# Pharmacokinetics of isoniazid in Indian children with tuberculosis on daily treatment

I. Shah,* N. Jadhao,* N. Mali,† S. Deshpande,† N. Gogtay,† U. Thatte†

*Paediatric Tuberculosis Clinic, Department of Paediatrics, B J Wadia Hospital for Children, Mumbai, †Department of Clinical Pharmacology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, India

——————————— S U M M A R Y

OBJECTIVE: To assess the pharmacokinetics of isoniazid (INH) at 10 mg/kg/day among Indian children.
METHODS: INH levels were estimated using liquid chromatography-tandem mass spectroscopy in 35 children aged 1–15 years on daily anti-tuberculosis treatment. Blood samples were collected 0, 1, 2, 3, 6 and 24 h after INH administration. The maximum concentration ($C_{max}$) and area under the curve ($AUC_{0-24}$) were determined. The normal therapeutic range for $C_{max}$ is 3–5 µg/ml. An AUC of <10.52 µg•h/ml for INH is low.
RESULTS: The mean $C_{max}$ was 8.3 ± 4.28 µg/ml and was attained in 1.22 ± 0.5 h, with a median time to $C_{max}$ ($T_{max}$) of 1 h. The mean AUC for INH was 46.23 ± 34.82 µg•h/ml. Children aged 1–4.9 years, 5–10 years and >10 years had a mean $C_{max}$ of respectively 9.87 ± 5.75 µg/ml, 7.62 ± 3.37 µg/ml and 7.21 ± 2.50 µg/ml

($P = 0.08$) and a mean AUC of respectively 60.97 ± 49.90 µg•h/ml, 38.95 ± 22.28 µg•h/ml and 36.09 ± 13.56 µg•h/ml ($P = 0.29$). The mean $C_{max}$ in children taking fixed-drug combinations and individual drugs was respectively 9.07 ± 4.67 µg/ml and 7.43 ± 3.71 µg/ml ($P = 0.26$); the mean AUC was respectively 50.48 ± 38.38 µg•h/ml and 41.20 ± 30.52 µg•h/ml ($P = 0.44$). Two children had hepatitis.
CONCLUSION: Most Indian children had higher than normal INH AUC and $C_{max}$ values. It is necessary to determine the ideal dose of INH in Indian children using the genotypic acetylator status of the patients and pharmacokinetic toxicity analysis.
KEY WORDS: INH; isoniazid; pharmacokinetics; children; India

TUBERCULOSIS (TB) is a widespread disease in India, with the highest incidence in the 5–20 years age group.[1] Isoniazid (INH) is one of the key components of anti-tuberculosis treatment regimens.[2,3] INH, an organic compound also known as iso-nicotyl-hydrazine, is bactericidal to rapid-growing mycobacteria, but bacteriostatic to slow-growing mycobacteria.[4,5] INH acts by inhibiting the synthesis of mycolic acid, which is required for mycobacterium cell wall synthesis.[1]

Response to INH treatment is related to the peak concentration attained in blood serum. To achieve steady-state pharmacokinetic (PK) levels of various anti-tuberculosis drugs in children, given the risk of drug-induced hepatotoxicity, the World Health Organization (WHO) recommends INH at 10 mg/kg (range 10–15 mg/kg), with a maximum dose of 300 mg/day.[6.] In Indian children, INH attains a much higher serum concentration than the normal therapeutic range (3–5 µg/l) for maximum plasma concentration ($C_{max}$) following a dose of 10 mg/kg.[7] Another Indian study also found that a daily dose of

