

## PHARMACOKINETICS OF ISONIAZID IN PULMONARY TUBERCULOSIS-A COMPARATIVE STUDY AT TWO DOSE LEVELS

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**Objectives:** To compare the pharmacokinetic parameters and the clinical efficacy of isoniazid, administered in 10 mg/kg or 5 mg/kg to children suffering from pulmonary tuberculosis. **Design:** A randomized, open, controlled clinical trial. **Setting:** Teaching hospital in New Delhi. **Subjects:** Twenty children suffering from pulmonary tuberculosis in the age group 6-12 years. **Interventions:** A three drug antitubercular regimen comprising of rifampicin (10 mg/kg), pyrazinamide (30 mg/kg) and isoniazid in a dose of either 10 mg/kg (Group I) or 5 mg/kg (Group II) was administered for fourteen days. On day fifteen serial blood samples were collected at 0,1,2,3,6 and 24 h of isoniazid administration and analyzed spectrofluorometrically. **Main outcome measures:** Serum isoniazid concentrations and clinical response in both the groups. **Results:** In both the groups, serum concentration of isoniazid were above the therapeutic range (0.5-2 ug/ml) at 6 h following drug administration. The minimum serum concentration of isoniazid was within or above minimum inhibitory concentration of the drug at 24 h in both the groups. The time to achieve maximum serum concentration, elimination half life, elimination rate constant, mean residence time, volume of distribution at steady state and plasma drug clearance were also comparable. At the end of 6 months follow up, all children showed comparable clinical and radiological improvement. **Conclusion:** Isoniazid in a dose of 5 mg/kg administered with other anti-tubercular drugs appears adequate for treatment of pulmonary tuberculosis in children.

**Key words:** Isoniazid, Pharmacokinetics, Minimum inhibitory concentration.

TUBERCULOSIS is a widespread disease in developing countries. In India, its incidence is highest in individuals between the ages of 5-20 yr(1). Isoniazid (INH) is considered to be an important drug and is included in all antitubercular regimens. Although the recommended daily dose of INH is 10-20 mg/kg(2), it has been shown that in children effective blood concentrations are achieved with small doses of 4-8 mg/kg(3-5). In view of the above, the International Union Against Tuberculosis and Lung Diseases and the

World Health Organization recommended a daily dose of 4-6 mg/kg in children with a total dose not exceeding 300 mg(6-8). However, these lower doses of INH are not prescribed due to lack of adequate supportive pharmacological data. The present study was designed to compare the pharmacokinetics of INH at 5 and 10 mg/kg. The clinical efficacy and adverse effects at these two doses were evaluated.

### Subjects and Methods

A randomized open controlled trial was

conducted in children suffering from pulmonary tuberculosis, attending the Outpatient Clinic of Lok Nayak Hospital. The study was approved by the Ethics committee. Informed consent was obtained from the parents or guardians of all the patients.

Twenty four newly diagnosed patients of tuberculosis were enrolled in the study. Diagnosis for tuberculosis was made according to the Kenneth Jones criteria and children with a score of seven and above were included(9). Twenty children suffering from pulmonary tuberculosis and fulfilling the inclusion criteria were finally inducted.

There were eleven boys and nine girls, in the age group 6-12 yr. The mean body-weight was 17.6 kg (range 15-21 kg). The levels of blood urea, serum creatinine, bilirubin, aspartate transaminase, alanine transaminase and alkaline phosphatase were normal. These patients were not taking any other drugs except the prescribed antitubercular treatment.

The patients were divided into two groups of 10 each. *Group I* received daily rifampicin (10 mg/kg), pyrazinamide (30 mg/kg) and INH (10 mg/kg) whereas *Group II* received all the above except that INH was given in a dose of 5 mg/kg. Medicines for 2 weeks were given to the patients after which they were asked to report back.

