

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Smythe, W; Merle, CS; Rustomjee, R; Gninafon, M; lo, MB; Bah-Sow, O; Olliaro, PL; Lienhardt, C; Horton, J; Smith, P; +2 more... McIlleron, H; Simonsson, USH; (2013) Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations. *Antimicrobial agents and chemotherapy*, 57 (9). pp. 4164-4171. ISSN 0066-4804 DOI: <https://doi.org/10.1128/AAC.00479-13>

Downloaded from: <http://researchonline.lshtm.ac.uk/1229522/>

DOI: <https://doi.org/10.1128/AAC.00479-13>

Usage Guidelines:

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations

Wynand Smythe, Corinne S. Merle, Roxana Rustomjee,
Martin Gninafon, Mame Bocar Lo, Oumou Bah-Sow, Piero L.
Olliaro, Christian Lienhardt, John Horton, Peter Smith,
Helen McIlleron and Ulrika S. H. Simonsson
Antimicrob. Agents Chemother. 2013, 57(9):4164. DOI:
10.1128/AAC.00479-13.
Published Ahead of Print 17 June 2013.

Updated information and services can be found at:
<http://aac.asm.org/content/57/9/4164>

These include:

REFERENCES

This article cites 42 articles, 15 of which can be accessed free
at: <http://aac.asm.org/content/57/9/4164#ref-list-1>

CONTENT ALERTS

Receive: RSS Feeds, eTOCs, free email alerts (when new
articles cite this article), [more»](#)

Information about commercial reprint orders: <http://journals.asm.org/site/misc/reprints.xhtml>
To subscribe to to another ASM Journal go to: <http://journals.asm.org/site/subscriptions/>

Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations

Wynand Smythe,^a Corinne S. Merle,^b Roxana Rustomjee,^c Martin Gninafon,^d Mame Bocar Lo,^e Oumou Bah-Sow,^f Piero L. Olliaro,^g Christian Lienhardt,^h John Horton,ⁱ Peter Smith,^a Helen McIlleron,^{a,j} Ulrika S. H. Simonsson^k

Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa^a; Faculty of Epidemiology & Population Health, Tropical Epidemiological Group, London School of Hygiene & Tropical Medicine, London, United Kingdom^b; Unit for Clinical & Biomedical TB Research, Medical Research Council (MRC), Durban, South Africa^c; Programme National de Lutte contre la Tuberculose, Cotonou, Benin^d; Programme National de Lutte contre la Tuberculose, Dakar-Fann, Senegal^e; Service Pneumo-physiologie, CHU Ignace Deen, Conakry, Guinea^f; UNICEF/UNDP/World Bank/WHO Special Programme on Research & Training in Tropical Diseases (TDR), World Health Organization, Switzerland^g; Institut de recherche pour le Développement (IRD), Paris, France^h; Tropical Projects, Hitchin, United Kingdomⁱ; Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa^j; Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden^k

A 4-month regimen of gatifloxacin with rifampin, isoniazid, and pyrazinamide is being evaluated for the treatment of tuberculosis in a phase 3 randomized controlled trial (OFLOTUB). A prior single-dose study found that gatifloxacin exposure increased by 14% in the combination. The aims of the study are to evaluate the initial and steady-state pharmacokinetics of gatifloxacin when daily doses are given to patients with newly diagnosed drug-sensitive pulmonary tuberculosis as part of a combination regimen and to evaluate the gatifloxacin dose with respect to the probability of attaining a pharmacokinetic/pharmacodynamic target. We describe the population pharmacokinetics of gatifloxacin from the first dose to a median of 28 days in 169 adults enrolled in the OFLOTUB trial in Benin, Guinea, Senegal, and South Africa. The probability of achieving a ratio of ≥ 125 for the area under the concentration time curve to infinity ($AUC_{0-\infty}$) for the free fraction of gatifloxacin over the MIC ($fAUC/MIC$) was investigated using Monte Carlo simulations. The median $AUC_{0-\infty}$ of 41.2 $\mu\text{g} \cdot \text{h}/\text{ml}$ decreased on average by 14.3% (90% confidence interval [CI], -90.5% to +61.5%) following multiple 400-mg daily doses. At steady state, 90% of patients achieved an $fAUC/MIC$ of ≥ 125 only when the MIC was $< 0.125 \mu\text{g}/\text{ml}$. We conclude that systemic exposure to gatifloxacin declines with repeated daily 400-mg doses when used together with rifampin, isoniazid, and pyrazinamide, thus compensating for any initial increase in gatifloxacin levels due to a drug interaction. (The OFLOTUB study has been registered at ClinicalTrials.gov under registration no. NCT00216385.)

Fluoroquinolones represent a promising class of drug for the treatment of tuberculosis. Gatifloxacin distributes widely throughout the body (1), achieving MICs for *Mycobacterium tuberculosis* observed *in vitro* of 0.031 to 0.5 $\mu\text{g}/\text{ml}$ (2, 3, 4), and demonstrates strong bactericidal activity in the mouse model (2, 5). Furthermore, gatifloxacin displays excellent early bactericidal activity (EBA), only slightly lower than that of isoniazid (6); replacing ethambutol with gatifloxacin in the standard first-line regimen resulted in accelerated killing of *M. tuberculosis* in the sputum of patients with pulmonary tuberculosis (7). A single-dose crossover study in healthy volunteers showed a reduction in the elimination rate of gatifloxacin resulting in a 14% increase in the area under the concentration time curve to infinity ($AUC_{0-\infty}$) when it was given together with rifampin, isoniazid, and pyrazinamide (8). Reports of dysglycemia related to the use of gatifloxacin in elderly patients with renal insufficiency (9, 10, 11, 12) have raised concerns that pharmacokinetic interactions may lead to an increased risk of toxicity related to higher gatifloxacin exposure. On the other hand, *in vitro* and *in vivo* studies suggest a target ratio of ≥ 125 for the free drug area under the concentration versus time curve to MIC ($fAUC/MIC$) for maximal bactericidal effect and prevention of resistance to fluoroquinolones (13, 14).

We aimed to evaluate the population pharmacokinetics of gatifloxacin after an initial dose and at steady state (28 days) when given in combination with rifampin, isoniazid, and pyrazinamide in African adult patients with newly diagnosed pulmonary tuber-

culosis. In addition, the probability of target ($fAUC/MIC \geq 125$) attainment (PTA) and the cumulative fraction of response (CFR) (15) across the MIC distribution of *M. tuberculosis* for 400, 600, and 800 mg once daily of gatifloxacin at steady state in combination with rifampin, isoniazid, and pyrazinamide were investigated with Monte Carlo simulations using the final model.

