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Received: 10 February 2021 | Revised: 30 May 2021 | Accepted: 1 June 2021

DOI: 10.1002/bdd.2294

WILEY

ORIGINAL ARTICLE

Population pharmacokinetics of oral levofloxacin in healthy volunteers and dosing optimization for multidrug-resistant tuberculosis therapy

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Funding information

Faculty of Medicine, Prince of Songkla University; Doctor Kasem Pangsrivongse Foundation

Abstract

Levofloxacin is considered a key component of a multidrug-resistant tuberculosis (MDR-TB) regimen. However, there is considerable concern regarding the subtherapeutic concentrations of the currently used doses and the development of drug resistance. Therefore, this study aimed to describe the population pharmacokinetics (PPK) of oral levofloxacin in healthy volunteers and to evaluate the probability of target attainment (PTA) in an attempt to optimize the dosing regimens for MDR-TB therapy. Data of levofloxacin in healthy volunteers from a previous study were used to construct a PPK model. Monte Carlo simulations were performed to derive the PTAs of various regimens. A two-compartment model with linear elimination and transit absorption compartments best described the pharmacokinetics (PK) of levofloxacin. The estimated PK parameters (interindividual variability, %) were: apparent clearance 8.32 L h^{-1} (22.6%), apparent central volume of distribution 35.8 L (45.2%), apparent peripheral volume of distribution 39.7 L, intercompartmental clearance 40.6 L h^{-1} (43.8%), absorption rate constant 7.45 h^{-1} (150%), mean absorption transit time 0.355 h (52.4%), and total number of transit compartments 6.01 (131.9%). Monte Carlo simulations using levofloxacin 750–1000 mg yielded a probability of achieving a target free area under the concentration–time curve/minimum inhibitory concentration (MIC) of 100 at greater than 90% for *Mycobacterium tuberculosis* with an MIC < 0.5 mg L^{-1}, while a dose of 1500 mg was required for strains with an MIC of 1 mg L^{-1}. A higher dose of levofloxacin might be needed to treat tuberculosis. However, further studies on the efficacy and safety of this dose are needed to confirm our findings.

KEYWORDS

levofloxacin, Monte Carlo simulations, multidrug-resistant tuberculosis, pharmacodynamics, population pharmacokinetics

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1 | INTRODUCTION

Tuberculosis (TB) is one of the major public health concerns worldwide. In 2018, the World Health Organization (WHO) reported that 10 million individuals developed TB, and 1.2 million people died from it (World Health Organization, 2018a). The situation has been worsened in recent years by the emergence and spread of drug-resistant TB. According to the latest WHO report, 3.5% of new TB patients and 18% of previously treated patients had been infected with *Mycobacterium tuberculosis* strains that are resistant to both isoniazid and rifampicin, the most effective first-line drugs (World Health Organization, 2018a). Treatment of multidrug-resistant tuberculosis (MDR-TB) is complex, lengthy, highly toxic, and expensive. It generally requires 18–20 months of treatment with at least four different second-line agents, including fluoroquinolones (FQs), bedaquiline, linezolid, and other group-B agents (World Health Organization, 2019). Even with a longer treatment duration, the treatment success rate for MDR-TB is only 55%, compared to 82% for drug-susceptible TB (World Health Organization, 2018a). Considering the prevalence of MDR-TB and the unique challenges of MDR-TB treatment, there is an exigent need to optimize the dose of currently used regimens and to develop new drugs or regimens.

FQs, including levofloxacin and moxifloxacin, are considered a key component of MDR-TB regimens (World Health Organization, 2019). Of the available FQs, levofloxacin is the preferred agent. It has similar efficacy to moxifloxacin for treating MDR-TB but has less effect on QT-prolongation. This makes levofloxacin more suitable to be used in combination with other anti-TB drugs that cause QT prolongation (Koh et al., 2013; Noel et al., 2003). Moreover, its affordability and availability, especially in high-burden and resource-limited countries, make it more preferable than moxifloxacin.

Levofloxacin exhibits a concentration-dependent activity against *M. tuberculosis*, and its efficacy has been shown to be correlated with the free area under the concentration–time curve (*f*AUC) to the minimum inhibitory concentration (MIC) (Deshpande et al., 2018; Ghimire et al., 2016; Johnson et al., 2006). According to this index, the dosing of levofloxacin could be optimized to maximize its activity and reduce the risk of acquired resistance during MDR-TB treatment. Therefore, the objectives of this study were to describe the population pharmacokinetic (PPK) parameters of levofloxacin and use this information to estimate the probability of target attainment (PTA) in an attempt to optimize the dosing regimens for MDR-TB therapy.

