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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.

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