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Population Pharmacokinetics and Pharmacodynamics of Ofloxacin in South African Patients with Multidrug-Resistant Tuberculosis

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Despite the important role of fluoroquinolones and the predominant use of ofloxacin for treating multidrug-resistant tuberculosis in South Africa, there are limited data on ofloxacin pharmacokinetics in patients with multidrug-resistant tuberculosis, no ofloxacin pharmacokinetic data from South African patients, and no direct assessment of the relationship between ofloxacin pharmacokinetics and the MIC of ofloxacin of patient isolates. Our objectives are to describe ofloxacin pharmacokinetics in South African patients being treated for multidrug-resistant tuberculosis and assess the adequacy of ofloxacin drug exposure with respect to the probability of pharmacodynamic target attainment (area under the time curve/MIC ratio of at least 100). Sixty-five patients with multidrug-resistant tuberculosis were recruited from 2 hospitals in South Africa. We determined the ofloxacin MICs for the *Mycobacterium tuberculosis* isolates from baseline sputum specimens. Patients received daily doses of 800 mg ofloxacin, in addition to other antitubercular drugs. Patients underwent pharmacokinetic sampling at steady state. NONMEM was used for data analysis. The population pharmacokinetics of ofloxacin in this study has been adequately described. The probability of target attainment expectation in the study population was 0.45. Doubling the dose to 1,600 mg could increase this to only 0.77. The currently recommended ofloxacin dose appeared inadequate for the majority of this study population. Studies to assess the tolerability of higher doses are warranted. Alternatively, ofloxacin should be replaced with more potent fluoroquinolones.

Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis resistant to rifampin and isoniazid (34), is of increasing concern. Globally, among previously treated TB patients, 18.5% have MDR-TB (37), and 3.2% of all new TB cases are MDR-TB (7). Fluoroquinolones have improved MDR-TB cure rates, although development of resistance to quinolones is a concern (10, 11, 22). Ofloxacin is a fluoroquinolone that is routinely administered to patients with MDR-TB in South Africa in accordance with national guidelines (26). However, ofloxacin has been found to be less effective than other fluoroquinolones, such as moxifloxacin and gatifloxacin, in clinical studies (27) and in *in vitro* studies (13). Ofloxacin, however, continues to be used for treatment of tuberculosis, perhaps because it is less expensive. The levorotatory isomer of ofloxacin, levofloxacin, has been found to have half the MIC of ofloxacin against *Mycobacterium tuberculosis* (13); therefore, it may be expected to be more potent than ofloxacin. Indeed, in mice it has been shown that double the ofloxacin dose is equivalent in antitubercular activity to the corresponding levofloxacin dose (18). However, the higher cost of levofloxacin remains a problem.

Ofloxacin is primarily renally eliminated with a combination of glomerular filtration and active secretion (19); the respective proportions of the drug eliminated through glomerular filtration and extraglomerular means are currently unknown. As expected, renal function influences ofloxacin elimination (33), that is, clearance decreases with decreasing renal function. Plasma protein binding is reported to be independent of the ofloxacin concentration; it was reported to be 25% in healthy volunteers (19) and was estimated as 32% from *in vitro* data (16).

The World Health Organization (WHO) suggests a drug susceptibility testing critical concentration for ofloxacin of 2.0 mg/liter for both solid and liquid media (35). Patients with MDR-TB strains with an ofloxacin MIC greater than 2.0 mg/liter should not receive ofloxacin as part of their treatment but should receive an alternative drug. The MIC of ofloxacin for clinical *Mycobacterium tuberculosis* isolates has been reported to be normally distributed, ranging between 0.25 and 1 mg/liter (2). However, these data were from a Swedish hospital, and South African MIC distributions may differ. Interestingly, susceptibility to ofloxacin has been shown to be reduced in the presence of rifampin resistance (20).

The pharmacokinetic-pharmacodynamic marker that best predicts the efficacy of fluoroquinolones, including ofloxacin, is the ratio of the free fraction of area under the time curve to the MIC (*f*AUC/MIC) (31). *In vitro* murine (29) and clinical studies have shown that fluoroquinolones have the greatest bactericidal activity against *Mycobacterium tuberculosis* and decreased probability of resistance when the *f*AUC/MIC ratio is ≥100 (9, 12, 29–31).

