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Ethionamide Population Pharmacokinetic Model and Target Attainment in Multidrug-Resistant Tuberculosis

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ABSTRACT Ethionamide (ETA), an isonicotinic acid derivative, is part of the multidrug-resistant tuberculosis (MDR-TB) regimen. The current guidelines have deprioritized ETA because it is potentially less effective than other agents. Our aim was to develop a population pharmacokinetic (PK) model and simulate ETA dosing regimens in order to assess target attainment. This study included subjects from four different sites, including healthy volunteers and patients with MDR-TB. The TB centers included were two in the United States and one in Bangladesh. Patients who received ETA and had at least one drug concentration reported were included. The population PK model was developed, regimens with a total of 1,000 to 2,250 mg daily were simulated, and target attainment using published MICs and targets of 1.0-log kill and resistance suppression was assessed with the Pmetrics R package. We included 1,167 ethionamide concentrations from 94 subjects. The final population model was a one-compartment model with first-order elimination and absorption with a lag time. The mean (standard deviation [SD]) final population parameter estimates were as follows: absorption rate constant, 1.02 (1.11) h⁻¹; elimination rate constant, 0.69 (0.46) h⁻¹; volume of distribution, 104.16 (59.87) liters; lag time, 0.43 (0.32) h. A total daily dose of 1,500 mg or more was needed for ≥90% attainment of the 1.0-log kill target at a MIC of 1 mg/liter, and 2,250 mg/day led to 80% attainment of the resistance suppression target at a MIC of 0.5 mg/liter. In conclusion, we developed a population PK model and assessed target attainment for different ETA regimens. Patients may not be able to tolerate the doses needed to achieve the predefined targets supporting the current recommendations for ETA deprioritization.

KEYWORDS population pharmacokinetics, tuberculosis, ethionamide, Monte Carlo simulation, target attainment, *Mycobacterium tuberculosis*, pharmacodynamics, pharmacokinetics

Tuberculosis (TB) contributed to more than a million deaths in 2018 (1). Efforts to end TB are hampered by the prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB. Recent MDR-TB guidelines have reclassified drugs based on their efficacy and the outcomes associated with their use. Many commonly used drugs have been deprioritized and replaced with newer, more-effective agents. However, the

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TABLE 1 Baseline characteristics for 94 subjects

Characteristic	Mean (SD) or no. (%)
Age (yr)	37.2 (11.4)
Wt (kg)	64.8 (16.6)
Female	27 (29)
Study population ^a	
Healthy volunteers	16 (17)
Bangladesh	57 (61)
TCID	20 (21)
AGH	1 (1)
Sample timing (h)	
≤1	264 (23)
>1–2	254 (21)
>2–4	196 (17)
>4–6	161 (14)
>6–12	222 (19)
>12	70 (6)

^aTCID, Texas Center for Infectious Diseases; AGH, A. G. Holley Hospital.

deprioritized agents might still be needed in case the top drugs cannot be used or are unavailable (2).

Ethionamide (ETA), an isonicotinic acid derivative, has been used as a second-line agent in MDR-TB treatment regimens for decades (3). In a large meta-analysis which included >12,000 patients, ETA was associated with no benefit against susceptible strains and worse outcomes against resistant strains. The adjusted odds ratios (aORs) (95% confidence intervals [CI]) for success and death in patients who received ETA and had susceptible strains were 0.8 (0.7 to 0.9) and 0.9 (0.8 to 1.0), respectively, while with resistant strains, the aORs (95% CI) for success and death were 0.6 (0.5 to 0.8) and 1.8 (1.4 to 2.2), respectively (4). Currently, ETA is not suggested to be used in drug-resistant TB if more-effective drugs are available (2); however, ETA still remains a potential therapy option. In addition, the success of therapy with ETA and its analogue, prothionamide, has been influenced by the occurrence of side effects. The most commonly described adverse events are gastrointestinal disorders and hypothyroidism (5). To mitigate these side effects, stepwise dose escalation at the start of therapy has been recommended (6). The currently recommended dose of ETA is 15 to 20 mg/kg of body weight/day (250 to 500 mg once to twice daily), starting with 250 mg daily and escalating over a week (2). Additionally, for both ETA and prothionamide used as part of multidrug regimens, arthralgia, visual and hearing disturbances, electrolyte disturbances, abdominal pain, and anorexia have been reported, but it is difficult to attribute those effects exclusively to ETA (7). To improve therapy outcomes with ETA, optimal dosing to achieve the best available pharmacokinetic/pharmacodynamic (PK/PD) target is needed.

