AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Short Form

Improved characterization of aminoglycoside penetration into human lung epithelial lining fluid via population pharmacokinetics

Eunjeong Shin,[1] Yongzhen Zhang,[1] Jieqiang Zhou,[1] Yinzhi Lang,[1] Alaa R. M. Sayed,[1] Carolin Werkman,[1] Yuanyuan Jiao,[2] Monika Kumaraswamy,[3,4] Zackery P. Bulman,[5] Brian M. Luna,[6] Jürgen B. Bulitta[1]

AUTHOR AFFILIATIONS See affiliation list on p. 4.

ABSTRACT Aminoglycosides are important treatment options for serious lung infections, but modeling analyses to quantify their human lung epithelial lining fluid (ELF) penetration are lacking. We estimated the extent and rate of penetration for five aminoglycosides via population pharmacokinetics from eight published studies. The area under the curve in ELF vs plasma ranged from 50% to 100% and equilibration half-lives from 0.61 to 5.80 h, indicating extensive system hysteresis. Aminoglycoside ELF peak concentrations were blunted, but overall exposures were moderately high.

KEYWORDS lung epithelial lining fluid (ELF), population pharmacokinetics, amikacin, arbekacin, gentamicin, netilmicin, tobramycin, plazomicin, model-based meta-analysis, S-ADAPT

Aminoglycosides are an important part of our armamentarium to treat serious lung infections caused by multidrug-resistant Gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, and often used in combination with β-lactam antibiotics (1–12). Aminoglycosides are polar polycations (Table S1) (13), have small volumes of distribution (11, 14, 15), low (<20%) protein binding (16–19), and diminished activity in acidic pH (20, 21). A few studies report lung epithelial lining fluid (ELF) concentrations to range from 10% to 30% of those in plasma or serum, though these values only considered one or two time points during the first 2 h after the start of a short-term infusion (22–25). In contrast, ELF-to-plasma concentration ratios increased over time and reached 100% in all studies that determined ELF concentrations over up to 6 to 24 h post dose (Fig. S1) (26–31).

Time-course modeling can estimate the rate and extent of penetration, as employed to assess penetration of other antibiotic classes into ELF (32–37), bone (38–41), and cerebrospinal fluid (42, 43). Physiologically based modeling has been applied to predict the pulmonary pharmacokinetics (PK) of fluoroquinolones (44). Population PK modeling is highly beneficial to handle data sets with sparse sampling (e.g., only one ELF concentration per patient) and has been employed to model ELF concentrations of aminoglycosides in mice (45–47). However, we are not aware of published PK modeling analyses of the rate and extent of ELF penetration for aminoglycosides in humans. Instead, all but one prior study reported ELF-to-plasma concentration ratios at single or several time points (22–30) without even applying a non-compartmental analysis (NCA) (48). One study used bronchoscopic micro-sampling and NCA to calculate the area under the curve (AUC) in ELF and plasma and reported a ratio of 67.6% for arbekacin (31). Thus, despite extensive clinical use of aminoglycosides to combat serious lung infections for decades, their extent and rate of human ELF penetration have never been characterized via time-course modeling. Consequently, the impact of system hysteresis with ELF

Editor James E. Leggett, Providence Portland Medical Center, Portland, Oregon, USA

Address correspondence to Jürgen B. Bulitta, jbulitta@cop.ufl.edu.

Eunjeong Shin and Yongzhen Zhang contributed equally to this article. Author order was determined both alphabetically and in order of increasing seniority.

The authors declare no conflict of interest.

See the funding table on p. 4.

Received 25 October 2023
Accepted 29 November 2023
Published 3 January 2024

concentrations lagging behind those in plasma has never been quantitatively examined (22). Failure to consider the time course of exposures may lead to underestimating drug exposures in ELF in patients.

We performed model-based meta-analyses by simultaneously modeling all data from each aminoglycoside based on eight published PK studies assessing the ELF penetration in humans after intravenous or intramuscular dosing (23, 24, 26–31). We excluded studies with inhaled dosing (14, 49), one study on plazomicin reported as a poster (25, 50), and one study (51) where tobramycin concentrations in bronchoalveolar lavage fluid were expressed as a function of creatinine. Plasma (or serum) and ELF concentration values were used as reported (23, 24, 26, 28) or digitized (27, 29–31) (see Table S2 for details). For each drug, all plasma (or serum) and ELF concentrations were analyzed by population PK modeling in the S-ADAPT (version 1.57; importance sampling algorithm) and SADAPT-TRAN software packages (52–54) using previously described approaches (41, 55–59). The systemic PK of aminoglycosides was described by linear one or two compartment models (Fig. S2), plus an additional ELF compartment with a small, non-influential volume of distribution (fixed to 0.1 L) (39, 58). We estimated the ratio (F_{ELF}) for the AUC in ELF vs plasma or serum and the ELF-to-plasma equilibration half-life ($t_{1/2,eq}$). The F_{ELF} characterizes the overall extent and $t_{1/2,eq}$ the rate of penetration.

