin was administered as empirical treatment and, in the majority of the patients, microorganisms susceptible to this antibiotic were not found. This is why, susceptibility data of isolates in Araba University Hospital ICU inpatients was used to calculate CFR values (**table 5**). Daptomycin did not prove to be useful for infections caused by *E. faecium*. For the other microorganisms, the dose required to reach high CFR values would vary, depending on the patients' Clcr or whether they were undergoing CRRT or not. In this regard, we should bear in mind that sensitivity may vary over time and between countries as well as between areas or health centres[31].

Selecting the most favourable dosage for an antimicrobial requires not only maximising efficacy, but also minimising side effects or toxicity. For this antibiotic $Cmin_{ss}$ values above 24.3 mg/L have been associated with creatinine-phosphokinase (CPK) elevations, which may precede daptomycin-related muscle toxicity[20]. Therefore, increasing the daptomycin dosage may lead not only to increased efficacy, but also to higher probabilities of achieving toxicity related drug concentrations. However, we should also bear in mind that it is not only dosage that would compromise toxicity, but also the patients' characteristics that influence the drug's PK. As an example, **table 6** shows that the probabilities of reaching $Cmin_{ss} \geq 24.3$ mg/L in critically ill patients are higher when administering 280 mg/qd to patients with Clcr values of 10 mL/min (87%) or 30 mL/min (38%), than in those subjects with a Clcr value of 130 mL/min receiving 840 mg/qd (15%). Based on these results, simulations considering the administration of daptomycin every 48 h were performed. PTA values higher than 90% for MICs of 1 mg/L were obtained only for patients without CRRT and Clcr ≤ 30 mL/min (data not shown). The results revealed that when administering 560 mg/q48h (if CLcr is 10 mL/min) or 840 mg/q48h (if CLcr is 30 mL/min), the probability of reaching $Cmin_{ss}$ levels ≥ 24.3 mg/L are 65% and 39%, respectively. These values are lower than those obtained for the same daily dose administered in a 24 h regimen (280 and 420 mg/qd), but still compromise safety.

Even though CPK levels are considered to be a sensitive marker of musculoskeletal damage related to daptomycin, it has recently been questioned whether high dosages are linked to a greater risk of elevated CPK, as no significant differences were found between standard and higher dosages[35]. Moreover, another study in healthy volunteers concluded that a daptomycin dosage of 12 mg/kg once daily for 14 days was well tolerated, as no evidence of adverse effects were recorded[4]. Although in this study 3 patients had a $Cmin_{ss}$ value ≥ 24.3 mg/L, none of them, nor the other 13, experienced an increase in CPK levels (**table 1**).

According to the results obtained in this study and considering that the MIC values of the majority of isolated bacteria were ≥ 1 mg/L, standard antibiotic dosages would not be appropriate to treat patients with Clcr values ≥ 60 mL/min. Patients with Clcr values between 60 and 90 mL/min would require 700 mg/qd, while 840 mg/qd should be administered to patients with higher Clcr. Although higher probabilities of success are expected in subjects with Clcr ≤ 30 mL/min, probabilities of reaching concentrations of daptomycin linked to toxicity are high. Therefore, the risk-benefit balance of the therapy should be studied. For patients undergoing CRRT, the dosage should be at least 560 mg/qd, although it would depend on the CL_{EC} (conditioned by Sc and Q_{ef}).

It also needs to be taken into consideration that when the MIC value of the bacteria is available or when susceptibility distribution data in a hospital or area is known, dosing regimens should be determined considering this information.

5. Conclusions

A population PK model has been developed for daptomycin in critically ill patients. Data best suited a one-compartment model. Drug CL depended on Clcr, and in patients undergoing CRRT, CL was also dependent on the CL_{EC}. The influence of the patient's characteristics on the PK profile was related to differences in the estimated probabilities of success and toxicity. Therefore, individualization of daptomycin therapy is advisable to improve the success of therapy and reduce toxicity. The probability of reaching toxic concentrations was highly dependent on the CL, and not only on the dose.

Chapter 3

Population pharmacokinetics of linezolid in critically ill patients

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ABSTRACT: Linezolid has a broad-spectrum activity against mycobacteria and most Gram-positive bacteria, and it is widely use in Intensive Care Units. The aim of this study was to develop a population pharmacokinetic model for linezolid in critically ill patients and to carry out a PK/PD analysis to estimate the probability of success of the therapy. A total of 41 critically ill patients were included in the population pharmacokinetic model, 23 of whom were subjected to CRRT. All of them received standard doses of linezolid (600 mg/12h). Blood and, when necessary, effluent samples were drawn after linezolid administration at previously defined time points. A population approach using NONMEM 7.3 was performed to analyse data. The pharmacokinetics of linezolid was best described by a two-compartment model. Elimination was conditioned by the creatinine clearance (Clcr) and by the extra-corporeal clearance when undergoing CRRT. Monte Carlo simulations were executed to evaluate the suitability of the standard dose and 600 mg/8h. The probabilities of achieving the PK/PD target value associated with treatment success (AUC_{24h}/MIC > 80) and to reach linezolid concentrations linked to toxicity (through concentration > 10 mg/L and AUC_{24h} > 400 mg*h/L) were calculated. The standard dose of linezolid was not able to cover infections caused by pathogens with MIC ≥ 2 mg/L. The probability of target attainment did not substantially improve with 600 mg every 8h, but increased the probability of reaching drug concentrations linked to toxicity. Continuous infusion may improve patients' outcome, especially if they renal function is conserved (Clcr≥ 60 mL/min).

1. Introduction

Linezolid, an oxazolidinone derivative, is an antibiotic with a broad spectrum of activity against mycobacteria and most Gram-positive bacteria, such as staphylococci, streptococci and enterococci. It is an antimicrobial that has shown activity towards methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE)[1,2]. This hospital drug is commonly employed in intensive care units (ICU) to manage pneumonia, skin and soft tissue infections or bacteraemia, since about 50% of bloodstream infections in critically ill patients are caused by Gram-positive bacteria, which are frequently multi-drug resistant strains (e.g. MRSA and VRE)[3,4].

Selecting the optimal antimicrobial posology becomes quite a challenge when treating infections in critically ill patients. On the one hand, because they are commonly subjected to aggressive medical interventions, such as mechanical ventilation or renal replacement techniques. On the other hand, as a result of several pathophysiological alterations that may occur and contribute to changes in the volume of distribution (V) or in the clearance (CL) (e.g. acute kidney injury or hypoalbuminemia). Moreover, these patients are likely to have higher

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[2] Ryvak MJ, Akins RL. Emergence of methicillin-resistant *Staphylococcus aureus* with intermediate glycopeptide resistance: clinical significance and treatment options. Drugs. 2001; 61:1-7.

[3] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

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pharmacokinetic (PK) variability and therefore, it becomes difficult to select the optimal dose, leading to sub-optimal patient outcomes in some cases[5,6].

Acute kidney injury (AKI) is one of the most common pathological conditions in the ICU, ranging from 30 to 60% of hospitalised subjects. Continuous renal replacement therapies (CRRT) are frequent procedures for AKI treatment, estimating that around 5% of the ICU patients undergo these techniques[7,8,9]. CRRT not only participate in the clearance of endogenous compounds, but also help eliminate drugs administered to patients. In this way, many antibiotics are significantly eliminated by these techniques, which should be taken into consideration to minimise the risk of underdosing and therapeutic failure or emergence of resistance.

There are many factors that are able to condition extracorporeal clearance (CL_{EC}), such as the volume of distribution or protein binding of the drug, the permeability of the membrane, the effluent flow, or the CRRT modality itself, among others[10]. All these factors contribute to the considerable variability observed in antibiotic concentrations in critically ill patients with CRRT[11]. Although only around a 30% of unchanged linezolid is eliminated through the

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[11] Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med. 2012; 40(5):1523-8.

kidneys, it has low protein binding (≈ 30% in healthy volunteers) and a low molecular weight (337.45 g/mol); thus, it is likely to be eliminated by these techniques, especially with high-flux membranes[12].

An improvement in clinical cure and survival has been described when pharmacokinetic/pharmacodynamic (PK/PD) targets are applied for antibiotic treatment optimisation procedures[13,14]. Therefore, the aim of this study was to develop a population pharmacokinetic model for linezolid in critically ill patients to quantify and identify the causes of PK variability, also studying the influence of CRRT. A secondary objective was to carry out a PK/PD analysis by Monte Carlo simulation to evaluate the probability of achieving efficient concentrations and safety-related profiles with the standard dose of linezolid (600 mg/12 h) and to propose new dosage regimens when necessary.

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[14] Tängdén T, Ramos Martín V, Felton TW, Nielsen EI, Marchand S, Brüggemann RJ, et al. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. Intensive Care Med. 2017;43(7):1021-32.

2. Patients and methods

2.1. Study design and settings

An open-label prospective multicentre study was performed in the intensive care unit (ICU) of three Spanish hospitals: Araba University Hospital (Vitoria-Gasteiz), Doce de Octubre University Hospital (Madrid) and Joan XXIII University Hospital (Tarragona). The protocol was approved by the Basque Clinical Research Ethics Committee (EPA2014025) and the Spanish Agency of Medicinal Products and Medical Devices (FJM-LIN-2012-01). All subjects, or their legal representatives, had previously signed a written informed consent. Patients were eligible for inclusion if i) they were admitted to the ICU; ii) they suffered from an infection probably caused by a Gram-positive microorganism and, therefore, were treated with linezolid; iii) they gave informed consent; and iv) it was possible to obtain plasma samples and also effluent samples from the extracorporeal device when undergoing CRRT. The exclusion criteria were age < 18 years, pregnancy, hypersensitivity to linezolid or any of the excipients and being on any medicinal product which inhibits monoamine oxidase A or B.

Table 1 displays demographic and biochemical data for the patients. The APACHE II health score (Acute Physiology and Chronic Health Evaluation II) has also been included. Creatinine clearance (Clcr) was estimated for each patient using the following equation: Clcr (mL/min) = (Cr_u x V_u)/ (Cr_p x 600 min), where Cr_p was the plasma creatinine concentration (mg/dL), Cr_u was the concentration of creatinine in urine (mg/dL) and V_u was the total urine volume (mL) collected in 10 h.

The fraction of the drug eliminated across the membrane during CRRT, known as sieving coefficient (Sc), was calculated as the ratio of the linezolid area under the effluent concentration curve (AUC_{ef}) to the area under the plasma

concentration curve (AUC_P) over the dosage interval. Extracorporeal clearance for linezolid was set as Sc times effluent flow (Q_{ef}).

Table 1. Hospital, demographic and biochemical data of the 41 patients and their APACHE II health score. AUH: Araba University Hospital; DOUH: Doce de Octubre University Hospital; JUH: Joan XXIII University Hospital; CRRT: continuous renal replacement therapies; BMI: body mass index; Clcr: creatinine clearance; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; CL_{EC}: extracorporeal clearance; CVVHDF: continuous venovenous hemodiafiltration; CVVHD: continuous venovenous haemodialysis.

	No CRRT		CRRT	
Patient characteristic	**n**	**Median (Range)**	**n**	**Median (Range)**
Hospital				
AUH	18		9	
DOUH	0		13	
JUH	0		1	
Demographic data				
Age (years)		72 (22-85)		68 (37-79)
Gender (M/F)	14/4		16/7	
Body weight (kg)		71 (60-95)		74 (55-110)
Height (m)		1.70 (1.60-1.85)		1.69 (1.53-1.85)
BMI (kg/m^2)		24.5 (20.8-31.3)		25.9 (21.2-33.1)
Biochemical data				
Clcr (mL/min)		71.2 (11.0-179.5)		6.0 (0.0-45.6)
Creatinine (mg/dL)		0.80 (0.40-2.10)		1.15 (0.56-2.60)
Glucose (mg/dL)		144 (73-187)		140 (69-210)
Haemoglobin (g/dL)		9.85 (7.00-15.50)		8.50 (6.70-11.40)
Haematocrit (%)		30.5 (20.0-46.0)		26.4 (18.7-34.7)
Albumin (g/dL)		2.8 (1.9-4.0)		2.2 (1.7-3.6)
Total proteins (g/dL)		5.8 (4.2-7.4)		5.2 (2.7-7.3)
Bilirubin (mg/dL)		0.65 (0.20-1.30)		0.80 (0.12-2.60)
GPT (U/L)		25 (6-340)		50 (5-570)
GOT (U/L)		33 (16-330)		43 (8-675)
APACHE II		16 (11-36)		22 (16-34)
CL_{EC} (L/h)			23	2.51 (0.79-3.09)
CVVHDF			18	2.61 (0.79-3.09)
CVVHD			5	1.06 (1.00-2.73)

2.2. Drug administration and sampling procedure

Each patient was administered 600 mg dose of linezolid (Zyvoxid®) every 12 hours by intravenous infusion over 30 min, except for one subject, whose perfusion lasted 60 min. In order to ensure steady-state linezolid concentrations, a mean of 8 doses was administered before starting sample collection. Blood samples were drawn at predose, end of infusion (0.5 h) and at 1, 2, 3, 6, 8 to 10 and 12 hours. They were drawn into sodium heparin Vacutainer™ tubes and centrifuged at 3,000 rpm for 10 min to harvest the plasma. Samples were immediately frozen at - 80º C until they were analysed. For patients undergoing CRRT, effluent samples were taken at the same times and stored straight away at - 80º C.