5 mg/kg/day appears to be adequate for the treatment of pulmonary TB (PTB) in children.[1] Studies conducted in African children have reported that children metabolise INH faster than adults, and require a higher dose of INH.[3] However, PK data on INH in Indian children is lacking and most PK analyses have been conducted in children on a thrice-weekly regimen.[8,9] Three studies from North India analysed INH levels in children on daily INH treatment at 10 mg/kg/day, and found the $C_{max}$ to range from 3.4 µg/ml to 10.10 µg/ml and the area under the curve (AUC) to range from 7 µg•h/ml to 61.29 µg•h/ml.[1,7,10] Upon comparing INH 5 mg/kg/day to INH 10 mg/kg/day, Roy et al. found that the AUC and $C_{max}$ of INH were above the therapeutic range in both groups; they suggested that INH 5 mg/kg/day is adequate for PTB treatment in Indian children.[1]

We undertook a study to assess PK of INH at steady state after oral administration of INH 10 mg/kg/dose in Indian children with TB as few studies in Indian children on daily INH treatment have been conducted.

## MATERIALS AND METHODS

### Patients

Children aged 1–15 years with TB on anti-tuberculosis treatment for a minimum of 2 weeks and up to 4 months after treatment initiation referred to the paediatric TB clinic at B J Wadia Hospital for Children, Mumbai, India, were included in the present study. Patients were excluded if they were aged >15 years, had a history of liver or kidney disease, were human immunodeficiency virus infected, were on drugs that interfered with the metabolism of anti-tuberculosis drugs or were deemed by the treating physician to be medically unfit for participation. The study protocol was approved by the Ethics Committee of the Seth Gordhandas Sunderdas Medical College, Mumbai, India.

The TB treatment regimen was administered in accordance with WHO guidelines,[6] either in fixed-dose combinations (FDCs) or as a single-drug regimen. TB diagnosis was made on clinical grounds or was bacteriologically confirmed.[11] Malnutrition was defined as weight-for-age <2 standard deviation (SD), in accordance with WHO guidelines.[12] The children were fasting at the time of dosing, but were fed 1 h after drug administration. Crushed tablets were mixed in 5 ml of water and the dose was adjusted in millilitres to give 10 mg/kg/day. Patients were on concomitant rifampicin (RMP) at the time of taking INH. However, other anti-tuberculosis drugs were taken after a gap of 4–6 h.

### Sample size

Using the formula for sample size calculation [$N = Z^2 * CV^2/(\%^2)$], where $N$ is the sample size; $Z$, the value associated with the desired level of confidence ('$z$' equal to 1.96 was used to establish 95% confidence intervals); CV, the coefficient of variation, and %, the percentage deviation from the mean, the CV for INH ranged around 9% and percentage deviation from the mean was ~3% for INH.[13] The required sample size was thus determined to be 35.

### Pharmacokinetic sampling and bioanalysis

On the day of blood collection, the daily dose of INH was given at 8 am. To estimate INH levels, six blood samples of 2 ml each were collected at 0 h (baseline) and at 1, 2, 3, 6 and 24 h after INH administration. Blood collected at 0 h before INH administration was also tested for markers of liver function. At each point, blood samples were immediately centrifuged and serum samples stored at −20°C at the hospital for 24–48 h. The stored serum samples were then transferred to the Department of Clinical Pharmacology, King Edward Memorial Hospital, Mumbai, for estimation of INH levels using liquid chromatography-tandem mass spectroscopy (LC-MS/MS).[3] The

method for estimating INH levels was validated in accordance with the US Food and Drug Administration's guidance on bioanalytical method validation.[14]

### Pharmacokinetic analysis

The lower limit of quantification (LLOQ) for INH in plasma was 0.5 μg/ml; that for the high quality control (HQC) was 40 μg/ml. Linearity was assessed over a range of 0.1 μg/ml to 60 μg/ml. The intra- and inter-day variability of INH in plasma was within 15% of CV. Only internally prepared INH, five sets each of LLOQ (0.5 μg/ml), medium quality control (MQC; 10 μg/ml) and HQC (50 μg/ml) were assessed during the intra- and inter-day validation programme. Internally prepared QC standards were used during sample analyses. All plasma samples were extracted using the liquid-liquid extraction technique, and quantification was performed using LC-MS/MS. The INH and internal standard (phenacetin) response was obtained in the 'area' from the LC-MS/MS instrument. These responses were quantified using a calibration standard curve to obtain QC concentrations and patient samples in μg/ml.

