Development of a Population Pharmacokinetic Model of Levofloxacin in Healthy Adults and Identification of Optimal Dosing Regimens

RES-003

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Introduction/Objective

Levofloxacin (LVX), a third-generation fluoroquinolone, is widely used for infections due to its broad-spectrum activity against Gram-positive, Gram-negative, atypical organisms (Mycoplasma, Chlamydia, Legionella), and Mycobacteria [1,2]. Its nearly 100% bioavailability enables oral-to-intravenous switch therapy and excellent tissue penetration for respiratory, urinary tract, and skin infections [3,4]. The fluorine atom at C-6 and the N-methylated piperazine ring at C-7 enhance permeability and absorption [5,6]. The key PK/PD index is the 24-h free AUC/MIC ratio (*f*AUC/MIC) [7,8]. FDA and EMA guidelines adjust LVX dosing only for CrCl <50 mL/min, applying uniform doses for CrCl ≥50 mL/min [5,9]. This overlooks augmented renal clearance (ARC; CrCl >130 mL/min/1.73 m²), common in critically ill, younger, or obese patients, which can increase LVX clearance and reduce exposure [10–14]. Proposed PK/PD targets (*f*AUC/MIC ≥30–40 for Gram-positive, ≥100–125 for Gram-negative) represent minimum thresholds and are difficult to apply without validated PK models requiring multiple blood samples. Bayesian-assisted dosing may enable individualized therapy but remains rare for LVX [7,15–21].This study used Monte Carlo simulations with a healthy-volunteer population PK model to test guideline-based dosing in patients with CrCl ≥50 mL/min and to evaluate regimens stratified by narrower CrCl intervals (10–19, 20–49, 50–89, 90–129, 130–170 mL/min). We hypothesized that CrCl-stratified dosing would improve target attainment and support evidence-based recommendations across diverse renal function.

Methods

This study was approved by the IRB at Hallym University Sacred Heart Hospital (IRB No. 2024-05-015). It was conducted in August 2024 with healthy adults aged 19–55 who passed comprehensive health screenings. Individuals with chronic diseases, past liver/kidney issues, allergies to study drugs, infectious diseases, or pregnancy were excluded. Participants received 500 mg of LVX via 1 h IV infusion. Blood samples were collected immediately before infusion initiation (0 min) and at 61 min, 75 min, 90 min, 4 h, 8 h, and 24 h post-infusion initiation at pre-specified time points, and plasma concentrations were measured using validated LC-MS/MS methods.

Population pharmacokinetic (PK) modeling was performed using NONMEM (version 7.5), testing one- to three-compartment models under first-order kinetics. The model incorporated interindividual variability (IIV) and residual variability using exponential and combined error models, respectively. Model selection was based on objective function value changes, goodness-of-fit diagnostics, and bootstrap validation. Significant covariates, including renal function indicators (e.g., Cockcroft-Gault, MDRD, CKD-EPI), were identified using a stepwise selection process.

Monte Carlo simulations were performed with a population PK model to evaluate FDA/EMA levofloxacin dosing. In the first simulation, 10,000 virtual adults with CrCl ≥50 mL/min received guideline regimens (500 mg q24h, 750 mg q24h, 500 mg q12h), and PTA for *f*AUC/MIC targets (≥30 for S. pneumoniae, ≥100 for E. coli, ≥125 for P. aeruginosa) was calculated using EUCAST MIC data (accessed 18 February 2025). In the second simulation, 1,000 virtual adults across five CrCl categories (10–19, 20–49, 50–89, 90–129, 130–170 mL/min) received various daily doses (125–1500 mg) to identify optimal regimens by renal function and MIC.

Results

The demographic and clinical characteristics of the 12 healthy adult subjects (8 females, 4 males) are listed in **Table 1**.