2.3. Analytical method

All collected samples were analysed using a previously validated high-performance liquid chromatography (HPLC) technique with ultraviolet detection (**appendix 1**). Plasma sample preparation consisted of a protein precipitation step with acetonitrile, where the internal standard (propyl-4-hydroxybenzoate) had been previously diluted. Afterwards, they were centrifuged (10 min at 15,000 rpm) and the supernatants were injected into the HPLC system. On the other hand, effluent samples were directly injected in the system and analysed. Separation was performed on a Symmetry® C8 column (4.6 mm x 150 mm x 5 μm). Linearity in plasma was established over the expected concentration range from 0.5 to 50 μg/mL, whereas for the effluent samples it was set from 0.2 to 30 μg/mL. The linezolid standard for quantification was kindly provided by Pfizer Pharmaceuticals.

Both intra and inter-day accuracy and precision assays were settled at the limit of quantification (0.5 and 0.2 μg/mL for plasma and effluent, respectively) and at three concentration levels in the linearity range: 1.5, 10 and 40 μg/mL for plasma, and 0.6, 5 and 24 μg/mL for the effluent samples. Calculated concentration

did not deviate more than 15% from nominal concentration. Moreover, intra and inter-day coefficient of variation was never above 15%.

2.4. Population pharmacokinetic model

2.4.1. Base model

Nonlinear mixed-effects modelling was implemented by NONMEM 7.3[15] to estimate linezolid PK population parameters using first-order conditional estimation method with interaction (FOCE + I). Compartmental models were used to explain the disposition of the total drug plasma concentrations. Logarithmical data transformation was considered. The model selection was based on the decrease in objective function value (OFV), the relative standard errors (RSE) of the parameters and the goodness-of-fit (GOF) plots. Residual error was shaped, and inter-individual variabilities (IIV) and possible covariance were also explored.

2.4.2. Covariate selection

Once the base model was selected, and in order to describe interindividual variability, all factors described in **table 1** were studied as potential covariates. When a covariate value was missing in five or less patients, the median of the rest of individuals was assigned to these subjects. Clcr was studied as a continuous covariate. Moreover, patients were categorised in five groups, regarding their Clcr: < 10 mL/min, ≥ 10 but < 30 mL/min, ≥ 30 but < 60 mL/min, ≥ 60 but < 130 mL/min and Clcr ≥ 130 mL/min. Furthermore, 3 more dichotomous covariates were created, depending whether patients included in the study had or not, one, two or three of the following biochemical parameters out of the normal range: bilirubin (normal

[15] Beal S, Sheiner, LB, Boeckmann, A, Bauer RJ. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

range: 0.3-1.9 mg/dL), GOT (normal range: 8-30 UI/L for males and 6-25 UI/L for females) and GPT (normal range: 8-35 UI/L for males and 6-25 UI/L for females).

Stepwise covariate model building was used (SCM tool in PsN 4.7.0) to identify covariate candidates. During the forward inclusion and backward deletion, $p<0.05$ and $p<0.01$ levels of significance were used, respectively. GOF plots were also used to confirm whether different models performed satisfactorily.

2.4.3. Model evaluation

GOF plots were analysed to describe the suitability of the final model. The GOF plots being assessed were individual and population predictions versus observations, the conditional weighted residuals (CWRES) against time after dose and the individual weighted residuals (IWRES) versus individual predictions.

Moreover, a VPC was built to explore the performance of the selected model (VPC tool in PsN 4.7.0). Thus, the 2.5th, 50th and 97.5th percentiles for observed data were plotted. Afterwards, a 1,000 sample dataset was simulated from the final model parameter estimates, and the 95% confidence intervals for the simulated 2.5th, 50th and 97.5th percentiles were represented for visual inspection, using the xpose4 package in R 3.4.0[16]. Additionally, parameter precision was evaluated by performing a 2,000 dataset bootstrap (Bootstrap tool in PsN 4.7.0). During the whole model estimation and population pharmacokinetics analysis, Pirana v.2.9.5 software was used to handle the model development process[17].

[16] Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. 1999;58(1):51-64.

[17] Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72-9.

2.4.4. External validation

A total of 44 plasma samples, collected from a separate group of 11 critically ill patients, were used for the external validation. Data was obtained prospectively from a study conducted at Araba University Hospital. Apart from the abovementioned inclusion criteria, only patients with Clcr > 40 mL/min and not undergoing CRRT were admitted to this study. **Table 2** shows demographic and biochemical data for the patients, plus the APACHE II health score. This data was compared against data from the 41 patients being included to develop the population PK model, to detect significant differences among the two groups. For continuous covariates, a t-test or Mann–Whitney U test was performed, regarding whether they were normally distributed or not. Concerning categorical data, Pearson's chi-squared test (χ^2) was applied. IBM SPSS statistic® programme (version 21) was used[18].

Patients included in the external validation study were administered 1,200 mg/qd (*quaque die*, per day) linezolid by intravenous continuous perfusion after a 600 mg loading dose over 30 min. One plasma sample per day was drawn over four consecutive days and linezolid concentrations were quantified using the same HPLC technique (**appendix 1**).

[18] IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

Table 2. Demographic and biochemical data of the patients included in the continuous perfusion study and their APACHE II health score; BMI: body mass index; Clcr: creatinine clearance; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase.

	Continuous perfusion	
Patient characteristic	**n**	**Median (Range)**
Demographic data		
Age (years)		60 (24-84)
Gender (M/F)	4/7*	
Body weight (kg)		80 (70-115)
Height (m)		1.67 (1.65-1.80)
BMI (kg/m^2)		28.5 (24.2-35.5)
Biochemical data		
Clcr (mL/min)		111 (45-240)*
Creatinine (mg/dL)		0.70 (0.50-1.10)*
Glucose (mg/dL)		136 (114-217)
Haemoglobin (g/dL)		10.3 (8.2-11.7)
Albumin (g/dL)		3.0 (2.5-3.6)*
Total proteins (g/dL)		5.4 (5.3-7.4)*
Bilirubin (mg/dL)		0.70 (0.50-2.10)
GPT (U/L)		37 (18-220)
GOT (U/L)		25 (16-74)
APACHE II		16 (6-25)*

*Statistically significant differences ($p<0.05$) among patients with continuous perfusion (n = 11) and patients with short perfusion (n = 41) (**table 1**).

For these patients, linezolid concentrations were predicted using the developed PK model. Five thousand subject simulations were performed for the following Clcr values: 40, 80, 120, 160, 200 and 240, which included Clcr values observed in the study population. The 2.5th, 50th and 97.5th percentiles of the concentrations were calculated for the simulated data and were compared against the observed data.

2.5. Monte Carlo simulation

2.5.1. Pharmacokinetic/pharmacodynamic analysis

Probability of target attainment (PTA) estimation

PTA is understood as the probability that at least a specific value of a pharmacodynamic index (e.g. AUC/MIC of 80) is achieved at a certain (minimum inhibitory) concentration[19].

Linezolid has a concentration-independent activity. The best predictors of its efficacy are the ratio between the area under the concentration-time curve of total linezolid over 24 hours in the steady state and the MIC (AUC_{24h}/MIC) and the percentage of time that plasma concentrations are above MIC ($T_{>MIC}$). It has been reported that high probabilities of success are observed when total drug AUC_{24h}/MIC > 80 to 120 or when $T_{>MIC}$ > 85%[20].

With the standard dosage regimen of linezolid (600 mg in a short intravenous infusion every 12h), studies of 5,000 subjects were simulated, distinguishing those who underwent CRRT from those who did not. Scenarios with different Clcr values were studied: 0, 10 and 30 mL/min for simulated subjects undergoing CRRT and 10, 30, 60, 90 and 130 mL/min for the rest. Since the CL_{EC} is significantly conditioned by the Q_{ef} ($CL_{EC} = Q_{ef} \times Sc$), different effluent flows (1.5, 2 and 3 L/h) were considered to evaluate their influence on the PTA. The Sc value used to calculate CL_{EC} was the mean value of the patients included in this study (0.8). Additionally, for the same groups of abovementioned patients, simulations of 30 min infusions of 600 mg every 8h were run. The probability of target

[19] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/ pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005;55(5):601-7.

[20] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003, 42:1411-23.

attainment was calculated over a range of doubling MICs between 0.25 and 4 mg/L. The simulations were performed using NONMEM 7.3.

Calculation of the cumulative fraction of response (CFR)

CFR is defined as the expected population PTA for a specific antibiotic dose and population of microorganisms. It allows us to determine the proportion of the population achieving a certain PK/PD value, given the Monte Carlo simulation and the MIC distribution of the target microorganisms[19]. It is calculated from the following equation:

$$CFR = \sum_{i=1}^{n} PTA_i \times F_i \qquad \textbf{(Eq. 1)}$$

where *i* indicates the MIC category ranked from lowest to highest MIC value of a population of microorganisms, *PTAi* is the PTA of each MIC category and *Fi* is the fraction of the population in each MIC category. CFR values were obtained for the standard dose (600 mg/12h) and for a higher dose of 600 mg/8h.

Susceptibility data of all isolates from ICU inpatients at Araba University Hospital from January 2013 to December 2015 were used to calculate CFR values for different bacteria: *Enterococcus faecalis, Enterococcus faecium, Staphylococcus epidermidis, Staphylococcus aureus* and coagulase negative staphylococci (**table 3**). The laboratory data from the Microbiology department was managed using Whonet[21].

[21] WHONET 5.6. Available at: *http://www.who.int/medicines/areas/rational_use/AMR_WHONET_SOFTWARE/en/* [Accessed: May 2018].

Table 3. MIC distributions for linezolid for *E. faecium*, *E. faecalis*, *S. epidermidis*, *S. aureus* and coagulase-negative staphylococci (CoNS) at Araba University Hospital from January 2013 to December 2015.

Microorganism	Clinical break point MIC (mg/L) [a]	no. of isolates	% of strains inhibited at a MIC (mg/L) of			
			1	2	4	8
Enterococcus faecium	2/4	18	22	78		
Enterococcus faecalis	2/4	53	26	72		2
Staphylococcus epidermidis	4	34		82	3	15
Staphylococcus aureus	4	60		92	8	
CoNS	4	70		88	3	9

[a]According to the Clinical and Laboratory Standard Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

For both PTA and CFR, values greater or equal to 90% were considered as optimal, while values between 90% and 80% were related to moderate probabilities of success[22,23].

2.5.2. Safety evaluation

In order to evaluate the safety profile of linezolid, the percentage of subjects that would reach plasma concentrations that have been associated with toxic

[22] Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J. 2003;22(11):982-92.

[23] Drusano GL, Preston SL, Hardalo C, Hare R, Banfield C, Andes D, et al. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob Agents Chemother. 2001;45(1):13-22.

events were taken into consideration: AUC_{24h} > 400 mg*h/L and $Cmin_{ss}$ > 10 mg/L[24,25]. These simulations were also performed using NONMEM 7.3.

3. Results

A total of 41 critically ill patients were included in the population pharmacokinetic model. Around 8 plasma samples per patient were analysed. In total, 311 concentration values were included in the data set to develop the model. The source of infection was pulmonary in 15 cases, abdominal in 10, neurological in 9, and biliary in 2, with other sources in the other 5 cases.

