Isoniazid Plasma Concentrations in a Cohort of South African Children with Tuberculosis: Implications for International Pediatric Dosing Guidelines

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Background. In most countries with a high burden of tuberculosis, children with tuberculosis are prescribed isoniazid at dosages of 4–6 mg/kg/day, as recommended by international authorities.

Methods. We studied isoniazid concentrations in 56 hospitalized children (median age, 3.22 years; interquartile range [IQR], 1.58–5.38 years) who received isoniazid daily (median dosage, 5.01 mg/kg/day; range, 2.94–15.58 mg/kg/day) as part of antituberculosis treatment. At 1 and 4 months after initiation of treatment, isoniazid concentrations were measured in plasma samples at 0.75, 1.5, 3, 4, and 6 h after a treatment dose, to describe pharmacokinetic measures by using noncompartmental analysis. The effects of dose in milogram per kilogram, acetylator genotype, age, sex, and clinical diagnosis of kwashiorkor and human immunodeficiency virus (HIV) infection on isoniazid concentrations were evaluated.

Results. Median peak concentrations of isoniazid in children prescribed a dose of 4–6 mg/kg were 58% lower than those in children prescribed a dose of 8–10 mg/kg (2.39 mg/L [IQR, 1.59–3.40] vs. 5.71 mg/L [IQR, 4.74–7.62]). Peak concentrations were <3 mg/L in 70% of children prescribed a dose of 4–6 mg/kg. In contrast, children prescribed a dose of 8–12 mg/kg achieved peak concentrations approximating those in adults treated with 300 mg of isoniazid daily. Intermediate or fast acetylator genotype independently predicted a 38% (95% confidence interval [CI], 21%–51%) reduction in peak concentrations, compared with the slow-acetylator genotype. Each 1-mg/kg increase in the dose and each year increase in age were associated with increases in peak concentrations of 21% (95% CI, 16%–25%) and 6% (95% CI, 3%–10%), respectively.

Conclusions. Younger children require higher doses of isoniazid per kilogram of body weight to achieve isoniazid concentrations similar to those in adults. A daily isoniazid dose of 8–12 mg/kg should be recommended.

Isoniazid plays a crucial role in the treatment and prevention of tuberculosis. It has potent bactericidal activity against metabolically active Mycobacterium tuberculosis and prevents the development of resistance to companion antituberculosis drugs [1].

Oral doses of isoniazid are rapidly absorbed and readily distributed throughout the body. The drug undergoes intestinal and hepatic first-pass metabolism and is eliminated primarily by acetylation and dehydrazination. The rate of elimination has a trimodal distribution determined by genetic polymorphisms of the arylamine N-acetyltransferase 2 gene (NAT2); individuals may be homozygous for the allele for a fast acetylator (hereafter, “fast genotype”), heterozygous for the allele for a fast acetylator (hereafter, “intermediate genotype”), or homozygous for the allele for a slow acetylator (hereafter, “slow genotype”) [2]. NAT2 genotype is a prominent determinant of isoniazid concentrations in adults and children [2, 3]. The frequencies of NAT2

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polymorphisms vary widely between different populations, and there are corresponding differences in isoniazid pharmacokinetics reported in different regions [3, 4]. Younger children tend to have more-rapid elimination of isoniazid and relatively larger volumes of distribution, in comparison with older children and adults [3, 5–7].

Studies involving adults with pulmonary tuberculosis have demonstrated dose-related efficacy, with regard to both early bactericidal activity [8, 9] and longer-term outcomes [10]. Numerous clinical trials leading to implementation of the 6-month multidrug regimen (rifampin and isoniazid during all 6 months, with pyrazinamide or pyrazinamide and ethambutol during the first 2 months) support a daily isoniazid dose of 300 mg (i.e., 6 mg/kg for a patient weighing 50 kg) for adults [11]. Extensive experience with pharmacokinetic studies involving adults suggests a minimum target of 3 mg/L for the peak concentration ($C_{\text{max}}$) following receipt of a 300-mg dose when isoniazid is administered daily [12]. Reduced isoniazid concentrations may predispose to the development of rifamycin-resistant organisms in patients with tuberculosis who have advanced immunosuppression due to increased periods of exposure to effective concentrations of rifamycin alone [13, 14].