The pharmacokinetics and pharmacodynamics of ofloxacin in patients with MDR-TB in a routine clinical setting have been studied to a very limited extent (33) and have not been studied in

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South Africans. This study characterizes ofloxacin pharmacokinetics and pharmacodynamics in patients with MDR-TB in the high-burden South African setting.

MATERIALS AND METHODS

Ethical approval was obtained from the University of Cape Town, the University of KwaZulu-Natal, the South African Department of Health, and the U.S. Centers for Disease Control and Prevention.

Clinical procedures. The study was conducted at two MDR-TB referral hospitals, one in Cape Town and the other in Durban. Patients were diagnosed with MDR-TB based on results of drug susceptibility tests and referred to the hospitals as part of routine clinical practice. Sixty-five adult patients with MDR-TB were recruited into the study before commencing treatment. Patients received daily weight-based doses of kanamycin (or amikacin), pyrazinamide, terizidone, and ethionamide, in addition to 800 mg of ofloxacin. All the subjects were inpatients, and drug intake was directly observed by hospital staff. A baseline sputum sample was obtained from each patient before commencing treatment to determine the ofloxacin MIC of *Mycobacterium tuberculosis*. In addition to standard therapy for MDR-TB, 12 of the 27 patients from Durban received a 600-mg daily dose of linezolid as part of a clinical trial (TBTC Study 30) in which they were coenrolled. In the TBTC Study 30, the 27 patients from Durban were randomized to receive 600 mg of linezolid or a placebo daily. Twelve of these patients actually received linezolid, while the remainder received the placebo.

Participants underwent pharmacokinetic sampling on one occasion at least 1 week after commencing treatment to ensure that steady-state pharmacokinetics had been attained. Patients in Cape Town received the ofloxacin dose after breakfast (oatmeal porridge, bread, and a cup of tea) as part of the standard hospital procedure. Patients in Durban received the ofloxacin dose on an empty stomach. The Cape Town pharmacokinetic sampling schedule was 0.5, 3.5, 5.5, 7.5, and 12 h after dose administration, while the Durban sampling schedule was 0, 1, 2, 4, 8, 11, and 24 h after dose administration. For Durban patients, blood samples were immediately placed on ice after collection and centrifuged and sera were separated and aliquoted within 30 min. Sera were placed on ice, transported, and stored at −70°C within 4 h of collection. For Cape Town patients, blood samples were immediately placed on ice after collection. Within 10 min thereafter, the samples were centrifuged and the sera were placed on dry ice before being transferred all at once to a −80°C freezer at the end of the day. Lithium heparin tubes were used for blood sampling for both study sites.

Laboratory procedures. The MIC was determined by the agar dilution method using 2-fold dilutions from an initial concentration of 8.0 mg/liter down to 0.03 mg/liter. Serial ofloxacin concentrations and a drug-free control were incorporated into Middlebrook 7H10 agar. A 1.0 McFarland standard of each *Mycobacterium tuberculosis* isolate from the patients was diluted to 10^{-4} before inoculation onto the drug-free control and drug-containing quadrants. A sensitive *M. tuberculosis* H37Rv control and a resistant *M. tuberculosis* A169 control were set up with each batch of MIC assays. The inoculated agar plates were allowed to air dry in a biosafety cabinet and then packed into CO_2-permeable plastic bags. The bags were sealed and incubated at 37°C, and the plates were read after 21 days. The lowest concentration on the agar plate that did not have growth was recorded as the MIC. The plates were done in triplicate to ensure reproducibility of the results. Drug plasma concentrations were determined using a validated high-performance liquid chromatography assay with tandem mass spectroscopy detection method (21). The assay was validated over the concentration range of 0.078 mg/liter to 20 mg/liter. The percent recovery for ofloxacin was greater than 70% and reproducible at low, medium, and high concentrations (21). The coefficient of variation during analysis of the study samples ranged from 4.4% to 6.0% and the accuracy from 94.0% to 102.9% for high, medium and low quality controls, showing that the method had good reproducibility.