Table 1. Characteristics of the participants

Variables	Median (min–max)		
	Total (*n* = 12)	Female (*n* = 8)	Male (*n* = 4)
Demographic characteristics			
Age, years	35.5 (29.0–44.0)	37.5 (29.0–44.0)	33.0 (30.0–44.0)
TBW, kg	68.0 (47.3–77.2)	58.4 (47.3–75.7)	72.8 (67.5–77.2)
LBM, kg [a]	47.9 (37.7–60.3)	43.6 (37.7–51.3)	58.1 (53.6–60.3)
Height, cm	165 (152–181)	161 (152–171)	174 (168–181)
Body surface area, m^2 [b]	1.75 (1.45–1.94)	1.63 (1.45–1.86)	1.89 (1.77–1.94)
Body mass index, kg/m^2	23.5 (18.3–28.9)	22.5 (18.3–28.9)	23.8 (21.3–26.8)
Laboratory characteristics			
Protein, g/dL	7.45 (6.80–8.00)	7.50 (6.80–8.00)	7.20 (6.90–7.50)
Albumin, g/dL	4.75 (4.40–5.20)	4.75 (4.40–5.20)	4.80 (4.60–4.90)
Creatinine, mg/dL	0.850 (0.560–1.11)	0.780 (0.560–0.900)	1.06 (0.880–1.11)
Cystatin C, mg/dL	0.880 (0.780–1.06)	0.880 (0.780–1.06)	0.885 (0.850–0.930)
Renal functions			
CrCl, mL/min [c]	106 (74.8–113)	99.6 (74.8–113)	106 (90.5–113)
$eGFR_{MDRD}$, mL/min/1.73 m^2 [d]	80.1 (69.8–121)	81.6 (69.8–121)	78.8 (77.8–99.1)
$eGFR_{CKD\text{-}EPI\_CR}$, mL/min/1.73 m^2 [e]	95.8 (83.1–120)	98.1 (83.1–120)	92.7 (91.6–116)
$eGFR_{CKD\text{-}EPI\_CRCC}$, mL/min/1.73 m^2 [f]	98.2 (81.3–119)	97.2 (81.3–119)	99.4 (94.0–113)

TBW— total body weight; LBM—lean body mass; CrCl—creatinine clearance; eGFR—estimated glomerular filtration rate; MDRD—modification of diet in renal disease; CKD-EPI—chronic kidney disease epidemiology collaboration; CR—creatinine; CC—cystatin C; min—the minimum of (CR or CC)/number and 1; max—the maximum of (CR or CC)/number and 1. [a] LBM (female) = 1.07 × TBW- 148 × (TBW/height)^2. LBM (male) = 1.1 × TBW-128 × (TBW/height)^2. [b] Body surface area = $0.007184 \times TBW^{0.425} \times height^{0.725}$ (Du Bois formula [23]). [c] CrCl = (140−Age) × TBW/CR × 72 (×0.85 if female). [d] $eGFR_{MDRD} = 175 \times CR^{-1.154} \times Age^{-0.203}$ (×0.742 if female). [e] $eGFR_{CKD\text{-}EPI\_CR}$ (female) = $142 \times \min(CR/0.7,1)^{-0.241} \times \max(CR/0.7,1)^{-1.200} \times 0.9938^{Age} \times 1.012$. $eGFR_{CKD\text{-}EPI\_CR}$ (male) = $142 \times \min(CR/0.9,1)^{-0.302} \times \max(CR/0.9,1)^{-1.200} \times 0.9938^{Age}$. [f] $eGFR_{CKD\text{-}EPI\_CRCC}$ (female) = $135 \times \min(CR/0.7,1)^{-0.219} \times \max(CR/0.7,1)^{-0.544} \times \min(CC/0.8,1)^{0.323} \times \max(CC/0.8,1)^{-0.778} \times 0.9961^{Age} \times 0.963$. $eGFR_{CKD\text{-}EPI\_CRCC}$ (male) = $135 \times \min(CR/0.9,1)^{-0.144} \times \max(CR/0.9,1)^{-0.544} \times \min(CYS/0.8,1)^{0.323} \times \max(CYS/0.8,1)^{-0.778} \times 0.9961^{Age}$.

Eighty-four plasma samples (**Figure 1**) were analyzed to characterize the PK profile of LVX, which was best described by a two-compartment model (**Table 2**). The selected two-compartment model included parameters such as the total clearance (CL), volume of distribution in the central compartment (V1), volume of distribution for the peripheral compartments (V2), and intercompartmental clearance between V1 and V2 (Q2). Covariate analysis identified CrCl (affecting CL) and lean body mass (LBM) (affecting V2) as significant factors. In the final model, the covariates CrCl and LBM were incorporated using a power model structure (Table 2). Specifically, CL was modeled as a function of CrCl, and V2 was modeled as a function of LBM.