2 | MATERIALS AND METHODS

2.1 | Study design

The individual concentration–time profiles of levofloxacin in healthy volunteers from a previous study were used to develop a PPK model. Details regarding the study design have been published (Jaruratanasirikul et al., 2018). Briefly, each healthy male subject had received a single dose of levofloxacin 500 mg tablet (Daiichi Pharmaceutical, Bangkok, Thailand) with 100 ml of water under fasting conditions. Blood samples (5 ml) were obtained through a peripheral venous catheter immediately prior to the dose (time 0) and then at the following times postdose: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 6, 8, 10, and 24 h. All blood samples were collected in heparinized tubes and centrifuged at 5000 rpm for 5 min. The plasma was separated and stored at −80°C until assayed within 1 week.

2.2 | PPK modeling

In the previous study noted above (Jaruratanasirikul et al., 2018), a levofloxacin pharmacokinetic (PK) model was developed using an individual compartment analysis approach without quantifying the interindividual and residual variability of the PK parameters. In order to use this PK knowledge to guide potentially optimal regimens for MDR-TB therapy, the PPK analysis, which explored the variability within the population and examining these variabilities in relation to patient characteristics such as age and body weight, was developed.

The PPK model-building was performed using a nonlinear mixed-effects model approach in NONMEM (v. 7.4; ICON Development Solution, Hanover, MD) along with Perl-Speaks-NONMEM (v. 4.9.0; Uppsala University, Sweden) and Pirana (v. 2.9.9; Certara, Princeton, NJ). The secondary PK parameters were obtained by using both individual model parameter estimates from NONMEM and non-compartmental analysis (PKanalix v. 2019R1; Lixoft SAS, Antony, France). Data processing and graphical evaluation were carried out using R software (v. 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). A first-order conditional estimation method with η-ε interaction was used for parameter estimation throughout the model-building process.

(i) Structural and Statistical Models. The plasma levofloxacin concentrations were fitted to one-, two-, and three-compartment models with first-order elimination using subroutines from the NONMEM library. The bioavailability (F) of levofloxacin could not be estimated, so specific parameters were estimated as ratios: apparent clearance (CL/F), apparent central volume of distribution (V_c/F), intercompartmental clearance (Q/F), and apparent peripheral volume of distribution (V_p/F). Various absorption models, including a first-order absorption with and without lag-time, zero-order absorption, parallel and sequential zero- and first-order absorption, a transit model, and a combined transit with zero- or first-order absorption model, were assessed. The interindividual variability (IIV) of each parameter was modeled using an exponential error model, and covariances between random effects were also investigated. Residual variability was evaluated by different error models containing additive, proportional, and combined error models. The model selections were based on several criteria, including a decrease in an objective function value (OFV) of 3.84 units ($p < 0.05$, $df = 1$) for nested models, and Akaike information criterion (AIC) for a non-nested model, the precision of parameter estimates, and goodness-of-fit (GOF) plots.

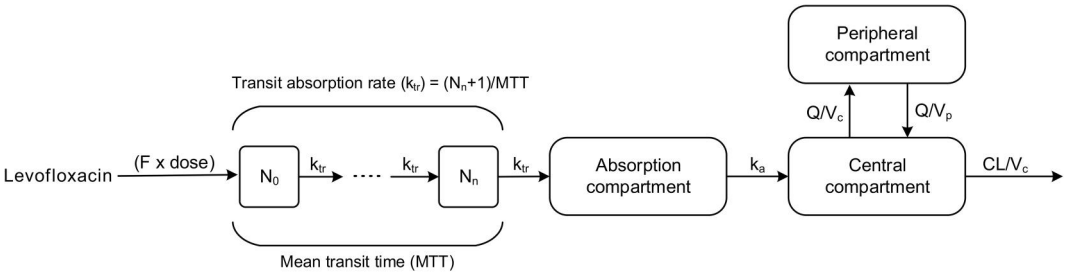

FIGURE 1 Schematic diagram of the final levofloxacin population pharmacokinetic model. N_0 to N_n represents the chain of hypothetical transit compartments used in the model to describe the delayed absorption process. F denotes bioavailability, and k_a is the absorption rate constant. V_c, V_p, CL, and Q are the central and peripheral volumes of distribution, clearance, and intercompartmental clearance, respectively

(ii) Covariate Model. Once a base model was selected, several covariates were evaluated and chosen for their impact on PK parameters. These covariates were age, body weight, and body mass index. The relationships between PK parameters and the covariates were first explored graphically. If a relationship was visibly evident, it was considered for inclusion in the base model. A covariate was retained in the model if it led to significant improvement of model fit, as evaluated by a decrease in OFV of 3.84 ($p < 0.05$, $df = 1$) for forward addition and an increase of OFV by 6.64 ($p < 0.01$, $df = 1$) for a backward deletion step.