Pharmacokinetic analysis. Concentration-time data from the two study sites were pooled for pharmacokinetic analysis using a nonlinear mixed effects modeling approach implemented in NONMEM version 7.1.2 (Icon, Inc., Verona, PA). An Intel Fortran compiler was used, and the runs were executed using Perl-speaks-NONMEM (http://psn.sourceforge.net/). Population pharmacokinetic parameter estimates and their variability were obtained using the first-order conditional estimation method with ε-η interaction (FOCE-I). The objective function value (OFV) and visual predictive checks were used for model building and evaluation. A decrease in the OFV of at least 3.84 points after the inclusion of one model parameter was regarded as statistically significant. Various structural models were evaluated, including a one- and two-compartment model with first-order elimination and mixed-order elimination. Absorption models that were evaluated include first-order absorption, zero-order absorption, sequential zero-order and first-order absorption, and a transit compartment (28) absorption model. The effects of covariates on several model parameters were investigated one at a time in a stepwise manner, using the OFV and parameter precision to decide whether the covariate was of significance or not. Covariates that were investigated included total body weight introduced using allometric scaling (1), lean body weight (15) introduced using allometric scaling, creatinine clearance, HIV infection, and meal administration (with a meal for patients in Cape Town, and without a meal for patients in Durban). Creatinine clearance in ml/min was calculated using total body weight in the Cockcroft-Gault equation using the formula below:

$$\text{creatinine clearance} = \frac{(140 - \text{age}) \cdot \text{total body weight} \cdot K}{\text{sCr}}$$

where K is a constant equal to 1.04 for women and 1.23 for men and sCr is serum creatinine concentration in μmol/liter.

Creatinine clearance was also calculated using lean body weight in a modified Cockcroft-Gault equation as shown below:

$$\text{creatinine clearance} = \frac{(140 - \text{age}) \cdot \text{LBW}}{\text{sCr}}$$

where LBW is the lean body weight. As the two different study sites had different pharmacokinetic sampling schedules, this had the potential to confound analyses when investigating the effect of food on drug administration. To evaluate the influence of pharmacokinetic sampling differences on the estimates of the model parameters of interest to be evaluated, a stochastic simulation-estimation experiment of 200 samples was undertaken using the Durban absorption model parameter estimates but with the Cape Town pharmacokinetic sampling schedule. The bias and precision of the parameters from the simulation-estimation experiment were obtained. However, it must be stated that another potential confounder is the study site, since only Cape Town patients received food with their tablets. This cannot be resolved by any means, and it is more likely that any differences would be due to food effects.

Probability of target attainment. The probability, based on Monte Carlo simulations, that a specific value of a pharmacodynamic index is achieved or exceeded within a population of individuals is known as the probability of target attainment (PTA) (23). The PTA is based upon integration of pharmacokinetic data in humans, using Monte Carlo simulations, with antimicrobial pharmacodynamics as has been performed previously (5, 25). In our case, the pharmacodynamic index target was a *f*AUC/MIC ratio of at least 100. Individual AUCs from the model were obtained by integrating drug concentration predictions from 0 to 24 h after drug administration. The AUC was then multiplied by 0.75, which is the unbound fraction of ofloxacin in humans (19), to obtain the *f*AUC. The final model was used to perform Monte Carlo simulations in 10,000 individuals to determine the PTA at various MICs (0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 mg/liter) and the PTA expectation based on the MIC distribution in our study population. The PTA expectation was calculated using the following equation:

$$\Sigma_{i=1}^{n} \text{PTA}_i \times F_i$$

where PTA_i is the PTA for each MIC category and F_i is the fraction of the

TABLE 1 MDR-TB patient characteristics, ofloxacin pharmacokinetic study, South Africa

Patient characteristic	Median (2.5, 97.5 percentile)
Wt (kg)	55 (39, 80)
Lean body wt (kg)	46 (32, 54)
Ht (m)	1.67 (1.34, 1.84)
Age (yr)	34 (20, 63)
Body mass index (kg/m^2)	19.3 (13.6, 36.4)
Creatinine clearance (ml/min)[a]	109 (69, 159)

[a] Calculated using Cockcroft-Gault equation using total body weight.

study population for the corresponding MIC category.