Population PK estimated the mean ELF-to-plasma AUC ratios (F_{ELF}) between 0.502 and 1.00 for all aminoglycosides with good precision (relative standard errors, RSE ≤12%, except for 31% for amikacin, Table 1). The between-patient variability of F_{ELF} was large for amikacin (84.4% coefficient of variation) and smaller for the other aminoglycosides (≤27.6%; Fig. 1; Fig. S3). The individual subject estimates for the ELF-to-plasma AUC ratio ranged from 0.138 to 1.60 for amikacin and from 0.468 to 1.94 for gentamicin, netilmicin, and tobramycin (Table 1).

The estimated $t_{1/2,eq}$ differed between aminoglycosides with a range of 0.857 to 5.80 h in patients and 0.613 h in healthy volunteers (Table 1). It is unknown, whether these differences arose from the aminoglycoside structures (Table S1) (13), clinical factors (e.g., type of infection and inflammation) (60, 61), or both. The longest half-life was observed in neonates receiving amikacin (Fig. 1; Fig. S1). Neonates might have had an altered expression of pulmonary transporters compared to adults (62–65). Future research on such transporters and their impact on lung penetration is warranted (66–71). Owing to the sparse nature of the data sets, the differences in $t_{1/2,eq}$ between aminoglycosides should be interpreted cautiously.

The system hysteresis (Fig. S1) yielded blunted peak concentrations (C_{max}) in ELF, which were on average 2.3- to 4-fold lower than those in plasma. Despite this, the AUC in ELF was 50% to 100% of the plasma AUC. Plazomicin modeling results are shown in Fig. S4 (50). Thus, estimating the system hysteresis via time-course modeling is important when determining the ELF penetration of aminoglycosides. To support future studies, we provided Monte Carlo simulation code to simulate ELF and plasma concentrations, as well as D-optimal sampling designs [in the PopED Lite software (72)] for amikacin, gentamicin, and tobramycin in the supplementary materials.

In mice, PK analyses estimated average ELF-to-plasma AUC ratios of 0.60 to 0.88 for amikacin, tobramycin, plazomicin, and apramycin (4, 45–47, 73), consistent with our results (Table 1). However, the ELF-to-plasma equilibration half-lives were substantially faster in mice [3 to 5 min for tobramycin and plazomicin (45, 46), and 22 to 36 min for amikacin (73)] compared to those in patients (0.857 to 5.80 h; Table 1).

This study represents the first time-course modeling to characterize the rate and extent of ELF penetration for five aminoglycosides in humans based on eight published studies. Our model-based meta-analyses revealed the average AUC in ELF to be 50% to 100% compared to those in plasma for humans. The individual subject ELF penetration ratios displayed considerable variability. Due to extensive system hysteresis, the C_{max} in ELF were blunted and lower than those in plasma. With both C_{max} and AUC being correlated to bacterial killing and clinical efficacy of aminoglycosides (2–11), future studies are warranted to assess whether or not blunted C_{max} in ELF are clinically