There are multiple obstacles to evaluating antituberculosis treatment regimens and their individual drug components for children [15, 16]. However, it is likely that good responses to treatment will be achieved in children, provided that they are given drug formulations and doses that achieve pharmacokinetics comparable to those that have demonstrated safety and efficacy among adults. Although some national programs, such as those in Japan, Mexico, the Philippines, and the United States, recommend isoniazid dosages of 10–15 mg/kg/day for children, international treatment guidelines recommend 4–6 mg/kg/day [17, 18].

The South African Tuberculosis Control Programme recommends isoniazid doses of 4–6 mg/kg for children receiving daily doses [19]. However, many pediatricians elect to use higher doses, particularly for children with severe disease. We studied the pharmacokinetics of isoniazid in children prescribed a range of isoniazid doses at the Brooklyn Hospital for Chest Diseases in Cape Town, South Africa.

**METHODS**

**Patients and treatments.** Children aged 3 months to 13 years who were referred to the Brooklyn Hospital for Chest Diseases for management of severe forms of tuberculosis were eligible to participate in the study. Parents or legal guardians gave written informed consent before enrollment of their children. Treatment was initiated ∼1 month before admission to the Brooklyn Hospital for Chest Diseases by the referring hospital, at which the diagnosis of tuberculosis or probable tuberculosis was made on the basis of ≥2 of the following criteria: gastric aspirate, sputum, or CSF culture result positive for *M. tuberculosis*; induration ≥5 mm in children with human immunodeficiency virus (HIV) infection or >10 mm in HIV-uninfected children at 48–72 h after a Mantoux test with 2 U of tuberculin RT23; household source case with sputum-microscopy smear test result positive for acid-fast bacilli in the preceding year; chest radiograph findings indicative of pulmonary tuberculosis; and findings on cranial computed tomography compatible with tuberculous meningitis and appropriate microscopic changes in the cerebrospinal fluid. HIV infection status was determined by enzyme-linked immunosorbent assay, with positive results confirmed by a second assay, or for children aged <18 months, HIV infection status was confirmed by polymerase chain reaction. The parents or legal guardians of the children were counseled and written informed consent was obtained before HIV testing. A clinical diagnosis of kwashiorkor was made in the presence of pitting edema. Children were classified as having fast, intermediate, or slow genotypes for NAT2 on the basis of previously described methods [3]; the fast and slow alleles are codominant [2]. The study was approved by the Institutional Review Board of the Faculty of Health Sciences of Stellenbosch University (2003/054/N) and was conducted in accordance with national research standards [20] and the Helsinki Declaration of 2000, revised in 2004.

Antituberculosis treatment regimens included daily doses of rifampin and isoniazid for 6 months with pyrazinamide for the first 2 months. Higher doses of isoniazid tended to be prescribed for children with disseminated disease, such as miliary tuberculosis or tuberculous meningitis. Ethionamide was added to the treatment regimen for children with tuberculous meningitis. Ethambutol was added during the intensive phase for other forms of tuberculosis when the use of 4 drugs was considered advisable. Isoniazid was administered as part of dispensable, pediatric, fixed-dose combinations (Rimcure Paed 3-FDC: each tablet contains 60 mg of rifampin, 30 mg of isoniazid, and 150 mg of pyrazinamide; Rimactazid Paed 60/30: each tablet contains 60 mg of rifampin and 30 mg of isoniazid; or Rimactazid Paed 60/60: each tablet contains 60 mg of rifampin and 60 mg of isoniazid; all manufactured by Sandoz). All the antituberculosis medicines were approved by the South African Medicines Control Council and were dispensed by the Brooklyn Hospital for Chest Diseases pharmacy.