Dosing simulations. To optimize the dosing, further Monte Carlo simulations were performed using higher ofloxacin doses ranging from 800 mg to 1,600 mg daily in 200-mg increments toward dose optimization that would lead to higher PTA expectation values. The final pharmacokinetic model implemented in the software NONMEM was used for the simulations. The simulations were carried out in 10,000 patients based on the covariate distribution of our current data set. For each dose, the *f*AUC for each patient was obtained. This was then used to calculate the PTA for each MIC in the observed range (0.25 to 8 mg/liter), followed by the PTA expectation as described above.

RESULTS

Thirty-eight patients were recruited from Cape Town and 27 patients from Durban, giving a total of 65 patients. Thirty-five (54%) (18 from Cape Town and 17 from Durban) of the 65 patients were HIV positive. There were 13 females (20%) in the study, all of whom were from the Durban site. Table 1 further describes the patient characteristics. Twenty-nine patients (16 from Cape Town and 13 from Durban) received antiretroviral therapy comprising efavirenz with 2 nucleoside reverse transcriptase inhibitors. Other concomitant medicines included vitamin B complex, vitamin B_6, and cotrimozaxole in HIV-positive patients.

MIC distributions. MIC data were available from 22 of the Durban patients and all 38 of the Cape Town patients. Five of the Durban patients did not have MIC results due to lack of a *Mycobacterium tuberculosis* isolate from these patients. Table 2 shows the percentages of MICs for each study site, together with the overall MIC percentages of the pooled data. The Cape Town MICs were significantly higher than the Durban MICs by approximately one dilution. The geometric means (95% confidence intervals) for the Cape Town and Durban MICs, respectively, were 1.5 (1.2 to 2.0) and 0.8 (0.6 to 1.1) (Wilcoxon rank-sum $P < 0.001$).

Ofloxacin pharmacokinetics. A transit compartment (28) model best described the absorption of ofloxacin, while a two-compartment model with first-order elimination best described the disposition of ofloxacin. Mixed-order elimination could not be supported by the data. As can be seen from the derived parameters in Table 3 and Fig. 1b, there is a short early distribution phase, followed by a longer terminal phase, similar to what has been reported previously for ofloxacin (19). The final model had two clearance pathways according to the equations below:

$$CL_{GFR} = \theta_1 \times \left(\frac{CrCl}{68}\right)$$

$$CL_{non\text{-}GFR} = \theta_2 \times \left(\frac{WT}{70}\right)^{\frac{3}{4}}$$

$$(CL/F)_i = [CL_{GFR} + CL_{non\text{-}GFR}] \cdot \exp(\eta_{CL})$$

where CL_{GFR} is the glomerular filtration of ofloxacin, θ_1 is the typical value that will be estimated by the model, CrCl is the creatinine clearance of the individual subject *i*, which had a median value of 68 ml/min, $CL_{non\text{-}GFR}$ is the extraglomerular excretion route of ofloxacin, θ_2 is the typical value that will be estimated, WT is the weight of individual *i*, $(CL/F)_i$ is the total oral clearance of ofloxacin for individual *i*, and η_{CL} is the population variability in oral clearance for individual *i*.

The excretion of ofloxacin was best described using two clearance pathways. One pathway represents glomerular filtration of ofloxacin. Creatinine clearance was a significant covariate for this route of excretion. Substitution of lean body

TABLE 2 Comparison of MICs for ofloxacin of multidrug-resistant *M. tuberculosis* isolates from 2 sites in South Africa

Study site	% of isolates with ofloxacin MIC (mg/liter) of[a]:				
	0.5	1	2	4	8
Cape Town ($n = 38$)	5	50	32	3	10
Durban ($n = 22$)	41	50	5	0	5
Total ($n = 60$)	18	50	22	2	8

[a] *P* value comparing proportion of isolates with specific MIC in Cape Town versus Durban was <0.001.