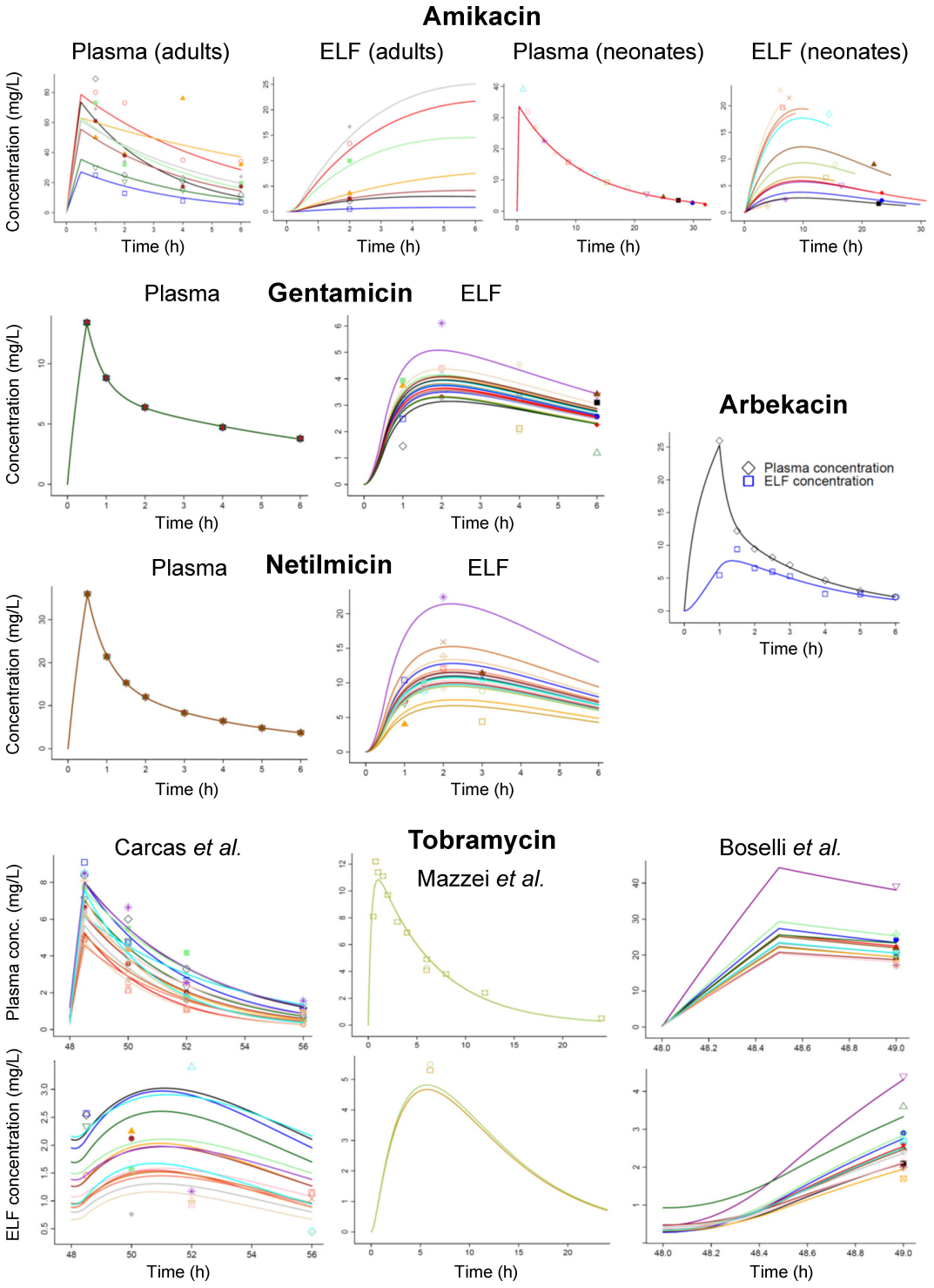

FIG 1 Fitted (lines) and observed (markers) plasma (or serum) and ELF concentrations based on published data of five aminoglycosides from eight human PK studies (23, 24, 26–31). The lines represent different subjects if individual subject data were reported (see Table S2 for details on data sets).

important. Moreover, future research is warranted to assess the impact of pH and different oxygen tensions on aminoglycoside efficacy for lung infections (74, 75). This study supports translational research to simulate the time course of ELF concentrations in *in vitro* infection models (76) and future clinical ELF penetration studies in animals and humans.

TABLE 1 Population PK parameter estimates for one- or two-compartment models describing plasma and lung ELF concentrations of five aminoglycosides after intravenous (or intramuscular) dosing[a]

Drug	Population	AUC_{ELF}/AUC_{Plasma}			$t_{1/2,eq}$ (h)	CL (L/h)	CLd (L/h)	*V*1 (L)	*V*2 (L)
		Mean (RSE[c])	BSV[b] (RSE[c])	Median [range]	Mean	Mean	Mean	Mean	Mean
Amikacin	ICU patients (with VAP)	0.502 (31%)	0.844 (39%)	0.461 [0.138–1.60]	5.80 (58%)	4.88		24.6	
Amikacin	Ventilated neonates					0.138		1.61	
Arbekacin	Healthy volunteers	0.535 (12%)	0.10 (fixed)	–[f]	0.613 (24%)	3.56	6.77	3.00	4.77
Gentamicin	VABP critically ill patients	0.600 (7%)	0.165 (160%)	0.600 [0.507–0.782]	0.857 (18%)	3.63	14.9	13.5	13.9
Netilmicin	ICU patients (ventilated, with pneumonia)[e]	1.00 (11%)	0.276 (67%)	0.989 [0.627–1.94]	1.68 (13%)	5.61	6.90	9.36	7.87
Tobramycin[d]	VABP critically Ill patients and healthy volunteers	0.642 (9%)	0.248 (84%)	0.635 [0.468–0.901]	3.38 (17%)	5.60		20.1	

[a]The volume of distribution of the ELF compartment was set to a small, non-influential value (0.1 L). The estimated ELF-to-plasma equilibration half-life characterized the extent of system hysteresis. AUC_{ELF}, area under the ELF concentration time curve from time zero to infinity (for a single aminoglycoside dose); AUC_{Plasma}, area under the plasma concentration time curve from time zero to infinity (for a single aminoglycoside dose); ICU, intensive care unit; $t_{1/2,eq}$, equilibration half-life between the ELF and the plasma compartment. This half-life characterizes the extent of system hysteresis and represents the slower rise of ELF concentrations compared to the rapid rise of the plasma or serum concentrations. If an aminoglycoside was dosed as a continuous infusion, the $t_{1/2,eq}$ would be the half-life of approaching a constant steady-state concentration in ELF; VAP / VABP, ventilator-associated (bacterial) pneumonia.
[b]BSV, between subject variability reported as coefficient of variation.
[c]Relative standard errors.
[d]The estimated absorption half-life ($t_{1/2,abs}$) after intramuscular dosing of tobramycin was 13.4 min.
[e]Patients were intubated and ventilated for a variety of reasons and received antibiotics due to the development of pneumonia.
[f]Not applicable.