The aim of this study was to develop a population pharmacokinetic model, perform Monte Carlo simulation, and calculate the probability of target attainment (PTA) for different ETA dosing regimens.

RESULTS

A total of 94 subjects were included in the study. Seventeen percent were healthy volunteers, and 29% ($n = 27$) were female. The median (range) age was 35 (17 to 76) years, and the median (range) weight was 52 (30 to 96) kg. In total, 1,167 ETA samples were included in the PK model (Table 1). Table S1 summarizes baseline characteristics and noncompartmental analysis results for each site. Figure S1 shows raw ETA concentrations per site.

The final population PK model was a one-compartment model with first-order absorption and elimination, and with a lag time for absorption (T_{lag}) and a gamma multiplicative error model. None of the covariates were included in the final model,

TABLE 2 Population parameter estimates for the final one-compartment population model^a

Parameter	Mean (SD)	CV (%)	Median	95% CI
k_a (h^{-1})	1.02 (1.11)	109.22	0.41	0.39–0.77
k_{el} (h^{-1})	0.69 (0.46)	66.35	0.49	0.40–0.65
V/F (liters)	104.16 (59.87)	57.48	89.68	72.18–116.8
T_{lag} (h)	0.43 (0.32)	75.88	0.42	0.31–0.59

^aCV, coefficient of variation; k_a , absorption rate constant; k_{el} , elimination rate constant; T_{lag} , lag time; V/F , apparent volume of distribution.

because they did not improve the fit or decrease interindividual variability. Table 2 shows the population parameter summary. The mean estimated parameters were as follows: elimination rate constant (k_{el}), 0.69 h^{-1} ; absorption rate constant (k_a), 1.02 h^{-1} ; T_{lag} , 0.43 h; apparent volume of distribution (V/F), 104.16 liters. Figure 1 shows the observed versus predicted population and individual concentrations of ethionamide. Figure S2 shows the probability of each population PK parameter (support points).

The results of Monte Carlo simulation are shown in Fig. 2 and 3. Table 3 shows the success rate for each regimen. For the target of an $fAUC_{0-24}/MIC$ (ratio of the area under the concentration-time curve from 0 to 24 h for the free, unbound fraction of the drug to the MIC) value of 10, all the regimens had a 90% or more PTA at a MIC of 0.5 mg/liter. However, at least 1,500 mg per day was required to achieve that target at a MIC of 1 mg/liter. None of the regimens led to 90% target attainment at a MIC of 2 mg/liter, and the highest PTA was 80%, achieved with 750 mg three times daily. For the $fAUC_{0-24}/MIC$ target of 42, all regimens failed to lead to 90% target attainment at all MICs, and only 750 mg three times daily led to 80% target attainment at the lowest tested MIC of 0.5 mg/liter.

DISCUSSION

This study included a large number of ETA samples from three unique cohorts in order to develop a one-compartment population PK model and simulate different dosing regimens so as to assess their abilities to achieve the $fAUC_{0-24}/MIC$ targets. None of the covariates were significantly associated with any of the PK parameters in the model, a result consistent with a previously published model of ETA population PK (8). We also found a wide dispersion of k_a values generated by our model, which might be due to combining data from healthy subjects with data from TB patients, who have different estimated k_a values. Healthy volunteers had k_a values of $<3 h^{-1}$, most of which were $<1 h^{-1}$, while Bangladeshi patients had more-dispersed k_a values, ranging up to $4 h^{-1}$ (Fig. S2). Differences in k_a between patients and healthy volunteers have been reported previously in the literature, with patients having k_a values as high as $0.66 h^{-1}$ while healthy volunteers' values were similar to those reported in our study (8). However, given the software and algorithm used (i.e., a nonparametric approach), we were able to capture this spread while ignoring the assumption of normality in the parameter distribution (9). Another factor that could affect k_a is between-patient variability in tolerating the drug administration (e.g., whether patients experienced vomiting).