When subjected to CRRT (n = 23), eight effluent samples per individual were collected. Eighteen patients underwent continuous venovenous haemodiafiltration (CVVHDF) and five subjects venovenous haemodialysis (CVVHD). The effluent flow was set at a range from 1.1 to 3.3 L/h. Fluid balance was prescribed according to clinical status. Anticoagulation was performed, if necessary, with unfractionated heparin at a dose of 0.1 to 5 UI/kg/h. The filters had polysulphone membranes (Aquamax HF 12; Fresenius, Germany) or AN69 membranes (Nephral ST400, Hospal, Bologna, Italy), with surface areas of 1.80 and 1.65 m^2, respectively.

[24] Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012; 67:2034-42.

[25] Cattaneo D, Orlando G, Cozzi V, Cordier L, Baldelli S, Merli S, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with Gram-positive infections. Int J Antimicrob Agents. 2013; 41:586-89.

3.1. Population pharmacokinetic model

3.1.1. Base model

Linezolid plasma concentrations were best described by a two-compartment model. Interindividual variability (IIV) was included for clearance (CL) and the central compartment volume of distribution (V_1), and no correlation was detected between the two parameters. Variability was modelled using an exponential model for IIV and a combined error model for the residual variability was found to be the most suitable.

3.1.2. Covariate selection

The linezolid CL was estimated as the sum of a non-renal (CL_{NR}) and a renal component (CL_R), which was influenced by Clcr. The inclusion of Clcr in the model reduced the IIV of the CL from 98.7% to 61.5%. In patients undergoing CRRT, the extracorporeal clearance contributed to the total CL. The exploratory analysis suggested a relationship between body weight and age in the apparent volume of distribution of the central compartment (V_1); however, it was not supported in the covariate selection process ($p > 0.05$). Bilirubin, GOT and GPT were grouped and studied as potential covariates; however, they were excluded from the final model, as did not support a better fit. Although patients with Clcr > 130 mL/min showed a higher apparent volume of distribution of the peripherical compartment (V_2) in the SCM, categorised Clcr was not included as a covariate in the final model; since no substantial improvement was observed in the predicted concentrations, while higher estimation errors were obtained. No other covariate resulted in a relevant reduction in the OFV.

3.1.3. Model evaluation

Table 4 shows the estimated parameter values of linezolid according to the PK population model and their RSE (%). Furthermore, bootstrap results have been also included, which reveal that all parameters were estimated precisely. GOF plots obtained with the final model (**Figure 1**) showed no trend in CWRES or IWRES over time or predicted concentrations of the drug, respectively. Moreover, there was a good correlation between observed and predicted concentrations for both individual and population data. On the other hand, the VPC (**Figure 2**) showed a good correlation between raw data and the confidence intervals obtained by simulation.

Table 4. Base and final population pharmacokinetic models estimates, shrinkage[a] values and bootstrap results for linezolid after short-term intravenous infusion.

Parameter	Base model Estimate, RSE (%)	Final model Estimate, RSE (%)	Bootstrap, median (5^{th}-95^{th} percentile)
CL (L/h) = CL_{NR} + CL_R+ CL_{EC}	5.59 (13) + CL_{EC}		
CL_{NR}		2.62 (18)	2.65 (2.02 – 3.65)
CL_R = θ x (Clcr/44)		4.35 (19)	4.33 (2.99 – 5.84)
V_1 (L)	16.1 (20)	16.2 (14)	16.6 (11.7 – 24.4)
Q (L/h)	72.3 (18)	71.7 (14)	69.5 (40.4 – 92.0)
V_2 (L)	29.1 (8)	29.0 (7)	28.6 (23.0 – 32.6)
IIV_{CL} (%)	98.7 (10)	61.5 (9)	59.3 (48.9 – 69.4)
IIV_{V1} (%)	66.6 (20)	65.9 (17)	62.4 (37.7 – 91.6)
Residual error_additive (mg/L)	0.260 (24)	0.266 (24)	0.267 (0.156 – 0.464)
Residual error_proport. (%)	0.160 (9)	0.159 (19)	0.157 (0.122– 0.183)

[a] $CL\eta sh$ = 1%; $V_1\eta sh$ = 18%; εsh = 11%

[b] Only for patients undergoing CRRT. The individual value of CL_{EC} was considered.

CL: total body clearance; CL_{NR}: non-renal clearance; CL_R: renal clearance; CL_{EC}: extracorporeal clearance; Clcr: creatinine clearance; V_1: apparent volume of distribution of the central compartment; V_2: apparent volume of distribution of the peripheral compartment; IIV: inter-individual variability; RSE: relative standard error; ηsh: shrinkage value for a parameter; εsh: shrinkage value for the residual error.

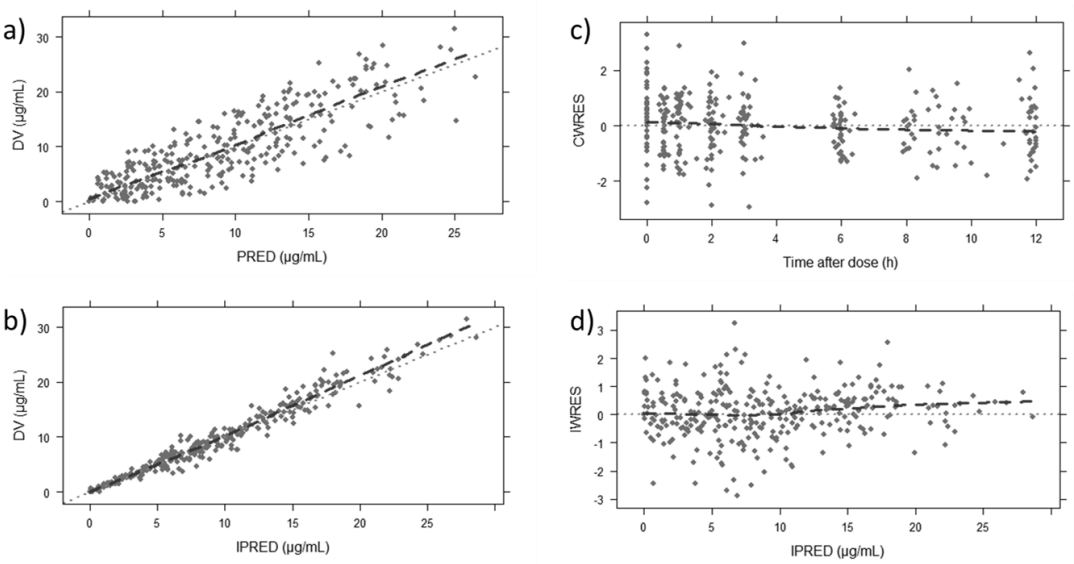

Figure 1. GOF plots obtained for the final model: population predictions (PRED)[(a)] and individual predictions (IPRED)[(b)] against observed linezolid plasma concentrations (DV, µg/mL), conditional weighted residuals (CWRES) versus time after dose (h)[(c)] and the individual weighted residuals (IWRES) versus individual concentration predictions (µg/mL)[(d)].

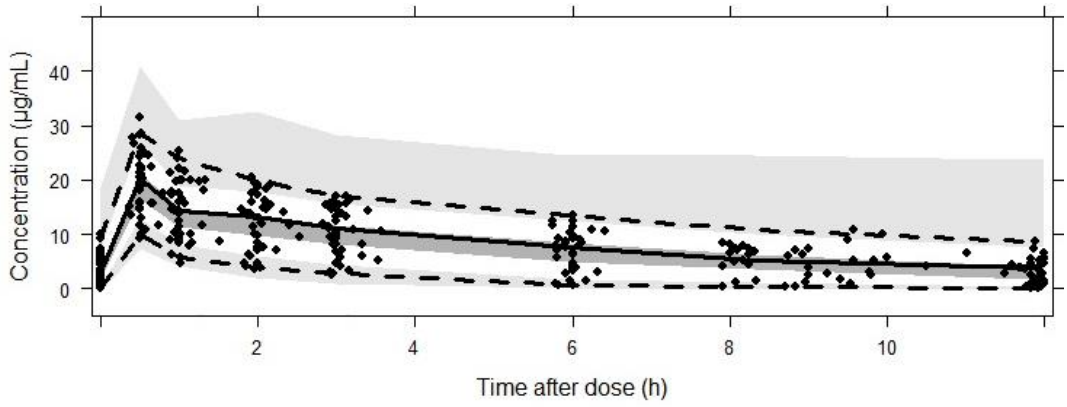

Figure 2. Results from the VPC from 0 to 12 h after dose. Dots correspond to the observed concentrations (µg/mL). The continuous line represents the median, while the dashed lines correspond to the 2.5th and 97.5th observed percentiles. Simulation-based 95% CIs for the median and both 2.5th and 97.5th percentiles are displayed by dark-grey and light-grey shading, respectively.

3.1.4. External validation

Figure 3 shows the comparison of the concentrations observed in the prospective study performed with 11 patients receiving linezolid by continuous infusion, and the median value and 2.5% and 97.5% percentiles obtained by simulation using the final model. As could be appreciated, our model was able to successfully predict patients' concentrations.

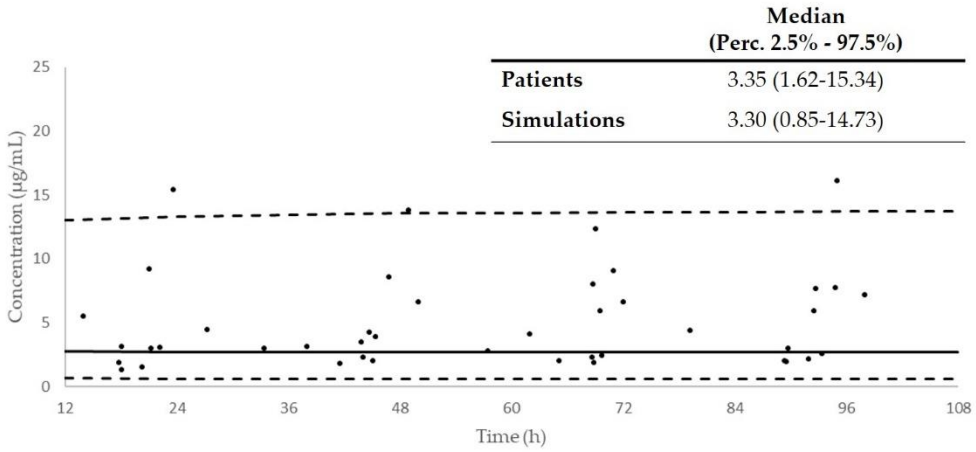

Figure 3. Comparison of the concentrations observed in continuous infusion, and the median value and 2.5% and 97.5% percentiles obtained by simulation using the final model.

3.2. Monte Carlo simulation

3.2.1. Pharmacokinetic/pharmacodynamic analysis

Probability of target attainment (PTA)

Table 5 shows the probability of achieving AUC_{24h}/MIC > 80 for different simulated scenarios. Overall, the greater the dose and the lower the Clcr, the higher the PTA. In patients without CRRT and Clcr ≤ 60 mL/min, 600 mg/12h covered infections caused by microorganisms with MIC values ≤ 1 mg/L. For MICs of 2 mg/L, this dose appears to be insufficient, except when the Clcr is ≤ 10 mL/min.

When increasing the dose to 600 mg/8h, no relevant improvement in probabilities of treatment success was observed for this MIC value, except for patients with Clcr values of 30 mL/min, where PTA increased from 68 to 88%

In patients undergoing CRRT, infections caused by microorganisms with MIC values ≤ 1 mg/L would be covered. In order to ensure high probabilities of treatment success for MIC values of 2 mg/L in patients with high Q_{ef} and/or Clcr values around 30 mL/min, 600 mg/8h would be required.

Cumulative fraction of response (CFR)

Table 6 features the CFR values obtained in this study. None of the dosing regimens provided high probabilities of success (≥ 90%) for infections caused by *S. epidermidis*. In patients without CRRT, infections caused by the other studied microorganisms would only be covered with the standard dose in patients with severe renal impairment (Clcr ≤ 10 mL/min). Overall, increasing the dose to 600 mg/8h would benefit patients with Clcr values between 10 and 30 mL/min, since the probability of treatment success is enhanced in these cases.

In patients undergoing CRRT, probabilities of treatment success for infections caused by *E. faecium, E. faecalis, S. aureus* or CoNS would vary depending on patients' Clcr and CL_{EC}. However, in general, it could be observed that even 600 mg/8h of linezolid would not properly cover infections caused by these microorganisms in patients with Clcr values around 30 mL/min or higher.