ACKNOWLEDGMENTS

This study was supported by awards R01AI136803 and R01AI130185 (to J.B.B.), and R01AI173064 (to Z.B., Y.L., and J.B.B.) from the National Institute of Allergy and Infectious Diseases. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, or the Department of Veterans Affairs.

AUTHOR AFFILIATIONS

[1]Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Orlando, Florida, USA
[2]Peking University Cancer Hospital, Beijing, China
[3]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, La Jolla, California, USA
[4]Infectious Diseases Section, VA San Diego Healthcare System, San Diego, California, USA
[5]Department of Pharmacy Practice, College of Pharmacy, University of Illinois Chicago, Chicago, Illinois, USA
[6]Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

AUTHOR ORCIDs

Zackery P. Bulman http://orcid.org/0000-0002-5396-911X
Jürgen B. Bulitta http://orcid.org/0000-0001-7352-3097

FUNDING

Funder	Grant(s)	Author(s)
HHS | NIH | National Institute of Allergy and Infectious Diseases (NIAID)	R01AI136803	Jürgen B. Bulitta
HHS | NIH | National Institute of Allergy and Infectious Diseases (NIAID)	R01AI130185	Jürgen B. Bulitta
HHS | NIH | National Institute of Allergy and Infectious Diseases (NIAID)	R01AI173064	Yinzhi Lang Zackery Bulman Jürgen B. Bulitta

AUTHOR CONTRIBUTIONS

Eunjeong Shin, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing | Yongzhen Zhang, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review and editing | Jieqiang Zhou, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review and editing | Yinzhi Lang, Data curation, Formal analysis, Funding acquisition, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing | Alaa R. M. Sayed, Formal analysis, Writing – original draft, Writing – review and editing | Carolin Werkman, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review and editing | Yuanyuan Jiao, Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing | Monika Kumaraswamy, Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review and editing | Zackery P. Bulman, Conceptualization, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review and editing | Brian M. Luna, Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review and editing | Jürgen B. Bulitta, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Tables S1 to S4, Fig. S1 to S4, optimal design analyses, and simulation model code (AAC01393-23-s0001.docx). Supplementary figures, tables. and simulation model code.

REFERENCES

1. Milatovic D, Braveny I. 1987. Development of resistance during antibiotic therapy. Eur J Clin Microbiol 6:234–244. https://doi.org/10.1007/BF02017607
2. Jiao Y, Moya B, Chen MJ, Zavascki AP, Tsai H, Tao X, Sutaria DS, Louie A, Boyce JD, Deveson Lucas D, Kim TH, Tsuji BT, Bonomo RA, Drusano GL, Bulitta JB. 2019. Comparable efficacy and better safety of double β-lactam combination therapy versus β-lactam plus aminoglycoside in Gram-negative bacteria in randomized, controlled trials. Antimicrob Agents Chemother 63:e00425-19. https://doi.org/10.1128/AAC.00425-19
3. Bland CM, Pai MP, Lodise TP. 2018. Reappraisal of contemporary pharmacokinetic and pharmacodynamic principles for informing aminoglycoside dosing. Pharmacotherapy 38:1229–1238. https://doi.org/10.1002/phar.2193
4. Lepak AJ, Trang M, Hammel JP, Sader HS, Bhavnani SM, VanScoy BD, Pogue JM, Ambrose PG, Andes DR, United States Committee on Antimicrobial Susceptibility Testing. 2023. Development of modernized *Acinetobacter baumannii* susceptibility test interpretive criteria for recommended antimicrobial agents using pharmacometric approaches. Antimicrob Agents Chemother 67:e0145222. https://doi.org/10.1128/aac.01452-22
5. Zavascki AP, Klee BO, Bulitta JB. 2017. Aminoglycosides against carbapenem-resistant *Enterobacteriaceae* in the critically ill: the pitfalls of aminoglycoside susceptibility. Expert Rev Anti Infect Ther 15:519–526. https://doi.org/10.1080/14787210.2017.1316193
6. Pai MP, Rodvold KA. 2014. Aminoglycoside dosing in patients by kidney function and area under the curve: the Sawchuk-Zaske dosing method revisited in the era of obesity. Diagn Microbiol Infect Dis 78:178–187. https://doi.org/10.1016/j.diagmicrobio.2013.10.011
7. Craig WA. 2011. Optimizing aminoglycoside use. Crit Care Clin 27:107–121. https://doi.org/10.1016/j.ccc.2010.11.006
8. Turnidge J. 2003. Pharmacodynamics and dosing of aminoglycosides. Infect Dis Clin North Am 17:503–528, https://doi.org/10.1016/s0891-5520(03)00057-6
9. Barclay ML, Begg EJ, Hickling KG. 1994. What is the evidence for once-daily aminoglycoside therapy? Clin Pharmacokinet 27:32–48. https://doi.org/10.2165/00003088-199427010-00004
10. Tulkens PM. 1990. Efficacy and safety of aminoglycosides once-a-day: experimental and clinical data. Scand J Infect Dis Suppl 74:249–257.
11. Pechere JC, Dugal R. 1979. Clinical pharmacokinetics of aminoglycoside antibiotics. Clin Pharmacokinet 4:170–199. https://doi.org/10.2165/00003088-197904030-00002
12. Serio AW, Keepers T, Andrews L, Krause KM, Bush K. 2018. Aminoglycoside revival: review of a historically important class of antimicrobials undergoing rejuvenation. EcoSal Plus 8. https://doi.org/10.1128/ecosalplus.ESP-0002-2018
13. O'Shea R, Moser HE. 2008. Physicochemical properties of antibacterial compounds: implications for drug discovery. J Med Chem 51:2871–2878. https://doi.org/10.1021/jm700967e
14. Touw DJ. 1998. Clinical pharmacokinetics of antimicrobial drugs in cystic fibrosis. Pharm World Sci 20:149–160. https://doi.org/10.1023/a:1008634911114
15. Tod M, Padoin C, Petitjean O. 2000. Clinical pharmacokinetics and pharmacodynamics of isepamicin. Clin Pharmacokinet 38:205–223. https://doi.org/10.2165/00003088-200038030-00002
16. Contrepois A, Brion N, Garaud JJ, Faurisson F, Delatour F, Levy JC, Deybach JC, Carbon C. 1985. Renal disposition of gentamicin, dibekacin, tobramycin, netilmicin, and amikacin in humans. Antimicrob Agents Chemother 27:520–524. https://doi.org/10.1128/AAC.27.4.520
17. Gordon RC, Regamey C, Kirby WM. 1972. Serum protein binding of the aminoglycoside antibiotics. Antimicrob Agents Chemother 2:214–216. https://doi.org/10.1128/AAC.2.3.214