MATERIALS AND METHODS

Patients. Newly diagnosed pulmonary tuberculosis patients participating in the multicenter phase 3 randomized controlled trial (OFLOTUB trial [ClinicalTrials.gov registration no. NCT00216385]) (16) at clinics in South Africa, Senegal, Guinea, and Benin were enrolled in the pharmacokinetic study, and those randomized to the 4-month regimen of gatifloxacin, rifampin, isoniazid, and pyrazinamide ($n = 169$) were included in this analysis. Written informed consent was obtained prior to enrollment. Adult males ($n = 116$) and nonpregnant females ($n = 53$), aged 18 to 58 years and weighing 35 to 80 kg were included in this analysis. HIV-infected patients ($n = 54$) were antiretroviral naive. During the first 2

Received 14 March 2013 Returned for modification 4 May 2013

Accepted 10 June 2013

Published ahead of print 17 June 2013

Address correspondence to Helen McIlleron, helen.mcilleron@uct.ac.za.

Copyright © 2013, American Society for Microbiology. All Rights Reserved.

doi:10.1128/AAC.00479-13

months of treatment, all patients received 400 mg gatifloxacin (Lupin Pharmaceuticals Pvt Ltd., Mumbai, India) daily irrespective of weight together with a fixed combination of rifampin, isoniazid, and pyrazinamide (Lupin Pharmaceuticals Pvt Ltd., Mumbai, India) as follows: rifampin, 150 mg; isoniazid, 75 mg; and pyrazinamide, 400 mg; patients weighing <50 kg received 3 tablets, and patients weighing ≥ 50 kg received 4 tablets. All doses were given orally for 6 days of the week, and dose taking was supervised using directly observed therapy (DOT) performed either by health center staff or designated representatives for the duration of the study.

Blood sampling. Three venous blood samples per patient were taken after the first dose (initial dose) and repeated after approximately 28 days (steady state) for the determination of gatifloxacin pharmacokinetics. Samples were drawn 1 to 2 and 2.5 to 3.5 h postdose from each patient on both occasions. Patients were block randomized to a time for the third sample. After the first dose, the third sample was taken 4 to 6 h postdose from one half of the patients, and the remaining patients had a sample taken 8 to 10 h postdose. At steady state, the third sample was taken either pre-dose, 4 to 6 h postdose, or 8 to 10 h postdose.

Drug quantification. Each 4-ml blood sample, collected in a heparinized vacuum plastic tube, was centrifuged at $750 \times g$ for 10 min to separate the plasma using a benchtop centrifuge. Samples were kept on crushed ice during preparation, and the plasma aliquots were stored at -80°C until drug quantification within 30 min of sampling. Concentrations of gatifloxacin in plasma were quantified using high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS). Inter- and intraday coefficients of variation were below 10%. The lower limit of quantification was set at 0.2 $\mu\text{g/ml}$ for pyrazinamide and 0.1 $\mu\text{g/ml}$ for rifampin, gatifloxacin, and isoniazid (8).

Population pharmacokinetic analysis. Data analysis was performed with a nonlinear mixed-effects approach, as implemented in NONMEM software, version 7.1.2 (Icon Development Solutions) (17), using Advan 13 and the first-order conditional estimation method with interaction (FOCE Inter). R (version 2.12.1) was used for graphical analysis and data management (18). Xpose (version 4.0) was used for data exploration and visualization as well as model diagnostics and model comparison (19). PsN, version 3.3.2 (20, 21), was used for stepwise covariate model building (SCM) (22), visual predictive checks (VPCs) (23, 24), and prediction-corrected VPCs (pcVPCs) (25) of the models. Model selection was performed using the objective function value (OFV) (which is minus twice the log likelihood of the data), standard error of parameter estimates, scientific plausibility, and goodness-of-fit plots together with VPC and, when indicated, pcVPC.

A total of 954 gatifloxacin concentration observations from 169 patients were included in the analysis. Twelve observations, from 12 individuals, falling below the lower limit of quantification (LLOQ = 0.1 $\mu\text{g/ml}$) were replaced with LLOQ/2. There was not more than one LOQ observation in each individual absorption or elimination phase. One- and two-compartment distribution models with first-order elimination were fitted to the data. Potential differences in gatifloxacin pharmacokinetic parameters were evaluated after initial and multiple doses. A transit absorption compartment model described by Savic et al. (26) and applied by Wilkins et al. (27) for multiple dosing was used to capture the delay in the absorption characteristics. The absorption model used hypothetical transit compartments to mimic a delay in the onset of absorption, producing a gradual increase in absorption rate in a physiologically plausible manner. Drug transfer between transit compartments occurred via the rate constant k_{tr} (equation 1):

$$k_{tr} = \frac{N + 1}{MTT} \quad (1)$$

where MTT is the mean transit time and N is the number of transit compartments. Drug transfer from the final transit compartment to the central compartment occurred via the first-order rate constant k_a .

Creatinine clearance (CL_{CR}) was estimated from serum creatinine using the Cockcroft-Gault formula (28) (equation 2):

$$CL_{CR} = \frac{(140 - \text{age}) \cdot \text{MASS} \cdot K}{\text{serum creatinine}} \quad (2)$$

where CL_{CR} is in ml/min, serum creatinine is in nmol/ml, age is recorded in years, K represents a constant of 1.23 for men and 1.04 for women, and MASS is the total body weight recorded in kilograms.

As gatifloxacin is excreted primarily via the kidneys (1), typical oral clearance, $TV(CL/F)$, was parameterized as the sum of $TV(CL/F_{GFR})$ (where GFR stands for glomerular filtration rate), accounting for drug passively filtered via the kidneys, and $TV(CL/F_{\text{other}})$, accounting for the remaining drug clearance (equation 3):

$$TV \frac{CL}{F} = TV \frac{CL}{F_{GFR}} + TV \frac{CL}{F_{\text{other}}} \quad (3)$$

The relationship between $TV(CL/F_{GFR})$ and CL_{CR} was parameterized using equation 4.

$$TV \frac{CL}{F_{GFR}} = \left(\frac{CL}{F_{GFR}} \right)_{STD} \cdot \left(\frac{CL_{CR,i}}{CL_{CR}(\text{median})} \right) \quad (4)$$

where $(CL/F_{GFR})_{STD}$ is the oral clearance in a typical patient with a median CL_{CR} of 94 ml/min and $CL_{CR,i}$ is the individual CL_{CR} . $TV(CL/F_{\text{other}})$ was scaled to a body size descriptor (MASS) and reported for a typical 70-kg patient [$(CL/F_{\text{other}})_{STD}$] (equation 5):

$$TV \frac{CL}{F_{\text{other}}} = \left(\frac{CL}{F_{\text{other}}} \right)_{STD} \cdot \left(\frac{\text{MASS}}{70} \right)^{\frac{3}{4}} \quad (5)$$

Allometric scaling, using various size descriptors (MASS), namely, total body weight (WT) (29, 30, 31, 32), fat-free mass (FFM) (32, 33), and normal fat mass (NFM) (33), was evaluated for both $TV(CL/F_{\text{other}})$ (equation 5) and the typical apparent volume of distribution, $TV(V/F)$ (equation 6):

$$TV \frac{V}{F} = \left(\frac{V}{F} \right)_{STD} \cdot \left(\frac{\text{MASS}}{70} \right) \quad (6)$$

where $(V/F)_{STD}$ is the typical apparent volume of distribution.

