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Pharmacokinetics and Safety of Bedaquiline in Human Immunodeficiency Virus-Positive and Negative Older Children and Adolescents With Rifampicin-Resistant Tuberculosis

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Background. Pharmacokinetic data for bedaquiline in children are limited. We described the pharmacokinetics and safety of bedaquiline in South African children and adolescents receiving treatment for multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) in routine care.

Methods. In this observational cohort study, children aged 6–17 years receiving bedaquiline at recommended doses as part of MDR/RR-TB treatment underwent semi-intensive pharmacokinetic sampling. Bedaquiline and the M2 metabolite plasma concentrations were quantified, and nonlinear mixed-effects modeling performed. Pediatric data were described using a pre-established model of bedaquiline pharmacokinetics in adults. The exposure reference was 187 μg · h/mL, the median weekly area under the curve (AUC) of adults at week 24 of treatment with bedaquiline. Safety was assessed through monthly clinical, blood and electrocardiogram monitoring, and treatment outcomes described.

Results. Fifteen children (3 human immunodeficiency virus [HIV]-positive) with median age 13.3 years (range 6.5–16.3) were included. A bedaquiline pharmacokinetic model was adapted to be allometrically scaled in clearance and volume, centered in the median child population weight. Bedaquiline bioavailability was 57% of that in adults. Overall bedaquiline exposures were below target, and AUC reference attainment was achieved in only 3 (20%) children. Ten children experienced 27 adverse events at least possibly related to bedaquiline; no adverse events led to bedaquiline withdrawal. Two adverse events (arthritis and arthralgia) were considered severe, and 2 children had mild QT interval corrected for heart rate using Fridericia's formula (QT) prolongation.

Conclusions. The evaluated doses of bedaquiline in children ≥ 6 years of age were safe but achieved slightly lower plasma concentrations compared to adults receiving the recommended dose, possibly due to delayed food intake relative to bedaquiline administration.

Keywords. bedaquiline; pharmacokinetics; safety; children; RR-TB.

An estimated total of 157 903 cases of rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB, resistance to rifampicin and isoniazid) were detected globally in 2020 [1]. The diarylquinoline bedaquiline, with a novel mechanism of action of mycobacterial adenosine triphosphate synthase inhibition [2–4], has been independently associated with reduced mortality and improved treatment outcomes in adults with MDR/RR-TB [5–10].

Approximately 30 000 children develop MDR-TB disease annually [11]. Pediatric pharmacokinetic, efficacy, and safety data for novel agents are currently limited, resulting in delayed access for children [12]. Data from the Phase 2 TMC207-C211 trial (NCT02354014) [13] led to US Food and Drug Administration approval for bedaquiline in children aged ≥ 5 years and weighing ≥ 15 kg [8]; early C211-trial data in children ≥ 5 years of age have recently been published [14]. A recent World Health Organization (WHO) rapid communication recommends bedaquiline for all children based on interim analyses of pharmacokinetic and safety data in children < 6 years from the Phase 1/2 IMPAACT P1108 trial (NCT02906007) [15, 16].

The pharmacokinetics of bedaquiline have been well described in adults [17–20]. Concomitant food intake increases bedaquiline oral bioavailability approximately 2-fold [21]. Bedaquiline is primarily metabolized in the liver by

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the cytochrome P-450 isoenzyme 3A4 (CYP3A4) into the N-monodesmethyl metabolite (M2) and is at risk for drug-drug interactions with CYP3A4 inducers and inhibitors [22].

Bedaquiline pharmacokinetic data in children are limited to the P1108 and C211 trials, with additional safety data available among adolescents receiving bedaquiline in routine care settings [14, 23]. There are no pharmacokinetic data from routine programmatic settings and little information from children with human immunodeficiency virus (HIV) on antiretroviral therapy (ART). We analyzed the pharmacokinetics and safety of bedaquiline in children ≥ 6 years of age with and without HIV who were routinely treated with bedaquiline-containing regimens for MDR/RR-TB as per standard of care in South Africa.