**Pharmacokinetic assessment.** Sample collection for pharmacokinetic analysis was performed at ~1 month after the initial admission to the referral hospital and again at 4 months after initiation of treatment. Children fasted overnight before blood sample collection at 0.75, 1.5, 3.0, 4.0 and 6.0 h after an observed treatment dose. Blood specimens were immediately placed on ice. Plasma (1 mL) was separated by centrifugation within 30 min and was stored at −80°C until analysis. Alanine
aminotransferase (ALT), body mass, and height were measured on the days of pharmacokinetic sample collection.

Plasma concentrations of isoniazid were quantified by tandem high-performance liquid chromatography mass spectrometry (API 2000; Applied Biosystems) with use of a 20 x 2.1-mm Betasil silica column (Thermo). An isocratic elution of 80% acetonitrile in 0.1% formic acid was used as the mobile phase, with a flow rate of 0.3 mL/min and an injection volume of 0.005 mL. The internal standard was sulfamoxole. Selected reaction-monitoring transitions of [M-H]+ precursor ions to product ions were isoniazid (mass-to-charge ratio [m/z], 138.0–121.2) and sulfamoxole (m/z, 254.0–92.2). Plasma protein was precipitated with 3 volumes of acetonitrile containing the internal standard. Samples were vortexed and centrifuged for 5 min at 750 g. Supernatant (0.005 mL) was injected into the column. Standard curves were linear in the range 0.1–15 mg/L. Quality-control samples covering the ranges were included with each run. Interday and intraday coefficients of variation were <10%.

Plasma concentrations at the time of dosing and those >20% below the limit of quantification (0.1 mg/L) were given a value of 0.05 mg/L. WinNonlin, version 4.1 professional (Pharsight), was used to determine Cmax and time to Cmax (Tmax) directly from the concentration-time data; the apparent elimination half-life (t1/2 = 0.693/k, where k is the slope of the log-linear regression of ≥3 final data points); and the area under the curve until the 6-h time point (AUC0–6) by the linear trapezoidal rule. AUC0–6 and t1/2 were not evaluated in patients with missing concentration data at the 4- or 6-h time points.

**Statistical analysis.** The data were summarized as median and interquartile range (IQR). The Wilcoxon rank-sum test, the Kruskal-Wallis test, and the Wilcoxon signed-rank test were used to determine whether 2 independent groups, 3 independent groups, or paired data, respectively, were statistically significantly different. For binominal data, differences between groups were determined using Fisher’s exact test. The Spearman rank correlation coefficient described associations between continuous variables. The natural logarithm transformation was applied to Cmax values for examination of the covariate effects of age, sex, HIV infection status, a diagnosis of kwashiorkor, isoniazid dose per kilogram of body weight, and NAT2 genotype (as a binary variable: slow genotype in one category; intermediate and fast genotypes in the other category) by use of linear regression. Effects of covariates that were found to be possibly associated (P < .2) with the log-transformed Cmax in the univariate analyses were further examined by multivariate regression analysis. The regression coefficients were back-transformed to express the percentage change in the dependent variable conferred by a 1-unit change in the relevant covariate. The model assumptions of constant variance, linearity, and the appropriate form of the covariates in the model were checked using methods based on the distribution of the residuals. The odds of developing transaminitis was evaluated for children treated with an isoniazid dose of 8–12 mg/kg, compared with children treated with a dose of 4–6 mg/kg, in a univariate logistic regression model. Stata, version 8.2 (StataCorp), was used to compute summary statistics and for statistical tests and regression analysis.