NFM was expressed for $TV(CL/F_{\text{other}})$ (equation 7) and $TV(V/F)$ (equation 8) as described by Anderson and Holford (33).

$$NFM_i = FFM_i + (F_{\text{fat}})_{\frac{CL}{F_{\text{other}}}} \cdot (WT_i - FFM_i) \quad (7)$$

$$NFM_i = FFM_i + (F_{\text{fat}})_{\frac{V}{F}} \cdot (WT_i - FFM_i) \quad (8)$$

where $(F_{\text{fat}})_{CL/F_{\text{other}}}$ and $(F_{\text{fat}})_{V/F}$ denote the estimated unique contribution of fat mass (i.e., body weight minus FFM) to CL/F_{other} and V/F , respectively.

Individual FFM values (FFM_i) were calculated as

$$FFM_i = \frac{WHS_{MAX} \cdot HT^2 \cdot WT}{WHS_{50} \cdot HT^2 + WT} \quad (9)$$

where WHS_{MAX} is 42.92 kg/m^2 and WHS_{50} is 30.93 kg/m^2 in men, WHS_{MAX} is 37.99 kg/m^2 and WHS_{50} is 35.98 kg/m^2 in women, HT is height in meters, and WT is total body weight in kg.

Interindividual variability (IIV) was modeled exponentially for all parameters. Furthermore, interoccasional variability (IOV) in the pharmacokinetic parameters was explored for all parameters (34). Covariance between parameters was also tested. Different residual error models were investigated, including proportional and slope-intercept models. Shrinkage was calculated for fixed and random effects as $1 - SD(\eta)/\omega$, where η is the between-individual and -occasion variation term and ω is the population model estimate of the standard deviation in η .

Once the basic model was developed, a covariate analysis was performed using stepwise covariate model building (SCM) (22) as implemented in PsN version 3.3.2 (20, 21). Sex, age, HIV status, and study site (South Africa versus West Africa) were investigated as covariate effects on the following parameters: CL/F_{GFR} , CL/F_{other} , V/F , k_a , MTT, and bioavailability (F). In the SCM, each parameter-covariate relationship was tested

TABLE 1 Demographics and covariates of patients included in the gatifloxacin population pharmacokinetic model^a

Characteristic (unit)	All sites	South Africa	Senegal	Benin	Guinea
Total no. of patients	169	99	26	25	19
No. of males/no. of females	116/53	62/37	23/3	20/5	11/8
No. of HIV ⁺ patients	54	51	0	3	0
FFM (kg)	45 (39–49)	45 (38–48)	49 (46–52)	46 (41–48)	45 (35–46)
Body wt (kg)	55 (51–60)	56 (51–61)	55 (52–59)	53 (46–57)	52 (50–55)
Age (yr)	29 (24–35)	30 (24–35)	28 (25–31)	30 (26–37)	25 (20–34)
CL _{CR} (ml · min ⁻¹)	94 (81–110)	100 (85–111)	87 (82–102)	75 (63–87)	89 (78–99)

^a Continuous variables are given as medians, with interquartile ranges in parentheses. FFM, fat-free mass; CL_{CR}, creatinine clearance.

in a univariate fashion within NONMEM. The covariate model that resulted in the best fit was carried forward to a multivariate search in which the remaining parameter-covariate relations were included based on a 5% significance level, and it was referred to as the “full forward model.” After identification of the full forward model, a backward deletion was performed to determine the final model. In the backward-deletion step, each parameter covariate relationship was left out one at a time and tested using a statistical significance criterion of 0.01%. This step was repeated until no further covariate could be excluded, and the resulting model was referred to as the “final model.” Continuous covariates were first introduced in a linear fashion (fractional change) and centered on the median covariate value. If a continuous covariate was included in a linear fashion, inclusion according to a nonlinear fashion (i.e., piece-wise linear, exponential, and power equation) was also tested. For categorical covariates, models were expressed as fractional change from the typical value.

Based on the final model, the AUC from zero hour to infinity (AUC_{0-∞}) was derived to describe exposure after the first dose and at steady state (day 28), respectively. Total oral clearance was simulated for 10,000 virtual patients and AUC_{0-∞} derived through the following equation:

$$AUC_{0-\infty} = \frac{F \cdot \text{dose}}{CL} \quad (10)$$

The individual percentage change in AUC_{0-∞} between first dose and steady state was calculated and reported as median (5th and 95th percentiles). The 10,000 virtual patients were derived by resampling subjects from the data used to develop the model.

As a pharmacokinetic/pharmacodynamic (PK/PD) index, we used the ratio of the day 28 free gatifloxacin AUC for a 24-h dosing interval and the MIC (fAUC/MIC), which has been shown to correlate to clinical outcome (35). The target PK/PD index was defined as fAUC/MIC of ≥ 125 , which corresponds to a surrogate for maximal bactericidal effect and reduced probability of resistance (13, 14). The probability of target attainment (PTA) (36) was investigated with Monte Carlo simulations. The final model describing the pharmacokinetics in our study population was used together with the MIC distribution from an *in vitro* study investigating the activity of gatifloxacin against 234 clinical strains of *M. tuberculosis* isolated in the southeast of Spain, published by Rodriguez et al. (3), with a MIC range of 0.06 to 16 $\mu\text{g/ml}$. The median MIC₅₀ from the aforementioned study was 0.125 $\mu\text{g/ml}$, while the median MIC₉₀ was 0.25 $\mu\text{g/ml}$ with only 6 strains (2.5%) having MICs of $>0.25 \mu\text{g/ml}$.

The acceptable level for the PTA is still under debate, as is the most appropriate value for the target ratio of fAUC/MIC for optimal activity of gatifloxacin against *M. tuberculosis*. Therefore, the target ratio of fAUC/MIC as a function of the MIC with the 80% and 90% confidence intervals (CI) was derived. The lower boundary in an 80% CI of the total probability function is equivalent to 90% PTA (36). The PK/PD breakpoint was defined as the MIC at which the calculated PTA was 90%.

Ten thousand individual fAUCs were simulated based on the final model by integrating predicted drug concentrations from 0 to 24 h at steady state and thereafter correcting for serum protein binding, which was assumed to be 20% (1, 37). The PTA, i.e., the probability of fAUC/MIC being ≥ 125 across the range of MICs described by Rodriguez et al.