TABLE 3 Parameter estimates from final model, ofloxacin pharmacokinetic study in patients with MDR-TB, South Africa[a]

Parameter	Typical value (% RSE)	PPV (% RSE)
Estimated parameter		
Glomerular filtration (liters/h/68 ml/min CrCl)	3.7 (30)	26 (9)[b]
Extraglomerular excretion (liters/h/70 kg)	4.7 (28)	26 (9)[b]
Central vol (liters/46 kg LBW)	52 (20)	30 (32)
Peripheral vol (liters/70 kg)	40 (25)	
Intercompartmental clearance (liters/h/70 kg)	59 (44)	
Durban mean transit time (h)	0.74 (18)	54 (14)
Cape Town mean transit time (h)	1.76 (11)	54 (14)
Number of absorption transit compartments	6 (15)	
Additive error (mg/liters)	0.6 (6)	
Proportional error (%)	9.6 (9.4)	
Covariance between random effects of clearance and central vol of distribution	0.56 (25)	
Derived parameters		
Alpha half-life (h)	0.3	
Beta half-life (h)	7.8	
$k_{el\alpha}$ (h^{-1})	2.7	
$k_{el\beta}$ (h^{-1})	0.09	
Peak concn in Durban patients (mg/liters)	10.4	
Peak concn in Cape Town patients (mg/liters)	8.8	
Time to peak concn in Durban patients (h)	1.2	
Time to peak concn in Cape Town patients (h)	3	

[a] RSE, relative standard error; PPV, population variability; CrCl, creatinine clearance calculated using LBW in Cockcroft-Gault equation; LBW, lean body weight; $k_{el\alpha}$, elimination rate constant for the alpha phase; $k_{el\beta}$, elimination rate constant for the beta phase.

[b] Variability was put on the overall clearance, which was the sum of the two different pathways.