**RESULTS**

**Patient characteristics and treatment doses.** A total of 60 children were enrolled in the study. Four HIV-infected children were withdrawn before pharmacokinetic assessment because they required transfer to other hospitals for management of complications. Of the remaining 56 children, 29 (52%) were male, and 22 (39%) were infected with HIV-1. Of the 56 children, 20 (36%) had slow genotypes, 24 (43%) had intermediate genotypes, and 8 (14%) had fast genotypes. (Genotyping results were not available for 4 participants with a mean age of 2.76 years, mean weight of 11.3 kg, and mean height of 82 cm). Their median age was 3.22 years (IQR, 1.58–5.38 years), median weight was 12.43 kg (IQR, 8.88–17.26 kg), and median height was 84.5 cm (IQR, 76.2–104.2 cm) at 1 month after initiation of antituberculosis treatment. The dose of isoniazid at the first pharmacokinetic assessment ranged from 2.94 to 15.58 mg/kg (median, 5.01 mg/kg; IQR, 4.35–9.24 mg/kg) or 52 to 317 mg/m² of body surface area (median, 119 mg/m²; IQR, 100–198 mg/m²). Infants (age, <1 year) were more likely to receive isoniazid doses of <4 or >12 mg/kg (3 of 6 infants vs. 6 of 50 children aged >1 year; P = .046, by Fisher’s exact test), and children who received a diagnosis of kwashiorkor tended to be prescribed higher doses than those without a diagnosis of kwashiorkor (median, 6.27 mg/kg [IQR, 4.90–9.72 mg/kg] vs. 4.82 mg/kg [IQR, 4.25–8.77 mg/kg]; P = .074, by Wilcoxon rank-sum test). Doses were not statistically significantly different between children with and children without HIV infection (median, 4.61 mg/kg [IQR, 4.23–7.33 mg/kg] vs. 5.14 mg/kg [IQR, 4.72–9.27 mg/kg]; P = .191, by Wilcoxon rank-sum test), between female and male patients (median, 5.23 mg/kg [IQR, 4.50–9.20 mg/kg] vs. 4.85 mg/kg [IQR, 4.25–9.27 mg/kg]; P = .372, by Wilcoxon rank-sum test), or among children with slow, intermediate, and fast genotypes (table 1).

**Pharmacokinetics.** Isoniazid concentrations at ~1 month after initiation of antituberculosis treatment were available for 56 participants. Isoniazid concentrations were not available for 4 and 13 samples obtained at the 4- and 6-h time points, respectively, because of our inability to maintain the intravenous line for the duration of sample collection or because of an insufficient sample for analysis of isoniazid concentrations. Two samples obtained at the 4-h time point and 3 samples obtained at the 6-h time point were below the limit of quantification. Plasma concentrations at each sample collection time

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varied widely among individuals (figure 1). Absorption was rapid, with a median \( T_{\text{max}} \) of 0.75 h. The dose, \( C_{\text{max}} \), \( t_{1/2} \), AUC\(_{0-\text{p}}\), and concentration at the 6-h time point (\( C_{6} \)) for children with slow, intermediate, and fast NAT2 genotypes are reported in table 1, and \( C_{\text{max}} \) and AUC\(_{n-a}\) for children receiving doses <4 mg/kg, 4–6 mg/kg, >6 and <8 mg/kg, 8–12 mg/kg, and >12 mg/kg are described in table 2. \( C_{\text{max}} \) and AUC\(_{n-a}\) were highly correlated (Spearman rank correlation coefficient, 0.938; \( P < .001 \)).

None of the 7 children (3 with slow genotypes and 4 with intermediate genotypes) who received isoniazid doses <4 mg/kg had a \( C_{\text{max}} \) above the recommended lower limit of 3 mg/L. Of 30 children prescribed doses of 4–6 mg/kg, 21 (70%) had a \( C_{\text{max}} \) <3 mg/L (4 [36%] of 11 with slow genotypes, 9 [90%] of 10 with intermediate genotypes, 6 [100%] of 6 with fast genotypes, and 2 [67%] of 3 with unknown genotypes). All children prescribed doses of 8–12 mg/kg had peak concentrations >3 mg/L (5 children with slow genotypes and median \( C_{\text{max}} = 7.10 \) mg/L, 8 children with intermediate genotypes and median \( C_{\text{max}} = 5.35 \) mg/L, 1 child with fast genotype and \( C_{\text{max}} = 5.58 \) mg/L, and 1 child with unknown genotype and \( C_{\text{max}} = 5.70 \) mg/L).