(iii) Model Validation. The appropriateness of the final PK model was validated with GOF plots, a visual predictive check (VPC), and bootstrap analysis. The VPC of the final model was carried out using the final parameter estimates to simulate 2000 new datasets, then the 5th, 50th, and 95th percentiles of the observed data were superimposed with a 95% confidence interval (CI) of the simulated data to assess model predictiveness. A nonparametric bootstrap resampling technique ($n = 1000$) was performed to evaluate the robustness of the final model and to construct the nonparametric confidence intervals of the parameter estimates.

2.3 | Simulation and dosing regimen optimization

The final PPK model was used to perform Monte Carlo simulations ($n = 5000$). Levofloxacin concentrations of different dosage regimens ranging from 500 to 1750 mg once daily were simulated. The $fAUC_{0\text{-}24}$ for each virtual subject was obtained by using the linear trapezoidal rule and multiplied by 0.75 for calculating the free fraction of levofloxacin. This *f*AUC was then used to calculate the probability of attaining a target *f*AUC/MIC ratio ≥100 and ≥146 against *M. tuberculosis* at various MICs (Deshpande et al., 2018; Peloquin et al., 2008).

3 | RESULTS

3.1 | Subjects

Forty-five healthy male volunteers were enrolled in this study. The mean age was 27.4 ± 6.1 years (range, 18–43 years), average bodyweight 60.8 ± 6.5 kg (range, 48–80 kg), and average body mass index 21.0 ± 2.3 kg m^{-2} (range, 16.6–27.7 kg m^{-2}). All participants had normal renal function with mean creatinine clearance ($CL_{CR\text{-}CG}$) of 93.0 ± 17.6 ml min^{-1} (range, 55.1–132.9 ml min^{-1}).

3.2 | Population pharmacokinetics

A total of 539 levofloxacin concentrations from the 45 subjects were used to develop the PPK model. The data below the lower limit of quantitation (LLOQ), which represented only 0.6% of the dataset, were imputed using the LLOQ/2 value. A two-compartment model with first-order elimination best described the levofloxacin concentration–time profiles. The transit absorption compartment model provided the lowest AIC value among all of the tested absorption models and was thus selected for further model development. A schematic illustration of the PPK model is shown in Figure 1. The IIV was able to be estimated in all parameters, but the IIV on V_p/F was very low, and therefore it was fixed to zero. Since there was a significant correlation between IIV on CL/F and V_c/F, a covariance term was incorporated, which resulted in a substantial improvement of the model fit (ΔOFV = −48.5). A proportional error model was selected to describe the residual variability. After covariates testing, neither demographic covariates nor laboratory profiles showed any influence on the levofloxacin PK.

The final parameter estimates, along with their precisions and corresponding secondary parameters, are summarized in Tables 1 and 2, respectively. All model parameters were estimated with acceptable precision. The parameters obtained from the final model were generally similar and contained within the 95% CIs from 1000 bootstrap runs, indicating the robustness of the model. The GOF plots showed a good agreement between observed and model-predicted concentrations (Figure 2). A majority of the conditional weighted residuals lay within two SDs and were symmetrically distributed around zero. Furthermore, the VPC plot (Figure 3) showed that the 5th, 50th, and 95th percentiles of observed data were within the 95% prediction interval, indicating good predictive performance of the final model. With regard to overall plots, the fit of this model seemed reasonably good, with no apparent visual biases.