Table 5. PTA values (%) of linezolid, taking into consideration AUC_{24h}/MIC > 80 pharmacodynamic target. Bold values represent PTA ≥ 90%. Italics correspond to PTA ≥ 80%.

Dose	**Clcr** (mL/min)	**No CRRT**					**CRRT**														
							Q_{ef} 1.5 L/h					**Q_{ef} 2.5** L/h					**Q_{ef} 3** L/h				
600 mg/12h	0						**100**	**100**	**100**	**93**	48	**100**	**100**	**100**	**90**	23	**100**	**100**	**100**	*87*	12
	10	**100**	**100**	**99**	**90**	54	**100**	**100**	**99**	*85*	27	**100**	**100**	**99**	78	11	**100**	**100**	**98**	74	4
	30	**100**	**100**	**96**	68	24	**100**	**100**	**95**	58	9	**100**	**100**	**93**	49	2	**100**	**98**	**92**	43	1
	60	**100**	**99**	*85*	40	7															
	90	**100**	**95**	*67*	23	2															
	130	**100**	*88*	47	10	1															
600 mg/8h	0						**100**	**100**	**100**	**99**	*81*	**100**	**100**	**100**	**99**	70	**100**	**100**	**100**	**98**	63
	10	**100**	**100**	**100**	**98**	79	**100**	**100**	**100**	**97**	65	**100**	**100**	**100**	**96**	50	**100**	**100**	**100**	**95**	42
	30	**100**	**100**	**99**	*88*	50	**100**	**100**	**99**	*85*	34	**100**	**100**	**99**	*81*	23	**100**	**100**	**99**	79	16
	60	**100**	**100**	**96**	70	23															
	90	**100**	**99**	*88*	47	11															
	130	**100**	**97**	75	29	4															
MIC (mg/L)		**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**	**0.25**	**0.5**	**1**	**2**	**4**

Table 6. CFR values (%) of linezolid for different bacteria taking into consideration frequency distributions of MICs in Araba University Hospital, from January 2013 to December 2015. Bold values represent CFR ≥ 90%. Italics correspond to CFR ≥ 80%.

		Dose NO CRRT		**Dose CRRT**					
				Q_{ef} 1.5 L/h		**Q_{ef} 2.5** L/h		**Q_{ef} 3** L/h	
Bacteria	**Clcr** (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
Enterococcus faecium	0			**95**	**99**	**92**	**99**	**90**	**99**
	10	**92**	**98**	*88*	**97**	*82*	**96**	*80*	**96**
	30	74	**91**	66	*88*	59	*85*	54	*83*
	60	50	75						
	90	33	56						
	130	18	39						
Enterococcus faecalis	0			**93**	**98**	**91**	**97**	89	**97**
	10	**91**	**97**	*87*	**96**	*82*	**95**	79	**94**
	30	74	*89*	67	*87*	60	*84*	55	*82*
	60	51	75						
	90	34	57						
	130	19	40						
Staphylococcus epidermidis	0			78	*87*	74	*83*	72	*82*
	10	77	*85*	70	*82*	64	*80*	61	79
	30	57	75	48	71	40	67	35	65
	60	33	58						
	90	19	39						
	130	8	24						
Staphylococcus aureus	0			**90**	**98**	*85*	**96**	*81*	**95**
	10	*87*	**96**	*80*	**94**	72	**92**	69	**90**
	30	65	*85*	54	*81*	45	76	39	74
	60	38	66						
	90	21	44						
	130	9	27						
CoNS	0			*85*	**92**	*81*	**90**	78	*89*
	10	*83*	**91**	76	*89*	69	*87*	66	*85*
	30	62	*80*	52	*77*	44	73	38	70
	60	36	63						
	90	20	42						
	130	9	26						

3.2.2. Safety evaluation

Tables 7 and **8** show the probability of achieving $Cmin_{ss}$ > 10 mg/L and AUC_{24h} > 400 mg*h/L, respectively, both associated with linezolid related toxicity. The standard dose (600 mg/12h) obtained low probabilities of reaching values associated with toxicity, except for patients without CRRT and Clcr ≤10 mL/min or anuric patients with low-effluent-flow CRRTs. Using a higher dose (600 mg/8h), the safety profile of linezolid would be substantially compromised, making patients with lower Clcr values (≤ 60 mL/min) and low effluent flows (when subjected to CRRT) particularly susceptible.

Table 7. Probability of achieving linezolid $Cmin_{ss}$ >10 mg/L.

	No CRRT		**Q_{ef} 1.5** L/h		**Q_{ef} 2** L/h		**Q_{ef} 3** L/h	
Clcr (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
0			32	92	9	87	3	83
10	43	88	15	81	3	73	1	68
30	16	65	4	53	1	43	0	36
60	4	36						
90	1	19						
130	0	8						

Table 8. Probability of achieving linezolid AUC_{24h} > 400 mg*h/L.

	No CRRT		**Q_{ef} 1.5** L/h		**Q_{ef} 2** L/h		**Q_{ef} 3** L/h	
Clcr (mL/min)	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**	**600 mg/ 12 h**	**600 mg/ 8 h**
0			26	65	5	45	1	34
10	38	66	11	44	1	27	0	17
30	13	35	2	18	0	8	0	4
60	3	12						
90	1	5						
130	0	1						

4. Discussion

A population pharmacokinetic model was developed for linezolid in critically ill patients. Data was best supported by a two-compartment model. This was in accordance with previously published manuscripts[26,27,28,29]. The estimated apparent total volume of distribution (V_{ss} = 45.2 L), which approximated the total body water, was similar to values obtained in studies performed on critically ill patients (e.g. Taubert et al.[27]: 41.55 L) and did not differ from patients with or without CRRT. Moreover, it was also similar to the volume of distribution described by Slatter et al.[30] or by MacGowan et al.[31] in healthy volunteers (30-50 L). The moderate lipophilic nature of linezolid may explain the lack of differences in this parameter among critically ill patients and healthy volunteers. Contrary to hydrophilic drugs, where V is conditioned by the increased extracellular fluids in the critically ill, the volume of distribution of lipophilic drugs hardly changes in these patients with respect to healthy subjects.

Regarding linezolid elimination, both non-renal and renal clearance were included in the model, the latter being influenced by patients' Clcr. The inclusion

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[26] Zoller M, Maier B, Hornuss C, Neugebauer C, Döbbeler G, Nagel D, et al. Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. Crit Care 2014; 18: R148.

[27] Taubert M, Zoller M, Maier B, Frechen S, Scharf C, Holdt LM, Frey L, et al. Predictors of Inadequate Linezolid Concentrations after Standard Dosing in Critically Ill Patients. Antimicrob Agents Chemother. 2016;60(9):5254-61.

[28] Ide T, Takesue Y, Ikawa K, Morikawa N, Ueda T, Takahashi Y, et al. Population pharmacokinetics/pharmacodynamics of linezolid in sepsis patients with and without continuous renal replacement therapy. Int J Antimicrob Agents. 2018 Feb 6. pii: S0924-8579(18)30032-3.

[29] Adembri C, Fallani S, Cassetta MI, Arrigucci S, Ottaviano A, Pecile P, et al. Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: Intermittent versus continuous infusion. Int J Antimicrob Agents. 2008; 31:122-9.

[30] Slatter JG, Stalker DJ, Feenstra KL, Welshman IR, Bruss JB, Sams JP, et al. Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [(14)C]linezolid to healthy human subjects. Drug Metab Dispos. 2001;29(8):1136-45

[31] MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrob Chemother. 2003;51 Suppl 2:ii17-25.

of this covariate in the PK model has been controversial. Thus, while some authors found a correlation between Clcr and total clearance[28,32,33] others concluded that no strong relationship could be demonstrated[27,34]. This might be attributable to the use of the Cockcroft-Gault equation to calculate creatinine clearance, which is not accurate enough for critically ill patients[35,36]. In this study, the inclusion of the Clcr as a covariate in the model decreased the inter-individual variability of the CL from 97.8% to 61.5%.

Since linezolid is partially eliminated by CRRT, the CL_{EC} value was included in the total body clearance equation[37]. The estimation of drug elimination in critically ill patients undergoing CRRT could become complex, since it is influenced by antibiotic-related and CRRT-related characteristics, such as surface area, composition and pore diameter of the membrane used, the effluent flow or the CRRT modality[38]. In this study the mean sieving coefficient value was around 0.8, similar to the unbound protein fraction observed in critically ill patients[33] and did not substantially vary depending on the technique or membrane used. The lack of differences in the Sc among the different techniques has been previously described, and might be due to the low molecular weight of the antibiotic[37]. However, the effluent flow justifies differences in CL_{EC} between continuous

[32] Matsumoto K, Shigemi A, Takeshita A, Watanabe E, Yokoyama Y, Ikawa K, et al. Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentrations and renal function in adult patients. Int J Antimicrob Agents. 2014;44:242-7.

[33] Tsuji Y, Holford NHG, Kasai H, Ogami C, Heo YA, Higashi Y, et al. Population pharmacokinetics and pharmacodynamics of linezolid-induced thrombocytopenia in hospitalized patients. Br J Clin Pharmacol. 2017;83(8):1758-72.

[34] Pea F, Furlanut M, Cojutti P, Cristini F, Zamparini E, Franceschi L, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother. 2010;54(11):4605-10.

[35] Kharbanda M, Majumdar A, Basu S, Todi S. Assessment of accuracy of Cockcroft-Gault and MDRD formulae in critically ill Indian patients. Indian J Crit Care Med. 2013;17(2):71-5.

[36] Sunder S, Jayaraman R, Mahapatra HS, Sathi S, Ramanan V, Kanchi P, et al. Estimation of renal function in the intensive care unit: the covert concepts brought to light. J Intensive Care. 2014;2(1):31.

[37] Villa G, Di Maggio P, De Gaudio AR, Novelli A, Antoniotti R, Fiaccadori E, et al. Effects of continuous renal replacement therapy on linezolid pharmacokinetic/pharmacodynamics: a systematic review. Crit Care. 2016;20(1):374.

[38] Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis. 2005;41(8):1159-66.

venovenous hemofiltration (CVVH), CVVHD or CVVHDF. In fact, lower extracorporeal clearance values have been obtained when using CVVH or CVVHD[39,40] as compared to CVVHDF[41], where higher effluent flows are commonly employed. The calculated extracorporeal values in this study (**table 1**) were consistent with the aforementioned research works[39,40,41].

It is well known that, at least in healthy volunteers, linezolid clearance occurs by both renal and hepatic mechanisms (around 30 and 65% respectively). Liver metabolism occurs by oxidation of the morpholine ring of the drug, without involvement of the cytochrome P450 system[30]. Taking this into consideration, the inclusion in the model of covariates associated with hepatic functionality was analysed. Despite using the available bilirubin and transaminases data to create three dichotomous covariates, none of them improved the PK model. This outcome might be due to the current lack of a reliable, economical and untroublesome indicator of hepatic functionality[42,43].

In the time-concentration profile of studied patients, a linezolid peak among 2 and 4h after dose was detected in around one third of cases. That sudden rise in concentrations turned out to be inexplicable with the two-compartmental model. As previous studies had demonstrated that linezolid presents biliary

[39] Pea F, Viale P, Lugano M, Pavan F, Scudeller L, Della Rocca G, et al. Linezolid disposition after standard dosages in critically ill patients undergoing continuous venovenous hemofiltration: a report of 2 cases. Am J Kidney Dis. 2004;44(6):1097-102.

[40] Meyer B, Kornek GV, Nikfardjam M, Karth GD, Heinz G, Locker GJ, et al. Multiple-dose pharmacokinetics of linezolid during continuous venovenous haemofiltration. J Antimicrob Chemother 2005; 56: 172-9.

[41] Roger C, Muller L, Wallis SC, Louart B, Saissi G, Lipman J, et al. Population pharmacokinetics of linezolid in critically ill patients on renal replacement therapy: comparison of equal doses in continuous venovenous haemofiltration and continuous venovenous haemodiafiltration. J Antimicrob Chemother. 2016;71(2):464-70.

[42] Watkins PB, Merz M, Avigan MI, Kaplowitz N, Regev A, Senior JR. The clinical liver safety assessment best practices workshop: rationale, goals, accomplishments and the future. Drug Saf. 2014;37 Suppl 1:S1-7.