The patients were admitted to the hospital and fasted overnight. INH was given at 6 a.m. followed one hour later by rifampicin and 6 hour later by pyrazinamide. A standard breakfast meal was given at 8 a.m. Venous blood (1.5 ml) samples were collected at 0,1,2,3,6 and 24 h after INH administration. Serum was separated and deproteinized with 5% trichloroacetic acid solution within 4 h of collection.

The supernatant solution was stored at  $-20^{\circ}$  C, till further assay. INH was estimated by the micro-spectrofluorometric method of Miceli *et al.*(10) using a spectrofluorometer model SFM-25, Kontron Instruments. The sensitivity of the method was 0.01ug/ml. The standard curve showed linearity over a concentration of 0.05-10 ug/ml. The reading was obtained at an excitation and emission wavelength of 392 and 478 nm, respectively.

The patients were then called every two weeks for six months to assess for clinical improvement and the occurrence of any side effects. The pharmacokinetic analysis of INH was undertaken using a computer software program 'Pharmkit' based on an open two-compartment model.

#### Statistical Analysis

The results are expressed as mean  $\pm$  SEM. Students 't' test for unpaired data was used for comparison and the differences considered significant when  $p < 0.01$

#### Results

The mean serum concentration-time profile of INH in the two groups of patients is shown in *Fig. 1*. The serum concentration, was predictably and significantly higher throughout the 24 h period in Group I. In this group at 6 h the serum INH concentration was  $2.69 \pm 0.44$  ug/ml (range 0.46-5.01 ug/ml), in Group II at 6 h the serum concentration was  $1.31 \pm 0.08$  ug/ml (range 0.72-1.72 ug/ml). The mean serum concentrations of INH in both the groups were within or above the minimum inhibitory concentration (MIC) range of 0.025-0.05 ug/ml for INH throughout the observed 24 h period (*Table I*). The minimum serum INH concentration ( $C_{\min}$ ) was within the MIC required for the tuberculostatic effect of INH in 18 patients. One patient in each group had  $C_{\min}$  below

the MIC (Fig. 2). In these patients, however, it was observed that the serum concentration at 6 h was much higher than the required therapeutic range of 0.5-3 ( $\mu\text{g}/\text{ml}$  of INH(5).

The other pharmacokinetic parameters, including time to achieve peak concentration ( $T_{\text{max}}$ ), elimination half life ( $t_{1/2}$  elim), mean residence time (MRT), elimination rate constant ( $k$ ), volume of distribution at steady state ( $V_{\text{ss}}$ ) and plasma clearance (CL) did not differ significantly between Groups I and II (Table I).

Symptomatic improvement was observed in all patients on a follow up of 6 mo. They were afebrile and an increase in appetite was reported. Weight gain was observed in 16 of 20 patients. Radiological improvement was seen in all subjects.

## Discussion

Age is an important factor capable of significantly altering the kinetic profile of an individual drug and hence its effect. Drug therapy in infancy and childhood

requires special dose calculation due to continuous change in body weight and body composition(11,12). Such changes may significantly influence relative disposition of drugs and their side effects.

Most studies on antitubercular drugs have been conducted in adults(7,13,14). The clinical efficacy and spectrum of INH as an antitubercular drug has also been based on studies in adults. The pediatric dose has mostly been extrapolated from these studies.

The response to treatment with INH is related to peak concentration attained in the serum(15). The growth of tubercle bacilli is inhibited soon after the start of chemotherapy with INH and no further multiplication occurs during treatment. The suitability of INH depends principally upon the length of time the bacterial multiplication is inhibited after exposure to the drug(16). It has been reported that a serum concentration of 0.5-3  $\mu\text{g}/\text{ml}$  maintained for at least 6 h a day is adequate in achieving good therapeutic results(5). All the 20