(3), was derived. The cumulative fraction of response (CFR) (36) was calculated, representing the proportion of the population achieving fAUC/MIC of ≥ 125 , given Monte Carlo simulation and the MIC distribution of *M. tuberculosis* for 400, 600, and 800 mg once daily of gatifloxacin at steady state in combination with rifampin, isoniazid, and pyrazinamide. The CFR was calculated using equation 11:

$$\sum_{i=1}^n \text{PTA}_i \times F_i \quad (11)$$

where *i* indicates the MIC category ranked from lowest to highest MIC value, PTA_{*i*} is the PTA of each MIC category, and *F* is the fraction of the *M. tuberculosis* population at each MIC category. *F* was calculated at each MIC as the number of isolates divided by the total number of isolates (234) yielding the frequency for each MIC.

RESULTS

The characteristics of the 169 patients contributing to this analysis are described in Table 1. More than one-half (59%) of the study participants were recruited at the South African study site, which had the highest frequency of HIV-infected patients (52% versus 12% in Benin and none in Guinea or Senegal).

The final gatifloxacin pharmacokinetic model described one-compartment with first-order elimination. Including an absorption transit model to account for the delay in absorption resulted in a drop in OFV of 125 points. The relationship between CL_{CR} and CL/*F* was described using equations 3 and 4 based on the prior knowledge that gatifloxacin is largely eliminated by the kidneys (1), and this resulted in OFV reductions of 19 and 24 points, respectively, compared to models not accounting for CL_{CR} or a combination of GFR-mediated- and non-GFR clearance. In a 70-kg patient, gatifloxacin total CL/*F* was estimated to be 11.28 liters/h. Approximately 55% (6.17 liters/h) of CL/*F* was accounted for by renal filtration (a route scaled with CL_{CR}). Allometric scaling was applied to the remaining 45% (5.11 liters/h) of CL/*F* and to *V*/*F* (141 liters/h) using FFM as the optimal size descriptor, and the estimates were reported for a 70-kg patient (Table 2). *F* was 11.7% lower at steady state (day 28) than at the first dose. Age, sex, and HIV status had significant effects on the absorption rate constant, reducing interindividual variability of the parameter by 6.5, 3.4, and 17.7%, respectively (Table 2). The final model adequately described the concentration in plasma-time data at initial dose and at steady state as judged by the VPC (Fig. 1). Shrinkage for random effects between individuals and occasions ranged from 17 to 25% and from 38 to 99%, respectively. Shrinkage rates in IIV and IOV for CL/*F* were 25% and 42%, respectively. The epsilon (residual error) shrinkage was 39%.

Based on 10,000 Monte Carlo patient simulations, the median AUC_{0-∞} (41.2 $\mu\text{g} \cdot \text{h/ml}$ after the first dose) decreased to 35.4 $\mu\text{g} \cdot$

TABLE 2 Parameter estimates based on the final gatifloxacin pharmacokinetic model^a

Parameter (unit)	Estimate	% RSE
$(CL/F_{\text{GFR}})_{\text{STD}}$ (liters/h)	6.17	9.7
$(CL/F_{\text{Other}})_{\text{STD}}$ (liters/h)	5.11	15.4
$(V/F)_{\text{STD}}$ (liters)	141	2.7
$F_{\text{first dose}}$	1 FIX	
$F_{\text{steady state}}$ (% change from $F_{\text{first dose}}$)	-11.7	17.4
k_a (h^{-1})	4.13	13.5
MTT (h)	0.65	8.1
N	12.6	19.7
Covariate relationships		
AGE- k_a (%)	3.2	15.2
SEX- k_a (%)	-54.8	10.7
HIV ⁺ - k_a (%)	61.9	38.4
IIV		
IIV _{CL/F} (%)	33.0	7.7
IIV _{V/F} (%)	22.1	10.9
IOV		
IOV _{CL/F} (%)	33.0	5.7
IOV _{V/F} (%)	13.2	13.9
IOV _{MTT} (%)	44.9	12.3
Residual variability		
Additive error ($\mu\text{g/ml}$)	0.341	5.1
Proportional error (%)	7.35	12.5
Predose additive error ($\mu\text{g/ml}$)	0.0418	40.7

^a IIV, interindividual variability expressed as coefficient of variation; IOV, interoccasion variability expressed as coefficient of variation; RSE, relative standard error reported on the approximate standard deviation scale; $(CL/F_{\text{GFR}})_{\text{STD}}$, the oral clearance in a typical patient with a median CL_{CR} of 94 ml/min, representing drug cleared via glomerular filtration (GFR); $(CL/F_{\text{Other}})_{\text{STD}}$, the oral clearance not due to GFR in a typical 70-kg male patient and with a fat-free mass (FFM) of 55 kg. $(V/F)_{\text{STD}}$, typical apparent volume of distribution scaled to FFM and reported for a 70-kg male patient; F , bioavailability; MTT, mean transit time; N , number of transit compartments; AGE- k_a , % increase in k_a for every year change from the median AGE of 29 years; SEX- k_a , % decrease in k_a for female patients relative to male patients; HIV⁺- k_a (%), % increase in k_a for patients with HIV relative to patients without HIV; predose additive error ($\mu\text{g/ml}$), additive error estimated uniquely for the predose concentrations following an unobserved dose; 1 FIX, fixed to 1 (not estimated).

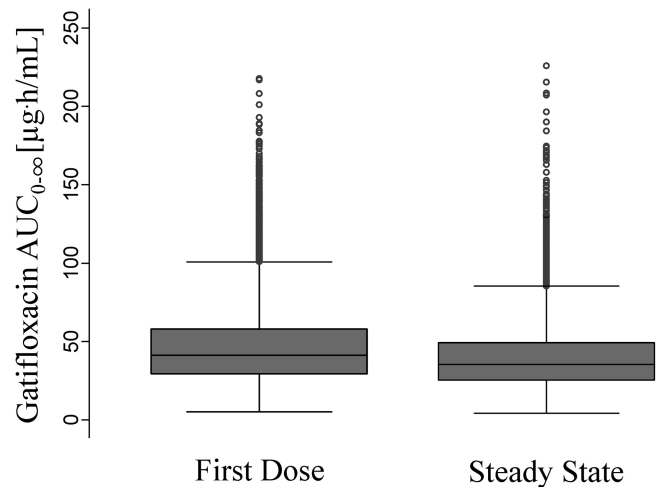


FIG 2 Box plot of gatifloxacin area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) at first dose and at steady state (day 28) based on 10,000 virtual patients and Monte Carlo simulations of 400 mg gatifloxacin daily together with rifampin, isoniazid, and pyrazinamide. In this population, the median gatifloxacin $AUC_{0-\infty}$ of 41.2 $\mu\text{g} \cdot \text{h/ml}$ (5th and 95th percentiles, 17.9 and 93.8) after the first dose was reduced on an individual level by 14.3% (5th and 95th percentiles, -90.4 and 61.5) to 35.4 $\mu\text{g} \cdot \text{h/ml}$ (5th and 95th percentiles, 15.2 and 80.4) at steady state (day 28).

h/ml at steady state, following daily 400-mg doses of gatifloxacin in combination with rifampin, isoniazid, and pyrazinamide (Fig. 2). The median decrease in $AUC_{0-\infty}$ was 14.3% (5th and 95th percentiles, -90.4%, +61.5%).