METHODS

Patient Population, Study Design, and Setting

This analysis was part of an observational study (MDR-PK2) aiming to characterize the pharmacokinetics and safety of moxifloxacin, levofloxacin and linezolid in children < 18 years of age routinely treated for clinically diagnosed or confirmed MDR/RR-TB between 2015 and 2020 in South Africa; study methods have been described elsewhere [24, 25]. In 2018 the National Tuberculosis Programme (NTP) recommended bedaquiline for all patients with MDR/RR-TB aged ≥ 6 years. Children undergoing pharmacokinetic sampling in MDR-PK2 who were receiving bedaquiline in routine care were included in this analysis.

Treatment of MDR/RR-TB

During the study period, routine MDR/RR-TB treatment provided through the NTP shifted from 12–18-month injectable-containing regimens to 9–11-month injectable-sparing regimens, which included repurposed and novel agents, such as bedaquiline. Those not eligible for the standardized 9–11-month regimen received an injectable-sparing individualized regimen (duration based on site and severity of disease and drug susceptibility of the isolate) containing at least four likely effective drugs [26]. Bedaquiline was administered according to recommended weight and age-based dosing: 200 mg once daily for 2 weeks (loading phase) followed by 100 mg thrice weekly for 22 weeks (maintenance phase) for children ≥ 6 years weighing 15–30 kg, and 400 mg once daily, then 200 mg thrice weekly in children weighing > 30 kg.

Pharmacokinetic Sampling

Each child underwent semi-intensive pharmacokinetic sampling 2–16 weeks after starting MDR/RR-TB treatment; some were sampled twice. Sampling was not specifically timed to the initiation of bedaquiline. On the day of pharmacokinetic sampling, all medications were administered after an overnight fast as either whole, crushed, or dispersed tablets. A standard meal was offered 1 hour after TB drug dosing. Blood samples were collected pre-dose and 1, 4, and 10 hours after TB drug administration, centrifuged, plasma separated and stored at −80°C within 30 minutes of collection. Some children underwent repeated pharmacokinetic sampling on 2 consecutive days, which allowed for analysis beyond 24 hours after bedaquiline administration. Bedaquiline and the M2 metabolite were analyzed with a validated liquid chromatography tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, University of Cape Town, as previously described (see Supplementary Methods) [23].

Pharmacokinetic Modeling

Nonlinear mixed-effects models were utilized and described typical pharmacokinetic characteristics and random variability in the population. Bedaquiline and M2 pharmacokinetic observations were modelled simultaneously. The observed concentrations were converted to molar units and log-transformed. The stochastic model included between-subject and between-occasion variability and residual variability. Individual parameters were assumed to be log-normally distributed. Due to the opportunistic nature of the sampling schedule and the sparsity of the data, a previously established pharmacokinetic model for bedaquiline in adults was used as a base structural model [17]. The original model includes 3 distribution compartments for bedaquiline and 1 for M2; bedaquiline absorption is described with 2 transit compartments with estimated parameters of the mean absorption time (MAT, typical time to achieve 90% complete absorption) and the fraction of MAT (FR). This FR is a parameter that delays the first-order absorption described with the transit compartments. The typical value of bioavailability (F) of bedaquiline was re-estimated, whereas the typical values the fraction of parent drug metabolized to M2 (f_m) was kept fixed to 1.

Covariates

Patient age, weight, HIV status, sex, race, weight-for-age z-score (WAZ), and height-for-age z-score (HAZ) were considered in the covariate analysis. The covariate exploration included covariate-parameter relationships previously described for bedaquiline [17–20], and other scientifically plausible covariates. We used a stepwise covariate model building procedure implemented in Perl Speaks NONMEM (PsN) software, based on a forward inclusion followed by a backward deletion approach; the levels of significance used to incorporate and keep the covariate in the model were set to 0.05 and 0.01, respectively.

Model Selection and Evaluation

Model selection was based on a likelihood ratio test, with a significance level of $P < .05$ used to accept model extension. Model evaluation and performance was done by prediction-corrected visual predictive checks [27]. A total of 1000 data sets with the

same characteristics as the original were simulated. Precision in parameter estimates was reported as standard errors as provided by the model. Pharmacokinetic analysis was carried out with the first-order conditional estimation method with interaction in the software NONMEM version 7.4 [28], using functionalities implemented in PsN [29]. Graphical analysis was conducted in R.

Pharmacokinetic Targets

A weekly area under the curve (AUC) at week 24 of treatment (steady state) of 187 μg h/mL, which is the median adult exposure reported with standard dosing [17], was used as the reference AUC.