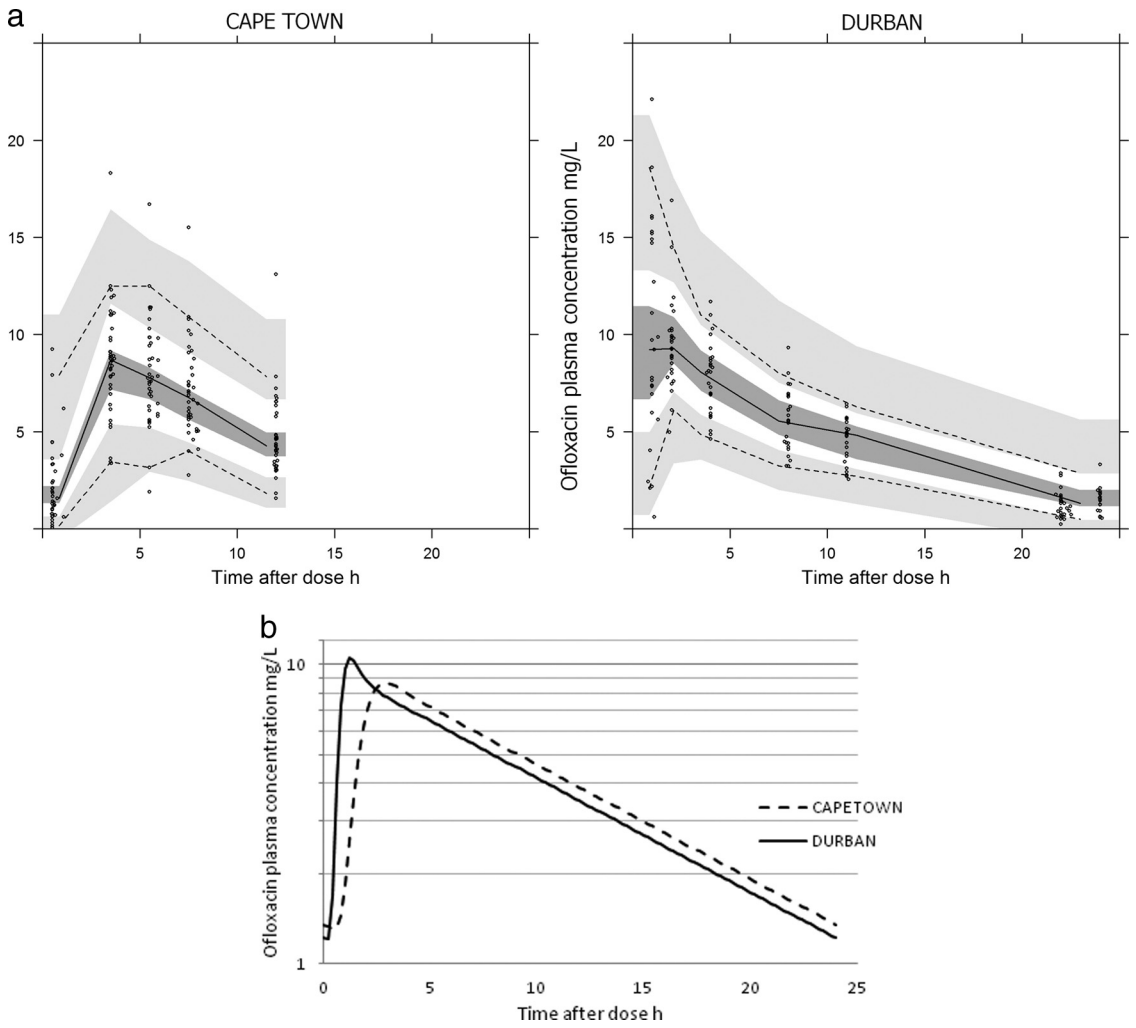

FIG 1 (a) Visual predictive check of ofloxacin plasma concentrations in South African patients with MDR-TB in the final model stratified by the study site. Open circles are the observations. Upper dotted line represents the 95th percentile of the observation. Continuous line represents the median of the observations. Lower dotted line represents the 5th percentile of the observations. Shaded areas are the simulated confidence intervals for the corresponding percentiles. (b) Log-normal plot showing ofloxacin concentration-time profile for the typical patient in Cape Town and in Durban.

weight (14) for total body weight in the Cockcroft-Gault equation further improved the model fit and resulted in a further 8-point decrease in the OFV ($P < 0.01$) compared to a model using total body weight. The second excretion route of ofloxacin in our model represents extraglomerular routes, which would be mainly active tubular secretion and a small amount of biliary excretion (16). A significant covariate on this extraglomerular excretion of ofloxacin was total body weight, which was introduced allometrically (1). We investigated lean body weight as a covariate instead of total body weight on the extraglomerular route of excretion but found it to result in a higher OFV than using total body weight. The central volume of distribution was allometrically scaled to lean body weight, while the peripheral volume was scaled to total body weight, as was the intercompartmental clearance. The central volume of distribution was initially scaled to the total body weight. This resulted in a typical female having a volume 70% higher than that for a male of the same weight and was accompanied by a 12-point drop in the OFV. However, when central volume was scaled to lean body weight in the final model, which described the data equally well, the gender effect on volume fell to 21% and was no longer statistically significant. HIV infection was not a significant covariate on ofloxacin pharmacokinetics. Administration of ofloxacin after a meal (Cape Town patients) resulted in a 2.4-fold increase in the mean transit time (MTT), meaning food significantly delays the rate of absorption. Table 3 contains population parameter estimates, variability, and precision from the final model. Figure 1 is a visual predictive check of the final model, and it shows that the model describes the data well.

As aforementioned, a stochastic simulation and estimation experiment was carried out to determine whether this finding could be an artifact of an altered sampling schedule. The bias and precision of the MTT from this finding were found to be +0.9% and 13%, respectively, thus confirming that the finding was independent of the sampling schedule.

Ofloxacin pharmacodynamics. The graphs of the PTA corresponding to various ofloxacin doses from Monte Carlo simula-