The PTA, i.e., the probability of patients achieving or exceeding the $fAUC/MIC$ ratio of 125 at steady state, given the frequency distribution of MICs reported from 234 clinical isolates of *M. tuberculosis*, is shown in Fig. 3. The CFR, i.e., the proportion of the population achieving an $fAUC/MIC$ of ≥ 125 for daily 400-mg doses of gatifloxacin in combination with rifampin, isoniazid, and pyrazinamide, was calculated to be 61.4%. The respective CFRs for 600- and 800-mg doses of gatifloxacin were 79.3% and 88%. The PK/PD breakpoint, defined as the MIC at which the calculated PTA was $\geq 90\%$, was 0.125 $\mu\text{g/ml}$ for daily gatifloxacin doses

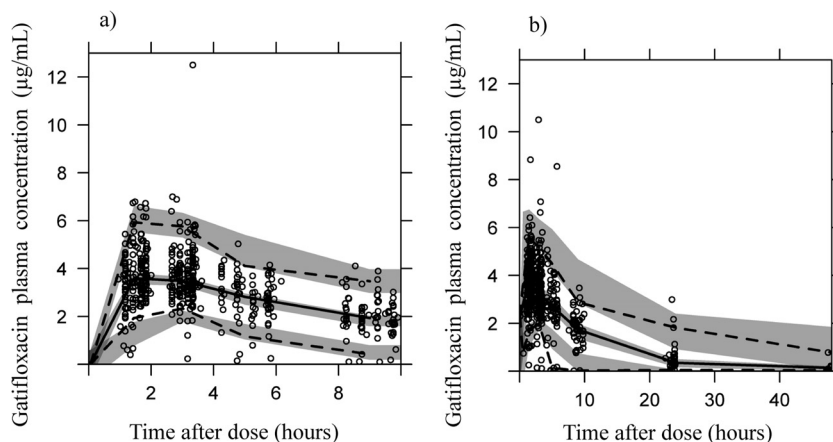


FIG 1 Visual predictive check (VPC) of the final gatifloxacin pharmacokinetic model stratified by occasion, i.e., first dose (a) and steady-state (day 28) (b). The solid line and the two dashed lines are the median and 5th and 95th percentiles, respectively, of the observed gatifloxacin concentrations in plasma. Shaded areas are the 90% prediction intervals for the median and 5th and 95th percentiles of simulated data. The open circles are observed concentrations.

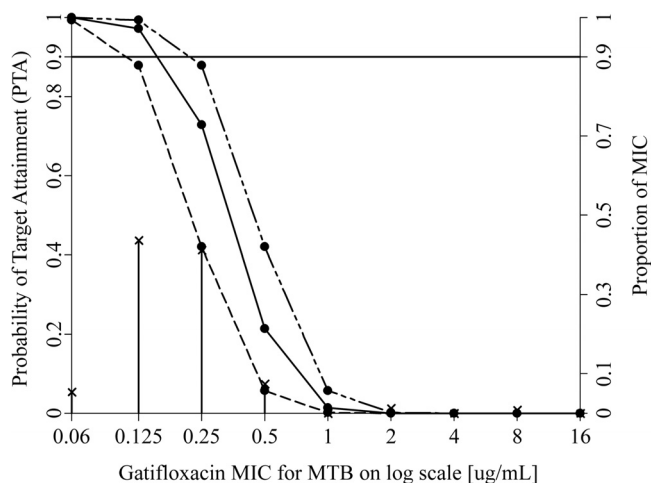


FIG 3 The probability of target attainment (PTA) versus *Mycobacterium tuberculosis* (MTB) MIC following daily administration of 400 mg (dashed line), 600 mg (solid line), and 800 mg (long dash-dot-dot line) gatifloxacin together with rifampin, isoniazid, and pyrazinamide based on 10,000 virtual patients and Monte Carlo simulations. The PTA was defined as the probability of achieving the target PK/PD index ratio of the area under the unbound concentration versus time curve from 0 h to infinity at steady state ($fAUC$) divided by MIC ($fAUC/MIC$) of ≥ 125 (a correlate of maximal bactericidal effect and reduced probability of resistance (10, 40)). The dashed horizontal line indicates the reference line of 90% PTA. The solid drop lines with crosses (×) represent the frequency distribution for MIC of gatifloxacin (y axis on the right) obtained from 243 clinical isolates of *M. tuberculosis* (37).

of 400 mg and 0.25 $\mu\text{g/ml}$ for 800-mg doses of gatifloxacin (dashed line in Fig. 3). The $fAUC/MIC$ as a function of the MIC is shown for 400-, 600-, and 800-mg doses in Fig. 4.

DISCUSSION

In our study, gatifloxacin exposure (bioavailability) was reduced following multiple doses when given together with rifampin, isoniazid, and pyrazinamide. This is in contrast to a single-dose study in healthy volunteers in which increased gatifloxacin exposure ($AUC_{0-\infty}$) was observed (8). Hence, any initial increase in gatifloxacin concentrations attributable to concomitant use of rifampin, isoniazid, and pyrazinamide was counteracted by a reduction in gatifloxacin concentrations with repeated doses of the four drugs in combination. Exposure-related toxicity is thus unlikely to increase with repeated doses of gatifloxacin when it is given with rifampin, isoniazid, and pyrazinamide.

Two interesting observations emerge when comparing exposure after single-agent and combination treatment. First, the steady-state gatifloxacin AUC achieved in our study was slightly lower than the steady-state AUC reported in studies where patients were given the drug alone (6, 38). Second, gatifloxacin pharmacokinetic parameters (including bioavailability) were reported not to change following multiple doses when the drug was given on its own (1, 39). Gatifloxacin is a known substrate of the transmembrane efflux transporter protein P-glycoprotein (Pgp) (40), and rifampin induces the expression of Pgp (41). Hence, repeated doses of rifampin may result in reduced gatifloxacin systemic bioavailability due to increased efflux by Pgp expressed on enterocytes and hepatocytes. Gatifloxacin is principally (>80%) cleared unchanged via the kidneys (1). The overall reduction in gatifloxacin concentrations, following multiple doses in combination with