The PK parameters, $C_{max}$ and time to $C_{max}$ ($T_{max}$), were determined by visual inspection of the data. The linear trapezoidal approach was used to estimate AUC in the absorption phase, and the logarithmic trapezoidal method in the excretion phase. INH half-life (t1/2) was calculated by plotting INH concentration against time interval and estimating the elimination. The actual values for plasma concentrations at various time points as determined using LC-MS/MS were considered for analysis. The normal therapeutic range of $C_{max}$ is considered to be 3–5 μg/ml.[3,7] AUC associated with 90% of the maximal killing of metabolically active bacilli present in sputum during the first 2 days of anti-tuberculosis treatment (EB$_{90}$) is reached at an INH AUC of 10.52 mg*h/l.[15] An INH level <10.52 mg*h/l was therefore considered to be low. The normal range of the minimum inhibitory concentration (MIC) was considered to be 0.025–0.05 μg/ml.[5]

### Determination of acetylator status

The PK of INH is strongly dependent on genetic polymorphism in $N$-acetyltransferase, a phase II metabolic enzyme.[16] We determined the acetylator status phenotypically from INH t1/2, as described in a population that included children.[17] Patients with an INH t1/2 of <1.8 h were considered to be fast acetylators and those with an INH t1/2 of >1.8 h were classified as slow acetylators.[17]

### Statistical analysis

Statistical analysis was performed using SPSS v 20 (IBM, Armonk, NY, USA). Continuous variables are described using summary statistics (number of observations, mean and SD). Categorical values were

**Table**   Effect of various parameters on $C_{max}$ and AUC

|  | Cases (n = 35) n | AUC µg•h/ml mean ± SD | AUC µg•h/ml median | $C_{max}$ µl/ml mean ± SD | $C_{max}$ µl/ml median | P value |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| Male | 19 | 49.7 ± 43.22 | 34.31 | 8.71 ± 5.18 | 7.57 | 0.56 |
| Female | 16 | 42.06 ± 21.74 | 41.76 | 7.86 ± 2.97 | 9.07 | |
| **Age group, years** | | | | | | |
| <5 | 13 | 60.97 ± 49.90 | 52.87 | 9.87 ± 5.75 | 9.09 | 0.08 |
| 5–10 | 11 | 38.95 ± 22.28 | 37.59 | 7.62 ± 3.37 | 7.05 | |
| >10 | 11 | 36.09 ± 13.56 | 34.31 | 7.21 ± 2.50 | 7.13 | |
| **Type of TB** | | | | | | |
| Pulmonary | 12 | 37.61 ± 18.49 | | 7.6 ± 2.60 | | 0.29 |
| Extra-pulmonary | 22 | 51.17 ± 41.41 | | 8.69 ± 5.06 | | |
| **Drug formulation** | | | | | | |
| FDC | 19 | 50.48 ± 38.38 | 42.32 | 9.07 ± 4.67 | 9.01 | 0.26 |
| Single-drug | 16 | 41.20 ± 30.52 | 32.6 | 7.43 ± 3.71 | 6.72 | |
| **Breaking of tablets** | | | | | | |
| Yes | 15 | 52.59 ± 48.47 | 34.31 | 8.84 ± 5.58 | 8.11 | 0.54 |
| No | 20 | 41.47 ± 19.58 | 38.53 | 7.93 ± 3.07 | 8.30 | |
| **Nutrition** | | | | | | |
| Malnourished | 11 | 40.25 ± 20.22 | 40.25 | 8.17 ± 3.30 | 8.30 | 0.88 |
| Healthy | 24 | 48.98 ± 39.87 | 35.95 | 8.39 ± 4.72 | 7.86 | |

$C_{max}$ = maximum concentration; AUC = area under the curve; SD = standard deviation; TB = tuberculosis; FDC = fixed-drug combination.

summarised using frequencies and percentages. Comparisons of AUC and $C_{max}$ in subgroup analysis in terms of age, sex, split tablets, FDCs and nutrition status were performed using the Kruskal-Wallis test or Mann-Whitney test. All P values were reported based on a two-sided significance test, and P < 0.05 was considered significant. Incidence of hepatitis (alanine transaminase [ALT] >3 times the upper limit of normal or bilirubin >2 mg/dl) was noted.