Simulating dosing with our specified targets showed significant underexposure with the current regimen of 500 mg twice daily and a low PTA at a MIC of 1 mg/liter for the 1.0-log kill target. Zhu et al. developed an ETA population PK model using a previous version of the nonparametric software (nonparametric expectation maximization [NPEM2]; USC*PACK, v10.7) including 55 TB patients (8). Using a MIC value of 1 mg/liter, the authors simulated different dosing regimens up to 1,000 mg daily and found that an AUC/MIC value of ≥ 10 is achievable with a total daily dose of 750 mg or more; however, that was the total, rather than the free, ETA exposure (8). Our simulations showed that at least 1,500 mg per day is needed for $\geq 90\%$ target attainment for an $fAUC_{0-24}/MIC$ target of 10 at a MIC of ≤ 1 mg/liter. Importantly, none of the regimens led to 90% target attainment for resistance suppression, and 2,250 mg per day was

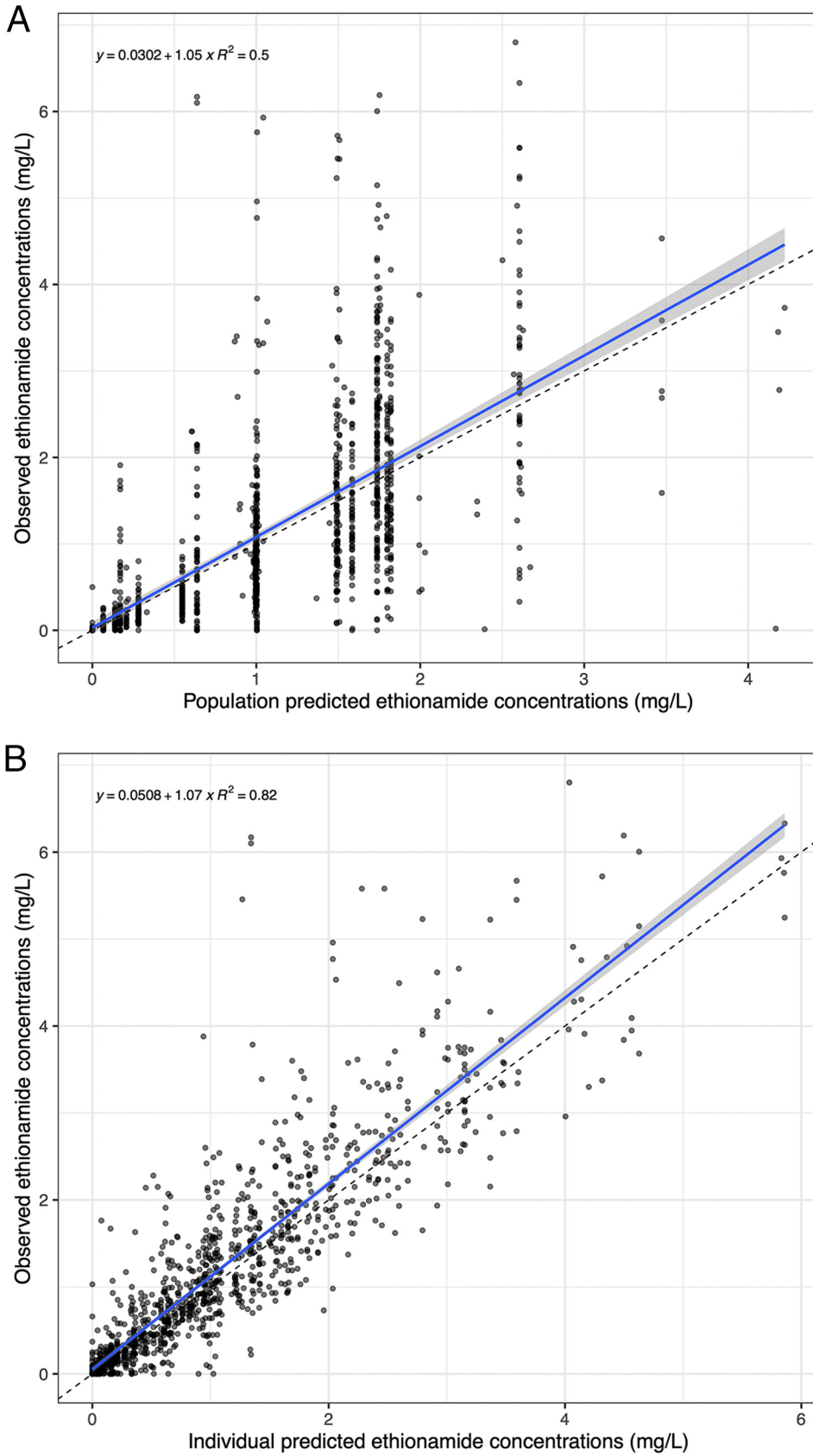


FIG 1 Observed versus predicted population (A) and individual (B) concentrations of ethionamide.