Univariate regression analyses found no association (\( P > .2 \)) between isoniazid \( C_{\text{max}} \) at 1 month after initiation of antituberculosis treatment and HIV infection status or between \( C_{\text{max}} \) at 1 month and the presence of kwashiorkor. Sex was weakly associated (\( P = .040 \)) in univariate analysis but did not contribute to the multivariate model. A multivariate model describing 71% of the variability in \( C_{\text{max}} \) found that each 1-mg/kg increase in dose was associated with a 21% increase (95% CI, 16%–25% increase) in \( C_{\text{max}} \) and that each 1-year increase in age was associated with a 6% increase (95% CI, 3%–10% increase) in \( C_{\text{max}} \). Participants with intermediate or fast NAT2 genotypes had 38% decreases (95% CI, 21%–51% decrease) in \( C_{\text{max}} \) compared with those with slow genotypes. The model included 51 observations, because NAT2 genotype was unknown for 4 participants and because there was 1 outlying observation (\( C_{\text{max}} = 20.08 \) mg/L; dose, 5.06 mg/kg; slow genotype; age, 2.41 years) that was excluded to satisfy the math-

### Table 1. Pharmacokinetic assessment at 1 month after initiation of antituberculosis treatment, according to arylamine \( N \)-acetyltransferase 2 (NAT2) genotype.

<table>
<thead>
<tr>
<th>Isoniazid measure</th>
<th>All patients</th>
<th>Slow</th>
<th>Intermediate</th>
<th>Fast</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, mg/kg</td>
<td>5.01 (4.35–9.24)</td>
<td>4.98 (4.12–7.99)</td>
<td>5.26 (4.43–9.37)</td>
<td>4.90 (4.68–7.38)</td>
<td>.748</td>
</tr>
<tr>
<td>( C_{\text{max}} ), mg/L</td>
<td>3.07 (1.82–5.66)</td>
<td>4.05 (2.72–5.74)</td>
<td>2.63 (1.61–5.25)</td>
<td>1.54 (1.22–4.14)</td>
<td>.067</td>
</tr>
<tr>
<td>( t_{1/2} ), h</td>
<td>1.59 (1.21–2.17)</td>
<td>2.23 (1.80–3.06)</td>
<td>1.36 (1.14–1.75)</td>
<td>1.12 (0.96–1.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AUC(_{0-\text{p}}), mg/h-L</td>
<td>8.73 (4.55–14.13)</td>
<td>10.60 (8.66–16.14)</td>
<td>6.45 (4.18–13.27)</td>
<td>2.31 (1.77–6.12)</td>
<td>.014</td>
</tr>
<tr>
<td>( C_{6} ), mg/L</td>
<td>0.26 (0.12–0.76)</td>
<td>0.76 (0.52–1.86)</td>
<td>0.14 (0.11–0.26)</td>
<td>0.08 (0.05–0.12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (interquartile range), unless otherwise indicated. NAT2 genotype was available for 52 of the 56 children in the study. AUC\(_{0-\text{p}}\) area under the curve until the 6-h time point; \( C_{\text{max}} \) peak concentration; \( C_{6} \) concentration at the 6-h time point; \( t_{1/2} \) half life.

\( a \) For dose and \( C_{\text{max}} \), \( n = 66 \); for \( t_{1/2} \), \( n = 40 \); for AUC\(_{0-\text{p}}\), \( n = 41 \); and for \( C_{6} \), \( n = 43 \). AUC\(_{0-\text{p}}\) and \( t_{1/2} \) were not determined for patients with missing samples at the 4- or 6-h time point. For 1 patient with a late \( C_{\text{max}} \) measured at 4 h after the treatment dose, \( t_{1/2} \) was not estimated.

