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Clinical Pharmacology of Isoniazid in Infants and Children

Gian Maria Pacifici*

Associate Professor of Pharmacology, via Saint Andrea 32, 56127 Pisa, Italy

Abstract

Isoniazid (isonicotinic acid hydrazide), is used, with pyrazinamide or rifampin, in the primary treatment and re-treatment of tuberculosis. Tuberculosis is still the most important infectious killer of humans. Isoniazid is bacteriastatic, and at high concentrations, is bactericidal against Mycobacterium tuberculosis. This antibiotic enters bacilli by passive diffusion, and is activated to its toxic form with the bacillus by KatG, multifunctional catalyses-peroxidise. Isoniazid is metabolized to acetylisoniazid by N-acethyltransferase-2, which is polymorphic. Acetylisoniazid formation rate is higher in faster than slower acetylators. Thus, isoniazid plasma concentration is lower in faster than slower acetylators, and this has therapeutic implications: isoniazid half-life is shorter in faster than slower acetylators. Isoniazid doses are 5 mg/kg, for the treatment of neonatal prophylaxis, 10 mg/kg, for treatment of neonatal latent tuberculosis infection, and 10 to 20 mg/kg in children. Isoniazid half-lives are 2 to 5 hours in infants and 1.5 to 2.5 hours in children. This antibiotic is safe in children; however increase of hepatic transaminase activities and excretion of vitamin B6 has been reported. Isoniazid migration into the breast-milk is poor and isoniazid concentration is not enough for tuberculosis prevention and prophylaxis. Infants, which are tuberculous-infected, should require appropriate antituberculosis chemotherapy. Isoniazid penetration into the cerebrospinal fluid is poor; however, isoniazid concentration is well above the MIC for Mycobacterium tuberculosis. Concomitant administration of isoniazid and rifampin induces hepatotoxicity in children. Isoniazid pharmacokinetics have been extensively studied in infants and children. Several bacteria may become resistant to isoniazid and the consequent isoniazid-resistance is an obstacle to treatment of tuberculosis. The aim of this study is to review the published data of isoniazid effects, metabolism, pharmacokinetics, and bacteria-resistance in infants and children.

Keywords: Isoniazid, effects, Metabolism, Pharmacokinetics, Bacteria-resistance, N-acetyltransferase-2, Acetylisoniazid, Infants, Children

Introduction

Isoniazid (isonicotinic acid hydrazide) is used, with pyrazinamide or rifampin, in the primary treatment and re-treatment of tuberculosis. Tuberculosis is still the most important infectious killer of humans. Guidance of dosing varies widely. Infants who come into contact with a case of active tuberculosis also merit prophylaxis. Isoniazid is bacteriastatic, and at high concentrations, is bactericidal against Mycobacterium tuberculosis. This antibiotic is active against both intracellular and extracellular bacilli, but resistance develops when given on its own, and at least another antibiotic, is always administered. A 9-month course of isoniazid monotherapy has long been the standard approach for latent infection, but studies in adults and children suggest that a 3- or 4-month course of isoniazid and rifampin may be better tolerated. There is no evidence that isoniazid is teratogenic. Isoniazid is safe in children, but isoniazid treatment increases the hepatic transaminase activities and the excretion of vitamin B6. Women should take 10 mg of pyridoxine, once-daily, in pregnancy and breastfeeding her infant. During lactation, the infant receives up to 20% of the maternal dose, on a weight-for-weight basis. Isoniazid is well absorbed after oral administration and excreted in the urine after inactivation in the liver. The half-life is long at birth (2 to 5 hours) but is substantially shorter in children (1.5 to 2.5 hours). Isoniazid is inactivated by N-acetyltransferase-2, which is polymorphic, faster acetylators eliminate isoniazid twice as faster as slow acetylators. Liver toxicity is not common in children but appears related to high-dose treatment and when combined with rifampin, and it is probably more common in slow acetylators. Haemolytic anaemia and agronuloytosis are rare complications, while a lupus-like syndrome, liver damage and gynaecomastia have been reported in adults. Treatment should stop and reviewed if toxicity is suspected. Use of isoniazid is usually contraindicated in patients with drug-induced liver disease and porphyria. Malnourished children also benefit from prophylactic pyridoxine, especially in the first year of life. Isoniazid can potentiate the effect of carbamazepine and phenytoin to the point where toxicity develops [1].