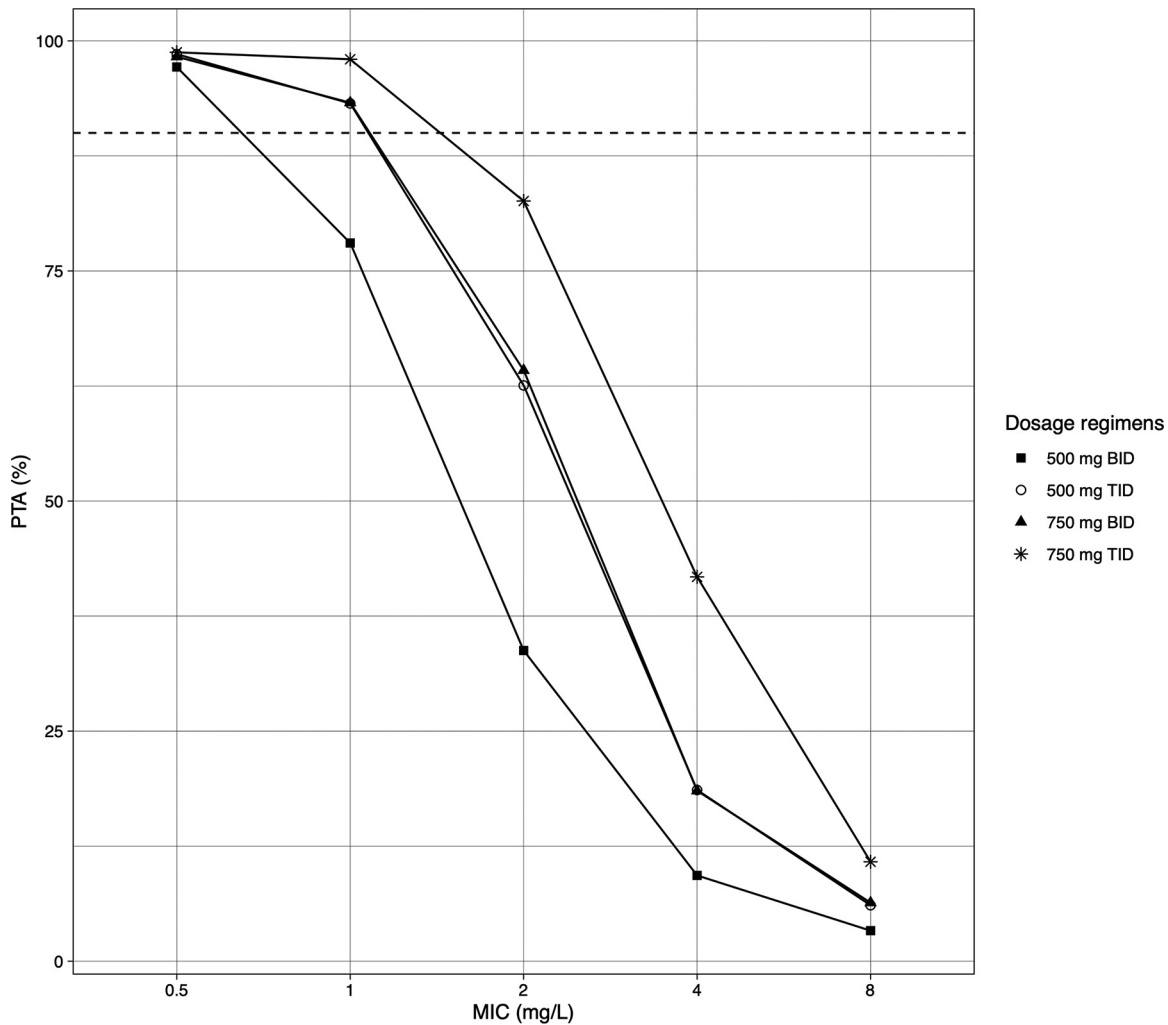


FIG 2 Probability of target attainment for ethionamide using an $fAUC_{0-24}/MIC$ value of 10 as the target. The horizontal dashed line indicates 90% target attainment. PTA, probability of target attainment; BID, twice daily; TID, three times daily.