18. Segal JL, Brunnemann SR, Eltorai IM. 1990. Pharmacokinetics of amikacin in serum and in tissue contiguous with pressure sores in humans with spinal cord injury. Antimicrob Agents Chemother 34:1422–1428. https://doi.org/10.1128/AAC.34.7.1422
19. Brunnemann SR, Segal JL. 1991. Amikacin serum protein binding in spinal cord injury. Life Sci 49:PL1–PL5. https://doi.org/10.1016/0024-3205(91)90030-f
20. Bodem CR, Lampton LM, Miller DP, Tarka EF, Everett ED. 1983. Endobronchial pH. relevance of aminoglycoside activity in Gram-negative bacillary pneumonia. Am Rev Respir Dis 127:39–41. https://doi.org/10.1164/arrd.1983.127.1.39
21. Blaser J, Lüthy R. 1988. Comparative study on antagonistic effects of low pH and cation supplementation on *in-vitro* activity of quinolones and aminoglycosides against *Pseudomonas aeruginosa*. J Antimicrob Chemother 22:15–22. https://doi.org/10.1093/jac/22.1.15
22. Rodvold KA, George JM, Yoo L. 2011. Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents. Clinical Pharmacokinetics 50:637–664. https://doi.org/10.2165/11594090-000000000-00000
23. Boselli E, Breilh D, Djabarouti S, Guillaume C, Rimmelé T, Gordien J-B, Xuereb F, Saux M-C, Allaouchiche B. 2007. Reliability of mini-bronchoalveolar lavage for the measurement of epithelial lining fluid concentrations of tobramycin in critically ill patients. Intensive Care Med 33:1519–1523. https://doi.org/10.1007/s00134-007-0688-x
24. Najmeddin F, Shahrami B, Azadbakht S, Dianatkhah M, Rouini MR, Najafi A, Ahmadi A, Sharifnia H, Mojtahedzadeh M. 2020. Evaluation of epithelial lining fluid concentration of amikacin in critically ill patients with ventilator-associated pneumonia. J Intensive Care Med 35:400–404. https://doi.org/10.1177/0885066618754784
25. Drwiega EN, Rodvold KA. 2022. Penetration of antibacterial agents into pulmonary epithelial lining fluid: an update. Clin Pharmacokinet 61:17–46. https://doi.org/10.1007/s40262-021-01061-7
26. Mazzei T, Novelli A, De Lalla F, Mini E, Periti P. 1995. Tissue penetration and pulmonary disposition of tobramycin. J Chemother 7:363–370. https://doi.org/10.1179/joc.1995.7.4.363
27. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G. 2005. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest 128:545–552. https://doi.org/10.1378/chest.128.2.545
28. Carcas AJ, García-Satué JL, Zapater P, Frías-Iniesta J. 1999. Tobramycin penetration into epithelial lining fluid of patients with pneumonia. Clin Pharmacol Ther 65:245–250. https://doi.org/10.1016/S0009--9236(99)70103-7
29. Valcke YJ, Vogelaers DP, Colardyn FA, Pauwels RA. 1992. Penetration of netilmicin in the lower respiratory tract after once-daily dosing. Chest 101:1028–1032. https://doi.org/10.1378/chest.101.4.1028
30. Tayman C, El-Attug MN, Adams E, Van Schepdael A, Debeer A, Allegaert K, Smits A. 2011. Quantification of amikacin in bronchial epithelial lining fluid in neonates. Antimicrob Agents Chemother 55:3990–3993. https://doi.org/10.1128/AAC.00277-11
31. Funatsu Y, Hasegawa N, Fujiwara H, Namkoong H, Asami T, Tasaka S, Kimizuka Y, Kamata H, Ishii M, Iketani O, Ogata H, Iwata S, Betsuyaku T. 2014. Pharmacokinetics of arbekacin in bronchial epithelial lining fluid of healthy volunteers. J Infect Chemother 20:607–611. https://doi.org/10.1016/j.jiac.2014.05.007
32. Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. 2011. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 55:1606–1610. https://doi.org/10.1128/AAC.01330-10
33. Lodise TP, Kinzig-Schippers M, Drusano GL, Loos U, Vogel F, Bulitta J, Hinder M, Sörgel F. 2008. Use of population pharmacokinetic modeling and Monte Carlo simulation to describe the pharmacodynamic profile of cefditoren in plasma and epithelial lining fluid. Antimicrob Agents Chemother 52:1945–1951. https://doi.org/10.1128/AAC.00736-06
34. Layios N, Visée C, Mistretta V, Denooz R, Maes N, Descy J, Frippiat F, Marchand S, Grégoire N. 2022. Modelled target attainment after temocillin treatment in severe pneumonia: systemic and epithelial lining fluid pharmacokinetics of continuous versus intermittent infusions. Antimicrob Agents Chemother 66:e0205221. https://doi.org/10.1128/AAC.02052-21