## RESULTS

The male:female ratio was 19:16. The age range was between 1 and 14 years, with 13 (37.2%) children aged 1–4.9 years, 11 (31.4%) aged 5–10 years and 11 (31.4%) aged >10 years. Twelve (34.3%) children had PTB, 22 (62.9%) had extra-pulmonary TB (EPTB) and 1 (2.8%) had latent tuberculous infection. Among those with EPTB, 7 (31.9%) patients had lymph node TB, 4 (18.2%) had bone TB, 7 (31.9%) had tuberculous meningitis (TBM), 2 (9.1%) had tuberculomas and 2 (9.1%) had epididymal TB. Twenty-five (71.4%) patients were in the intensive phase of anti-tuberculosis treatment and 10 (28.6%) were in the continuation phase. Nineteen (54.2%) received FDC and 16 (45.7%) were on individual drugs. Twenty (57.1%) patients swallowed the whole tablet; tablets had to be split before consumption for 15 (42.9%) patients. Three (8.6%) children had increased levels of ALT on the day of PK sampling, one of whom was found to have hepatitis A co-infection. Thus, 2 (5.7%) children were suspected to have drug-induced hepatitis. Malnutrition was present in 11 (31.4%) patients. The mean dose of INH given to patients was 9.93 ± 1.16 mg/kg/day.

The INH concentration at one time-point could not be analysed in three patients due to haemolysis of the blood sample (Patient 1, baseline sample; Patient 2, sample at 3 h; and Patient 3, sample at 24 h). The mean $C_{max}$ was 8.3 ± 4.28 µg/ml (median 8.11, range 2.88–24.74). The mean $T_{max}$ was 1.22 ± 0.5 h (median 1 h). Twenty-seven (77.1%) patients had $C_{max}$ more than the recommended therapeutic range of 3–5 µg/ml, 7 (20%) had $C_{max}$ within the therapeutic range and 1 (2.9%) had $C_{max}$ below the therapeutic range. All patients had an INH concentration above the recommended MIC. The mean AUC was 46.23 ± 34.82 µg•h/ml (median 38.53, range 6.63–192.11). The mean t1/2 was 2.45 ± 1.17 h (median 2.32, range 01.16–6.68). The effect of various parameters, such as age and sex, on $C_{max}$ and AUC are given in the Table.

Nine (25.7%) children were fast acetylators and 26 (74.3%) were slow acetylators. $C_{max}$ and AUC in fast acetylators was respectively 6.15 ± 2.74 µg/ml and 20.18 ± 9.03 µg•h/ml compared with $C_{max}$ 9.08 ± 4.50 µg/ml and AUC 55.25 ± 35.98 µg•h/ml in slow acetylators (P = 0.07 and P = 0.007, respectively). The mean t1/2 in fast acetylators was 1.39 h compared with 2.8 h in slow acetylators.

Three patients developed hepatitis. The mean dose of INH in these patients was 10.43 ± 0.75 mg/kg; the mean ALT level was 130.3 ± 14.6 units. The average AUC in children with hepatitis was 36.71 ± 27.53 µg•h/ml and mean $C_{max}$ was 6.73 ± 3.75 µg/ml compared with AUC 47.13 ± 35.66 µg•h/ml and $C_{max}$ 8.47 ± 4.35 µg/ml in children without hepatitis. No correlation was observed between the AUC and $C_{max}$ of children with drug-induced hepatitis and those without hepatitis.