needed to reach 80% target attainment at a MIC of 0.5 mg/liter, yet such a dosing regimen would be difficult to implement given the dose-related toxicity profile and common gastrointestinal intolerance. Early studies of ETA at doses of 500 mg reported intolerability in as many as 76% of patients (3). Among the most common dose-related adverse events was gastrointestinal intolerance of ETA, including anorexia, a metallic taste, nausea, vomiting, upper abdominal discomfort, and diarrhea (5). Therefore, our results provide informed PK/PD support for the most recent guidelines, which suggest using other, more-potent drugs while deprioritizing ETA (2). Of interest, however, companion drugs consisting of inhalable ETA and a booster are being investigated for an improved antimycobacterial activity and toxicity profile, which could reintroduce ETA as a desirable agent for MDR-TB patients (10–12).

It is noteworthy that these simulated regimens are assumptions based on *in vitro* models. Factors such as protein binding, penetration into lesions, and penetration and activity within macrophages can modify the predicted performance of ETA. For example, the concentrations in the lungs, especially within granulomas, cavities, or caseous lesions, might differ from those measured in the plasma. Since we do not have information regarding how much active drug reached the infection site, a PK/PD target was chosen based on the available hollow fiber data, which have been predictive of microbiological outcomes in cohorts treated with ETA for MDR-TB (13). In addition, the simulations provide initial dosing guidance, and therapy should be individualized for