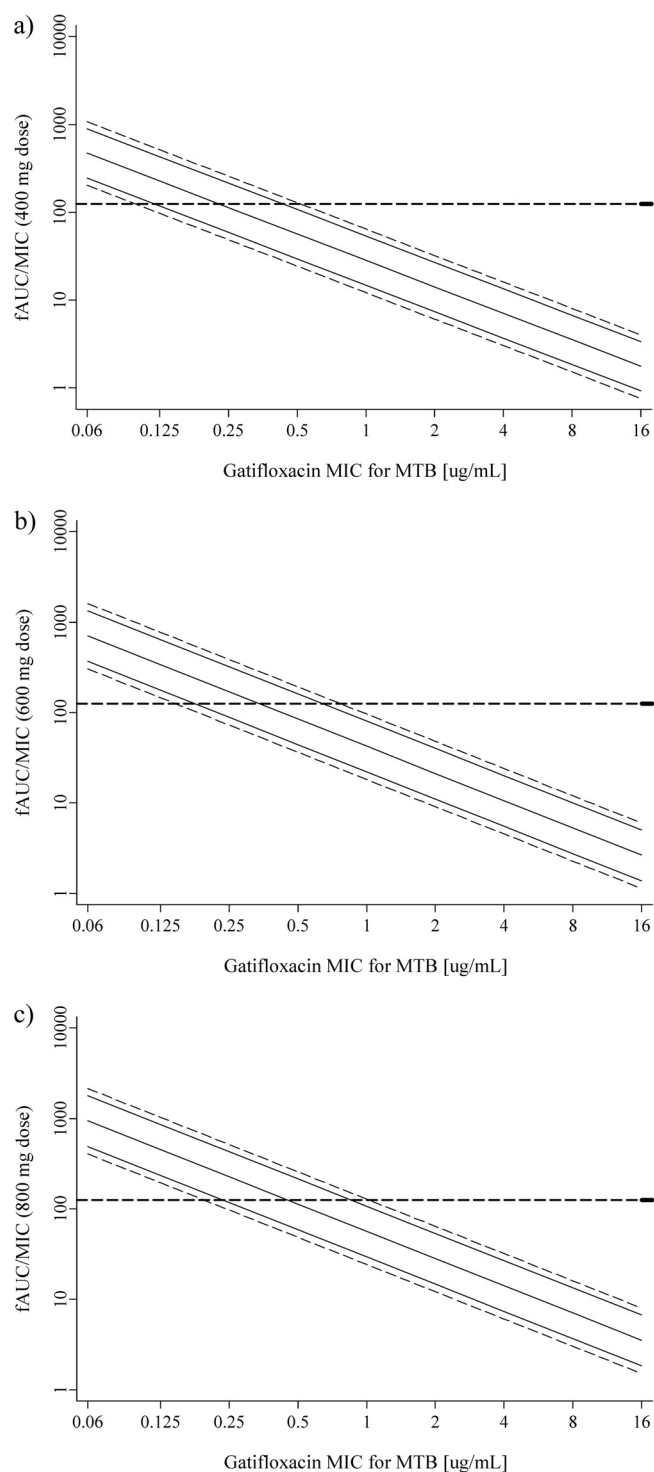


FIG 4 Median (solid thick line) total probability function, irrespective of the target, as a function of the *Mycobacterium tuberculosis* (MTB) MIC, with the 80th (solid lines) and 90th (dashed lines) percentiles following daily administration of 400 (a), 600 (b), and 800 (c) mg of gatifloxacin together with rifampin, isoniazid, and pyrazinamide. The lower boundary in the 80th percentile of the total probability function is equivalent to 90% PTA. The dashed horizontal line indicates the reference line ($fAUC/MIC = 125$).

rifampin, isoniazid, and pyrazinamide, is thus likely to be the net result of drug-drug interactions observed both following single doses and at steady state.

Reduced gatifloxacin clearance and recovery in urine were reported following concomitant dosing with probenecid, suggesting that tubular secretion may contribute to its elimination (1). In our study, gatifloxacin clearance increased with creatinine clearance (CL_{CR}) and patient weight (FFM). Scaling drug clearance to both FFM and CL_{CR} allowed us to estimate that approximately 53% of the dose was cleared via glomerular filtration. Using CL_{CR} as our proxy for renal filtration might, however, overestimate the contribution of this pathway to drug clearance, since creatinine is actively secreted by the peritubular capillaries of the kidney (42). The remaining 47% of gatifloxacin's clearance was scaled to FFM and accounted for drug cleared via all pathways other than glomerular filtration.

Gatifloxacin bioavailability was predicted to be approximately 12% lower at steady state than after an initial dose. This, combined with increased patient weight (FFM) and CL_{CR} ($\text{ml} \cdot \text{min}^{-1}$) at the second occasion, resulted in a 14.3% reduction of $AUC_{0-\infty}$ at steady state. The reduction in gatifloxacin exposure following multiple doses is unlikely to be clinically significant, as on an individual level gatifloxacin $AUC_{0-\infty}$ could increase by as much as 90% or decrease by as much as 62% between the two occasions due to the high IOV in CL/F . Age, sex, and HIV infection status were also identified as having significant covariate effects on the absorption rate constant. However, these covariates are also unlikely to be clinically relevant, as changes of the absorption rate do not alter the average steady-state concentration.

Based on 10,000 Monte Carlo simulations using the final model, 62, 79, and 88% of our study population were predicted to achieve the target $fAUC/MIC$ ratio of ≥ 125 following daily 400-, 600-, and 800-mg respective doses of gatifloxacin. Only when the MIC of gatifloxacin fell below $0.125 \mu\text{g/ml}$ could 90% of the study population, irrespective of dose, achieve the target ratio. The simulations showed that at 800-mg daily doses of gatifloxacin, approximately 90% of the population would achieve the target ratio when the MIC was $\leq 0.25 \mu\text{g/ml}$. These results suggest that the current 400-mg daily dosing of gatifloxacin does not achieve optimal drug exposure with respect to the MIC distribution used. However, using the target plasma $fAUC/MIC$ ratio of ≥ 125 to predict the optimal dose of gatifloxacin in this context is a simplification and has its limitations. Forrest et al. (13) demonstrated that bacteriological and clinical outcomes correlated best with the pharmacodynamic index of an AUC/MIC of ≥ 125 in 74 acutely ill patients treated with ciprofloxacin for lower respiratory tract infections. In that study, an AUC/MIC ratio of ≥ 125 was significantly correlated with a faster bacterial eradication rate, which may decrease the likelihood of antibacterial resistance. Setting the target to a lower value (i.e., targets of AUC/MIC ratios of < 125) could potentially create needless selective pressure, increasing the chance of resistance especially with a long duration of therapy (e.g., 4 months). Notably, in a review by Schentag et al. (14), the pharmacodynamic index target AUC/MIC ratio of ≥ 125 is recommended for both Gram-positive and Gram-negative organisms. Although $fAUC/MIC$ is widely accepted as a correlate of fluoroquinolone efficacy (43), more work is required to determine whether an AUC/MIC of ≥ 125 truly correlates with *in vivo* efficacy against *M. tuberculosis*. In this work, we also pres-