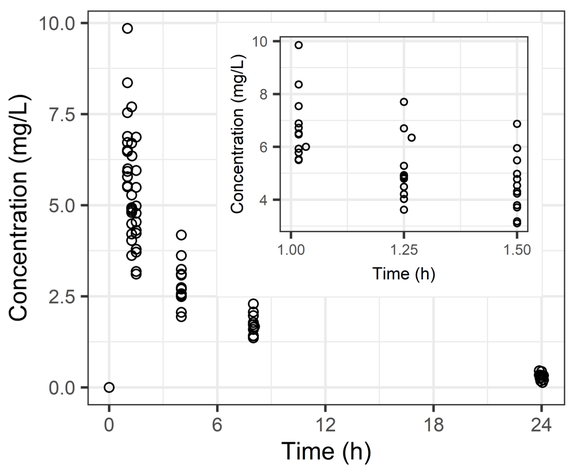


Figure 1. Levofloxacin concentration–time profile in healthy adults. The main plot represents the entire sampling period, and the inset highlights the concentration–time profile during the early phase (1.0–1.5 h). The open circles are observed drug concentrations.

Table 2. Parameter estimates and bootstrap medians (95% confidence intervals) for the final PK model of piperacillin

Parameter	Estimates	RSE (%) [Shrinkage, %]	Bootstrap Median (95% CI)
	Structural model		
$CL = \theta_1 \times (CrCl/105.71)^{\theta 2}$			
θ_1 (L/h)	13.4	3.36	13.4 (12.6–14.5)
θ_2	0.901	16.8	0.900 (0.392–1.26)
V1	34.3	8.93	34.5 (29.6–41.3)
Q	72.8	10.9	72.4 (56.6–86.2)
$V2 = \theta_3 \times (LBM/47.91)^{\theta 4}$			
θ_3 (L)	67.7	3.42	67.4 (62.1–71.9)
θ_4	1.75	12.5	1.76 (1.32–2.27)
	Interindividual variability		
CL (%)	8.99	15.3 [3.58]	8.23 (4.65–11.1)
Q (%)	36.0	30.6 [10.2]	35.3 (0.000–53.0)
	Residual variability		
Proportional error (%)	6.99	13.8 [7.09]	6.72 (4.68–8.24)

RSE—relative standard error; CI—confidence interval; CL—total clearance; V1—central volume of distribution; V2—volume of distribution for the first peripheral compartment; Q—intercompartmental clearance between V1 and V2; CrCl—individual creatinine clearance estimated using the Cockcroft–Gault equation (mL/min, with 105.71 mL/min used as the median reference value); LBM—individual lean body mass (kg), with 47.91 kg used as the median reference value.

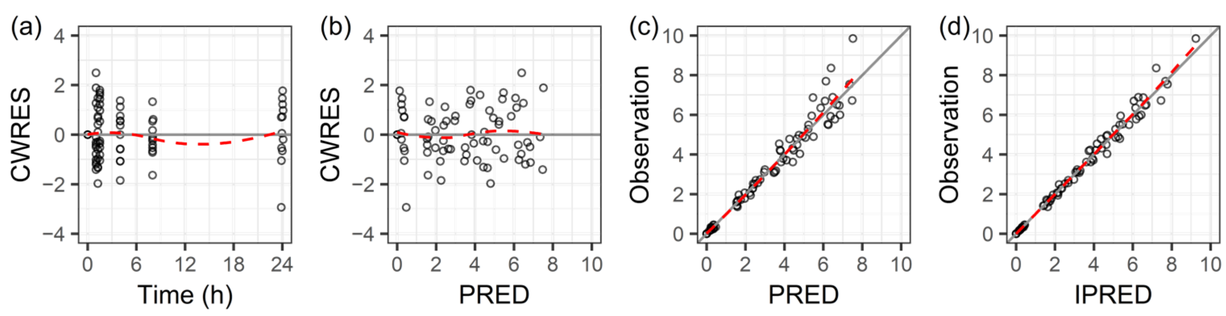


Figure 2. Goodness-of-fit plots for the final PK model of levofloxacin: (a) conditional weighted residuals (CWRESs) vs. time, (b) CWRESs vs. population-predicted concentration (PRED), (c) observed concentration vs. PRED, and (d) observed concentration vs. individual-predicted concentration (IPRED). The dashed red lines represent smooth curves.