TABLE 1 Final population pharmacokinetic parameters of levofloxacin

Parameter	Estimate (%RSE)	Bootstrap median (95% CI)	Shrinkage (%)
CL/F (L h^{-1})	8.32 (3.9)	8.30 (7.74–8.94)	
V_c/F (L)	35.80 (8.7)	35.36 (30.72–41.33)	
V_p/F (L)	39.70 (4.3)	39.73 (36.78–44.18)	
Q/F (L h^{-1})	40.60 (14.3)	40.27 (31.08–56.48)	
Ka (h^{-1})	7.45 (26.4)	7.60 (4.68–14.88)	
MTT (h)	0.355 (8.3)	0.351 (0.29–0.47)	
NN	6.01 (25.8)	6.33 (3.77–10.09)	
Interindividual variability (IIV), %CV			
IIV_{CL}	22.56 (24.4)	22.14 (16.91–27.59)	1.2
IIV_{Vc}	45.17 (23.4)	44.42 (34.14–55.40)	2.9
IIV_{Vp}	0[a]	–	–
IIV_{Q}	43.82 (48.4)	43.11 (20.07–66.93)	28.9
IIV_{Ka}	150.00 (25.8)	149.74 (114.31–193.55)	23.6
IIV_{MTT}	52.35 (48.5)	50.58 (31.48–76.22)	17.8
IIV_{NN}	131.91 (32.9)	127.83 (63.62–169.44)	20.0
Covariance between CL and V_c	0.087 (25.1) (r = 0.854)	0.08 (0.05–0.13)	–
Residual unexplained variability, %CV			
Proportional	12.61 (17.4)	10.60–14.61	18.1

Abbreviations: %RSE, percent relative standard error; CI, confidence interval; CL/F, apparent clearance; CV, coefficient of variation; IIV, interindividual variability; Ka, first-order absorption rate constant; MTT, mean absorption transit time; NN, number of transit compartments; Q/F, intercompartmental clearance; V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution.

[a]Fixed to zero.

TABLE 2 Secondary pharmacokinetic parameters of levofloxacin

Parameter	Description	NCA[a]	Model-derived parameter[b]
$t_{1/2}$ (h)	Elimination half-life	7.03 (±1.0)	6.85 (±0.66)
$AUC_{0\text{-}24}$ (mg h L^{-1})	Area under the concentration–time curve from 0 to 24 h	61.31 (±13.21)	61.61 (±12.73)
C_{MAX} (mg L^{-1})	Maximum concentration	9.93 (±3.77)	9.84 (±3.83)
T_{MAX} (h)	Time to maximum concentration	0.75 (0.50–1.12)[c]	0.74 (0.51–1.09)[c]

[a]NCA, noncompartmental analysis, mean parameter estimates (±SD) obtained using noncompartmental analysis.

[b]Mean parameter estimates (±SD) obtained from post-hoc Bayesian predictions in NONMEM.

[c]Median (interquartile range).

3.3 | Simulation and dosing regimen optimization

Monte Carlo simulations were performed to calculate the steady-state AUC of levofloxacin and derive the probabilities of achieving PK/pharmacodynamic (PD) targets at *f*AUC/MIC ≥ 100 and ≥ 146. The PTAs for the different dosing regimens of levofloxacin and the PTA overlays with international MIC distributions of *M. tuberculosis* (European Committee on Antimicrobial Susceptibility Testing, 2020) are presented in Figure 4. Considering $fAUC_{0\text{-}24}$/MIC ≥ 100 as the target, the standard dosage regimens of 750–1000 mg once daily were sufficient for MICs up to 0.5 mg L^{-1} but failed to achieve 90% PTA for higher MIC values. For an MIC of 1 mg L^{-1}, a dose higher than 1500 mg once daily appeared to be necessary to achieve 90% PTA. None of the dosage regimens showed good target attainment when the MIC ≥ 2 mg L^{-1}. In order to achieve the target *f*AUC/MIC ≥ 146, a dose of 1250 mg once daily was required for treating pathogens with MICs less than 0.5 mg L^{-1}. For pathogens with an MIC ≥ 1 mg L^{-1}, even higher doses of up to 1750 mg daily still failed to achieve 90% PTA.

The PTA sensitivity analysis of different protein binding values used to derive *f*AUC is shown in Table 3. A regimen of 750 mg once daily only irregularly achieved the desired 90% PTA for pathogens

