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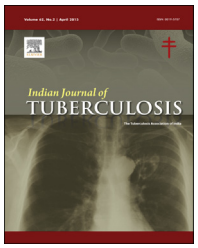

Original Article

Blood levels of isoniazid in Indian children with tuberculosis

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ABSTRACT

Background: Under the Revised National Tuberculosis Control Program (RNTCP) in India children are receiving antituberculosis treatment (ATT) as per a weight band system. In this children may be receiving antituberculosis drugs in doses which may be more or less than that recommended in mg/kg body weight doses. The recommended dose of isoniazid (INH) for intermittent therapy under the RNTCP is 8–12 mg/kg body weight and by the World Health Organization (WHO) for daily therapy is 10–15 mg/kg body weight.

Aims: To evaluate the blood levels and pharmacokinetics of INH, in children suffering from tuberculosis, at doses administered under the weight band system of the Revised National Tuberculosis Control Program (RNTCP) 2009 of India.

Design: Prospective, open label, non-randomized single-dose study conducted in 20 children in the age group 5–12 years attending the outpatient, chest clinic of a tertiary care hospital.

Results: Group I (n = 8) included children who received INH in a dose of 10 mg/kg body weight or more and Group II (n = 12) included those who received INH in a dose less than 10 mg/kg body weight. The mean peak INH concentration (C_{max}) was 6.03 ± 1.4 μg/mL and this was achieved in 2 hours (T_{max}). The mean serum INH concentration was significantly higher in children who received INH in dose more than 10 mg/kg (Group I) as compared to those who received INH in doses lesser than 10 mg/kg body weight (Group II) at all-time points except at 2 hours ($P < 0.05$). The C_{max} was also lower in Group II patients in comparison to Group I patients. Area under the concentration time curve (AUC) was significantly lower in Group II patients (P value 0.002). The elimination half-life of INH was 4.3 ± 0.4 h, elimination rate constant 0.16 ± 0.01/h, the volume of distribution 44.05 ± 5.3 L and clearance 7.1 ± 0.8 L/h.

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Conclusions: Lower blood levels and AUC of INH were achieved in children receiving doses of INH lesser than 10 mg/kg body weight. Long elimination half-life of INH is indicative of a slower rate of metabolism. Lower INH levels despite a slower rate of drug metabolism indicate caution with the INH doses being administered to children for intermittent therapy under the RNTCP.

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1. Introduction

Under the Revised National TB Control Program (RNTCP) in India, children are administered thrice weekly doses of antituberculosis drugs according to a weight band system.[1] Under RNTCP 2009, INH was being administered at a dose of 10 mg/kg body weight (8–12 mg/kg) thrice weekly to both adults and children. Recently the RNTCP has been revised and INH dose has been specified as 10 mg/kg body weight to a maximum of 300 mg for intermittently (thrice weekly) therapy.[2] The World Health Organization (WHO) has recommended INH in an oral dose of 10–15 mg/kg body weight in children, to be administered daily.[3] The WHO has also recommended that in countries with a high prevalence of HIV, antituberculosis treatment should not be given intermittently to children.[4]

In India under the RNTCP INH has been administered in a dose range lesser than that recommended by WHO, intermittently to children. India also has a high prevalence of HIV infection. Under the weight band system of RNTCP 2009, some children were getting doses lesser than 10 mg/kg body weight of INH, a dose which is at the lower end of the dose range recommended by the WHO for daily therapy and the average dose according to RNTCP guidelines for intermittent therapy. The basis of intermittent therapy is that appropriate peak drug levels be achieved, which will inhibit mycobacterial growth sufficiently till the administration of the next dose of the drug. Low doses of antituberculosis drugs administered intermittently may result in inadequate drug concentrations in the body. This may contribute to treatment failure, relapse and drug resistance.

There is lack of sufficient data in Indian pediatric patients on the blood levels of INH achieved with the weight band system of RNTCP 2009. This study was conducted to observe the blood levels of INH achieved in children falling under Weight band 2 and 3 of RNTCP.

2. Methods

An open-label, prospective, non-randomized single dose study was conducted in newly diagnosed children suffering from tuberculosis attending the chest clinic of Lok Nayak Hospital, New Delhi, India. The study was conducted between 2011 and 2012, prior to the official announcement of the change in guidelines for pediatric tuberculosis in 2013. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from parents or guardians of all the children and written informed assent was obtained from all the subjects above 7 years of age.

2.1. Subjects

A total of twenty children in the age group of 5–12 years, newly diagnosed with pulmonary or lymph node tuberculosis, were enrolled in the study. Diagnosis of tuberculosis was based on relevant clinical history, physical examination, chest X-ray, Mantoux test and fine needle aspiration cytology of accessible lymph nodes, wherever required. Patients with hematological, hepatic and renal functions within normal range were included. Children with severe tuberculosis requiring hospital admission, presence of any other diseases and having history of any concomitant or long term drug intake were excluded from the study.

2.2. Study design

Patients fulfilling the inclusion criteria were admitted one day prior to study commencement in the Paediatric ward of Lok Nayak Hospital. After overnight fasting, a single dose of INH was administered at 6.00 am. Children with body weight between 11 and 17 kg (Weight Band 2) were given a single oral INH tablet 150 mg and those with body weight between 18 and less than 25 (Weight Band 3) were administered single oral dose of INH 225 mg. These doses were administered as per RNTCP 2009 guidelines for intermittent therapy of tuberculosis in children. A standard breakfast and lunch was administered 2 and 6 h after INH administration, respectively. Regular antituberculosis treatment began 24 h later.

2.3. Sample collection

Venous blood samples (1.5 mL) were collected at 0, 1, 2, 4, 6, 10 and 24 h. Serum was separated within 1 h, deproteinized within 4 h and stored at −20 °C till isoniazid estimation.

2.4. Assay method

Estimation of isoniazid was done by the microspectrofluoro metric method of Miceli et al.[5]

The INH dose administered to individual patients was converted to mg/kg dose and the patients were divided into two groups. Group I consisted of those patients who received INH in a dose of 10 of mg/kg or more and Group II who received INH in a dose lesser than 10 mg/kg. Comparison of serum INH concentrations over different time points, and pharmacokinetic parameters, peak serum concentration (C_{max}), time to achieve the peak concentration (T_{max}), area under the serum concentration vs time curve from zero to twenty four hours and zero to infinity ($AUC_{(0-24)}$, and $AUC_{(0-\infty)}$), elimination half-

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