Safety

After study enrolment, clinical and laboratory safety monitoring was conducted 1–2 times monthly, or when clinically indicated. Children were followed until treatment completion. All adverse events recorded during study participation were assessed for attribution to TB drugs, including bedaquiline, by the study investigator and graded for severity using the DAIDS Adverse Events Grading Tables [30, 31].

During pharmacokinetic sampling, 12-lead electrocardiograms (ECGs) were done in triplicate pre-dose, and 1, 4, and 10 hours post-dose to pair with drug concentrations. Routine ECGs were also done monthly in routine care. All study ECGs were evaluated by a single pediatric cardiologist. The QT interval was corrected for heart rate using Fridericia's formula (QTcF) and graded as follows: Grade 1 (mild), ≥450 to <480 milliseconds; Grade 2 (moderate), ≥480 to <500 milliseconds; Grade 3 (severe), ≥500 milliseconds; Grade 4 (life-threatening), arrhythmia.

Statistical Analysis

Clinical and demographic characteristics were described using summary statistics, with continuous variables reported using medians and interquartile ranges (IQRs) and categorical variables using frequencies and percentages. WAZ and HAZ were calculated using the British 1990 growth curve [32]. Any adverse events, and those attributed to bedaquiline, were displayed by grade using frequencies. The mean QTcF from each set of triplicate ECGs on pharmacokinetic sampling days was calculated and the maximum values per child per sampling occasion were visualized over time on bedaquiline. Treatment outcomes were described according to standard research definitions [33]. Data were analyzed using Stata 16.0 Special Edition software (Stata Statistical Software: Release 16, 2019. StataCorp LP, College Station, Texas, USA).

Ethics

Written informed consent was provided by the parent/s or legal guardians, and written informed assent by participants aged ≥ 7 years. Study ethics approval was provided by the Health Research Ethics Committee of Stellenbosch University (N15/02/012) and by the local department of health.

RESULTS

Fifteen children, median age 13.3 years (range, 6.5–16.3 years), were included. Median weight on the day of pharmacokinetic sampling was 33.2 kg (range, 18.6–57.6 kg) and 4 (27%) children had WAZ below −2. Three children (20%) were HIV-positive on ART; Table 1 shows demographic and clinical features. Treatment regimens comprised of a median of eight (range, 7–12) anti-tuberculosis medications (Supplementary Table 1). Bedaquiline was started a median of 1.0 week (IQR 0.0, 5.9) after initiation of MDR/RR-TB treatment, and all 15 children received bedaquiline for at least 24 weeks (median 26.3 weeks, IQR 25.9, 32.0). Ten children swallowed bedaquiline

Table 1. Demographic and Clinical Characteristics of Children Receiving Bedaquiline-containing Treatment Regimens for Multidrug-resistant/Rifampicin-resistant Tuberculosis (N = 15)

Median age in years at TB treatment initiation (IQR)	13.6 (11.5, 13.9)
Age 6 to < 12 years (%)	4 (26.7)
Age 12 to < 18 years (%)	11 (73.3)
Male gender (%)	7 (46.7)
Ethnicity (%)	
Black	5 (33.3)
Mixed race	10 (66.7)
TB classification (%)	
Bacteriologically confirmed TB[a]	13 (86.7)
Clinically diagnosed TB	2 (13.3)
Drug resistance pattern determining treatment regimen (%)	
Rifampicin mono-resistance	4 (26.7)
Resistance to rifampicin and isoniazid	9 (60.0)
Resistance to rifampicin and isoniazid plus fluoroquinolone and second-line injectables	2 (13.3)
TB disease type (%)	
Pulmonary TB only	12 (80.0)
Extrapulmonary TB only	1 (6.7)
Both pulmonary and extrapulmonary TB	2 (13.3)
HIV-positive (%)	3 (20.0)
Median CD4 absolute count (IQR) [n = 2]	211 (92, 330)
Antiretroviral therapy regimen (%)	3 (100)
Lopinavir-ritonavir and 2 NRTIs	2 (66.7)
Nevirapine and 2 NRTI	1 (33.3)
Median weight-for-age Z-score, at enrolment (IQR)	−1.48 (−2.36, −0.68)
Weight-for-age Z-score < −2, at enrolment (%)	6 (40.0)
Median height-for-age Z-score, at enrolment (IQR) [n = 14]	−1.18 (−1.39, −0.56)
Height-for-age Z-score < −2, at enrolment (%) [n = 14]	3 (21.4)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; TB, tuberculosis.