ent the total probability function for different gatifloxacin doses, which is not dependent on the target (Fig. 4). The lower boundary in the 80th percentile of the total probability function is equivalent to 90% PTA. The 90% PTA for any new future target can be visualized from this plot. Interestingly, a plasma AUC/MIC ratio of 112 to 220 was associated with optimal survival among patients with tuberculosis meningitis who were treated with a regimen containing gatifloxacin, levofloxacin, or ciprofloxacin in addition to standard antituberculosis treatment (44). Although this ratio is in keeping with the target AUC/MIC of ≥ 125 , the optimal values for the plasma AUC/MIC ratios for pulmonary tuberculosis and tuberculosis meningitis are likely to differ due to differences in tissue penetration and immunity at the site of action. Drug action occurs within pulmonary compartments, including epithelial cells and macrophages, where drug concentrations exceed those found in plasma (45). Assuming higher $fAUC$ in pulmonary compartments, more patients could achieve the target $fAUC/MIC$ ratio of ≥ 125 . On the other hand, there are concerns that administering higher doses of gatifloxacin would increase the risk of toxicity such as dysglycemia. Lastly, the optimal dose of gatifloxacin would need to take into account the efficacy and safety profiles of the drug in the context of the contributions from companion drugs in the multidrug regimen and patient immunity.

Further limitations of our study include failure to measure free gatifloxacin concentrations and lack of study-specific information about the MICs. We assumed a 20% plasma protein binding for gatifloxacin that is independent of concentration (1), and we used the MIC distribution obtained from 234 clinical isolates of *M. tuberculosis* from Spain (3). The *M. tuberculosis* population reported in the Spanish study was slightly more sensitive to gatifloxacin than to moxifloxacin and levofloxacin, with reported MIC_{90s} of 0.25 and $0.5 \mu\text{g/ml}$, respectively. In agreement with the Spanish study, a similar gatifloxacin MIC_{90} of $0.25 \mu\text{g/ml}$ was reported against clinical isolates of *M. tuberculosis* obtained from numerous sources with broad geographical distribution (46). Additionally, the aforementioned study reported an MIC_{50} and distribution range of MIC for *M. tuberculosis* similar to that reported in the Spanish study. Thus, our assumption that the frequency distribution of gatifloxacin MIC reported in the Spanish study correlates to the MIC distribution found within our study population appears to be valid. Nonetheless, as demonstrated by Peloquin et al. (38), a change in the MIC distribution (i.e., published versus actual MICs determined from clinical isolates obtained from study patients) can radically change the $fAUC/MIC$ ratio. Since our study did not measure the MICs of *M. tuberculosis* in the study population, it is feasible that the true effective MIC could be lower. Moreover, the MICs reflect the activity of gatifloxacin alone; we did not account for synergism or antagonism within the regimen. The relevance of these findings needs to be evaluated alongside the eventual clinical outcomes of the study overall.

Conclusion. Although increased gatifloxacin exposure was observed in a previous single-dose study, gatifloxacin exposure, expressed as $AUC_{0-\infty}$, declined following multiple doses of the 4 drugs in the multidrug regimen. Hence, exposure-related toxicity is unlikely to increase with repeated doses of gatifloxacin when given concomitantly with rifampin, isoniazid, and pyrazinamide. Based on predictions of $fAUC/MIC$ and the derived proportion of the population achieving optimal bactericidal effect and reduced

probability of resistance (CFR), the CFR of the clinically used dose of 400 mg daily was 61%; simulations showed that doubling the dose would result in increasing the CFR to 88%. However, the pharmacokinetics of gatifloxacin needs to be studied in relation to efficacy and safety in pulmonary tuberculosis patients on the multidrug regimen in order to evaluate the optimal gatifloxacin exposures in this context.

ACKNOWLEDGMENTS

The study was supported by grant ICA4-CT 2002-10057 from the World Health Organization (WHO)/Special Programme for Research and Training in Tropical Diseases (TDR) and the Research Institute for Development (IRD).

We acknowledge the contributions of the clinical sites and patients, without which this study would not have been possible.

P.L.O. and C.L. are staff members of the WHO.

We are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy, or views of the WHO.