[43] Wicha SG, Frey OR, Roehr AC, Pratschke J, Stockmann M, Alraish R, et al. Linezolid in liver failure: exploring the value of the maximal liver function capacity (LiMAx) test in a pharmacokinetic pilot study. Int J Antimicrob Agents. 2017;50(4):557-63.

excretion[44,45], a model for enterohepatic circulation was evaluated to try to explain the peak observed in the concentration-time profile of some individuals. Unfortunately, our data was not powerful enough to cope with this model.

The overall high variability found among patients (IIV_{CL} = 61.5% and IIV_{V1} = 65.9%), was consistent with other population PK models performed in critically ill patients, such as that described by Taubert et al.[27] where a variability of 58% and 37% in terms of coefficients of variation was estimated for IIV_{CL} and IIV_{V1}, respectively. In this scenario, therapeutic drug monitoring has been suggested by some authors[25,32,46]. On the contrary, in a recent study carried out by Galar et al.[47] no clear correlation was observed between clinical outcome and abnormal trough levels of linezolid, and, therefore, drug monitoring would not be justified. Regardless of these discrepancies, monitoring drug plasma levels is not always feasible, as health personnel could not often cope with the required time and resources. Therefore, integrated PK/PD analysis and Monte Carlo Simulation become a noticeably helpful tool to predict the probability of success of a certain posology and to give advice on prescription to enhance the likelihood of a favourable outcome for the treatment[48]. As an example, in the present study it has been demonstrated that the PK model performed was able to properly predict linezolid plasma concentrations in patients where continuous perfusion was administered. Although statistically significant differences in demographic and biochemical data were observed among patients with short and continuous

[44] Pea F, Viale P, Lugano M, Baccarani U, Pavan F, Tavio M, et al. Biliary penetration and pharmacodynamic exposure of linezolid in liver transplant patients. J Antimicrob Chemother. 2009; 63(1):167-9.

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[46] Pea F, Furlanut M, Cojutti P, Cristini F, Zamparini E, Franceschi L, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother. 2010;54(11):4605-10.

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[48] Asín-Prieto E, Rodriguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother. 2015;21(5):319-29.

linezolid infusion, they did not result relevant for a proper concentration prediction.

Taking into consideration simulations performed in this study, acceptable probabilities of reaching AUC_{24h}/MIC > 80 would be achieved with the approved dose of linezolid (600 mg/12h) for infections caused by bacteria with MIC values of 1 mg/L, as far as Clcr values are ≤ 60 mL/min. Moreover, except for patients with Clcr ≤ 10 mL/min, or anuric patients undergoing CRRT, infections caused by microorganisms with MIC of 2 mg/L would not be covered, which is the clinical breakpoint for enterococci by the Clinical and Laboratory Standard Institute (CLSI)[49]. Likewise, in all simulated scenarios, 600 mg/12h linezolid would be insufficient for the treatment of infections due to microorganisms with MIC ≥ 4 mg/L, the clinical breakpoint for staphylococci and enterococci by the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[50].

In this study, linezolid was administered as empiric treatment and susceptible bacteria were not found in most of the samples obtained from the patients, which made it impossible to perform a direct pharmacodynamic correlation. In this context, susceptibility to isolates data from January 2013 to December 2015 in Araba University Hospital ICU inpatients was used to calculate CFR values (**table 6**). As the majority of isolate strains have MIC values equal to or higher than 2 mg/L (**table 3**), low cumulative fractions of response were obtained from the simulations.

In order to know whether treatment success probabilities would increase, simulations were performed for a higher linezolid dosage of 600 mg every 8h. As shown in **table 5**, the proposed posology would not substantially improve probabilities of target attainment, whilst the likelihood of overexposure to the drug, and therefore adverse effects, would increase considerably (**tables 7** and **8**).

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[49] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 28th Edition. M100-S28. CLSI, Wayne, PA, USA, 2018.

[50] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018. Available at: http://www.eucast.org [Accessed: March 2018].

The major side effect related to linezolid administration is reversible myelosuppression, especially thrombocytopenia[32,51]. Risk factors associated with this process are chronic liver impairment[52], prolonged duration of linezolid therapy (> 14 days), low body weight or renal failure[53,54]. In this research study none of the patients had a $Cmin_{ss}$ value > 10 mg/L nor an AUC_{24h} > 400 mg*h/L, and no adverse events related to linezolid were experienced. Even though many of the patients suffered from renal failure, the majority of them were subjected to CRRT, only one exceeded 14-day linezolid therapy and half of the patients were overweight or obese (BMI > 25 kg/m^2).

Administration of a continuous infusion of linezolid could be an alternative option that may avoid the toxicity problems that could occur when increasing the dose, which has already been suggested by different authors[27,55]. In all patients used for external validation, plasma concentrations above 1 mg/L were obtained, while 86% of measured concentrations were above 2 mg/L. Therefore, continuous infusion of linezolid seems to be a good option to treat critically ill patients with infections caused by bacteria with MIC values of 2 mg/L, even in patients with augmented renal function. Two of the patients had, at least, one plasma concentration higher than 10 mg/L, which could be associated with toxic events. However, it should be taken into consideration that this threshold was stated for short perfusion, where higher antibiotic concentrations are observed over the whole dosing interval, and it should not be compared with achieving a constant 10

[51] Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. He**m**atologic Effects of Linezolid: Summary of Clinical Experience. Antimicrob Agents Chemother. 2002; 46(8): 2723-26.

[52] Ikuta S, Tanimura K, Yasui C, Aihara T, Yoshie H, Iida H, et al. Chronic liver disease increases the risk of linezolid-related thrombocytopenia in methicillin-resistant *Staphylococcus aureus*-infected patients after digestive surgery. J Infect Chemother. 2011; 17(3):388-91.

[53] Echeverría-Esnal D, Retamero A, Pardos SL, Grau S. Severe thrombocytopenia caused by linezolid poisoning in an underweight critically ill patient with renal impairment treated with the recommended doses. Enferm Infecc Microbiol Clin. 2016;34(3):213-4.

[54] Natsumoto B, Yokota K, Omata F, Furukawa K. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014; 42(6):1007-12.

[55] Richards GA, Brink AJ. Therapeutic drug monitoring: linezolid too? Critical Care. 2014; 18:525.

mg/L concentration. Thus, further studies are needed to assess the most indicative concentration linked to toxicity for continuous perfusion.

5. Conclusions

A population pharmacokinetic model for linezolid was developed using data from intensive care unit patients. Data was best described by a two-compartment model. Total clearance was the sum of a non-renal clearance and a renal clearance (affected by CLcr) and, in patients undergoing CRRT, extracorporeal elimination. The model was useful to estimate the probability of treatment success according to PK/PD criteria. The standard dose of linezolid (600mg/12h) was not able to cover infections caused by pathogens with MICs ≥ 2 mg/L. Increasing the dosage to 600 mg every 8 h did not substantially improve the probability of target attainment but increased the probability of reaching drug concentrations linked to toxicity. Using continuous infusion may improve patients' outcome, especially if they present conserved renal function with Clcr ≥ 60 mL/min.

DISCUSSION

Discussion

The current complexity in the management of infectious diseases and the increase in antibiotic resistance makes it essential to optimise the use of antibiotics. It has been described that up to 50% of hospital antibiotic use might be improved and that in 30-40% of patients the care received is not based in scientific evidence[1].

The indication of antibiotics should be a decision-making process in which clinical, epidemiological, microbiological and pharmacological information is integrated, as infectious diseases not only threaten individual health, but also the welfare of global public health. Moreover, preserving the public good and protecting individual liberty may conflict with each other in some situations[2]. The multidisciplinary approach would be potentially beneficial in high-care complexity services, such as intensive care units.

Taking into consideration that empirical treatment accounts for two-thirds of all antimicrobial prescriptions in hospitals, empiric treatments for specific diseases should be stablished, considering local and national guidelines and local antimicrobial susceptibility profiles[3,4]. The design and optimisation of protocols would improve the clinical outcome, since the early administration of an adequate

[1] Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. Lancet Infect Dis. 2010; 10(3):167-75.

[2] Hernández-Marrero P, Martins Pereira S, de Sá Brandão PJ, Araújo J, Carvalho AS. Toward a bioethical framework for antibiotic use, antimicrobial resistance and for empirically designing ethically robust strategies to protect human health: a research protocol. J Int Med Res. 2017;45(6):1787-93.

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[4] Campion M, Scully GJ. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. Intensive Care Med. 2018 Jan 1:885066618762747. doi:10.1177/0885066618762747.

empiric antibiotic treatment is associated with lower mortality rates[5,6,7,8]. To do so, an antimicrobial resistance surveillance system is essential, with common standards for methods, data-sharing and coordination at local, national and global levels[9]. However, ensuring a satisfactory empiric coverage, should not be the sole aim of the treatment. Microbiological diagnosis may facilitate the choice for an optimal therapy, since it provides not only information about the microorganisms, but also their susceptibility to the most used antibiotics. Hence, early identification could become valuable to improve clinical outcome and reduce side effects[4,6].

In general, infections caused by Gram-negative microorganisms have been assessed as the most critical priority for research, due to their incidence and emerging antibiotic resistance[10]. However, infections due to Gram-positive bacteria should not be underestimated. In fact, it has been described that between one third and half of the bloodstream infections in critically ill patients might be caused by Gram-positive bacteria, representing one of the dominant species in the

[5] Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596.

[6] Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence. 2016;7(3):267-79.

[7] Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, Kelesidis T, Weisenberg SA, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect Dis. 2014;14(12):1220-7.

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ICUs[6,11,12,13]. Some of the most common diseases caused by these bacteria are health care associated pneumonia, particularly ventilator-associated pneumonia (which is often caused by MRSA), and bacteraemia associated with advanced invasive devices, such as ventricular assisted devices or intravenous catheters[13].

Vancomycin has been one of the most used antibiotics for the treatment of infections caused by Gram-positive bacteria in critically ill patients, such as methicillin-resistant *Staphylococcus aureus* or *Enterococcus spp*. Nevertheless, the increased use of this antibiotic has led to high rates of resistance and, in some cases, to the elevation of minimum-inhibitory concentrations of vancomycin (known as the "MIC-creep")[14,15,16]. As a result, vancomycin resistant Enterococci (VRE) and vancomycin resistant *S. aureus* (VRSA) have emerged as microorganisms responsible for nosocomial infections, which are likely to provoke treatment failures. Therefore, alternatives to this antimicrobial should be considered. In recent years, newer drugs against Gram-positive bacteria have played an important role in the management of these infections (e.g. ceftaroline, tigecycline, daptomycin and linezolid).

Given the risk of developing resistance against antibiotics and the reduced available therapeutic arsenal, adequate antibiotic dosing is of paramount importance for proper management of critically ill infected patients. Hence, the

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[13] Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study. CMAJ Open. 2016;4(4):E569-E577.

[14] Rengaraj R, Mariappan S, Sekar U, Kamalanadhan A. Detection of Vancomycin Resistance among *Enterococcus faecalis* and *Staphylococcus aureus*. J Clin Diagn Res. 2016;10(2):DC04-6.

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[16] Díaz R, Ramalheira E, Afreixo V, Gago B. Evaluation of vancomycin MIC creep in *Staphylococcus aureus*. J Glob Antimicrob Resist. 2017;10:281-4.

optimisation of antimicrobial dosage-regimens considering specific factors of the patients remains essential. For this purpose, population pharmacokinetic approach becomes a profitable tool to describe the population parameters in critically ill patients, identifying relations between the variability associated with the pharmacokinetic profile and their physiopathological characteristics.

Pharmacokinetic/pharmacodynamic (PK/PD) analysis integrates pharmacokinetic information and data about the susceptibility of the microorganisms (MIC values) for a specific antimicrobial agent. This analysis allows to select the most suitable antibiotic and dosing regimen for each individual and infectious process, to ensure the optimal antibiotic effect and to minimise side effects and the emergence of resistance.

The main limitation of using MIC values when applying PK/PD analysis is that they are estimated after incubation of the bacteria in presence of a static concentration of antibiotic. Therefore, no information about the evolution of the bacteria growth in the presence of changing antibiotic concentrations is provided, which correlates better with the actual situations in human body fluids. Even though pharmacodynamic models based on *in vitro* time-kill kinetics studies might provide a closer approach to what happens in the patients, they are not usually implemented, as they are often time-consuming and expensive[17,18].