[a]Among 13 children classified as having bacteriologically confirmed TB, 12 cases were confirmed with positive *Mycobacterium tuberculosis* cultures and one was confirmed with a positive XpertMTB/Rif Ultra result on cerebrospinal fluid (but *M. tuberculosis* culture was negative).

tablets whole, 4 had them crushed, and 1 received them dispersed in water.

The timing of pharmacokinetic sampling ranged from 1.6 to 19.7 weeks following initiation of bedaquiline; 5/15 (33%) children had evaluable repeat pharmacokinetic sampling on two consecutive days. In total there were 87 pharmacokinetic observations for bedaquiline and 87 for M2, including 16 bedaquiline observations from the loading phase and 71 from the maintenance phase (Figure 1). All available samples from all 15 children were included in the analysis.

Pharmacokinetic Model

Efforts to model the pediatric data without using a base model resulted in an unsuccessful fit of the data, rendering nonphysiological clearance estimates. Therefore, the final model developed by Svensson et al [17] was used as a base model. Attempts to describe the pediatric data with the unmodified adult model allowing for residual variability re-estimation resulted in over-predictions of bedaquiline plasma concentrations but not of M2 plasma concentrations over time (Supplementary Figure 1). Based on the model over-prediction and in part because patients received bedaquiline without food, bioavailability was re-estimated to be 0.568 with good precision (Table 2).

The covariate modelling resulted in inclusion of body weight on clearance and volume parameters, allometrically scaled with fixed coefficients of 0.75 and 1, respectively. A clearance scaling coefficient of 0.18 was previously reported by Svensson et al [17] but resulted in a worse fit on these data. The estimated scaling coefficient for clearance was 0.79; therefore, the standard value of 0.75 for scaling size-related changes from adults to children was conserved.

No statistically significant relationships could be identified for the remaining covariates assessed. Importantly, no age effect could be established with these data which is not surprising given the older age of the cohort, and no significant effect were identified of race, bedaquiline preparation (crushed versus whole or dispersed), or HIV status. The concentration-time profiles among the 3 HIV-positive children were not qualitatively different than HIV-negative children (Figure 2). The 2 children receiving lopinavir/ritonavir had similar exposures to HIV-negative children.

The final model estimates are reported in Table 2, where all the parameters are fixed except bioavailability and metabolite clearance. This estimation of bioavailability allowed for an adequate description of the pediatric data (Supplementary Figure 2).

Bedaquiline and M2 concentrations were mostly below the typical adult concentrations simulated using the model from Svensson et al [17], during the 2-week loading and the 22-week maintenance phases (Supplementary Figure 3). The model-derived Week 24 AUCs in this pediatric cohort were below the adult AUC reference of 187 µg h/mL [17]. The median Week 24 AUCs were 127 µg h/mL (IQR 75.2–173.2) overall, 161.6 µg · h/mL (IQR 91.4–165.1) in children ≤ 30 kg, and 112.5 µg h/mL (IQR 71.2–173.9) in children > 30 kg. AUC reference attainment was achieved in only 3 (20%) children; 1 weighed ≤ 30 kg, and 2 weighed > 30 kg (Figure 3).

Safety

Twenty-seven adverse events at least possibly related to bedaquiline were reported among 10 children; all but 2 adverse events were considered mild or moderate (Table 3). Electrocardiogram data were available in all 15 children (Figure 4). Two children had grade-1 QTcF prolongation.