\( b \) By Kruskal-Wallis test to determine the probability of equality between the genotype groups.

\( c \) For dose and \( C_{\text{max}} \), \( n = 20 \); for \( t_{1/2} \), \( n = 14 \); for AUC\(_{0-\text{p}}\), \( n = 15 \); and for \( C_{6} \), \( n = 16 \).

\( d \) For dose and \( C_{\text{max}} \), \( n = 24 \); for \( t_{1/2} \) and AUC\(_{0-\text{p}}\), \( n = 20 \); and for \( C_{6} \), \( n = 21 \).

\( e \) For dose and \( C_{\text{max}} \), \( n = 8 \); and for \( t_{1/2} \), AUC\(_{0-\text{p}}\), and \( C_{6} \), \( n = 4 \).
emathetical assumptions of the model. Substitution of dose in mg/kg and age with dose in mg/m² body surface area resulted in a simplified multivariate model that described the data equally well (r² = 71%; intermediate and fast genotypes were associated with a 36% lower [95% CI, 19%–49% lower] Cmax compared with slow genotypes; and each 25-mg/m² increase in the isoniazid dose resulted in a 24% increase [95% CI, 20%–31% increase] in Cmax).

One child with HIV infection and 1 child without HIV infection were discharged from the hospital after completion of the first pharmacokinetic evaluation. The remaining 54 children underwent additional pharmacokinetic evaluation at ∼4 months after initiation of antituberculosis treatment. Children had statistically significant growth during the intervening 3 months; the median weight gain was 0.48 kg (IQR, −1.00 to 1.35 kg; P < .001, by Wilcoxon signed-rank test), and the median increase in height was 1.75 cm (IQR, 0.55–3.00 cm; P < .001, by Wilcoxon signed-rank test). Isoniazid doses were adjusted to keep pace with weight gain; therefore, doses in mg/kg were not significantly different at 1 and 4 months (median dose change, −0.05 mg/kg; IQR, −0.46 to 0.18 mg/kg; P = .384, by Wilcoxon signed-rank test). The pharmacokinetics of isoniazid at 1 and 4 months after initiation of antituberculosis treatment were similar. At 4 months, isoniazid concentrations were not available for 3 and 10 samples obtained at the 4- and 6-h time points, respectively. One and 3 samples obtained at the 4- and 6-h time points, respectively, were below the limit of quantification. Median changes in pharmacokinetic variables were as follows: Cmax, 0.10 mg/L (IQR, −0.79 to 1.18 mg/L; P = .446, by Wilcoxon signed-rank test); Css, 0.02 mg/L (IQR, −0.05 to 0.09 mg/L; P = .479, by Wilcoxon signed-rank test); AUC0–6, 1.39 mg·h/L (IQR, −1.40 to 3.48 mg·h/L; P = .343, by Wilcoxon signed-rank test), and t1/2, −0.02 h (IQR, −0.39 to 0.24 h; P = .550, by Wilcoxon signed-rank test). Multivariate regression confirmed the important effects of dose (mg/kg) and NAT2 genotype at 4 months on the systemic concentrations of isoniazid. Age, sex, HIV infection, and kwashiorkor were not associated with Cmax after adjustment for the 2 dominant covariates.