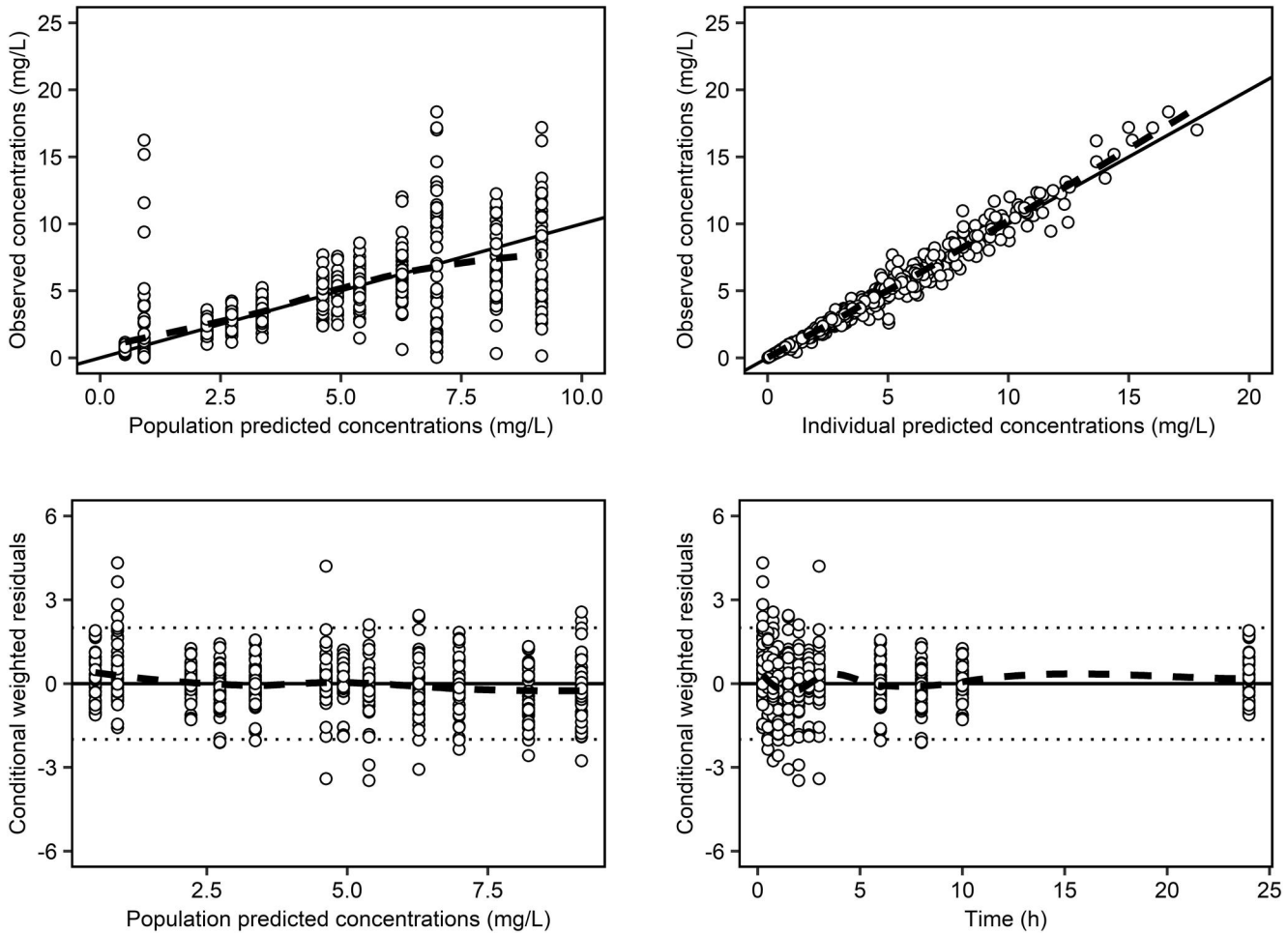

FIGURE 2 Goodness-of-fit plots of the final levofloxacin pharmacokinetic model. Solid lines represent the line of identity, and the dashed line is the locally weighted least-square regression line to indicate trends

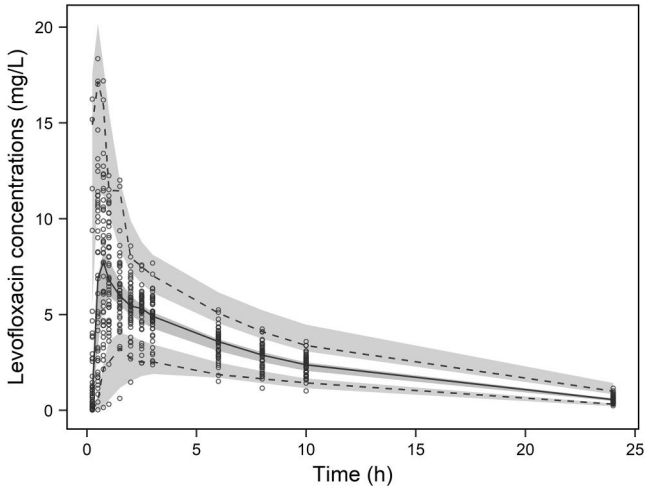

FIGURE 3 Visual predictive check of the final population pharmacokinetic model. Open circles indicate observed concentrations. The solid line represents the 50th percentiles of the observations, and dashed lines represent the 5th and 95th percentiles of the observations. The shaded areas are the 95% CIs around the 5th, 50th, and 95th percentiles of the simulated data

with an MIC $\leq$ 0.5 mg L^{-1}, while a dose greater than 1000 mg once daily produced more consistent target attainment.