One child experienced severe arthralgia 1 month after starting treatment and was diagnosed with grade-3 arthritis 5

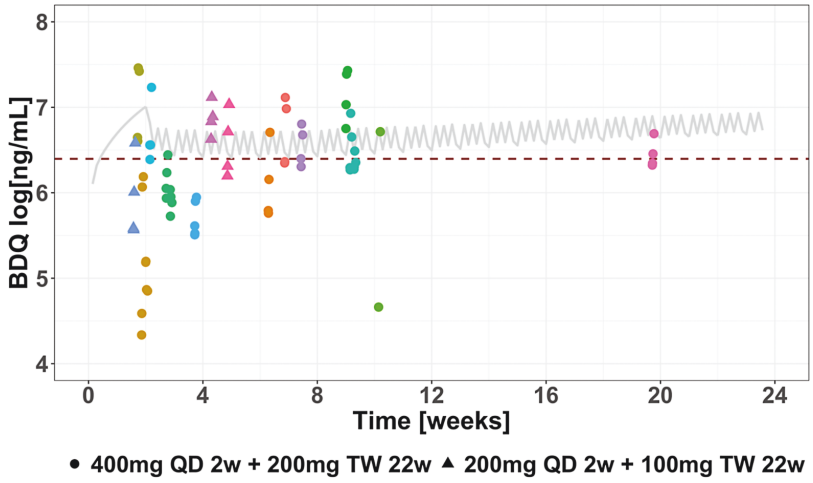

Figure 1. Raw data showing the concentrations of bedaquiline (BDQ) with respect to time, showing the entire treatment interval. Different colors represent different individuals, and different shapes different treatment schedule. Gray lines represent the simulated profile of a typical adult. Red dashed line represents the median target concentration (600 ng/mL).

Table 2. Parameter ESTIMATES With Uncertainty of the Final Pharmacokinetic Model of Bedaquiline and Metabolite M2 Among Children Receiving Bedaquiline-Containing Treatment Regimens for Multidrug-Resistant/Rifampicin-Resistant Tuberculosis (N = 15)

Parameter	Estimate (SE%)
MAT, fraction of 6 hours[a]	0.87
FR[a]	0.91
CL [L/h][a]	2.28
V [L][a]	94.1
Q1 [L/h][a]	3.19
VP1 [L][a]	4050
Q2 [L/h][a]	6.41
VP2 [L][a]	1280
CLM2/fm [L/h]	6.37 (9)
VM2/ fm [L][a]	1050
F	0.54 (2)
BSV CL [CV%][a]	39.11
BSV CLM2 [CV%][a]	46.04
Correlation BSV CL-CLM2 [%][a]	36.74
BSV V [CV%][a]	41.23
BSV Q1 [CV%][a]	42.42
BSV VM2 [CV%][a]	38.73
BSV F [CV%]	42.07 (36)
BOV MAT [CV%][a]	107.70
Additive residual error BDQ [ng/mL]	687.37 (6)
Proportional residual error M2	0.14 (7)

Parameters are scaled based on the median weight of the studied population (33.2 Kg).

Abbreviations: BDQ, bedaquiline; BOV, Between Occasion Variability; BSV, between subject variability; CI, confidence interval; CL, clearance; CV, coefficient of variation calculated with sqrt(exp(OMEGA)-1) where OMEGA is the estimated variance; F, bioavailability; fm, fraction metabolized; FR, fraction of MAT which is delay in the transit compartments; MAT, mean absorption time; M2, BDQ metabolite; Q, intercompartmental clearance; SE%, standard error in percentage; V, volume of distribution central compartment; VP, volume of distribution peripheral compartment.

[a]Fixed parameters from the reference adult model.