Neonatal prophylaxis

Give infants exposed to infection 5 mg/kg once a day by mouth. Dose adjustment is not necessary for poor renal function. If the infant is tuberculin negative at 3 months treatment can be stopped and Bacille Calmette-Guèrin given. Treat for 6 months if the tuberculin test is positive [1].

Correspondence to: Gian Maria Pacifici, Associate Professor of Pharmacology, via Saint Andrea 32, 56127 Pisa, Italy, Tel: 3388250108; Email: pacifici44@tiscali.it

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Treating latent infection

Give 10 mg/kg of isoniazid and 10 mg/kg of rifampin once a day for 3 months [1].

Treating overt infection

Give infants, over a month old 10 mg/kg once a day by mouth [1].

Isoniazid is an important antibiotic for the chemotherapy of drug-susceptible bacteria strain. All infected children should receive isoniazid in isoniazid-sensitive strains of the tubercle bacillus. The use of combination therapy (isoniazid + pyrazinamide + rifampin) provides the basis for short-course therapy and improves therapy. Isoniazid enters bacilli by passive diffusion. The drug is not directly toxic to the bacillus but must be activated to its toxic form with the bacillus by KatG, multifunctional catalyses-peroxidise [2]. KatG catalyzes the production of an isonicotinoyl radical, from isoniazid, that subsequently interacts with mycobacterial NAD and NAPD to produce a dozen adducts [3]. One of these, a nicotinoyl-NAD isomer, inhibits the activities of enoyl acyl carrier protein reductase (InhA) and KasA. [4]. Inhibition of these enzymes inhibits synthesis of mycolic acid, an essential component of the mycobacterial cell wall, leading to bacterial cell death. Another adduct, a nicotitinoyl-NDAP isomer, potently inhibits (K_i < 1 nM) mycobacterial dihydrofolate reductase, thereby interfering with nucleic acid synthesis [3]. Other products of KatG activation of isoniazid include superoxide, H_2O_2, alkyl hydroperoxides, and the NO radical, which may also contribute to the mycobactericidal [5]. Mycobacterium tuberculosis could be especially sensitive to damage from these radicals because the bacilli have a defect in the central regulator of the oxidative stress response *oxy*R. Backup defence against radicals is provided by alkyl hydroperoxide reductase (encoded by *ahp*C), which detoxifies organic peroxidises. Increased expression of *ahp*C reduces isoniazid effectiveness. The isoniazid MICs, with clinical Mycobacterium tuberculosis strains vary from country to country. In the US, for example, the MICs are 0.025 to 0.05 µg/ml against Mycobacterium bovis and Mycobacterium kansasii. Isoniazid has poor activity against Mycobacterium avium complex. It has no activity against any other microbial genus. Isoniazid bioavailability, following oral administration, absorption rate is about 100% for 300 mg dose [2]. Isoniazid pharmacokinetics are best described by a two-compartment model [6]. The ratio of isoniazid in the epithelial lining fluid to that in plasma is 1 to 2 and for cerebrospinal fluid is 0.9 [7]. Approximately 10% of isoniazid is bound to protein. From 75% to 95% of isoniazid dose is excreted in the urine within 24 hours, mostly as acetylisoniazid and isoninicotinic acid. Isoniazid is metabolized by hepatic arylamine NAT2, encoded by a variety of N-acetyltransferase-2 (NAT2)* alleles. Isoniazid clearance in patients has been traditionally classified as: "slow" and "fast" acetylators. Recently, the phenotypic groups have been expanded to fast, intermediate, and slow acetylators, and isoniazid population pharmacokinetic parameters have been estimated and related to NAT2* genotype, and the number of NAT2*4 alleles accounts for 88% of variability of isoniazid clearance. The frequency of each acetylation phenotype is not influenced by sex or age. Fast acetylation is the predominant in Inuit and Japanese. Slow acetylators are the predominant phenotype in most Scandinavians Jews, and North African whites [7]. The high N-acethyltransferse-2 activity is inherited as an autososomal dominant trait, fast isoniazid acetylators. Isoniazid microbial kills, as well as resistance emergence, is best explained by the ratios of $AUC_{0\text{-}24\ hours}$ to MIC and C_{pma}/MIC [6, 8]. Because AUC is proportional to dose/clearance, this means that efficacy is most dependent on drug dose and clearance and thus on the activity of NAT2 polymorphic forms. Thus, rapid acetylators are more likely to have reduced microbial cure, increased relapse, and increased acquired resistance [9]. Isoniazid is available as a pill, as an elixir, and for parental administration.