4 | DISCUSSION

The PK of levofloxacin is linear and predictable after both single and multiple dosing in adults. Concerning peak and total drug exposure, levofloxacin's dose linearity has previously been reported for doses ranging from 50 to 1500 mg (Janssen Pharmaceutical Companies, 2020). In the current study, we estimated the PPK parameters of a single 500-mg oral dose of levofloxacin in healthy volunteers. None of the covariates was shown to have a significant effect on PK parameters, which might be attributed to the homogeneity of our study population. The final PK parameters reported in the present study were comparable with previously published oral levofloxacin PPK studies in healthy subjects, patients with infectious diseases, and TB patients (Alsultan et al., 2015; Cojutti et al., 2017; Kempker et al., 2015; Kervezee et al., 2016; Peloquin et al., 2008; Tanigawara et al., 1995; van den Elsen et al., 2018; Zhang

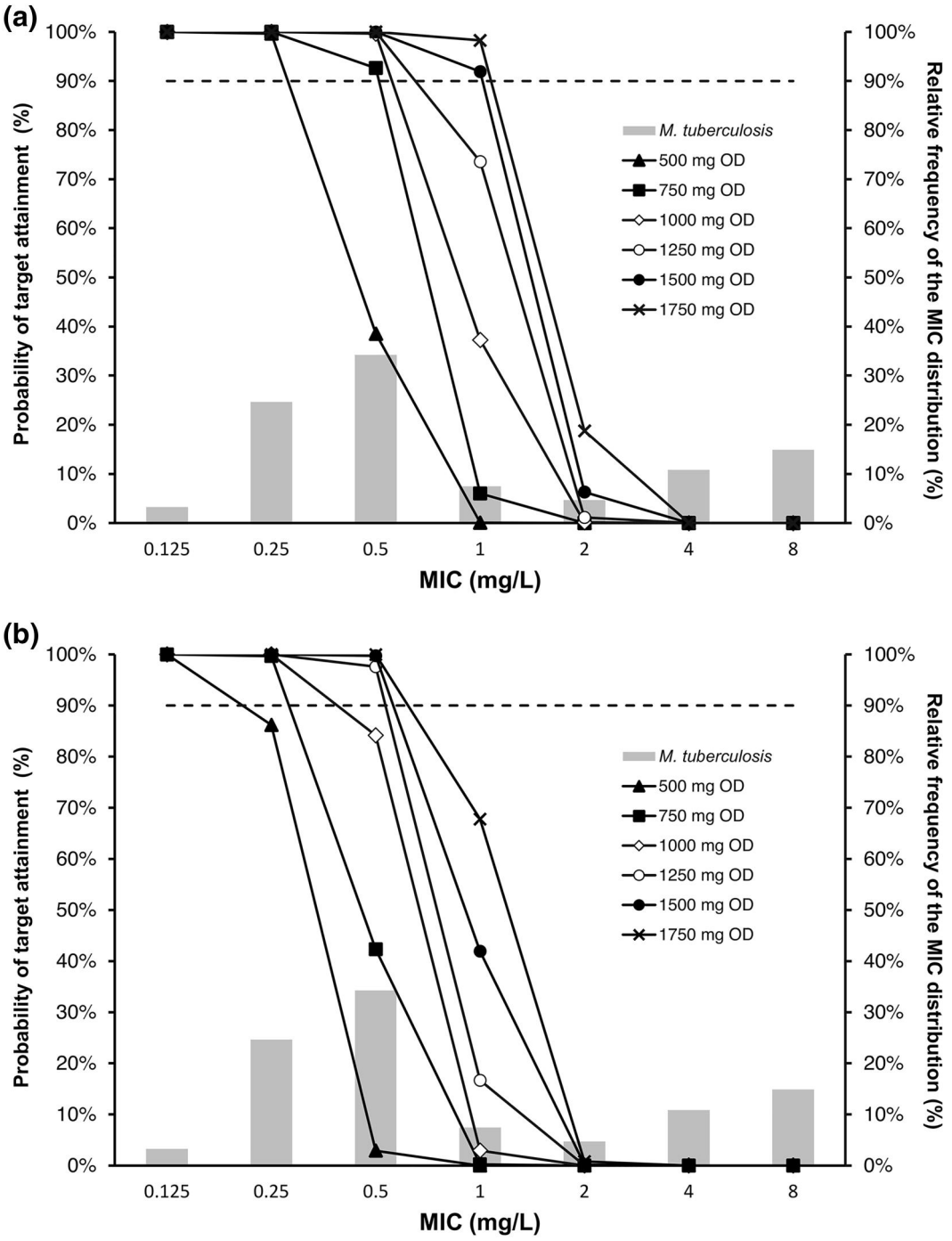

FIGURE 4 Probability of target attainment (PTA) for levofloxacin regimens achieving free area under the concentration–time curve (*f*AUC)/minimum inhibitory concentration (MIC) ≥ 100 (a) and *f*AUC/MIC ≥ 146 (b) at various MICs. The dashed line indicates a PTA of 90%. The histograms represent the international MIC distributions of *Mycobacterium tuberculosis*

et al., 2009). In particular, the volume of distribution (V_D/F) 75.5 L and CL/F 8.32 L h^{-1} was in the range of those previously reported in TB patients with normal renal function (V_D/F 49.4–140.5 L and CL/F 6.22–10.1 L h^{-1}) (Alsultan et al., 2015; Kempker et al., 2015; Peloquin et al., 2008; van den Elsen et al., 2018). The IIVs of the PK parameters in the current study were high, particularly the IIV on k_a (150%). This high variability