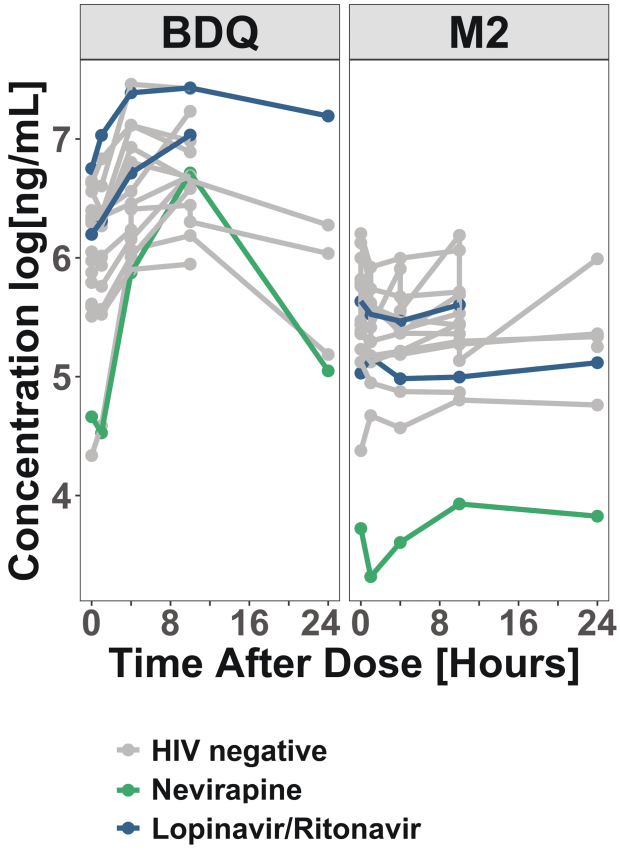

Figure 2. Bedaquiline (BDQ) and M2 metabolite concentrations over time in HIV negative and HIV positive children. Abbreviation: HIV, human immunodeficiency virus.

months later. The joint pains improved following intra-articular steroid injections, discontinuation of levofloxacin, and completion of the 24-week course of bedaquiline, which occurred all around the same time. One child experienced intermittent syncopal episodes shortly after starting bedaquiline, with occasional mild bradycardia documented later in treatment. These events were considered possibly related to bedaquiline and/or clofazimine, but there was not sufficient concern to withhold either drug. The child received 2 6-month courses of bedaquiline during prolonged treatment for extensively drug-resistant TB. There was no evidence of QTc-interval prolongation on the available ECGs throughout study participation and the syncope resolved during the second course of bedaquiline, suggesting it was unrelated.

Treatment Characteristics and Outcomes

Nine children had positive *Mycobacterium tuberculosis* cultures from respiratory samples at diagnosis and had follow-up samples taken; all 9 had culture-negative respiratory samples by eight weeks on MDR/RR-TB treatment. The median total duration of treatment was 11.5 months (IQR 9.5, 17.9), and all 15 children had a successful treatment outcome.

DISCUSSION

We analyzed the pharmacokinetics and safety of bedaquiline in 15 older children and adolescents, including 3 with HIV, who were all routinely treated per standard of care for MDR/RR-TB; we found that bedaquiline was well tolerated, and treatment outcomes were excellent. The pharmacokinetic properties of bedaquiline have not previously been reported in children treated for MDR/RR-TB outside of clinical trials, and we observed that bedaquiline exposure overall was lower than the average adult AUC reference of 187 µg h/mL at 24 weeks [17], with only 3 (20%) children achieving the adult AUC reference. Given the lack of an established target, we compared the median AUC (127 µg h/mL) in our cohort (median AUC 162 µg h/mL in children weighing ≤ 30kg; median AUC 112.5 µg h/mL in children > 30 kg) to previous reports among children. Moodliar et al [14] reported a weekly mean AUC, during the maintenance phase at week 24, of 134 and 124 µg h/mL for children weighing > 35 kg and ≤ 35 kg, respectively, and compared

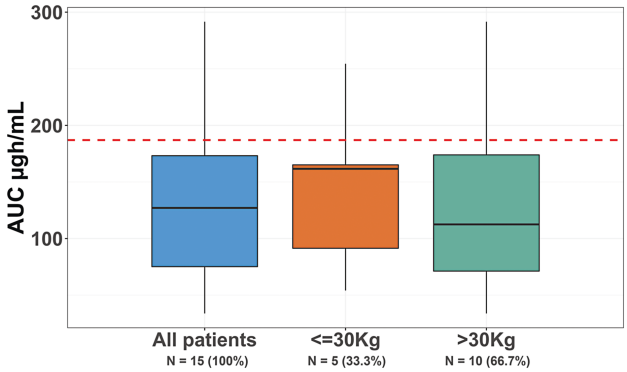

Figure 3. Bedaquiline exposure as weekly AUC at the end of treatment for all the children included in the study, overall and split by weight. Median weight on the pharmacokinetic sampling day among all 15 children was 33.2 kg (range 18.6–57.6). The median weight (interquartile range) on the sampling day for the 10 children > 30kg was 41.4 kg (33.2, 48.5) and for the 5 children ≤ 30 kg was 24.2kg (20.6, 27.1). The dashed horizontal line corresponds to the reference AUC used, 187 µg h/mL as the median weekly AUC of the adult exposure. Abbreviation: AUC, area under curve.

these with an adult reference exposure of weekly AUC of 144 µg h/mL.