## DISCUSSION

The mean $C_{max}$ was higher than required in 77.1% of patients. $C_{max}$ was attained within 1.23 h of drug ingestion. Only one patient had subtherapeutic $C_{max}$. Patients on daily treatment with INH 10 mg/kg/day achieved a higher $C_{max}$ than what is required. Whether this means that the dose should be reduced in patients on daily INH treatment needs to be assessed further. Similar results were obtained in Roy et al.'s study, in which a dose of INH 5 mg/kg/day had a $C_{max}$ of 4.75 µg/ml and AUC of 26.57 µg•h/ml, and a dose of 10 mg/kg/day had a $C_{max}$ of 10.1 µg/ml and AUC of 61.29 µg•h/ml. In both groups, $C_{max}$ was higher than normal.[1] The WHO[18] recommends increasing the INH dose from 5 mg/kg/day to 10 mg/kg/day based on data from African populations;[3,19] however, whether this recommendation is applicable to Indians, who have a different ethnicity, must be assessed. Most of the study patients were slow acetylators, and this could be one of the reasons why $C_{max}$ was higher in these patients. Singh et al. found that the distribution of slow, intermediate and fast acetylators was respectively 55%, 32% and 13% in an Indian population when tested for *NAT2* polymorphisms.[20]

INH AUC in Indian adults is usually 30.63 ± 12.98 µg•h/ml.[21] Indian studies have found AUC in children to vary from 1.5 µg•h/ml to 26.57 µg•h/ml for patients on 5 mg/kg/day, and from 7 µg•h/ml to 61.29 µg•h/ml for patients on 10 mg/kg/day.[1,7,10] Rangari et al. showed that AUC and $C_{max}$ was higher in children who received INH 10 mg/kg and lower in those who receive INH <10 mg/kg/day.[22] Schaaf et al. reported that AUC in slow acetylators among South African children was 8.35 µg•h/ml, and 5.3 µg•h/ml in fast acetylators.[3] In another study among African children where INH was given at a dose of 5 mg/kg/day, AUC was 10.6 µg•h/ml in slow acetylators and 2.3 µg•h/ml in fast acetylators.[19] In a study from Malawi, where INH was given at a dose of 10 mg/kg/day, AUC was 11.48 µg•h/ml and $C_{max}$ was 3.37 µg/ml.[23] In our study, AUC was 55.52 ± 35.97 µg•h/ml and $C_{max}$ 9.08 µg/ml in slow acetylators and AUC 20.18 ± 9.07 µg•h/ml and $C_{max}$ 6.14 µg/ml in fast acetylators, which is higher than in the South African studies. Pea et al. found an AUC of 16.5 µg•h/ml in fast acetylators on 5 mg/kg/day and 36.42 µg•h/ml in slow acetylators, suggesting that slow acetylators may need INH at 5 mg/kg/day.[13] Our results are consistent with the studies by Seth et al.[7] and Roy et al.,[1] both of which suggested that INH <10 mg/kg/day may be needed for Indian children, as most are slow acetylators.[20]

Most of the studies mentioned above used high-performance liquid chromatography to estimate AUC and $C_{max}$, whereas our study was conducted using LC-MS/MS. Among the various methods used to measure plasma drug levels, LC-MS/MS is the most sophisticated and sensitive, and only a few studies in children with TB have used this assay.[3,19] A study by the All India Institutes of Medical Sciences, New Delhi, India, conducted in children on daily INH treatment at 5 mg/kg/day and at 10 mg/kg/day that measured AUC up to 4 h post-ingestion found the AUC to be respectively 1.5 µg•h/ml and 7 µg•h/ml.[10] However, as AUC was calculated only up to 4 h post-ingestion, those results were not comparable to our study findings. As AUC in the study by Schaaf et al. was estimated at 2–5 h, results were not comparable with our study.[3] Mukherjee et al. found no association between low plasma drug concentrations and poor outcomes;[10] whether a higher dose of INH is required needs to be assessed, as most patients in India are slow acetylators.[20]