35. Das S, Fitzgerald R, Ullah A, Bula M, Collins AM, Mitsi E, Reine J, Hill H, Rylance J, Ferreira DM, Tripp K, Bertasini A, Franzoni S, Massimiliano M, Lahlou O, Motta P, Barth P, Velicitat P, Knechtle P, Hope W. 2020. Intrapulmonary pharmacokinetics of cefepime and enmetazobactam in healthy volunteers: towards new treatments for nosocomial pneumonia. Antimicrob Agents Chemother 65:e01468-20. https://doi.org/10.1128/AAC.01468-20
36. Felton TW, Ogungbenro K, Boselli E, Hope WW, Rodvold KA. 2018. Comparison of piperacillin exposure in the lungs of critically ill patients and healthy volunteers. J Antimicrob Chemother 73:1340–1347. https://doi.org/10.1093/jac/dkx541
37. van Hasselt JGC, Rizk ML, Lala M, Chavez-Eng C, Visser SAG, Kerbusch T, Danhof M, Rao G, van der Graaf PH. 2016. Pooled population pharmacokinetic model of imipenem in plasma and the lung epithelial lining fluid. Br J Clin Pharmacol 81:1113–1123. https://doi.org/10.1111/bcp.12901
38. Landersdorfer CB, Kinzig M, Höhl R, Kempf P, Nation RL, Sörgel F. 2020. Physiologically based population pharmacokinetic modeling approach for ciprofloxacin in bone of patients undergoing orthopedic surgery. ACS Pharmacol Transl Sci 3:444–454. https://doi.org/10.1021/acsptsci.0c00045
39. Landersdorfer CB, Kinzig M, Bulitta JB, Hennig FF, Holzgrabe U, Sörgel F, Gusinde J. 2009. Bone penetration of amoxicillin and clavulanic acid evaluated by population pharmacokinetics and Monte Carlo simulation. Antimicrob Agents Chemother 53:2569–2578. https://doi.org/10.1128/AAC.01119-08
40. Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sörgel F. 2009. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. Clin Pharmacokinet 48:89–124. https://doi.org/10.2165/00003088-200948020-00002
41. Landersdorfer CB, Kinzig M, Hennig FF, Bulitta JB, Holzgrabe U, Drusano GL, Sörgel F, Gusinde J. 2009. Penetration of moxifloxacin into bone evaluated by Monte Carlo simulation. Antimicrob Agents Chemother 53:2074–2081. https://doi.org/10.1128/AAC.01056-08
42. Panjasawatwong N, Wattanakul T, Hoglund RM, Bang ND, Pouplin T, Nosoongnoen W, Ngo VN, Day JN, Tarning J. 2020. Population pharmacokinetic properties of antituberculosis drugs in Vietnamese children with tuberculous meningitis. Antimicrob Agents Chemother 65:e00487-20. https://doi.org/10.1128/AAC.00487-20
43. Kennedy JL, Bulitta JB, Chatham-Stephens K, Person MK, Cook R, Mongkolrattanothai T, Shin E, Yu P, Negron ME, Bower WA, Hendricks K. 2022. Postexposure prophylaxis and treatment of *Bacillus anthracis* infections: a systematic review and meta-analyses of animal models, 1947-2019. Clin Infect Dis 75:S379–S391. https://doi.org/10.1093/cid/ciac591
44. Aulin LBS, Tandar ST, van Zijp T, van Ballegooie E, van der Graaf PH, Saleh MAA, Välitalo P, van Hasselt JGC. 2022. Physiologically based modelling framework for prediction of pulmonary pharmacokinetics of antimicrobial target site concentrations. Clin Pharmacokinet 61:1735–1748. https://doi.org/10.1007/s40262-022-01186-3
45. Louie A, Liu W, Fikes S, Brown D, Drusano GL. 2013. Impact of meropenem in combination with tobramycin in a murine model of *Pseudomonas aeruginosa* pneumonia. Antimicrob Agents Chemother 57:2788–2792. https://doi.org/10.1128/AAC.02624-12
46. Drusano GL, Liu W, Fikes S, Cirz R, Robbins N, Kurhanewicz S, Rodriquez J, Brown D, Baluya D, Louie A. 2014. Interaction of drug- and granulocyte-mediated killing of *Pseudomonas aeruginosa* in a murine pneumonia model. J Infect Dis 210:1319–1324. https://doi.org/10.1093/infdis/jiu237
47. Becker K, Aranzana-Climent V, Cao S, Nilsson A, Shariatgorji R, Haldimann K, Platzack B, Hughes D, Andrén PE, Böttger EC, Friberg LE, Hobbie SN, ENABLE consortium. 2021. Efficacy of EBL-1003 (apramycin) against *Acinetobacter baumannii* lung infections in mice. Clin Microbiol Infect 27:1315–1321. https://doi.org/10.1016/j.cmi.2020.12.004
48. Bulitta JB, Holford NHG. 2008. An introductory guide to non-compartmental analysis, p 1–28. In D'Agostino RB, Sullivan L, Massaro J (ed), Wiley encyclopedia of clinical trials. John Wiley & Sons, Inc, Hoboken, NJ.
49. Akkerman-Nijland AM, Akkerman OW, Grasmeijer F, Hagedoorn P, Frijlink HW, Rottier BL, Koppelman GH, Touw DJ. 2021. The pharmacokinetics of antibiotics in cystic fibrosis. Expert Opin Drug Metab Toxicol 17:53–68. https://doi.org/10.1080/17425255.2021.1836157