Results (continued)

Figure 2 presents diagnostic goodness-of-fit plots for the final PK model of LVX. The conditional weighted residuals (CWRESs) and concentrations were primarily evenly distributed around the x axis or line of identity (y = x), indicating that the structural models were appropriately fitted and unbiased. **Figure 3** presents the visual predictive check (VPC) for LVX. The observed 10th, 50th, and 90th percentiles were aligned within the 95% CIs of the corresponding simulated percentiles, confirming that the final PK models accurately reflected the observed drug concentrations and exhibited strong predictive capabilities. Figure A4 shows the VPC as a function of the CrCl. Similar to Figure 2, the observed percentiles were well captured by the simulated pre-diction intervals, supporting the adequacy of the covariate model in describing the relationship between CrCl and the LVX PK model.

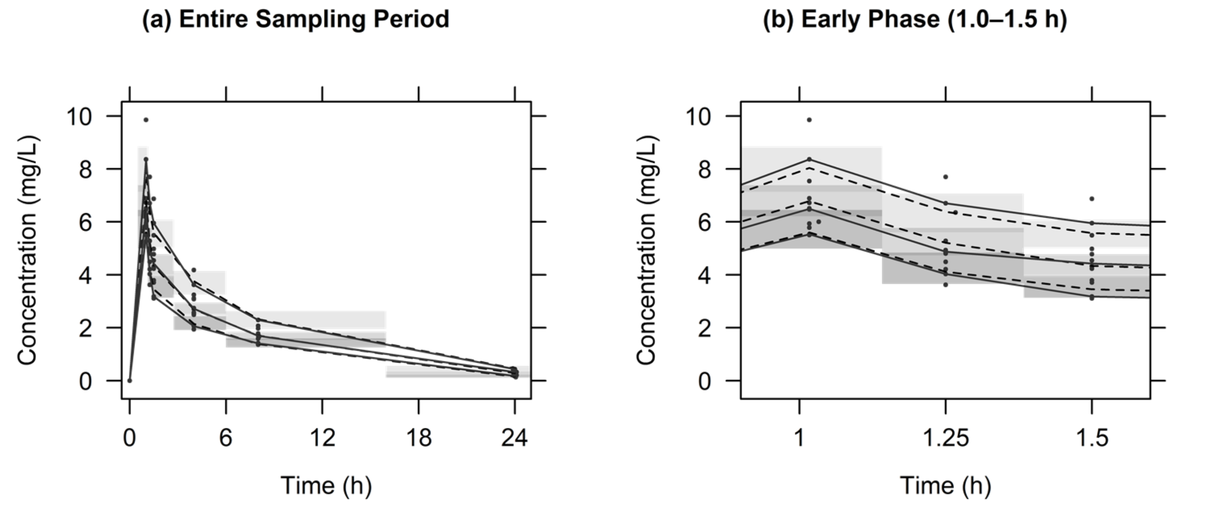


Figure 3. Visual predictive check from simulated concentrations of 1,000 virtual datasets of piperacillin (a) and tazobactam (b): closed circles, observed concentrations; solid lines, 10th, 50th, and 90th percentiles of observations; dashed lines, 10th, 50th, and 90th percentiles of simulated concentrations and shaded areas, 95% confidence intervals for the 10th, 50th, and 90th percentiles of the simulated concentrations.

In the first simulation, the current dose regimens in patients with normal CrCl were assessed to achieve a PTA of at least 90% for the following PK/PD indices: *f*AUC/MIC ≥30 for Streptococcus pneumoniae, ≥100 for Escherichia coli, and ≥125 for Pseudomonas aeruginosa (**Figure 4**). All dosing regimens met the target attainment criteria at low MIC values; however, the PTA significantly decreased at higher MIC values. For S. pneumoniae, the PTA dropped notably at MIC values ≥2 mg/L, particularly with the 500 mg q24h regimen. For E. coli and P. aeruginosa, the PTA sharply declined at MIC values ≥0.5 mg/L across all tested dosing regimens, suggesting the limited effectiveness of cur-rent standard doses against pathogens with elevated MICs and highlighting the potential need for more precise CrCl-based dosing adjustments.