We did not find any difference between $C_{max}$ and AUC values in males and females, which is consistent with the study findings of Verhagen et al.[24] Schaaf et al.[3] and McIlleron et al.[19] reported that younger children metabolise and eliminate INH faster than older children and adults. Children aged <5 years had shorter INH t1/2 than the other two age groups; however, no statistically significant correlation was observed between the two age groups in their study,[15] suggesting faster metabolism of INH in this age group, although this needs to be confirmed by measuring INH elimination. Similar results were observed in our study, whereby $C_{max}$ and AUC decreased with increasing age. However, these results were not statistically significant. Unlike findings from other studies,[10,25] $C_{max}$ and AUC did not differ in children with PTB and EPTB.

The WHO has recently recommended using dispersible FDC tablets for paediatric patients; these are manufactured according to newly recommended specifications.[26,27] Several studies have reported that FDCs interfere with drug absorption compared with individual drugs.[28,29] In our study, no significant difference in $C_{max}$ or AUC values was observed between patients using FDCs and those on individual drugs.

Our study is the first of its kind to compare PK in patients who split tablets. Breaking tablets is common practice when administering anti-tuberculosis treatment in children, particularly in younger children with low weight. As both groups in our study had similar results, we conclude that FDCs can be used to reduce the pill burden and achieve better treatment adherence.

There is a close interaction between drug disposition and nutritional status. The pathophysiological changes associated with malnutrition can alter PK processes, drug responses and toxicity.[30] Various studies have shown that malnourished children achieve lower drug levels than healthy children.[3,25,31,32] However, our results showed no

difference in $C_{max}$ and AUC between malnourished and healthy children, in line with findings reported by Mukherjee et al.[10]

In our study, 8.6% children had increased ALT levels on the day of PK sampling, one of whom was found to have hepatitis A co-infection. Whether INH 10 mg/kg/day was responsible for hepatitis or whether other co-administered drugs such as RMP and pyrazinamide were also responsible needs to be assessed. Studies have shown that most patients with TB tend to develop hepatitis during the intensive phase,[33] and it is likely hepatitis is due to drugs other than INH. Although study patients had higher AUC and $C_{max}$, drug-induced liver injury was not observed. There was no clear dose-toxicity relationship in the case of INH-induced hepatotoxicity;[3] whether higher AUC or higher $C_{max}$ leads to hepatotoxicity thus could not be established.

Our study had limitations. We determined acetylator status based on t1/2 and not on the genotypic acetylator status of patients. We conducted the study with INH at only 10 mg/kg/day. It would be worthwhile to compare different doses of INH and the corresponding AUC and $C_{max}$ values. Therapeutic drug monitoring of other anti-tuberculosis drugs such as RMP and pyrazinamide were not assessed.

In conclusion, most Indian children on daily INH treatment of 10 mg/kg/day had higher INH AUC and $C_{max}$ values than the normal therapeutic range for $C_{max}$ (3–5 µg/l).

*Conflicts of interest:* none declared.

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**RÉSUMÉ**

OBJECTIF : Evaluer la pharmacocinétique de l'isoniazide (INH) à 10 mg/kg/jour parmi des enfants indiens.

MÉTHODE : Les niveaux d'INH ont été estimés par chromatographie liquide couplée à la spectrométrie de masse en tandem chez 35 enfants âgés de 1 à 15 ans sous traitement antituberculeux quotidien. Des échantillons de sang ont été recueillis à 0, 1, 2, 3, 6, 24 h après l'administration de l'INH. La concentration maximale ($C_{max}$) et la zone sous la courbe ($AUC_{0-24}$) ont été déterminées. La fourchette normale thérapeutique de la $C_{max}$ est de 3 à 5 µg/ml. L'AUC <10,52 µg•h/ml est faible.