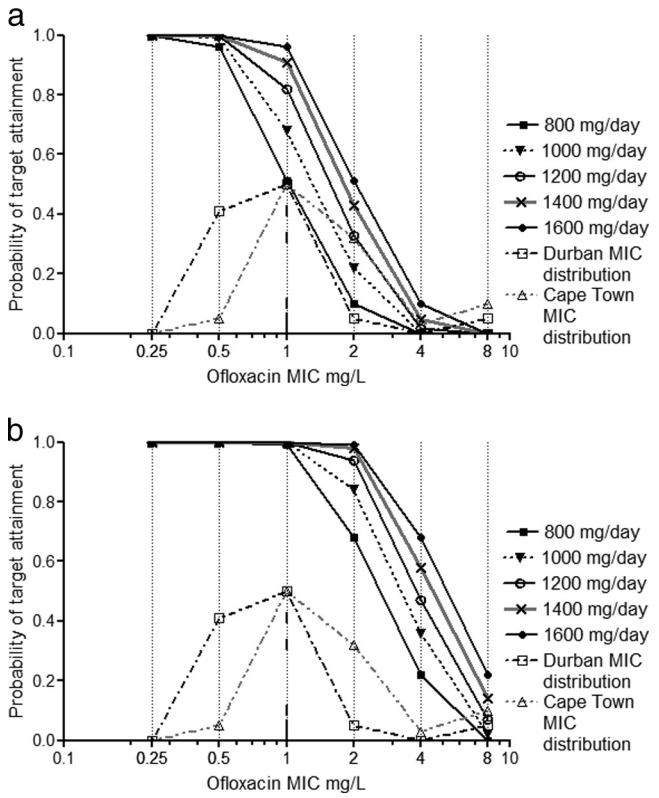

FIG 2 (a) Probability of target attainment (*f*AUC/MIC ≥ 100) by *Mycobacterium tuberculosis* isolate MIC for ofloxacin for various daily doses of ofloxacin. The fraction of the population with each MIC is also shown on the same graph for both Durban and Cape Town patients. (b) Probability of target attainment (*f*AUC/MIC ≥ 40) by *Mycobacterium tuberculosis* isolate MIC of ofloxacin for various daily doses of ofloxacin. The fraction of the population with each MIC is also shown on the same graph for both Durban and Cape Town patients.

tions are shown in Fig. 2. Using the WHO recommended critical concentration of 2.0 mg/liter, none of the doses examined (800 mg to 1,600 mg) resulted in a PTA greater than 0.9. The 800-mg dose provided a PTA greater than 0.9 only for patients with MICs less than or equal to 0.5 mg/liter (Fig. 2), that is, 5.3% of Cape Town patients and 40.9% of Durban patients. A dose of 1,400 mg was the minimum dose achieving a PTA greater than 0.9 in patients with an MIC equal to 1 mg/liter. The PTA expectation values for the pooled study population and those for each study site are shown in Table 4. Our simulations show that a 1,600-mg daily dose of ofloxacin will achieve a PTA expectation value higher than 0.9 in the Durban population, where the MICs were significantly lower than for the Cape Town cohort.

DISCUSSION

This is the first report describing the pharmacokinetics and pharmacodynamics of ofloxacin, taking into account *Mycobacterium tuberculosis* susceptibility data from MICs in the study population. We found that a high proportion of South African patients fail to achieve the target *f*AUC/MIC of 100. We found significantly higher MICs to ofloxacin for isolates in Cape Town (in the Western Cape Province in South Africa) than in Durban (in KwaZulu-Natal Province in South Africa). Due to the limited sample size, these data may not represent the general epidemiological situation, so further study of ofloxacin MICs in South Africa is warranted. However, resistance of the W-Beijing strain to fluoroquinolones has been documented (6), and the W-Beijing strain is rapidly increasing in Cape Town (4). It is, however, difficult to attribute the higher MICs found in Cape Town to the W-Beijing strain, since Durban has a high prevalence of the F15/LAM4/KZN strain (24), which is also resistant to fluoroquinolones. Further studies to determine the prevalence of different types of strains across South Africa and their susceptibilities to different drugs are needed.

This is the first report to quantitatively describe ofloxacin excretion by glomerular and extraglomerular means, together with the covariates influencing the different pathways. However, these findings should be interpreted with caution since no direct intrarenal drug sampling was performed and the results are derived solely from a mathematical perspective. Our finding that calculation of glomerular filtration using lean body weight rather than total body weight described the glomerular clearance better is in agreement with the fact that renal function is more closely related to lean body weight (15). This finding is especially important in our setting where some of the patients are obese according to their high body mass indices. Although some papers indicate that hyperfiltration may occur in obesity (3), more recent papers show that using the Cockcroft and Gault formula with an adjustment for lean body weight is the best measure for renal function in obesity (17). From our model, it can be seen that patients with renal insufficiency or patients with lower body weight would have lower clearance of the drug and hence higher plasma concentrations. When considering administration of higher doses of ofloxacin, it may be important to consider individual variation in body weight and renal function. HIV infection did not significantly alter ofloxacin pharmacokinetics, in accord with previous reports (33).