in k_a was consistent with previous studies in which the IIVs on k_a ranged from 92%–146% (Kervezee et al., 2016; Tanigawara et al., 1995; Zhang et al., 2009). The factors that contribute to a large IIV in the k_a of levofloxacin have not been identified. A previous study suggested that it could be due to variations in gastrointestinal (GI) physiology between individuals such as gastric emptying time or GI motility (Kervezee et al., 2016). A parameter sensitivity analysis was performed to investigate the influence of k_a variability on AUC, which is the parameter related to its bactericidal activity. The sensitivity analysis showed that varying k_a

TABLE 3 Deviations in the probability of $fAUC_{0-24}/MIC$[a] ≥ 100 attainment based on the difference of protein binding values used for estimation of unbound concentration

	PTA (%)							
	MIC 0.5 mg L^{-1}				MIC 1 mg L^{-1}			
Protein binding (%)	750 mg	1000 mg	1500 mg	1750 mg	750 mg	1000 mg	1500 mg	1750 mg
5	99.24	100.00	100.00	100.00	29.38	75.12	99.28	99.88
10	98.68	100.00	100.00	100.00	22.42	67.86	98.70	99.74
15	97.62	99.98	100.00	100.00	15.22	58.60	97.34	99.42
20	95.90	99.88	100.00	100.00	10.00	47.98	95.44	99.02
25	92.62	99.66	100.00	100.00	6.02	37.26	91.90	98.28
30	87.46	97.08	100.00	100.00	3.60	27.66	86.52	96.34
35	80.08	97.94	100.00	100.00	1.76	17.68	78.14	93.00
40	69.08	95.44	100.00	100.00	0.78	10.62	67.86	87.24

Abbreviations: *f*AUC, free area under the concentration–time curve; MIC, minimum inhibitory concentration; PTA, probability of target attainment.
[a]AUCs for free drug (*f*AUC) were estimated by multiplying the individual AUCs by (100%-protein binding values).

ranges from 0.08 up to 100 h^{-1}, while other PK parameters kept the same had little effect on AUC changes (Supplementary Figure 1S).