The observed bedaquiline peak concentration in children was lower than predicted by the adult model. Therefore, the decision to re-estimate the bioavailability parameter was reasonable and resulted in a bioavailability of 0.57 as compared to the adult value of 1. This lower bioavailability may be partly explained by a delay in administration of food after bedaquiline dosing on pharmacokinetic sampling days, although the exposures in our study are comparable to other pediatric data in similar age groups. As this study protocol was not originally designed to characterize bedaquiline pharmacokinetics [24, 25], we did not have information on the typical type or timing of food intake with bedaquiline on non-sampling days. Additionally, the elimination and disposition parameters of bedaquiline and its metabolite were allometrically scaled based on the median child weight. Svensson et al reported no statistically significant difference in the bioavailability of bedaquiline crushed or suspended in water compared to tablets swallowed whole in healthy adult volunteers [34]; bedaquiline preparation did not appear to affect bioavailability in our cohort either. Although the number of HIV-positive children was small, it is reassuring that there were no substantial differences in bedaquiline exposures of the 2 children treated with lopinavir/ritonavir.

End-of-treatment outcomes were excellent despite most children having bacteriologically confirmed and severe forms of MDR/RR-TB, some with poor nutritional status, extensive drug resistance patterns, and some children with HIV. None of the adverse events observed in this cohort led to bedaquiline withdrawal. Assigning attribution of events to individual drugs is complicated by the administration of multidrug regimens containing many anti-tuberculosis medications with overlapping toxicities. The adverse event profile presented here is a conservative and likely over-estimate of the events truly attributable to bedaquiline alone, particularly as the rate of events is similar to that described in a non-bedaquiline treated cohort of children with MDR/RR-TB at the same site [35]. Common adverse events attributed to bedaquiline in adults include

Table 3. Adverse Events Among Children with Multidrug-Resistant/Rifampicin-Resistant Tuberculosis (N = 15) at Least Possibly Attributed to Bedaquiline

	Adverse Effects Possibly, Probably, Definitely Attributed to Bedaquiline by Grade					
Adverse Event	No. of Patients With Event	Grade 1	Grade 2	Grade 3	Grade 4	Total No. of events
Gastrointestinal disorders						
Vomiting	4	4	1	0	0	5
Abdominal Pain	1	1	0	0	0	1
Nausea	2	2	0	0	0	2
Hepatobiliary disorders						
ALT, high	4	3	2	0	0	5
Skin disorders						
Pruritus	1	1	0	0	0	1
Acneiform rash	3	3	0	0	0	3
Other						
Arthritis	2	0	1	1	0	2
Arthralgia	2	1	0	1	0	2
Headache	2	1	1	0	0	2
Syncope	1	0	1	0	0	1
QT prolongation	2	2	0	0	0	2
Chest pain	1	0	1	0	0	1
Elevated lactate	1	1	0	0	0	1
Fatigue	1	0	1	0	0	1

Abbreviations: ALT, alanine transaminase; QTcF, QT interval corrected for heart rate using Fridericia's formula.