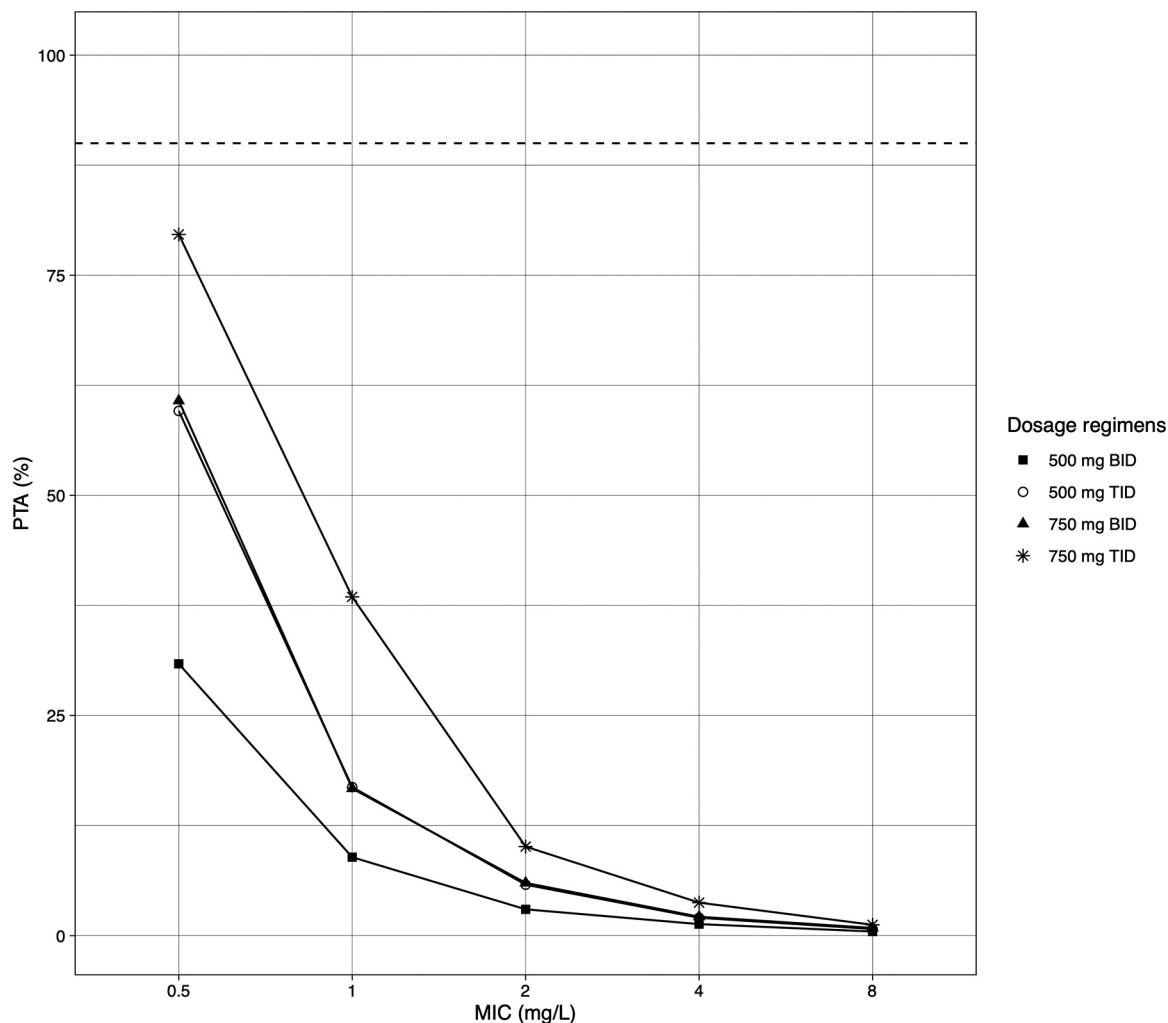


FIG 3 Probability of target attainment for ethionamide using an $fAUC_{0-24}/MIC$ value of 42 as the target. The horizontal dashed line indicates 90% target attainment. PTA, probability of target attainment; BID, twice daily; TID, three times daily.

each patient by performing therapeutic drug monitoring, which is also beneficial in improving adherence to therapy and assessing intolerance and toxicity (2).

One of the strengths of our study was its modeling of a range of clinically observed MIC values (14, 15). We acknowledge that MIC values may differ when one is testing the same *Mycobacterium tuberculosis* isolate on different platforms, such as solid or liquid culture media; that commercial platforms may test differing dilutions of a drug; and that a single MIC value from a clinical specimen may represent only the subgroup of cultured isolates selected for secondary drug susceptibility testing. Therefore, MIC thresholds associated with target attainment for ETA dosing, as with all anti-TB drugs, should account for the specific testing platform and the performance characteristics of

TABLE 3 PTAs for four dosing regimens on the sixth day of therapy

Dosing regimen	PTA (%) with the following target:			
	$fAUC/MIC = 10$		$fAUC/MIC = 42$	
	MIC, 1 mg/liter	MIC, 2 mg/liter	MIC, 1 mg/liter	MIC, 2 mg/liter
500 mg twice daily	80	32	8	3
500 mg three times daily	94	66	15	6
750 mg twice daily	93	62	16	6
750 mg three times daily	98	83	38	9

that MIC platform (13, 16). Nevertheless, our simulations were remarkably similar to those generated by Deshpande et al. (13), who concluded that ETA target attainment would be likely only with a MIC of <2.5 mg/liter by the Sensititre MYCOTB plate assay (Trek Diagnostics, Cleveland, OH, USA) or a MIC of 1.0 mg/liter based on MGIT liquid medium (BD, Franklin Lakes, NJ, USA) and conventional Middlebrook solid agar medium. Thus, while ETA retains activity equivalent to those of other commonly used anti-TB drugs, such as isoniazid and ethambutol, in preclinical models (13, 17), our data support the need for quantitative susceptibility testing in the form of ETA MIC results for a patient's cultured *M. tuberculosis* isolate before one initiates treatment with ETA and uses the higher doses that are required even for the lower end of observed MIC ranges. While whole-genome sequencing of isolates or even direct sputum smears have aided in genotypic susceptibility testing for other anti-TB drugs, correlates of quantitative change in the MIC of ETA, such as sequence-specific mutations in the *ethA* and *ethR* genes, have yet to be fully elucidated (18).

This study has its limitations. First, we did not include comedications in the covariate analysis. Second, we did not evaluate correlations with the occurrence of adverse events, since attribution, especially for gastrointestinal intolerance, is difficult to quantify in terms of the degree of the effect. Third, we quantified the total ETA concentration and assumed the free fraction, and these concentrations might not reflect the concentration at the site of infection. Fourth, in many countries, prothionamide is used instead of ethionamide. While prothionamide is similar, the PK/PD characteristics may differ, so these results do not necessarily apply to prothionamide. Finally, our simulations did not take into consideration the effect of combination anti-TB agents, which can be investigated *in vitro* to assess the additivity, synergy, and antagonism of any combination and to determine what level of drug exposure is needed to kill the mycobacteria and prevent the emergence of resistance.