50. Cass R, Kostrub CF, Gotfried M, Rodvold K, Tack KJ, Bruss J. 2013. A double-blind, randomized, placebo-controlled study to assess the safety, tolerability, plasma pharmacokinetics and lung penetration of intravenous plazomicin in healthy subjects [poster 1637]. Abstracts from the European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany.
51. Braude AC, Hornstein A, Klein M, Vas S, Rebuck AS. 1983. Pulmonary disposition of tobramycin. Am Rev Respir Dis 127:563–565. https://doi.org/10.1164/arrd.1983.127.5.563
52. Bulitta JB, Bingölbali A, Shin BS, Landersdorfer CB. 2011. Development of a new pre- and post-processing tool (SADAPT-TRAN) for nonlinear mixed-effects modeling in S-ADAPT. AAPS J 13:201–211. https://doi.org/10.1208/s12248-011-9257-x
53. Bulitta JB, Landersdorfer CB. 2011. Performance and robustness of the Monte Carlo importance sampling algorithm using parallelized S-ADAPT for basic and complex mechanistic models. AAPS J 13:212–226. https://doi.org/10.1208/s12248-011-9258-9
54. Bauer RJ, Guzy S, Ng C. 2007. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. AAPS J 9:E60–E83. https://doi.org/10.1208/aapsj0901007
55. Bulitta JB, Duffull SB, Kinzig-Schippers M, Holzgrabe U, Stephan U, Drusano GL, Sörgel F. 2007. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother 51:2497–2507. https://doi.org/10.1128/AAC.01477-06
56. Bulitta JB, Okusanya OO, Forrest A, Bhavnani SM, Clark K, Still JG, Fernandes P, Ambrose PG. 2013. Population pharmacokinetics of fusidic acid: rationale for front-loaded dosing regimens due to autoinhibition of clearance. Antimicrob Agents Chemother 57:498–507. https://doi.org/10.1128/AAC.01354-12
57. Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sörgel F. 2009. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. Clin Pharmacokinet 48:89–124. https://doi.org/10.2165/00003088-200948020-00002
58. Jiao Y, Yan J, Vicchiarelli M, Sutaria DS, Lu P, Reyna Z, Spellberg B, Bonomo RA, Drusano GL, Louie A, Luna BM, Bulitta JB. 2023. Individual components of polymyxin B modeled via population pharmacokinetics to design humanized dosage regimens for a bloodstream and lung infection model in immune-competent mice. Antimicrob Agents Chemother 67:e0019723. https://doi.org/10.1128/aac.00197-23
59. Wittau M, Paschke S, Kurlbaum M, Scheele J, Ly NS, Hemper E, Kornmann M, Henne-Bruns D, Bulitta JB. 2017. Population pharmacokinetics and target attainment of ertapenem in plasma and tissue assessed via microdialysis in morbidly obese patients after laparoscopic visceral surgery. Antimicrob Agents Chemother 61:e00952-16. https://doi.org/10.1128/AAC.00952-16
60. Peteranderl C, Sznajder JI, Herold S, Lecuona E. 2017. Inflammatory responses regulating alveolar ion transport during pulmonary infections. Front Immunol 8:446. https://doi.org/10.3389/fimmu.2017.00446
61. Chai AB, Ammit AJ, Gelissen IC. 2017. Examining the role of ABC lipid transporters in pulmonary lipid homeostasis and inflammation. Respir Res 18:41. https://doi.org/10.1186/s12931-017-0526-9
62. Arya V, Demarco VG, Issar M, Hochhaus G. 2006. Contrary to adult, neonatal rats show pronounced brain uptake of corticosteroids. Drug Metab Dispos 34:939–942. https://doi.org/10.1124/dmd.105.007419
63. Brouwer KLR, Aleksunes LM, Brandys B, Giacoia GP, Knipp G, Lukacova V, Meibohm B, Nigam SK, Rieder M, de Wildt SN, Pediatric Transporter Working Group. 2015. Human Ontogeny of drug transporters: review and recommendations of the pediatric transporter working group. Clin Pharmacol Ther 98:266–287. https://doi.org/10.1002/cpt.176