DISCUSSION

We describe the pharmacokinetics of isoniazid and NAT2 genotypes in a cohort of 56 children with severe forms of tuberculosis. Although previous studies have characterized the concentrations of isoniazid in South African children treated with higher doses [3], the pharmacokinetics of the 4–6 mg/kg dose that is recommended by international authorities, including the World Health Organization, has not been described in South African children. Peak concentrations were below the recommended reference range in 70% of children (21 of 30, including 4 [36%] of 11 children with slow genotypes) who were prescribed isoniazid doses of 4–6 mg/kg at 1 month after initiation of antituberculosis treatment. Thus, even among populations with a high prevalence of slow genotypes, a substantial proportion of children may achieve relatively low isoniazid con-
centrations. In contrast, all children prescribed isoniazid doses of 8–12 mg/kg, irrespective of NAT2 genotype, achieved a \( C_{\text{max}} > 3 \) mg/L, with a median \( C_{\text{max}} \) comparable to that reported in South African adults (6.5 mg/L; IQR, 4.9–8.7 mg/L) who were treated with 300 mg of isoniazid daily [21].

Children prescribed doses <4 mg/kg had low isoniazid concentrations, and infants were at greater risk than were older children of receiving low or high doses. Thus, the importance of accurate weighing of young children should be emphasized, as should the need to increase doses in line with growth and weight gain during treatment. It is relevant to note that the South African National Tuberculosis Control Programme and the package inserts for the fixed-dose combination formulations used in this study recommend that children who weigh 3–4.9 kg should be prescribed one-half of a fixed-dose combination tablet containing 30 mg of isoniazid [19, 22–24]. Thus, a child with a weight of 4.9 kg would receive only 3.06 mg/kg of isoniazid if the tablet was accurately halved. Likewise, 1 tablet is recommended for children who weigh 5–7 kg, and a dose of 3.80 mg/kg is recommended for a child who weighs 7.9 kg.

Dose in mg/kg of body weight and NAT2 genotype were the dominant determinants of isoniazid concentrations. After adjustment for the effects of dose and NAT2 genotype, age was associated with isoniazid concentrations at ~1 month after initiation of treatment. Age was noncontributory to the model describing the effects of genotype and dose in mg/m² body surface area on \( C_{\text{max}} \), which suggests that dosing based on body surface area may result in less variability in isoniazid concentrations among young children than might dosing based on weight. Age did not improve the model describing the effects of genotype and dose in mg/kg on \( C_{\text{max}} \) after 4 months of treatment. The fact that the children were older might explain in part the lack of association; however, the multivariate analysis at 4 months described only 48% of the variability in \( C_{\text{max}} \) compared with 71% in the earlier analysis indicating greater residual variability unexplained by the covariates investigated. Nonetheless, this finding highlights the need for further evaluation of isoniazid concentrations in infants (only 6 children included in this study were aged <1 year). The similarity in isoniazid pharmacokinetics at 1 and 4 months after initiation of antituberculosis treatment suggests that any physiological changes affecting isoniazid concentrations related to disease severity in this group of children had resolved within 1 month of treatment. Thus, the pharmacokinetic results are likely to reflect results for children with milder disease.

Data relating to treatment outcomes were not available. Although this is an important limitation, the assessment of response to antituberculosis treatment in a standardized manner is difficult in children because reliable markers of treatment response have not been developed [15, 16].

Severe isoniazid-related hepatitis is rare in children [25]. Although the risk of transaminitis tended to be increased in those receiving higher doses of isoniazid, this finding was not statistically significant and may have been confounded by disease-related factors, because children with disseminated tuberculosis tended to be prescribed higher doses. All children received a multivitamin supplement that supplied (at least) the recommended daily allowance of pyridoxine. None of the cohort developed peripheral neuropathy. It is our clinical experience (and that of others [26, 27]) that peripheral neuropathy is very rare in HIV-uninfected children treated with isoniazid, even at doses of up to 20 mg/kg. However, pyridoxine supplementation is prudent for children with HIV infection or nutritional deficiency.

In conclusion, in this group of young children, a dose of 4–6 mg/kg was insufficient to achieve isoniazid concentrations comparable to those deemed necessary for optimal response in adults. Conversely, a dose of 8–12 mg/kg achieved comparable peak concentrations to a 300-mg dose in adults.

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References

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