The quantitative relationship between a pharmacokinetic parameter and microbiological parameter is known as PK/PD index. There are three PK/PD indices linked to the effect of antibiotics: the time during which the concentration of the antimicrobial is over the MIC ($T_{>MIC}$), the peak concentration to the MIC ratio (Cmax/MIC), and the ratio of the area under concentration-time curve (usually in a 24 hour period) divided by the MIC (AUC_{24h}/MIC). Moreover, apart from

[17] Nielsen EI, Cars O, Friberg LE. Predicting in vitro antibacterial efficacy across experimental designs with a semimechanistic pharmacokinetic-pharmacodynamic model. Antimicrob Agents Chemother. 2011;55(4):1571-9.

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selecting the adequate PK/PD index, the magnitude of the index that is linked to antimicrobial efficacy must be defined; that is, the pharmacodynamic target (PDT).

Once a PK model is developed and the interrelationship of the PK and PD parameters have been studied, predictions on the probable outcome of the therapy and assessment of the probability of success of alternative dosages could be done, by performing Monte Carlo simulation. Therefore, in order to obtain reliable PK/PD breakpoints, it would be mandatory to use a validated population PK model for a specific population, as well as a truthful PDT related to efficacy. Otherwise, the results obtained would be biased and useless.

In line with the aforementioned, we have designed and evaluated population pharmacokinetic models for two antimicrobial drugs used in critically ill patients against Gram-positive bacteria, daptomycin and linezolid. Moreover, the adequacy of the dosage regimens has been studied, by applying PK/PD analysis and Monte Carlo simulation, taking into consideration the efficacy and safety profiles.

Thereby, in the second chapter, a population pharmacokinetic model for daptomycin is presented. Data was best described by a one-compartment model, and, according to it, a mean volume of distribution of 12.3 L was estimated. The elimination of the antibiotic was conditioned by a non-renal clearance (0.16 L/h) and a renal clearance (mean value of 0.37 L/h), the latter being dependent on the creatinine clearance. Moreover, in subjects undergoing CRRT the extracorporeal clearance (CL_{EC}) was also included in the clearance equation, which accounted from 39 to 80% of the total CL. Since a contribution of the CL_{EC} in total clearance higher than 25% is considered significant[19], it can be concluded that daptomycin is eliminated notably by renal extracorporeal techniques. Although daptomycin has shown a 90% protein binding in healthy volunteers, it has been widely described that in critically ill patients the protein binding of the antibiotics is usually lower

[19] Schetz M, Ferdinande P, Van den Berghe G, Verwaest C, Lauwers P. Pharmacokinetics of continuous renal replacement therapy. Intensive Care Med. 1995;21(7):612-20.

(due to hypalbuminaemia, among other reasons)[20]. Therefore, the sieving coefficient observed in the studied patients (mean value: 0.2) could correlate with the free daptomycin fraction in blood.

Even though daptomycin is recommended to be dosed according to the weight of the patients, the inclusion of this parameter as a covariate did not improve the model. This could be due to the small cohort size of the patients included in the study (n = 16), as well as to the fact that the majority of the patients (75%) were obese or overweight. Even though the no inclusion of the weight was in accordance with other studies[21,22], caution should be taken when using this population model to predict concentrations or optimal dosages in patients with much lower body-weights.

Daptomycin is approved at a dose of 4 mg/kg for the treatment of complicated skin and soft-tissue infection (SSTI) and at 6 mg/kg for *S. aureus* bloodstream infections, including treatment of right-sided endocarditis[23]. Moreover, it has been also used off label for the treatment of central nervous system infections caused by Gram-positive bacteria or for the treatment of VRE bacteraemia[24,25]. Daptomycin possess a good anti-biofilm activity, which represents

[20] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99-110.

[21] Di Paolo A, Tascini C, Polillo M, Gemignani G, Nielsen EI, Bocci G, et al. Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. Int J Antimicrob Agents. 2013;42(3):250-5.

[22] Falcone M, Russo A, Venditti M, Novelli A, Pai MP. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2013;57(11):1568-76.

[23] European Medicines Agency. Cubicin®: summary of product characteristics. Available at: *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf* [Accessed May 2017].

[24] Rybak JM, Barber KE, Rybak MJ. Current and prospective treatments for multidrug-resistant gram-positive infections. Expert Opin Pharmacother. 2013;14(14):1919-32.

[25] Mohr JF, Friedrich LV, Yankelev S, Lamp KC. Daptomycin for the treatment of enterococcal bacteraemia: results from the Cubicin Outcomes Registry and Experience (CORE). Int J Antimicrob Agents. 2009;33(6):543-8.

a potential advantage when catheters or other devices are the source of infection[26]. Furthermore, it has been described that, when a *S. aureus* bloodstream infection is suspected, an empiric treatment with high-dose daptomycin (8-10 mg/kg/day) may be more effective than empiric regimen with glycopeptides or beta-lactams, especially when high local prevalence of MRSA is observed[27].

However, there is no consensus concerning the optimal daptomycin dosage. The PK/PD analysis and Monte Carlo simulations performed in this study showed that the standard dosages of daptomycin would not cover infections caused by MIC values of 4 mg/L, which is the clinical breakpoint for enterococci reported by the Clinical and Laboratory Standard Institute (CLSI)[28] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[29]. Moreover, these dose levels would only cover infections caused by microorganism with MICs of 1 mg/L (the clinical breakpoint for streptococci and staphylococci) if patients suffer from renal insufficiency (≤ 30 mL/min) and are not subjected to CRRT. These results are consistent with the Guidelines from the Infectious Diseases Society of America (IDSA) and with previous studies that questioned standard dosages in favour of higher ones (8-12 mg/kg/qd or 560-840 mg/qd)[21,22,30,31].

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[26] Bauer J, Siala W, Tulkens PM, Van Bambeke F. A combined pharmacodynamic quantitative and qualitative model reveals the potent activity of daptomycin and delafloxacin against *Staphylococcus aureus* biofilms. Antimicrob Agents Chemother. 2013;57(6):2726-37.

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[28] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 28th Edition. M100-S28. CLSI, Wayne, PA, USA, 2018.

[29] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018. Available at: http://www.eucast.org [Accessed: March 2018].

[30] Senneville E, Caillon J, Calvet B, Jehl F. Towards a definition of daptomycin optimal dose: Lessons learned from experimental and clinical data. Int J Antimicrob Agents. 2016;47(1):12-9.

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In Chapter 3, a population pharmacokinetic model for linezolid was built. Plasma levels of antibiotic were measured in 41 ICU patients and time-concentration data was best described by a two-compartment model. Interindividual variability (IIV) was included for clearance (CL) and the central compartment volume of distribution (V_1). High variability among patients was observed, 61.5% and 65.9% for CL and V_1, respectively.

The estimated apparent total volume of distribution (V_{ss} = 45.2 L), approximated the total body water and was similar to that obtained in other studies performed on critically ill patients (e.g. Taubert et al.[32] : 41.55 L). Due to the lipophilic nature of the drug, this value did not either differ from estimated values for healthy volunteers[33,34]. Regarding linezolid elimination, both non-renal and renal clearance were included in the model, the latter being influenced by patients' Clcr. Since only the 30% of unaltered linezolid is supposed to be eliminated by the kidneys, the influence of Clcr on total clearance has been controversial. However, a strong relationship between the Clcr and CL was observed, and the inclusion of Clcr as a covariate decreased the inter-individual variability of the CL from 97.8% to 61.5%.

Since linezolid is partially eliminated by CRRT, the CL_{EC} value was included in the total body clearance equation[35]. The contribution of CL_{EC} to the total CL ranged from 5% to 67%, and was mainly conditioned by the Clcr. Thus, a higher proportion of the drug was eliminated by CRRT in anuric patients or in those with very limited kidney functionality. The mean sieving coefficient value

[32] Taubert M, Zoller M, Maier B, Frechen S, Scharf C, Holdt LM, Frey L, et al. Predictors of Inadequate Linezolid Concentrations after Standard Dosing in Critically Ill Patients. Antimicrob Agents Chemother. 2016;60(9):5254-61.

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[35] Villa G, Di Maggio P, De Gaudio AR, Novelli A, Antoniotti R, Fiaccadori E, et al. Effects of continuous renal replacement therapy on linezolid pharmacokinetic/pharmacodynamics: a systematic review. Crit Care. 2016;20(1):374.

calculated in this study (0.8) was similar to the unbound protein fraction observed in critically ill patients[36].

Linezolid is authorized for the treatment of pneumonia and SSTIs. However, it has been also used off label to treat secondary MRSA bacteraemia or tuberculous meningitis, among others[37,38,39]. Considering that respiratory tract infections, particularly pneumonia, represent the most common infection in the ICUs, and that they have some of the highest mortality rates, linezolid becomes a very valuable antibiotic for the treatment of infections in critically ill patients[40].

The clinical breakpoints for linezolid by CLSI[28] and EUCAST[29] are 2-4 mg/L for enterococci and 4 mg/L for staphylococci. According to the PK/PD analysis performed in this study, the standard dose of linezolid (600 mg/12h) would not always ensure a high probability of treatment success in critically ill patients. In fact, only patients with Clcr values ≤ 10 mL/min, or anuric patients when undergoing CRRT, would be covered when infections are caused by microorganisms with MIC values of 2 mg/L. Increasing the dose to 600 mg/8h would not improve substantially the probabilities of achieving efficacy, while would compromise the safety of the patients. In order to avoid the potential toxicity problems linked to a higher dose, results obtained from the present study confirm the need to explore new dosing strategies, including continuous perfusion.

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[37] Park HJ, Kim SH, Kim MJ, Lee YM, Park SY, Moon SM, et al. Efficacy of linezolid-based salvage therapy compared with glycopeptide-based therapy in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteremia. J Infect. 2012;65(6):505-12.

[38] Pereira NM, Shah I, Ohri A, Shah F. Methicillin resistant *Staphylococcus aureus* meningitis. Oxf Med Case Reports. 2015;19;2015(11):364-6.

[39] Sun F, Ruan Q, Wang J, Chen S, Jin J, Shao L, et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother. 2014;58(10):6297-301.

[40] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198-208.

Although this strategy has been especially suggested for beta-lactams[41,42], it has been also proposed by several authors for linezolid[32,43]. Continuous perfusion could be particularly beneficial for patients with augmented renal function, where poor probabilities of treatment success are achieved with short infusion administration. Even though results obtained in this study for continuous perfusion are promising, further research is needed in this field.

Some limitations of the present study should be contemplated. On the one hand, as said before, PK/PD analysis has been performed using MIC-based approach, and, therefore, only static values have been considered. On the other hand, the infection site has not been taken into consideration for dosage recommendations, and only plasma concentrations have been used. Moreover, the effects on resistance emergence has not been studied, which could become valuable if taking into consideration that evolution of resistance has already been observed for these antibiotics. In this sense, the existence of linezolid and daptomycin resistant *Staphylococcus aureus*[44,45], or linezolid resistant *Staphylococcus epidermidis*[46] have been reported, among others.

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CONCLUSIONS

Conclusions

1. A Population PK model has been developed for daptomycin in critically ill patients. Concentration-time data was best suited by a one-compartment model. The total body clearance was the result of the sum of non-renal and renal clearance (affected by creatinine clearance). Moreover, in patients undergoing continuous renal replacement techniques, clearance was also dependent on the extracorporeal clearance.

2. Standard dosages of daptomycin might be insufficient for several critically ill patients. Subjects without kidney injury or those subjected to continuous renal replacement therapies would be particularly vulnerable to be under-dosed, as low probabilities of treatment success would be achieved for MIC values of 1 mg/L (the clinical breakpoint for streptococci and staphylococci) or 4 mg/L (the clinical breakpoint for enterococci).

3. According to the PK/PD analysis, and in order to ensure high probabilities of daptomycin treatment success, patients with Clcr values between 60 and 90 mL/min would require 700 mg/qd, while 840 mg/qd should be administered to patients with higher Clcr values. Although higher probabilities of success are expected in subjects with Clcr ≤ 30 mL/min, probabilities of reaching concentrations of daptomycin linked to toxicity are higher than desired. Therefore, the risk-benefit balance of the therapy should be studied. For patients undergoing CRRT, the dosage should be at least 560 mg/qd, although it would depend on the extracorporeal clearance.