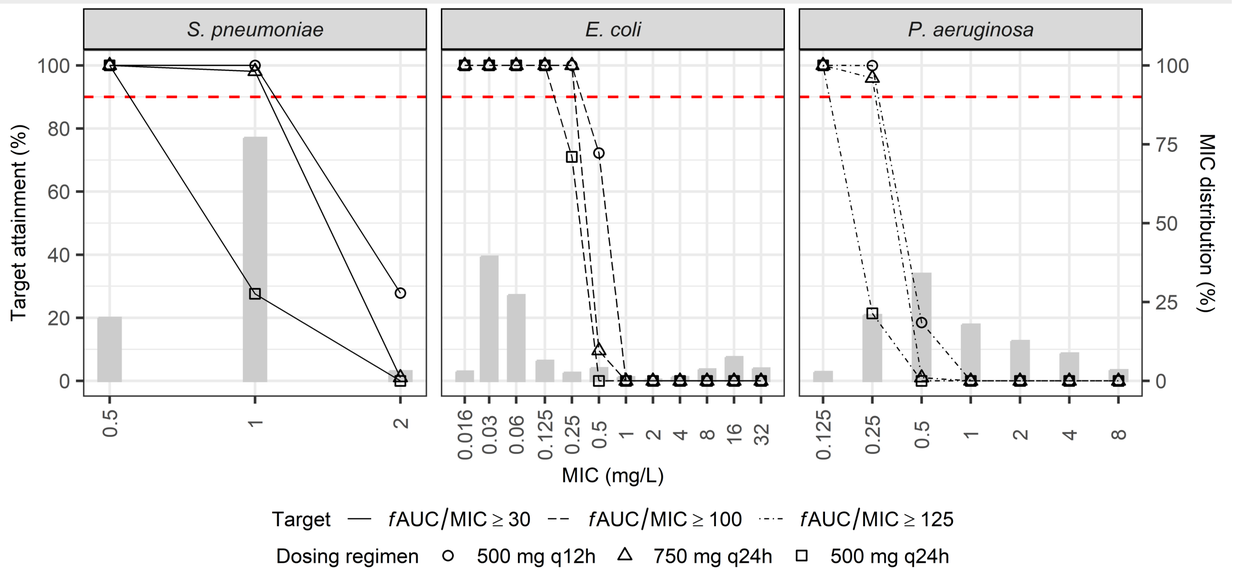
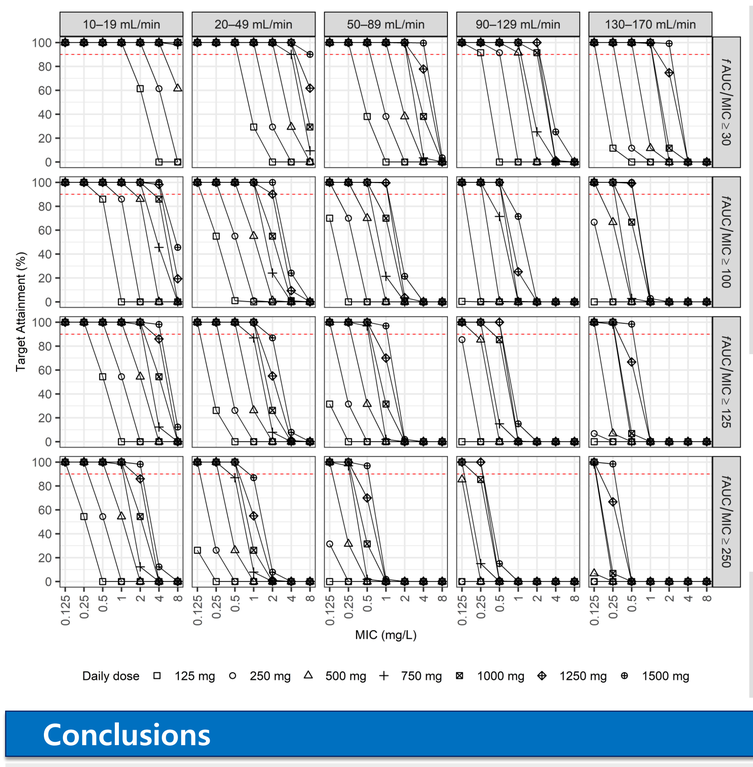


Figure 4. Probability of target attainment (PTA) versus MIC for the empirical piperacillin/tazobactam regimen (4 g/0.5 g q6h) in virtual subjects with normal renal function. Panels show PTA for different infusion durations (0.5, 1, 2, 3, and 4 h) against (A) *Pseudomonas aeruginosa* (Target: 50%$fT_{>MIC}$), (B) *Escherichia coli* (Target: 77%$fT_{>MIC}$), and (C) *Klebsiella pneumoniae* (Target: 100%$fT_{>MIC}$). Gray bars represent the MIC frequency distribution for each pathogen. Horizontal dashed lines denote the 90% PTA threshold.