RÉSULTATS : La $C_{max}$ moyenne a été de 8,3 ± 4,28 µg/ml et a été atteinte en 1,22 ± 0.5 h avec un temps nécessaire pour atteindre la $C_{max}$ ($T_{max}$) médiane à 1 h. L'AUC moyenne a été de 46,23 ± 34,82 µg•h/ml. Les

enfants entre 1 et 4,9 ans, entre 5 et 10 ans et au-dessus de 10 ans ont eu une $C_{max}$ moyenne de 9,87 ± 5,75 µg/ml, 7,62 ± 3,37 µg/ml et 7,21 ± 2,50 µg/ml ($P=0,08$) et une AUC de 60,97 ± 49,90 µg•h/ml, 38.95 ± 22.28 µg•h/ml et 36,09 ± 13,56 µg•h/ml, respectivement ($P=0,29$). La $C_{max}$ moyenne des enfants prenant des médicaments en combinaison à dose fixe et des médicaments séparés a été de 9,07 ± 4,67 µg/ml et 7,43 ± 3,71 µg/ml, respectivement ($P=0,26$) et l'AUC a été de 50,48 ± 38,38 µg•h/ml et 41,20 ± 30,52 µg•h/ml, respectivement ($P = 0,44$). Deux enfants avaient une hépatite.

CONCLUSION : La plupart des enfants indiens semblent avoir des niveaux d'AUC et de $C_{max}$ d'INH. Il est nécessaire de déterminer la dose idéale d'INH pour les enfants indiens en étudiant leur statut génotypique d'acétyleurs et l'analyse de toxicité pharmacocinétique.

**RESUMEN**

OBJETIVO: Evaluar las características farmacocinéticas de la isoniacida (INH) administrada en dosis de 10 mg/kg/día en los niños de la India.

MÉTODOS: Se determinaron las concentraciones de INH mediante cromatografía líquida y espectrometría de masas en tándem en 35 niños de 1 año a 15 años de edad que recibían tratamiento antituberculoso diario. Se obtuvieron muestras sanguíneas a las 0, 1, 2, 3, 6 y 24 h después de la administración de INH. Se determinaron la concentración máxima ($C_{max}$) y el área bajo la curva de concentración plasmática y tiempo de 0 a 24 h ($AUC_{0-24}$). El intervalo terapéutico normal de la $C_{max}$ es de 3–5 µg/ml. Un $AUC_{0-24}$ < 10,52 µg•h/ml se considera baja.

RESULTADOS: La $C_{max}$ promedio fue 8,3 ± 4,28 µg/ml y se alcanzaba en 1,22 ± 0,5 h con una mediana del tiempo máximo ($T_{max}$) de 1 h. El AUC promedio fue 46,23 ± 34,82 µg•h/ml. La $C_{max}$ promedio fue 9,87 ±

5,75 µg/ml en los niños de edad 1–4,9 años; 7,62 ± 3,37 µg/ml en los niños de 5–10 años; y 7,21 ± 2,50 µg/ml en los >10 años ($P=0,08$). En estos grupos el AUC fue 60,97 ± 49,90 µg•h/ml, 38,95 ± 22,28 µg•h/ml y 36,09 ± 13,56 µg•h/ml, respectivamente ($P = 0,29$). La $C_{max}$ promedio en niños que recibían asociaciones en dosis fijas fue 9,07 ± 4,67 µg/ml y en los que recibían fármacos individuales fue 7,43 ± 3,71 µg/ml ($P=0,26$) y el AUC fue 50,48 ± 38,38 µg•h/ml y 41,20 ± 30,52 µg•h/ml, respectivamente ($P = 0,44$). Dos niños presentaron hepatitis.

CONCLUSIÓN: La mayoría de los niños indios parece tener valores más altos del AUC y de la $C_{max}$ de INH. Es necesario determinar la dosis óptima de INH en los niños de la India, investigando el genotipo acetilador de estos pacientes y con análisis farmacocinéticos de toxicidad.