64. Smits A, Annaert P, Van Cruchten S, Allegaert K. 2020. A physiology-based pharmacokinetic framework to support drug development and dose precision during therapeutic hypothermia in neonates. Front Pharmacol 11:587. https://doi.org/10.3389/fphar.2020.00587
65. Allegaert K, Simons SHP, Tibboel D, Krekels EH, Knibbe CA, van den Anker JN. 2017. Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: filling the gaps beyond developmental pharmacology. Eur J Pharm Sci 109S:S27–S31. https://doi.org/10.1016/j.ejps.2017.05.023
66. Brillault J, De Castro WV, Harnois T, Kitzis A, Olivier J-C, Couet W. 2009. P-glycoprotein-mediated transport of moxifloxacin in a Calu-3 lung epithelial cell model. Antimicrob Agents Chemother 53:1457–1462. https://doi.org/10.1128/AAC.01253-08
67. Aoki M, Iguchi M, Hayashi H, Shibasaki S, Kurosawa T, Hayashi M. 2009. Active uptake of ulifloxacin from plasma to lung that controls its concentration in epithelial lining fluid. Biol Pharm Bull 32:1095–1100. https://doi.org/10.1248/bpb.32.1095
68. Deguchi Y, Sun J, Tauchi Y, Sakai S, Morimoto K. 2003. Distribution characteristics of grepafloxacin, a fluoroquinolone antibiotic, in lung epithelial lining fluid and alveolar macrophage. Drug Metab Pharmacokinet 18:319–326. https://doi.org/10.2133/dmpk.18.319
69. Kim YH, Kim K-J, D'Argenio DZ, Crandall ED. 2021. Characteristics of passive solute transport across primary rat alveolar epithelial cell monolayers. Membranes 11:331. https://doi.org/10.3390/membranes11050331
70. Rotoli BM, Barilli A, Visigalli R, Ferrari F, Frati C, Lagrasta CA, Lascia MD, Riccardi B, Puccini P, Dall'Asta V. 2020. Characterization of ABC transporters in EpiAirway, a cellular model of normal human bronchial epithelium. Int J Mol Sci 21:3190. https://doi.org/10.3390/ijms21093190
71. Sun J, Deguchi Y, Tauchi Y, He Z, Cheng G, Morimoto K. 2006. Distribution characteristics of orally administered olamufloxacin, a newly synthesized fluoroquinolone antibacterial, in lung epithelial lining fluid and alveolar macrophage in rats. Eur J Pharm Biopharm 64:238–245. https://doi.org/10.1016/j.ejpb.2006.04.009
72. Aoki Y, Sundqvist M, Hooker AC, Gennemark P. 2016. PopED lite: an optimal design software for preclinical pharmacokinetic and pharmacodynamic studies. Comput Methods Programs Biomed 127:126–143. https://doi.org/10.1016/j.cmpb.2016.02.001
73. Luna BM, Bulitta JB. Development and pharmacokinetic challenges of a murine model for *Acinetobacter baumannii* infection. Advancing animal models for antibacterial drug development workshop. FDA Center for Drug Evaluation and Research, Silver Spring, MD, March 5, 2020.
74. Shohet I, Yellin A, Meyerovitch J, Rubinstein E. 1987. Pharmacokinetics and therapeutic efficacy of gentamicin in an experimental pleural empyema rabbit model. Antimicrob Agents Chemother 31:982–985. https://doi.org/10.1128/AAC.31.7.982
75. König C, Simmen HP, Blaser J. 1993. Effect of pathological changes of pH, pO_2 and pCO_2 on the activity of antimicrobial agents *in vitro*. Eur J Clin Microbiol Infect Dis 12:519–526. https://doi.org/10.1007/BF01970957
76. Bulitta JB, Hope WW, Eakin AE, Guina T, Tam VH, Louie A, Drusano GL, Hoover JL. 2019. Generating robust and informative nonclinical *in vitro* and *in vivo* bacterial infection model efficacy data to support translation to humans. Antimicrob Agents Chemother 63:e02307-18. https://doi.org/10.1128/AAC.02307-18