4. A Population pharmacokinetic model has been developed for linezolid in critically ill patients. The pharmacokinetics of linezolid was best described by a two-compartment model. The total body clearance depended on Clcr. Moreover, in patients undergoing continuous renal replacement techniques, clearance was also dependent on the extracorporeal clearance.

5. Standard dosage of linezolid (600 mg/12h) would not achieve high probabilities of treatment success for MIC values of 2 and 4 mg/L, which are the clinical breakpoints for enterococci and staphylococci by CLSI and EUCAST.

6. Increasing the dose of linezolid to 600 mg/8h would not improve substantially the probabilities of target attainment, whilst the likelihood of an overexposure to the drug would increase notably. Therefore, other dosage regimens, such as the continuous infusion, should be explored.

APPENDIX I

APPENDIX I. Quantification of daptomycin and linezolid in plasma and effluent samples from critically ill patients by HPLC

1. Chemicals and reagents

Daptomycin and linezolid standards were kindly supplied by Novartis Pharma AG and Pfizer Pharmaceuticals, respectively. Propyl 4-hydroxybenzoate (P4HB) and ammonium phosphate-were purchased form Sigma-Aldrich (Barcelona, Spain), and acetonitrile from Merck (Darmstadt, Germany). Ultrapure water was obtained from Milli-Q® Plus apparatus (Millipore). Fresh human plasma was purchased from The Basque Center for Blood Transfusion and Human Tissues (Vitoria-Gasteiz, Spain).

2. Sample processing and analysis

The quantification of antibiotics in both plasma and effluent samples was performed by a high-performance liquid chromatography (HPLC) technique with ultraviolet (UV) detection. **Table 1** shows chromatographic conditions employed in the quantification of daptomycin and linezolid.

Table 1. Chromatographic conditions used for the quantification of the studied antibiotics.

	Chromatographic conditions	
	Daptomycin	**Linezolid**
Column	Symmetry® C8 4.6 mm x 150 mm x 5 μm	Symmetry® C8 4.6 mm x 150 mm x 5 μm
Wavelength (nm)	224	254
Temperature (ºC)	30	30
Injection volume (μL)	20	20
Flow rate (mL/min)	1.2	1
Mobile phase	Ammonium phosphate (0.5%): Acetonitrile (62:38, v: v)	Ammonium phosphate (0.5%): Acetonitrile (66:34; v: v)

Plasma sample processing was initiated precipitating the plasma proteins, by adding acetonitrile (where the internal standard, propyl 4-hydroxybenzoate, was previously diluted). Subsequently, samples were vortexed (30 seconds) and centrifugated for 10 minutes, at 4ºC. From the obtained sample supernatants, 20 μL were injected into the chromatographic system. **Figure 1** represents the plasma sample processing method employed for each antibiotic.

Regarding the effluent samples, they were not subjected to any processing. Thus, after thawing the samples, they were introduced directly into micro-vials to be injected into the chromatographic system.

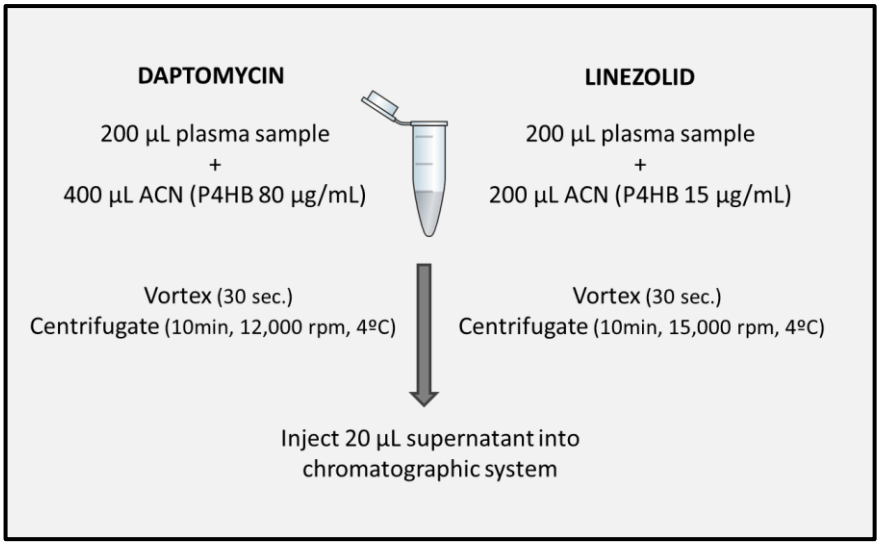

Figure 1. Plasma sample processing method used for daptomycin and linezolid. ACN: acetonitrile; P4HB: propyl 4-hydroxybenzoate.

3. Validation of the analytical method

The main goal of a validation process is to test the reliability of a particular method for the quantification of an analyte concentration in a specific biological matrix (e.g. blood, plasma or urine).

In this research work, the validation of the analytical methods to quantify daptomycin and linezolid in both plasma and effluent samples was carried out following the EMA's *Guideline on bioanalytical method validation*[1]. As stated in this

[1] European Medicines Agency. Guideline on bioanalytical method validation. Committee for Medical Products for Human Use (CHMP), 2011. Available at: *www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf* [Accessed: March 2018]

protocol, the main characteristics that are essential to ensure the acceptability of the efficiency and reliability of analytical results are: selectivity, linearity, accuracy, precision and stability.

3.1. Selectivity

The analytical method should be able to differentiate the analyte(s) of interest and internal standard (IS) from endogenous components in the matrix or other components in the sample. Selectivity should be proved using at least 6 individual sources of the appropriate blank matrix, which are individually analysed and evaluated for interference. Thus, absence of interferences is accepted where the response is less than 20% of the lower limit of quantification for the analyte and 5% for the internal standard.

The selectivity assay was performed using human plasma from 6 different donors. The possible appearance of interfering peaks of the analyte at the retention time of the IS and vice versa was also evaluated. To do so, there were analysed a plasma sample (blank), another sample in which the internal standard was included, and a third plasma sample containing the antibiotic at the lowest concentration level of the linearity range.

3.2. Linearity

Linearity can be defined as the ability of the method to obtain, within a certain interval, a linearly proportional response to the concentration of the analyte. That interval will be determined by the lower and upper limits of quantification (LLOQ and ULOQ).

To measure the linearity of the method, solutions of antibiotic were prepared in plasma and effluent at LLOQ and ULOQ. Moreover, at least six more different antibiotic concentration solutions were also formulated within the

studied linearity range. The samples were prepared in triplicate, on three different days, studying the linearity between the antibiotic concentration and the ratio of the area of the antimicrobial and P4HB (IS).

The calculation of the percent of the relative error (E%) for each case, was performed using the following equation:

$$E\ \% = \frac{Theoretical\ concentration - Calculated\ concentration}{Theoretical\ concentration} \times 100 \qquad \textbf{(Eq.1)}$$

In order to conclude that the analytical technique fulfils the criteria of linearity, the E% of each calibration standard should be lower than 15% of the nominal concentration, except for the lower limit of quantification, that should not exceed 20%.

3.3. Accuracy and precision

The accuracy describes the closeness of the determined value obtained by the method to the nominal concentration of the analyte (expressed in E%). It should be assessed for the LLOQ and on samples spiked with known amounts of the analyte; that is, the quality control (QC) samples. These controls should be within three times the LLOQ (low QC), around 30-50% of the calibration curve range (medium QC), and at least at 75% of the upper limit of quantification (high QC). Samples are analysed against the calibration curve, and the obtained concentrations are compared with the theoretical value. Accuracy should be evaluated within a single run (the intra-run accuracy) and in different runs (inter-run accuracy).

The precision of the analytical method describes the closeness of repeated individual measures of analyte. Precision is expressed as the coefficient of variation (CV, %). As for the accuracy, precision should be demonstrated for the LLOQ and QC samples, within a single run and between different runs. The limit of

quantification is the lowest concentration within the calibration line that can be measured accurately and precisely.

3.4. Stability

The analysis of the biological samples is not usually carried out immediately after their collection. Therefore, it is essential to establish the conditions in which the drugs remain stable during the storage period. Stability is a quality of the analyte that allows it to remain unchanged over time and after suffering different manipulation processes. It is evaluated using low and high QC samples, which are analysed immediately after preparation and after the applied storage conditions that are to be evaluated. The QC samples are analysed against a calibration curve, obtained from freshly spiked calibration standards, and the calculated concentrations are compared to the nominal concentrations. The mean concentration at each level should be within ±15% of the nominal concentration.

For the confirmation of this quality, the following stability studies were carried out:

3.4.1. Stability of the analyte in the biological matrix during storage

The stability of the samples in plasma was studied with 3 samples of the low and high QC under storage conditions (-80ºC and -20ºC) and over different time periods.

3.4.2. *Freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature*

Three samples of the low and high QC were stored at -80 ° C. They were subjected to three cycles of freeze-thawing, keeping them, at least, 12h in the freezer in each cycle. Three aliquots were analysed and stability was calculated.

3.4.3. *Stability in the chromatographic system*

The aliquots were analysed and maintained in the chromatographic system. They were analysed again 24 hours later, in order to detect differences between the two measurements.

3.4.4. *Stability of the stock solution of the analyte and internal standard*

Samples solutions of both antibiotic and the internal standard were prepared in triplicate. The chromatographic response (area) of the solutions after 24 h was compared with the freshly prepared solution.

Since plasma samples processing was more complex, and in order not to expand excessively, only plasma results have been included in this appendix. Even though, the validation of the analytical method was performed also for effluent samples.

4. Daptomycin: validation results

4.1. Selectivity

It was found that, in all the analysed samples, the response (chromatographic area) of the interfering peaks at the retention time of daptomycin was less than 20% of the response of the limit of quantification. Moreover, the responses of the interfering peaks at the internal standard's retention time were also less than 5% of the internal standard response to the concentration used in the study (80 μg/mL).

Figure 2 shows the chromatogram of one of the six human plasma used:

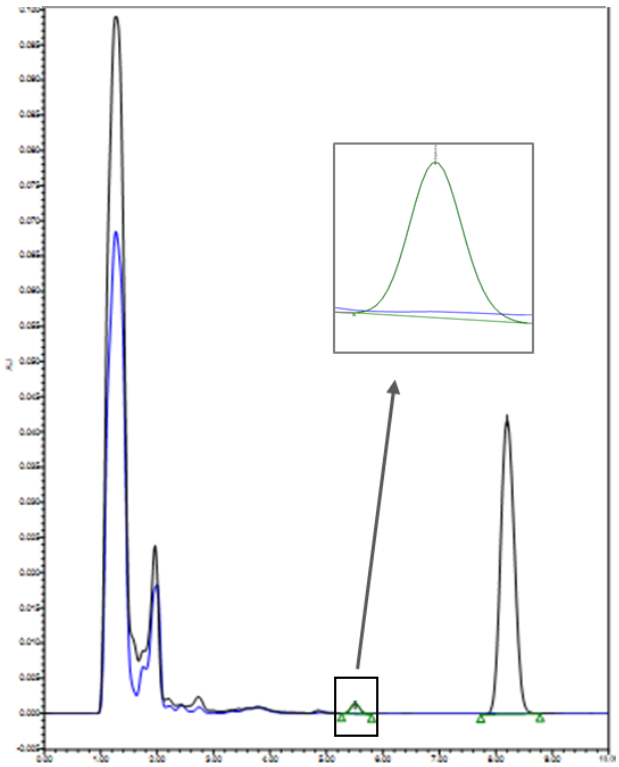

Figure 2. Chromatograms for the blank and for the sample including daptomycin and P4HB (internal standard). Retention times were 5.5 minutes for daptomycin and 8.2 minutes for P4HB.

4.2. Linearity

Table 2 shows the results obtained in the linearity study. The values of the slope (a), the intercept (b), the correlation coefficient (r) and the coefficient of determination (r^2), calculated for each of the calibration curve have been included in **table 3**.

Taking into account the results obtained, it can be concluded that the analytical technique meets the criteria of linearity at the studied concentration range; since the E% of standard was always lower than 15% of the nominal concentration, and for the lower limit of quantification it did not exceed 20%.

Table 2. Results of the linearity assay.

