VALIDATION OF THE 10 MG/KG ISONIAZID DAILY DOSE IN YOUNG INFANTS. NON-COMPARTMENTAL PHARMACOKINETIC ANALYSIS OF EXPERIMENTAL DATA

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Introduction

In 2010, increased daily doses of first-line anti-tuberculosis medicines in children were recommended by WHO. Isoniazid (INH) daily dose was increased from 5 to 10-15 mg per kg of body weight; the 10 mg/kg once-daily INH dose has been validated in infants aged >3 months. However, *"The Committee acknowledged the WHO conclusion that no dosing recommendation can be made in children less than three months due to the lack of specific data*".

We aimed to characterize the pharmacokinetics of the once-daily isoniazid dose at 10 mg/kg of body weight in children aged less than 6 months.

Methods

We aimed to document the pharmacokinetics of INH in neonates (n=8, Group A) and infants 1-3 months (n=8, Group B), as compared to a control group of infants aged 3-6 months (n=16, Group C) in a multicentric cross-sectional post-authorization observational study (EPA-OD) in Spain. We investigated as well the effect of clinical covariates, including age, gender, nutritional status, type of TB infection, concomitant treatment with other anti-TB drugs and the N-acetyltransferase 2 (NAT2) acetylator status.

Blood samples were drawn at 1, 3 and 6 or 2, 4 and 8 hours following INH dosing. The maximum drug concentration (Cmax; main objective: Cmax over 3 mg/L, as per adult PK/PD studies) in serum, the time to Cmax (tmax) and the area under the concentration-time curve (AUC) were calculated. The NAT2 gene was analyzed to determine the acetylation status. Data were analyzed using the non-compartmental pharmacokinetic software Winonlin®.

Conclusions

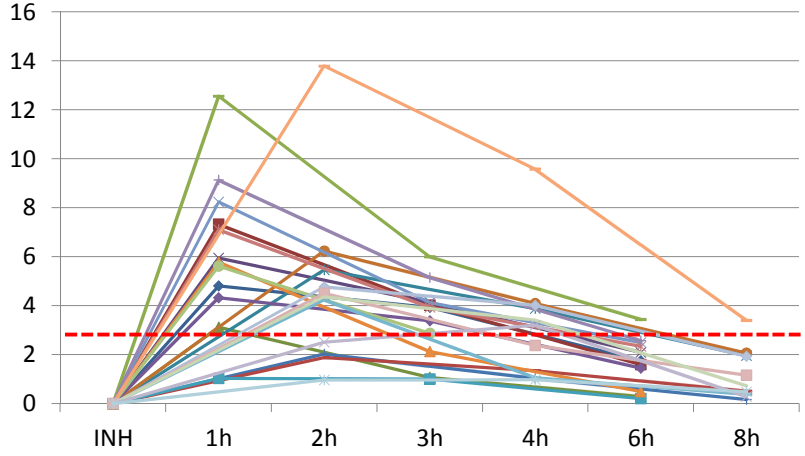
In our series of young infants receiving the currently recommended dose of INH, no major safety concerns were raised.

Target INH adult levels were not reached in 17% of cases and we could not identify any associated risk factor.

Results

Twenty-three pharmacokinetic profiles were performed in 20 infants (8 females) at a median (IQR) age of 19.0 (12.6-23.3) weeks, treated because of primary chemoprophylaxis (n=14) or tuberculosis (n=6). According to NAT2 genotypes, the acetylator status were homozygous fast (n=1), heterozygous intermediate (n=13) and homozygous slow (n=7).

Non-compartmental pharmacokinetic analysis showed a median (IQR) isoniazid Cmax of 4.80 (3.72-6.67) mg/L and in 4 cases (17.4%) the Cmax >3 mg/L target recommended in adults was not reached. Median (IQR) isoniazid area under the concentration-time curve and half-life were 23.50 (13.36-36.65) mg*h/L and 2.92 (2.01-3.17) hours, respectively.



Age at assessment or acetylator status had no impact on Cmax values, but a trend towards larger isoniazid AUC (p=0.053) and longer half-life (p=0.057) was observed in homozygous slow acetylators.

Treatment was well tolerated in all patients and mildly elevated levels of alanine aminotransferase (range, 61-76 UI/L) were observed in 3 out of 22 cases (13.6%).

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