In the second simulation, the PTA was evaluated for various daily doses of LVX across narrower CrCl intervals (i.e., CrCl: 10–19, 20–49, 50–89, 90–129, and 130–170 mL/min), considering four PK/PD targets (i.e., *f*AUC/MIC: ≥30, 100, 125, and 250) (**Figure 5**). For the lowest PK/PD target (*f*AUC/MIC ≥30), lower doses (125–500 mg/day) generally provided adequate PTAs (≥90%) for pathogens with MIC values ≤0.5 mg/L, particularly in patients with CrCl rates between 10 and 49 mL/min. However, as the CrCl increased to ≥50 mL/min, higher daily doses (≥750 mg/day) were necessary to maintain adequate PTAs.

Figure 5. PTA across various levofloxacin daily doses stratified according to narrower CrCl intervals (CrCl: 10–19, 20–49, 50–89, 90–129, and 130–170 mL/min). Simulations were performed at four PK/PD targets (fAUC/MIC ≥30, 100, 125, and 250) across different MIC values. The dashed red horizontal lines indicate the PTA threshold of 90%.

To further enhance the clinical applicability of our findings, a user-friendly Shiny app has been developed (available at https://dhlee.shinyapps.io/lvfx/).

Conclusions

This study demonstrated that current guideline-recommended dosing regimens of levofloxacin may be insufficient for patients with CrCl ≥50 mL/min, particularly those with augmented renal clearance. A population PK model incorporating CrCl and LBM effectively described LVX pharmacokinetics in healthy adults and provided standardized reference values. Monte Carlo simulations revealed that individualized dosing strategies stratified by narrower CrCl intervals and MIC values significantly improved the probability of target attainment. Therefore, to optimize therapeutic efficacy and reduce the risk of resistance, clinicians should consider adopting model-informed, renal function–based individualized dosing strategies for LVX in clinical practice.

