Pharmacokinetics and pharmacodynamics of high-dose isoniazid for the treatment of multidrug-resistant tuberculosis in Indonesia

Background: Pharmacokinetic data on high-dose isoniazid for multidrug-resistant tuberculosis (MDR-TB) treatment are limited. We aimed to describe the pharmacokinetics of high-dose isoniazid, estimate exposure target attainment, identify predictors of exposures, and explore exposure-response relationships in MDR-TB patients.

Methods: We performed an observational pharmacokinetic study, with exploratory pharmacokinetic/pharmacodynamic analyses, in Indonesian adults aged 18-65 years treated for pulmonary MDR-TB with standardized regimens containing high-dose isoniazid (10-15 mg/kg/day) for 9-11 months. After a minimum of two weeks of treatment, intensive pharmacokinetic sampling was performed at 0, 1, 2, 3, 4 and 8 hours after drug administration. Main pharmacokinetic parameters, including total plasma drug exposures (AUC_{0-24}) and peak concentrations (C_{max}) were assessed using non-compartmental analyses. AUC_{0-24}/minimum inhibitory concentration (MIC) ratio of 85 and C_{max}/MIC ratio of 17.5 were used as exposure targets. Multivariable linear and logistic regression analyses were used to identify predictors of drug exposures and responses, respectively.

Results: We consecutively enrolled 40 patients (median age 37.5 years). The geometric mean isoniazid AUC_{0-24} and C_{max} were 35.4 h·mg/L and 8.5 mg/L, respectively. Lower AUC_{0-24} and C_{max} values were associated with non-slow acetylator phenotype and a kanamycin-containing (*vs.* bedaquiline-containing) regimen, and lower C_{max} values were associated with male sex (all $p<0.05$). Of the 26 patients with MIC data, less than 25% achieved the proposed targets for isoniazid AUC_{0-24}/MIC (n=6/26) and C_{max}/MIC (n=5/26). Lower isoniazid AUC_{0-24} values were associated with delayed sputum culture conversion after more than 2 months of treatment (adjusted odds ratio 0.18 [95% CI 0.04–0.89]).

Conclusion: Isoniazid exposures below targets were observed in most patients, and certain risk groups for low isoniazid exposures, particularly non-slow acetylators and those taking concomitant kanamycin, may require dose adjustment. The effect of low isoniazid exposures on delayed culture conversion deserves attention as it may have implications for TB transmission and poor outcome.

Key words: High-dose isoniazid, multidrug-resistant tuberculosis, pharmacokinetics, pharmacodynamics, sputum culture conversion, efficacy.