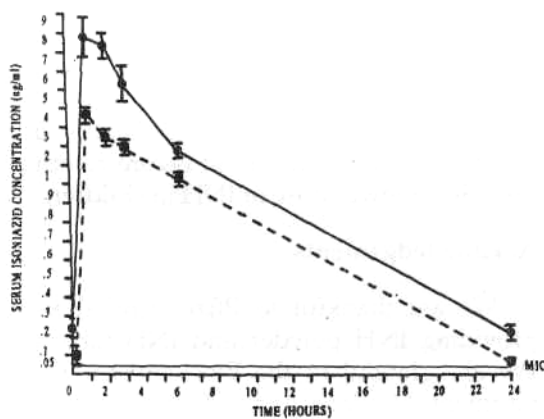


Fig. 1. Serum concentration time curve of INH in a dose of 10 mg/kg (.) and 5 mg/kg (-). Each point represents mean  $\pm$  SEM ( $n=10$  each group).

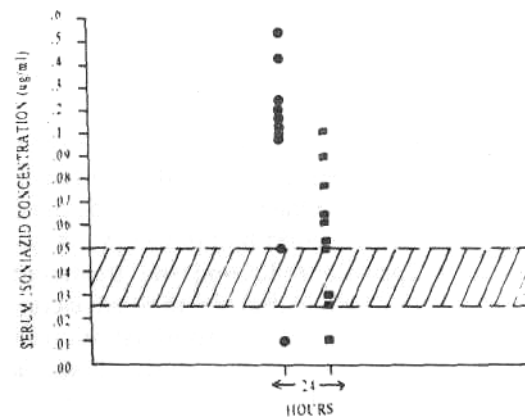


Fig. 2. Serum INH concentration ( $\mu\text{g}/\text{ml}$ ), at 24 hours. The shaded area indicates the minimum inhibitory concentration of INH for *Mycobacterium tuberculosis*; (.) 10 mg/kg; (-) 5 mg/kg.

TABLE I—INH Pharmacokinetics in Children with Pulmonary Tuberculosis

Pharmacokinetic parameter	Unit	Group I (10 mg/kg)	Group II (5 mg/kg)
Maximum plasma concentration	µg/ml	10.10±0.88	4.75±0.31*
Time to achieve maximum plasma concentration	h	1.40±0.16	1.20±0.20
Minimum plasma concentration	µg/ml	0.21±0.05	0.06±0.01**
Area under the plasma concentration time curve from zero to twenty four hours	µg/h/ml	61.29±7.39	26.57±1.92**
Area under the plasma concentration time curve from zero to infinity	µg/h/ml	63.01±7.51	27.91±1.64**
Elimination half life	h	4.61±0.59	3.77±0.23
Mean residence time	h	5.29±0.53	4.83±0.25
Elimination rate constant	per h	0.17±0.02	0.19±0.01
Volume of distribution at steady state	L	20.68±4.17	26.7±5.76
Plasma drug clearance	ml/min	53.30±10.62	62.69±7.69

\* p <0.01; \*\* p <0.001

patients in the present study had serum INH levels, well above this required therapeutic range after 6 h. Even 24 hours after drug administration, 18 out of 20 patients had serum INH concentration within or above the MIC, for *Mycobacterium tuberculosis*(2).

$T_{max}$  was in the range of 1-2 h in 19 of 20 patients and conforms to that reported in the literature(2). One patient had a delayed  $T_{max}$  at 3 h. This child had developed a voracious appetite following the treatment and it was possible that she may have consumed food prior to the administration of INH on the day of the study. Food is known to delay absorption of INH(17).

Our findings suggest that effective, therapeutic blood levels are achieved with a lower dose of 5 mg/kg of INH. The pharmacokinetics in the 2 groups

receiving INH in either 5 or 10 mg/kg per day were comparable. No obvious adverse effects were reported. A dose of 5 mg/kg INH is adequate for treatment of pulmonary tuberculosis when administered with other anti-tubercular drugs. However, more studies involving a larger sample size and correlation with the acetylator status in children need to be carried out before recommending a lower dose of INH in children.

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