References

1. Fish, D.N.; Chow, A.T. The clinical pharmacokinetics of levofloxacin. Clin. Pharmacokinet. 1997, 32, 101–119. https://doi.org/10.2165/00003088-199732020-00002.
2. Wimer, S.M.; Schoonover, L.; Garrison, M.W. Levofloxacin: A therapeutic review. Clin. Ther. 1998, 20, 1049–1070. https://doi.org/10.1016/s0149-2918(98)80104-5.
3. Langtry, H.D.; Lamb, H.M. Levofloxacin. Its use in infections of the respiratory tract, skin, soft tissues and urinary tract. Drugs 1998, 56, 487–515. https://doi.org/10.2165/00003495-199856030-00013.
4. Croom, K.F.; Goa, K.L. Levofloxacin: A review of its use in the treatment of bacterial infections in the United States. Drugs 2003, 63, 2769–2802. https://doi.org/10.2165/00003495-200363240-00008.
5. U.S. Food and Drug Administration. Levofloxacin Injection. Available online: https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/699fbdb8-a6fd-476a-9b80-08197d869534/spl-doc?hl=levofloxacin (ac-cessed on 2 January 2025).
6. Pham, T.D.M.; Ziora, Z.M.; Blaskovich, M.A.T. Quinolone antibiotics. Medchemcomm 2019, 10, 1719–1739. https://doi.org/10.1039/c9md00120d.
7. Wright, D.H.; Brown, G.H.; Peterson, M.L.; Rotschafer, J.C. Application of fluoroquinolone pharmacodynamics. J. Antimicrob. Chemother. 2000, 46, 669–683. https://doi.org/10.1093/jac/46.5.669.
8. Craig, W.A. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. 1998, 26, 1–10; quiz 11–12. https://doi.org/10.1086/516284.
9. European Medicines Agency. Tavanic. Available online: https://www.ema.europa.eu/en/medicines/human/referrals/tavanic (accessed on 2 January 2025).
10. Udy, A.A.; Baptista, J.P.; Lim, N.L.; Joynt, G.M.; Jarrett, P.; Wockner, L.; Boots, R.J.; Lipman, J. Augmented renal clearance in the ICU: Results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations*. Crit. Care Med. 2014, 42, 520–527. https://doi.org/10.1097/CCM.0000000000000029.
11. Bilbao-Meseguer, I.; Rodriguez-Gascon, A.; Barrasa, H.; Isla, A.; Solinis, M.A. Augmented Renal Clearance in Critically Ill Patients: A Systematic Review. Clin. Pharmacokinet. 2018, 57, 1107–1121. https://doi.org/10.1007/s40262-018-0636-7.
12. Chen, I.H.; Nicolau, D.P. Augmented Renal Clearance and How to Augment Antibiotic Dosing. Antibiotics 2020, 9, 393. https://doi.org/10.3390/antibiotics9070393.
13. Sistanizad, M.; Hassanpour, R.; Pourheidar, E. Are Antibiotics Appropriately Dosed in Critically Ill Patients with Augmented Renal Clearance? A Narrative Review. Int. J. Clin. Pract. 2022, 2022, 1867674. https://doi.org/10.1155/2022/1867674.
14. Shi, A.X.; Qu, Q.; Zhuang, H.H.; Teng, X.Q.; Xu, W.X.; Liu, Y.P.; Xiao, Y.W.; Qu, J. Individualized antibiotic dosage regimens for patients with augmented renal clearance. Front. Pharmacol. 2023, 14, 1137975. https://doi.org/10.3389/fphar.2023.1137975.
15. Lacy, M.K.; Lu, W.; Xu, X.; Tessier, P.R.; Nicolau, D.P.; Quintiliani, R.; Nightingale, C.H. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against Streptococcus pneumoniae in an in vitro model of infection. Antimicrob. Agents Chemother. 1999, 43, 672–677. https://doi.org/10.1128/AAC.43.3.672.
16. Bhavnani, S.M.; Forrest, A.; Hammel, J.P.; Drusano, G.L.; Rubino, C.M.; Ambrose, P.G. Pharmacokinetics-pharmacodynamics of quinolones against Streptococcus pneumoniae in patients with community-acquired pneumonia. Diagn. Microbiol. Infect. Dis. 2008, 62, 99–101. https://doi.org/10.1016/j.diagmicrobio.2008.04.008.
17. Pai, M.P.; Cojutti, P.; Pea, F. Levofloxacin dosing regimen in severely morbidly obese patients (BMI ≥ 40 kg/m2) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin. Pharmacokinet. 2014, 53, 753–762. https://doi.org/10.1007/s40262-014-0154-1.
18. Boonpeng, A.; Jaruratanasirikul, S.; Wattanavijitkul, T.; Nawakitrangsan, M.; Samaeng, M. Population pharmacokinetics of oral levofloxacin in healthy volunteers and dosing optimization for multidrug-resistant tuberculosis therapy. Biopharm. Drug Dispos. 2021, 42, 329–337. https://doi.org/10.1002/bdd.2294.
19. Canoui, E.; Kerneis, S.; Morand, P.; Enser, M.; Gauzit, R.; Eyrolle, L.; Leclerc, P.; Contejean, A.; Zheng, Y.; Anract, P.; et al. Oral levofloxacin: Population pharmacokinetics model and pharmacodynamics study in bone and joint infections. J. Antimicrob. Chemother. 2022, 77, 1344–1352. https://doi.org/10.1093/jac/dkac031.
20. Setiawan, E.; Abdul-Aziz, M.H.; Cotta, M.O.; Susaniwati, S.; Cahjono, H.; Sari, I.Y.; Wibowo, T.; Marpaung, F.R.; Roberts, J.A. Population pharmacokinetics and dose optimization of intravenous levofloxacin in hospitalized adult patients. Sci. Rep. 2022, 12, 8930. https://doi.org/10.1038/s41598-022-12627-1.
21. He, Y.Y.; Sun, J.; Wu, Y.E.; Wang, Y.B.; van den Anker, J.; Hao, G.X.; Sun, D.Q.; Zhao, W. Population pharmacokinetics and dose optimization of levofloxacin in elderly patients with pneumonia. Br. J. Clin. Pharmacol. 2024, 90, 1213–1221. https://doi.org/10.1111/bcp.16003.