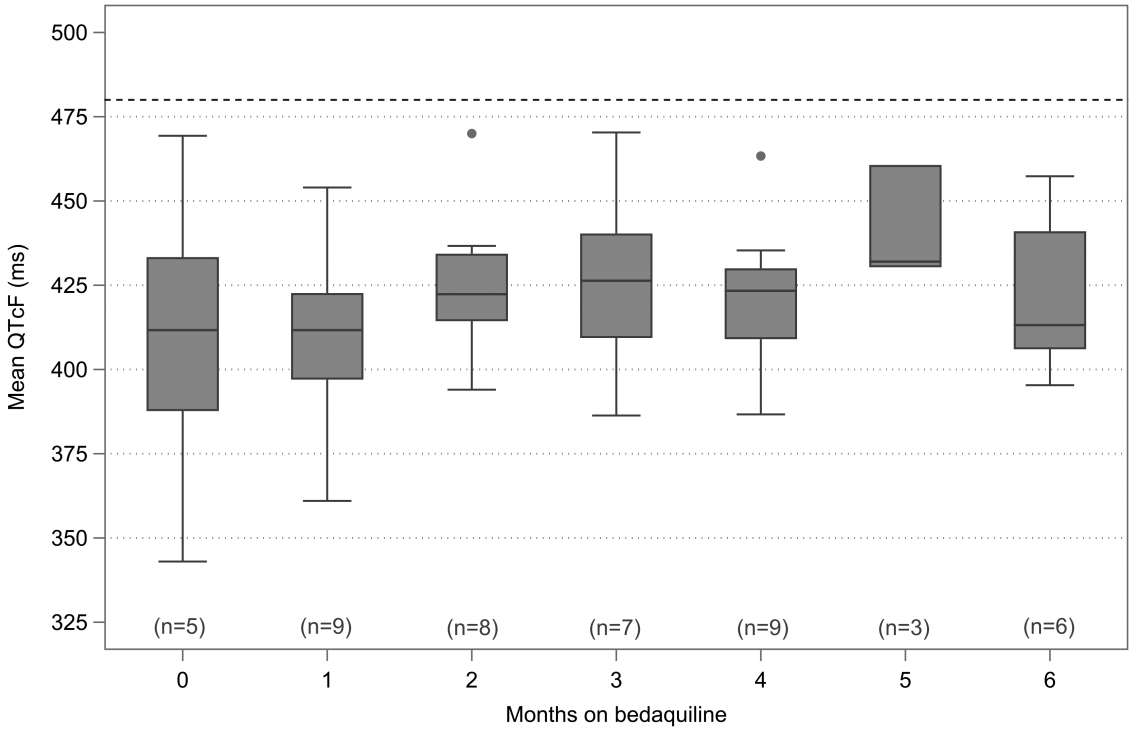

Figure 4. Electrocardiogram data indicating maximum mean corrected (Fridericia) QTc interval on pharmacokinetic sampling days in all 15 children receiving second-line tuberculosis treatment, over time on bedaquiline. Abbreviation: QTcF, QT interval corrected for heart rate using Fridericia's formula.

QTc-interval prolongation, linked to the metabolite M2 [36], elevated transaminases, and arthralgia [8, 37]. Published data from 30 children aged 5–18 years in the C211 trial indicated that arthralgia, acne, elevated blood creatinine phosphokinase and prolonged prothrombin time occurred frequently (>20%), and bedaquiline was discontinued in 3 children with elevated liver enzymes [14]. Although gastrointestinal symptoms were commonly reported in our cohort, severe hepatotoxicity was not observed. Joint pains were reported relatively frequently and considered possibly related to bedaquiline; however, many children were treated with regimens containing pyrazinamide and levofloxacin, also known causes of arthralgia. Only 2 children had mild QTc-interval prolongation, but none had grade-2 or higher cardiac events, despite co-administration of clofazimine (n = 9), delamanid (n = 3), and moxifloxacin (n = 2). Electrocardiogram data prior to bedaquiline initiation were not available for comparison to characterize longitudinal changes in QTcF from baseline in this cohort. Given the small number of children in our analysis, and the tendency to treat MDR/RR-TB with multiple QT-prolonging drugs, further evaluation of cardiac toxicity in children remains warranted.

Our study is limited by small numbers and the opportunistic sampling design. Nevertheless, these data may complement those from other studies with fixed timing and different pharmacokinetic sampling time points and could potentially be pooled and jointly modeled in future. Although QTc-interval prolongation was uncommon, we did not specifically obtain ECGs at the end of the loading phase when the concentration and QT prolongation risk is highest. We were not able to characterize the pharmacokinetic profile of bedaquiline in children without the adult model as background. The effect of previously defined covariates such as age or race, or important covariates such as nutritional status, HIV status, or concomitant medication could not be identified due to the small sample size and lack of power. Given the stated limitations we did not attempt to simulate alternative dosing strategies. Data from ongoing trials are awaited to guide optimal dosing of bedaquiline in children [13, 15].

In conclusion, our data suggest that the currently recommended, weight-based doses of bedaquiline in children ≥ 6 years of age administered in a routine care setting were safe and achieved only slightly lower plasma concentrations compared to those in adults receiving the recommended dose. Further evaluation of safety and pharmacokinetics of child-friendly formulations of bedaquiline in larger pediatric cohorts, including children < 6 years of age and those with HIV, should be prioritized to ensure access to effective, safe, and tolerable treatment regimens for children with MDR/RR-TB.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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