Levofloxacin is frequently used for the treatment of TB. Earlier studies have reported high in vitro and in vivo bactericidal activity of this drug against *M. tuberculosis*, with MIC ranges from 0.25 to 2 mg L^{-1} (Ji et al., 1995; Rodriguez et al., 2001). The efficacy of this agent for treating TB in humans has also been demonstrated, and favorable responses to its standard dose were observed when the MIC value was less than 0.5 mg L^{-1} (Johnson et al., 2006; Peloquin et al., 2008). Based on the dose linearity property and similarity of the levofloxacin PK profiles between healthy volunteers and TB patients with normal renal function, the final PK parameters were used to perform the Monte Carlo simulations to determine the optimal regimens for MDR-TB therapy. Our simulation results agree with the results of a previous study (Van't Boveneind-Vrubleuskaya et al., 2017), reporting that the currently recommended dosage of 750 to 1000 mg daily was sufficient to reach the target *f*AUC/MIC ≥ 100 only for strains with MIC values ≤0.5 mg L^{-1}. For an MIC of 1 mg L^{-1}, which is the WHO-recommended critical concentration of levofloxacin against *M. tuberculosis* (World Health Organization, 2018b), a dose of at least 1500 mg daily was necessary to achieve the desired 90% PTA. However, in a weight-based dosing simulation by Alsultan et al. (2015), a dose of 20 mg kg^{-1} or 1400 mg daily in a 70-kg patient was not adequate to attain the target *f*AUC/MIC ≥ 100 at an MIC of 1 mg L^{-1}. The differences in these results may be due to the differences in protein binding values used for the calculation of unbound concentrations (40% vs. 25%). The published protein binding values of levofloxacin ranged from 24% to 38% (Fish & Chow, 1997). We used a lower binding value in this range (25%) because reduced albumin levels is a common problem among TB patients (Alvarez-Uria et al., 2013). To explore this issue further, a sensitivity analysis of different protein binding values used on PTA was performed. The results suggested that a higher dose of 1000 mg for an MIC of 0.5 mg L^{-1} and 1750 mg daily for an MIC of 1 mg L^{-1} might be needed to overcome the uncertainty of individual protein binding levels on achieving the PK/PD target. The need for a higher dose was further strengthened by the recent suggestion of a new PD target for TB. This target was proposed based on the results from a hollow fiber system model for the development of antituberculosis drug experiments, which revealed that the *f*AUC/MIC of 146 was associated with a maximal *M. tuberculosis* kill (Deshpande et al., 2018). In order to achieve this target, regimens of 1250–1500 mg daily were necessary for a strain with an MIC ≤ 0.5 mg L^{-1}. However, none of the tested regimens was associated with an acceptable PTA when the MIC was 1 mg L^{-1}.

Increasing the dose of levofloxacin for treating TB could raise safety concerns, in particular, a QT prolongation. FQs prolong the QT interval by blocking the cardiac potassium channel. The potency of inhibitory effects varies by agent. Gatifloxacin and moxifloxacin have a moderate inhibiting effect on the potassium channel, whereas levofloxacin and ciprofloxacin have a relatively minor effect (Crouch et al., 2003; Kang et al., 2001). Noel et al. (2004) conducted a study to assess the effect of levofloxacin on the QT interval in healthy subjects. The mean changes in QTc after exposure to levofloxacin 1000 and 1500 mg were 1.38–2.79 and 3.50–7.73 ms, respectively. These small increases in QTc suggest that levofloxacin has little effect on prolonging ventricular repolarization. However, these results were the effect of single-dose levofloxacin in a small population with subjects who lacked other risk factors for cardiac arrhythmias. Therefore, higher doses of levofloxacin would need to be assessed carefully before prescribing the drug for TB patients with a high risk of QT prolongation.

The recruitment of a large enough number of participants and the intensive plasma sampling, which facilitated a well-evaluated and robust PK model, was the primary strength of this analysis. However, the study also had some limitations. First, similar to most levofloxacin PK studies, the total concentrations of levofloxacin were measured, while only the free fraction is antibacterial-active. We used the

published protein binding values to estimate the free fractions, but direct measurement of the unbound fractions would be more accurate. Second, the study was conducted only in healthy male subjects; thus, any extrapolation of these results to TB patients must be done with caution. Lastly, the proposed dosage regimens are based on a mathematical model. Therefore, exposure–response and exposure–safety relationship studies are needed to justify these dosages.

5 | CONCLUSION

In conclusion, our results suggest that the current recommended dose of levofloxacin might be suboptimal for the treatment of TB. The use of a higher dose of 1500–1750 mg once daily might be needed to improve its efficacy. However, further studies on the efficacy and safety of this dose are needed to confirm our findings.

ACKNOWLEDGMENTS

The authors thank Mr. David Patterson, Ms. Maria Mullet, and Dr. Adam Joseph Osman Dede for proofreading the article. This work was supported by a grant from the Faculty of Medicine, Prince of Songkla University, Thailand, and the Doctor Kasem Pangsrivongse Foundation provided financial support for purchasing the NONMEM® software.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Boonpeng, A., Jaruratanasirikul, S., Wattanavijitkul, T., Nawakitrangsan, M., Samaeng, M. (2021). Population pharmacokinetics of oral levofloxacin in healthy volunteers and dosing optimization for multidrug-resistant tuberculosis therapy. *Biopharmaceutics and Drug Disposition*, 1–9. https://doi.org/10.1002/bdd.2294