Nominal concentration (μg/mL)	Calculated concentration (μg/mL)			% Relative error (E%)		
	Curve 1	Curve 2	Curve 3	Curve 1	Curve 2	Curve 3
2.5	2.44	2.63	2.38	2.44	-5.11	5.02
5	4.95	5.02	5.12	1.08	-0.34	-2.36
10	9.16	9.41	9.57	8.40	5.94	4.32
25	25.73	24.83	25.74	-2.93	0.70	-2.95
50	56.43	50.92	54.94	-12.86	-1.84	-9.87
100	100.78	98.62	92.92	-0.78	1.38	7.08
150	143.01	151.08	151.84	4.66	-0.72	-1.23

Table 3. Values obtained for the slope (a), the intercept (b), the correlation coefficient (r) and the coefficient of determination (r^2), for each plasma calibration curve.

Parameter	Curve 1	Curve 2	Curve 3
a	0.012	0.012	0.011
b	0.004	0.007	-0.001
r	0.998	0.999	0.998
r^2	0.996	0.999	0.996

4.3. Accuracy and precision

Table 4. shows the results for the precision and accuracy study.

Table 4. Results of the accuracy and precision study in plasma samples.

	Nominal concentration (μg/mL)	Calculated concentration Mean ± SD (μg/mL)	Intra-assay (n = 6) CV (%)	Intra-assay E (%)
Day 1	**2.5**	2.41 ± 0.16	6.51	3.59
	7	6.7 ± 0.27	4.00	4.10
	40	44.39 ± 1.08	2.44	-0.97
	120	133.39 ± 4.35	3.27	-11.16
Day 2	**2.5**	2.67 ± 0.18	6.74	-6.72
	7	6.93 ± 0.02	1.93	0.95
	40	37.22 ± 1.31	3.51	6.99
	120	114.83 ± 7.18	6.25	4.31
Day 3	**2.5**	2.25 ± 0.14	6.06	10.43
	7	6.65 ± 0.32	4.87	5.03
	40	41.66 ± 0.94	2.26	-4.15
	120	132.34 ± 5.33	4.03	-10.28
	Nominal concentration (μg/mL)	**Calculated concentration Mean ± SD (μg/mL)**	**Inter-assay (n = 18) CV (%)**	**Inter-assay E (%)**
	2.5	2.44 ± 0.23	9.51	2.32
	7	6.77 ± 0.27	3.99	3.32
	40	41.09 ± 3.22	7.84	-2.72
	120	126.85 ± 10.28	8.11	-5.71

*SD: standard deviation; CV: coefficient of variation; E: relative error.

The coefficient of variation and the relative error of the quality controls were never higher than 15%. In the case of 2.5 μg/mL daptomycin control, the individual relative error, as well as the coefficients of variation and the inter-assay and intra-assay relative errors were lower than 20%. Thus, it has been demonstrated that the analytical method possesses the sufficient accuracy and

precision to determine the concentration of 2.5 μg/mL, and, therefore, this concentration was set as the limit of quantification.

4.4. Stability

4.4.1. Stability of the analyte in the biological matrix during storage

Table 5 shows the results of the stability study of the samples under storage conditions. As it can be seen, in all cases the deviation was lower than 15%. Therefore, it could be said that daptomycin is stable in plasma at -20 and -80ºC at least for one month.

4.4.2. Freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature

Table 5 shows the stability study data after three freeze-thaw cycles. The error in each of the samples was always below 15%, which indicates that daptomycin in samples was stable after the freeze-thaw process.

4.4.3. Stability in the chromatographic system

As it could be appreciated in **table 5**, daptomycin in samples was stable for at least 24h in the chromatographic system, since the error was never higher than 15%.

Table 5. Results obtained in the stability study.

Nominal concentration (μg/mL)	7		120	
	Calculated concentration mean ± SD	E (%)	Calculated concentration mean ± SD	E (%)
Stability during storage				
1 month (-20ºC)	7.48 ± 0.32	-1.04	113.33 ± 0.80	9.64
1 month (-80ºC)	6.88 ± 0.04	7.03	115.29 ± 1.29	8.08
Stability after freeze-thaw cycles	7.14 ± 0.38	3.51	116.04 ± 1.51	7.48
Stability in the chromatographic system (24 h)	7.37 ± 0.39	0.40	118.37 ± 1.336	5.62

*SD: standard deviation; E: relative error.

4.4.4. Stability of the stock solution

Table 6 shows the mean and standard deviation of daptomycin and internal standard stock solutions, at time 0 and at 24 h. The area of the solutions studied over time was comprised between 95-105% of the area of the same solution at time 0; that is, the relative error was always lower than 5%.

Table 6. Stability of stock solutions at time 24 h.

Stock solution (μg/mL)	Area ± SD		Error % (respected to t= 0 h)
	t = 0 h	t = 24 h	
Daptomycin			
50	1,506,860 ± 84,485	1,518,243 ± 20,492	-0.76
500	15,094,098 ± 134,168	15,076,133 ± 197,449	0.12
Internal standard			
80	98,4168 ± 20,603	1,006,699 ± 1,860	-2.29

*SD: standard deviation; E: relative error.

5. Linezolid: validation results

5.1. Selectivity

It was found that, in all the analysed samples, the response (chromatographic area) of the interfering peaks in the retention time of linezolid was less than 20% of the response of the limit of quantification. Moreover, the responses of the interfering peaks in the internal standard's retention time were also less than 5% of the internal standard response to the concentration used in the study (15 μg/mL).

Figure 3 shows the chromatogram of one of the six human plasma used:

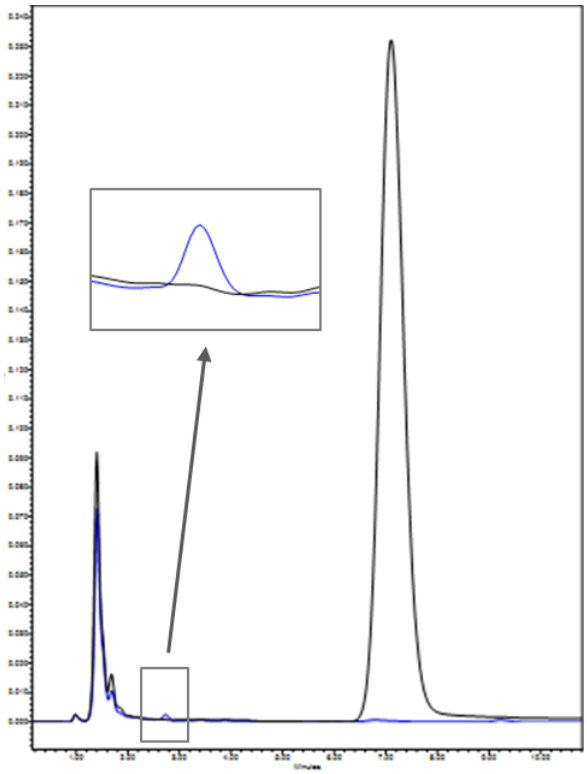

Figure 3. Chromatograms for the blank and for the sample that includes linezolid and P4HB. Retention times were 2.8 minutes for linezolid and 7.2 minutes for P4HB.

5.2. Linearity

Table 7 shows the results obtained in the linearity study. The values of the slope (a), the intercept (b), the correlation coefficient (r) and the coefficient of determination (r^2), calculated for each of the three calibration curves performed have been included in **table 8**.

Taking into account the results obtained, it can be concluded that the analytical technique meets the criteria of linearity at the studied concentration range; since the E% of standard was always lower than 15% of the nominal concentration, and for the lower limit of quantification it did not exceed 20%.

Table 7. Results of the plasma linearity assay.

Nominal concentration (μg/mL)	Calculated concentration (μg/mL)			% Relative error (E%)		
	Curve 1	Curve 2	Curve 3	Curve 1	Curve 2	Curve 3
0.5	0.46	0.45	0.41	8.91	8.94	18.70
2	2.10	1.96	2.25	-5.00	2.22	-12.58
5	5.11	5.51	5.31	-2.27	-0.24	-6.09
20	20.28	20.23	19.73	-1.37	-1.12	1.36
30	30.86	30.82	31.33	-2.87	-2.73	-4.44
50	48.70	48.53	48.48	2.61	2.93	3.04

Table 8. Values obtained for the slope (a), the intercept (b), the correlation coefficient (r) and the coefficient of determination (r^2), for each plasma calibration curve.

Parameter	Curve 1	Curve 2	Curve 3
a	0.003	0.007	0.014
b	0.035	0.040	0.036
r	1.000	0.999	0.999
r^2	0.999	0.999	0.998

5.3. Accuracy and precision

Table 9 shows the results for the precision and accuracy study.

Table 9. Results of accuracy and precision study in plasma samples.

	Nominal concentration (μg/mL)	Calculated concentration Mean ± SD (μg/mL)	Intra-assay (n = 5) CV (%)	Intra-assay E (%)
Day 1	**0.5**	0.48 ± 0.04	9.19	3.52
	1.5	1.49 ± 0.05	3.54	0.35
	10	10.94 ± 0.30	2.77	-9.44
	40	40.11 ± 1.26	3.15	-0.29
Day 2	**0.5**	0.47 ± 0.08	17.50	7.00
	1.5	1.54 ± 0.06	4.17	-2.41
	10	9.36 ± 0.13	1.39	6.36
	40	40.56 ± 3.63	8.94	-1.41
Day 3	**0.5**	0.43 ± 0.03	7.67	14.48
	1.5	1.50 ± 0.09	6.35	0.33
	10	11.26 ± 0.30	2.63	-12.61
	40	44.14 ± 1.64	3.71	-10.34
	Nominal concentration (μg/mL)	**Calculated concentration Mean ± SD (μg/mL)**	**Inter-assay (n = 15) CV (%)**	**Inter-assay E (%)**
	0.5	0.46 ± 0.02	5.22	8.33
	1.5	1.51 ± 0.07	4.66	-0.58
	10	10.52 ± 0.89	8.46	-5.23
	40	41.60 ± 2.91	6.99	-4.01

*SD: standard deviation; CV: coefficient of variation; E: relative error.

The coefficient of variation and the relative error of the quality controls were never higher than 15%. In the case of 0.5 μg/mL linezolid control, the individual relative error, as well as the coefficients of variation and the inter-assay and intra-assay relative errors were lower than 20%. Thus, it has been demonstrated that the analytical method possesses the sufficient accuracy and

precision to determine the concentration of 0.5 μg/mL, and, therefore, this concentration was set as the limit of quantification.

5.4. Stability

5.4.1. Stability of the analyte in the biological matrix during storage

Table 10 shows the results of the stability study of the samples under storage conditions. As it can be seen, in all cases the deviation is lower than 15%. Therefore, linezolid was stable in plasma at -20 and -80ºC at least for one month.

5.4.2. Freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature

Table 10 shows the stability study data after three freeze-thaw cycles. The error in each of the samples was always below 15%, which indicates that linezolid in plasma samples was stable after the freeze-thaw process.

5.4.3. Stability in the chromatographic system

As it could be appreciated in **table 5**, linezolid in samples was stable for at least 24h in the chromatographic system, since the error was never higher than 15%.

Table 10. Results obtained in the stability study.

Nominal concentration (μg/mL)	1.5		40	
	Calculated concentration mean ± SD	E (%)	Calculated concentration mean ± SD	E (%)
Stability during storage				
1 month (-20ºC)	1.56 ± 0.02	-4.00	37.11 ± 1.03	7.22
1 month (-80ºC)	1.56 ± 0.02	-4.00	43.49 ± 1.96	-8.73
Stability after freeze-thaw cycles	1.49 ± 0.02	0.67	41.67 ± 1.03	-4.19
Stability in the chromatographic system (24 h)	1.72 ± 0.10	-14.67	44.78 ± 1.23	-11.96

*SD: standard deviation; E: relative error.

5.4.4. Stability of the stock solution

Table 11 shows the mean and standard deviation of linezolid and internal standard stock solutions, at time 0 and at 24 h. The area of the solutions studied over time was comprised between 95-105% of the area of the same solution at time 0; that is, the percentage relative error was always lower than 5%.

Table 11. Stability of stock solutions at time 24 h.

Stock solution (μg/mL)	Area ± SD		Error % (respected to t=0 h)
	t = 0 h	t = 24 h	
Linezolid			
10	541,053 ± 2,953	556,340 ± 3,880	2.82
100	4,910,858 ± 24,212	5,029,011 ± 28,178	2.4
Internal standard			
15	1,445,212 ± 5,370	1,466,392 ± 25,763	1.46

*SD: standard deviation; E: relative error.

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