REFERENCES

- Nakashima M, Uematsu T, Kosuge K, Kusajima H, Ooie T, Masuda Y, Ishida R, Uchida H. 1995. Single- and multiple-dose pharmacokinetics of AM-1155, a new 6-fluoro-8-methoxy quinolone, in humans. *Antimicrob. Agents Chemother.* 39:2635–2640.
- Alvarez-Freites EJ, Carter JL, Cynamon MH. 2002. In vitro and in vivo activities of gatifloxacin against *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.* 46:1022–1025.
- Rodriguez JC, Ruiz M, Lopez M, Royo G. 2002. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*. *Int. J. Antimicrob. Agents* 20:464–467.
- Singh M, Chauhan DS, Gupta P, Das R, Srivastava RK, Singh PUP, Srivastava K, Faujdar J, Jaudaun GPS, Yadav VS, Sharma VD, Venkatesan K, Sachan S, Sachan P, Katoch K, Katoch VM. 2009. *In vitro* effect of fluoroquinolones against *Mycobacterium tuberculosis* isolates from Agra & Kanpur region of north India. *Indian J. Med. Res.* 129:542–547.
- Cynamon MH, Sklaney MR, Shoen C. 2007. Gatifloxacin in combination with rifampicin in a murine tuberculosis model. *J. Antimicrob. Agents Chemother.* 60:429–432.
- Johnson JL, Hadad DJ, Boom WH, Daley CL, Peloquin CA, Eisenach KD, Jankus DD, Debanne SM, Charlebois ED, Maciel E, Palaci M, Dietze R. 2006. Early and extended bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis.* 10:605–612.
- Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, Reddy C, Sturm AW, Sireg FA, Allen J, Coleman DJ, Fourie B, Mitchison DA. 2008. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis.* 12:128–138.
- McIlleron H, Norman J, Kanyok TP, Fourie PB, Horton J, Smith PJ. 2007. Elevated gatifloxacin and reduced rifampicin concentrations in a single-dose interaction study amongst healthy volunteers. *J. Antimicrob. Agents Chemother.* 60:1398–1401.
- Ambrose PG, Bhavnani SM, Cirincione BB, Piedmonte M, Grasela TH. 2003. Gatifloxacin and the elderly: pharmacokinetic–pharmacodynamic rationale for a potential age-related dose reduction. *J. Antimicrob. Chemother.* 52:435–440.
- Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dressler L, Low DE, Mamdani MM. 2006. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N. Engl. J. Med.* 354:1352–1361.
- Mehlhorn AJ, Brown DA. 2007. Safety concerns with fluoroquinolones. *Ann. Pharmacother.* 41:1859–1866.
- LaPlante KL, Mersfelder TL, Ward KE, Quilliam BJ. 2008. Prevalence of and risk factors for dysglycemia in patients receiving gatifloxacin and levofloxacin in an outpatient setting. *Pharmacotherapy* 28:82–89.
- Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. 1993. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob. Agents Chemother.* 37:1073–1081.
- Schentag JJ, Gilliland KK, Paladino JA. 2001. What have we learned from pharmacokinetic and pharmacodynamic theories? *Clin. Infect. Dis.* 32:S39–S46.
- Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. *J. Antimicrob. Chemother.* 55:601–607.
- Merle CS, Sismanidis C, Bah Sow O, Gninafon M, Horton J, Lapujade O, Lo MB, Mitchinson DA, Perronne C, Portaels F, Odhiambo J, Olliaro P, Rustomjee R, Lienhardt C, Fielding K. 2012. A pivotal registration phase III, multicenter, randomized tuberculosis controlled trial: design issues and lessons learnt from the Gatifloxacin for TB (OFLOTUB) project. *Trials* 13:61.
- Beal S, Sheiner LB, Boeckmann A, Bauer RJ. 2009. NONMEM user's guides 1989–2009. Icon Development Solutions, Ellicott City, MD.
- The R Foundation for Statistical Computing. 2 June 2011. R. A language and environment for statistical computing. <http://www.R-project.org>.
- Jonsson EN, Karlsson MO. 1999. Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput. Methods Programs Biomed.* 58:51–64. <http://xpose.sourceforge.net/>. Accessed 9 June 2011.
- Lindbom L, Ribbing J, Jonsson EN. 2004. Perl-speaks-NONMEM (PsN)—a Perl module for NONMEM related programming. *Comput. Methods Programs Biomed.* 75:85–94. <http://psn.sourceforge.net/>. Accessed 9 June 2011.
- Lindbom L, Pihlgren P, Jonsson EN. 2005. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput. Methods Programs Biomed.* 79:241–257. <http://psn.sourceforge.net/>. Accessed 9 June 2011.
- Jonsson EN, Karlsson MO. 1998. Automated covariate model building within NONMEM. *Pharm. Res.* 15:1463–1468.
- Holford NHG. 2005. PAGE 14. Abstract 738. <http://www.page-meeting.org/?abstr=738>.
- Holford NHG, Karlsson MO. 2008. PAGE 17. Abstract 1434. <http://www.page-meeting.org/?abstr=1434>.
- Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. 2011. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 13:143–151.
- Savic RM, Jonker DM, Kerbusch T, Karlsson MO. 2007. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. *J. Pharmacokinet. Pharmacodyn.* 34:711–726.
- Wilkins JJ, Savic RM, Karlsson MO, Langdon G, McIlleron H, Pillai G, Smith PJ, Simonsson USH. 2008. Population pharmacokinetics of rifampin in pulmonary tuberculosis patients, including a semimechanistic model to describe variable absorption. *Antimicrob. Agents Chemother.* 52:2138–2148.
- Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41.
- Holford NHG. 1996. A size standard for pharmacokinetics. *Clin. Pharmacokinet.* 30:329–332.
- West GB, Brown JH, Enquist BJ. 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276:122–126.
- West GB, Brown JH, Enquist BJ. 1999. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* 284:1677–1679.
- Anderson BJ, Holford NH. 2008. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu. Rev. Pharmacol. Toxicol.* 48:303–332.
- Anderson BJ, Holford NH. 2009. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug Metab. Pharmacokinet.* 24:25–36.
- Karlsson MO, Sheiner LB. 1993. The importance of modelling interoccasion variability in population pharmacokinetic analyses. *J. Pharmacokinet. Biopharm.* 21:735–750.
- Pasipanodya J, Gumbo T. 2011. An oracle: antituberculosis pharmacokinetics–pharmacodynamics, clinical correlation, and clinical trial simulations to predict the future. *Antimicrob. Agents Chemother.* 55:24–34.
- Mouton JW, Punt N, Vinks AA. 2005. A retrospective analysis using Monte Carlo simulation to evaluate recommended ceftazidime dosing regimens in healthy volunteers, patients with cystic fibrosis, and patients in the intensive care unit. *Clin. Ther.* 27:762–772.
- Gajjar DA, LaCreta FP, Uderman HD, Kollia GD, Duncan G, Birkhofer

- MJ, Grasele DM. 2000. A dose-escalation study of the safety, tolerability, and pharmacokinetics of intravenous gatifloxacin in healthy adult men. *Pharmacotherapy* 20:49S–58S.
38. Peloquin CA, Hadad DJ, Molino LP, Palaci M, Boom WH, Dietze R, Johnson JL. 2008. Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis. *Antimicrob. Agents Chemother.* 52:852–857.
 39. Mignot A, Guillaume M, Brault M, Gualano V, Millérioux L, Göhler K, Stahlberg HJ. 2002. Multiple-dose pharmacokinetics and excretion balance of gatifloxacin, a new fluoroquinolone antibiotic, following oral administration to healthy Caucasian volunteers. *Chemotherapy* 48:116–121.
 40. Kwatra D, Vadlapatla RK, Vadlapudi AD, Pal D, Mitra AK. 2010. Interaction of gatifloxacin with efflux transporters: a possible mechanism for drug resistance. *Int. J. Pharm.* 395:114–121.
 41. Schuetz EG, Schinkel AH, Relling MV, Schuetz JD. 1996. P-glycoprotein: a major determinant of rifampicin-inducible expression of cytochrome P4503A in mice and humans. *Proc. Natl. Acad. Sci. U. S. A.* 93:4001–4005.
 42. Crawford B. 1948. Depression of the exogenous creatinine/inulin or thio-sulphate clearance ratios in man by diodrast and p-aminohippuric acid. *J. Clin. Invest.* 27:171–175.
 43. Ginsburg AS, Grosset JH, Bishai WR. 2003. Fluoroquinolones, tuberculosis, and resistance. *Lancet Infect. Dis.* 3:432–442.
 44. Thwaites GE, Bhavnani SM, Chau TTH, Hammel JP, Török ME, Van Wart SA, Mai PP, Reynolds DK, Caws M, Dung NT, Hien TT, Kulawy R, Farrar J, Ambrose PG. 2011. Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. *Antimicrob. Agents Chemother.* 55:3244–3253.
 45. Honeybourne D, Banerjee D, Andrews J, Wise R. 2001. Concentrations of gatifloxacin in plasma and pulmonary compartments following a single 400 mg oral dose in patients undergoing fibre-optic bronchoscopy. *J. Antimicrob. Chemother.* 48:63–68.
 46. Fung-Tomc J, Minassian B, Kolek B, Washo T, Huczko E, Bonner D. 2000. *In vitro* antibacterial spectrum of a new broad-spectrum 8-methoxy fluoroquinolone, gatifloxacin. *J. Antimicrob. Chemother.* 45:437–446.