Our simulations of higher doses are based on first-order elimination of ofloxacin. We investigated mixed-order elimination of the drug in our study population, but this was not found to be statistically significant at daily doses of 800 mg. Hence, our model would underpredict exposure at higher doses, if saturable kinetics occurs.

With a MIC of 2.0 mg/liter (the WHO critical concentration), none of the doses simulated would result in an acceptable PTA,

TABLE 4 PTA expectation values, ofloxacin pharmacokinetic study in patients with MDR-TB, Cape Town and Durban, South Africa

Ofloxacin daily dose (mg)	Overall PTA expectation	Cape Town PTA expectation	Durban PTA expectation
*f*AUC/MIC ≥ 100			
800	0.45	0.33	0.65
1,000	0.57	0.46	0.76
1,200	0.66	0.57	0.83
1,400	0.73	0.64	0.89
1,600	0.77	0.70	0.91
*f*AUC/MIC ≥ 40			
800	0.83	0.77	0.94
1,000	0.87	0.83	0.95
1,200	0.90	0.87	0.96
1,400	0.92	0.89	0.97
1,600	0.93	0.91	0.97

suggesting that the critical concentration should be revised downward. Indeed, other authors have proposed a cutoff of ≤1.0 mg/liter based upon the MIC distribution from clinical strains in Sweden (2). Our PTA expectation results support this argument. This is apparent even though the MIC determination method in our study differs slightly from the Swedish study, which defined the MIC as the lowest concentration of drug that inhibited >99% of the bacterial population. This would result in a PTA greater than 0.9 but only when using a daily dose of at least 1,400 mg (Fig. 2a). The safety of these higher ofloxacin doses needs evaluation, as fluoroquinolones have side effects such as dysglycemia, tendonitis, anemia (16), and QT interval prolongation (8), whose incidence and severity may increase with higher doses. This is especially of concern when one considers the long duration of MDR-TB treatment. For the current 800-mg daily dose, we propose a cutoff of 0.5 mg/liter, as can be seen in Fig. 2a. However, if a target *f*AUC/MIC ratio of 40 is used, a breakpoint of 1 mg/liter is recommended, as can be seen in Fig. 2b. In either case, ofloxacin should not be used in patients with a MIC of >1 mg/liter. Therefore, one can speculate that the way ofloxacin is currently being used might even be promoting resistance among fluoroquinolones since it is known that there is cross-resistance among the fluoroquinolones (9, 32).

Perhaps ofloxacin continues to be used because it is relatively inexpensive. However, it is unclear whether this is rational drug use since our data suggest otherwise. As mentioned above, levofloxacin has about half the MIC of ofloxacin; hence, one can expect a similar dose of levofloxacin to do much better than ofloxacin. The same goes for moxifloxacin. Use of these alternative drugs would significantly increase the PTA expectation in patients with tuberculosis and decrease the likelihood of development of resistance.

Limitations. We have used a *f*AUC/MIC ratio of 100 as the ideal minimum value based upon studies using animals infected with *Mycobacterium tuberculosis* (31) and data from human studies (30) and *in vitro* studies (12). There is some disagreement over what the ideal AUC/MIC ratio should be for fluoroquinolones (29), which may vary for different types of bacteria (36) and during different phases of TB treatment. We have assumed concentration-independent protein binding of ofloxacin in accordance with findings in healthy volunteers (19). However, it is possible that at higher concentrations, ofloxacin protein binding may be concentration dependent as reported in a murine study (31).

Conclusion. Our data suggest that the currently recommended ofloxacin dose of 800 mg per day is too low for the treatment of MDR-TB in South Africa. If higher doses of ofloxacin cannot be used due to safety reasons, a more potent fluoroquinolone such as levofloxacin or moxifloxacin should be used.

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