Conclusions. We developed an ETA population PK model and calculated target attainment for multiple dosing regimens. At least 500 mg three times daily is needed to achieve the 1.0-log kill target at a MIC of 1 mg/liter. Our findings were in concordance with the recent guidelines and suggest that ETA should not be used as a preferred agent in MDR-TB. The total daily dose required to achieve the predefined targets can potentially be toxic for patients and should be considered only when the results of quantitative susceptibility testing are known.

MATERIALS AND METHODS

Study population. This study included populations from previous studies that had both healthy volunteers and TB patients. In the first study, healthy volunteers received a single 500-mg ETA dose and had blood samples drawn before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24, 36, and 48 h after the dose (19). The second study was a prospective PK study of adult patients newly diagnosed with MDR-TB in Bangladesh (ClinicalTrials registration no. NCT03559582). In addition to ETA, patients received other TB medications, including fluoroquinolones, bedaquiline, clofazimine, cycloserine, kanamycin or capreomycin, linezolid, and pyrazinamide. The daily dose range of ETA was 500 to 1,250 mg, and patients had blood samples drawn 1, 2, 6, and 12 h after the dose during week 2 of therapy and at 2 and 6 h during weeks 4 and 8 of therapy. The third data set included data collected retrospectively for MDR-TB patients admitted to two U.S. TB centers, the Texas Center for Infectious Diseases and the A. G. Holley Hospital, between 1984 and 2015, who received ETA, with doses ranging from 500 to 1,500 mg/day, and had serum ETA concentrations measured at least once. The blood sampling was random. Common data collected from all cohorts were age, sex, weight, ETA dose and frequency, and ETA concentrations and times of sampling.

ETA quantification in plasma samples. Plasma samples were stored at -80°C until the time of quantification. For the study done in Bangladesh, the ETA concentrations were measured at the Infectious Disease Pharmacokinetics Laboratory (University of Florida) using a validated high-performance liquid chromatography–tandem mass spectrometry assay. Analysis was performed on the Thermo Scientific TSQ Endura or TSQ Quantum Ultra system. The range of detection was 0.1 to 10 mg/liter. Samples with concentrations above the range were diluted and reanalyzed. The intrabatch and interbatch precision ranges were 1.95 to 7.41% and 3.19 to 4.10%, and the intrabatch and interbatch accuracy ranges were 101.80 to 116.48% and 104.55 to 118.57%, respectively. ETA in healthy subjects' samples was quantified as described by Auclair et al. (19). For the retrospective data from the Texas Center for Infectious Diseases and the A. G. Holley Hospital, ETA concentrations were collected from the medical records.

Population pharmacokinetic modeling. PK modeling and Monte Carlo simulation were done using the Nonparametric Adaptive Grid (NPAG) algorithm within the Pmetrics package (v1.5.2) in R (v3.6.1) (20). One- and two-compartment models with first-order absorption and elimination were tested and parameterized using V/F , k_{el} , k_{cp} , and T_{lag} . We accounted for assay error (standard deviation) and environmental noise using error polynomials as a function of observed concentration (standard deviation = $C_0 + C_1 \times$ observed concentration) using C_0 (intercept) and C_1 (slope) values of 0.1. Gamma multiplicative and lambda additive error models were tested to estimate residual error (21). The models were assessed using the population and individual goodness-of-fit plots that presented the linear regression of the observed versus predicted population and individual concentrations. The final base model was chosen based on the lowest Akaike information criterion (AIC) and the best goodness-of-fit plots. Then we tested for covariates, including age, sex, and weight, using a forward addition and backward deletion method. Significant covariates were included in the final model if they had a P value of <0.01 , improved the goodness of fit, and minimized interindividual variability.

Monte Carlo simulation and target attainment. Each support point generated by the population model has one value for each parameter in the model and an associated probability of that set of parameter values. In the Monte Carlo simulation, the nonparametric support points in the population model serve as the mean of one multivariate normal distribution in a multimodal, multivariate joint distribution. The weight of each multivariate distribution is equal to the probability of the point. Simulations were performed using regimens of 500 to 750 mg two or three times daily. For each regimen, 2,500 patients were simulated. We assessed target attainment for the PK/PD targets of $fAUC_{0-24}/MIC$ values of 10 for 1.0-log kill and 42 for resistance suppression over a MIC range of 0.5 to 8 mg/liter at day 6 of the simulated regimens (13, 22). A free ETA fraction of 70% was assumed (23).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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There are no conflicts of interest to disclose.

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