Literature search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was July 2019. The following key words: "isoniazid infants effects", "isoniazid children effects", "isoniazid infants metabolism", "isoniazid children metabolism", "isoniazid infants pharmacokinetics", "isoniazid children pharmacokinetics", "isoniazid infants resistance", and "isoniazid children resistance" were used. In addition, the book Neonatal Formulary [1] was consulted. The manuscript is prepared according to the "Instructions for Authors".

Results

Isoniazid efficacy and safety in infants and children

le Roux et al. [10] investigated the incidence of and risk factors for severe liver injury in HIV-infected children receiving long-term isoniazid-preventive-therapy. Randomised trial of isoniazid-preventive-therapy or placebo were given daily or thrice-weekly to HIV-infected children aged ≥ 8 weeks. ALT was measured at baseline, 6-monthly, and during illness. An ALT increase of ≥ 10 the upper limit of normal was defined severe liver injury. Of 324 children enrolled, 297 (91.6%) received isoniazid-preventive-therapy (559 person-years). Baseline median age was 23 months. A total of 207 children (63.9%) received a combination of antiretroviral therapy: 19 children (5.9%) developed severe liver injury, 16 children (4.9%) while receiving isoniazid-preventive-therapy. Among these there were 8 cases (2.5%) of viral hepatitis (5 cases [1.5%] with hepatitis A), 2 antiretroviral-induced liver injuries and 1 case (0.3%) of abnormal tuberculosis. Isoniazid-preventive-therapy induced severe liver injury that occurred in 1.7% and no child developed hepatic failure, and all children subsequently tolerated isoniazid-preventive-therapy. The present results suggest that long-term isoniazid-preventive-therapy has a low toxicity risk in HIV-infected children. Isoniazid-preventive-therapy and long-term isoniazid-preventive-therapy has a low toxicity risk in HIV-infected children. Isoniazid-preventive-therapy can be safely reintroduced following recovery from liver injury.

Ayieko et al. [11] evaluated isoniazid efficacy in the prevention of tuberculosis morbidity and mortality in children, aged 15 years or younger, by performing a meta-analysis of randomized control trials. Eight studies comprising 10,320 children were included in the analysis. Upon combining data from all eight studies, isoniazid-prophylaxis was found to be efficacious in preventing development of tuberculosis. Among the sub-group-analysis conducted, only young children yielded dramatic differences in the estimate of isoniazid efficacy, suggesting that age might be an effect modifier of isoniazid efficacy among children, with no effect realized in children initiating isoniazid therapy at four months of age or earlier and an effect being present in older children. Isoniazid-prophylaxis reduces the risk of developing tuberculosis by 59% among children, aged 15 years or younger, excluding children initiated during early infancy for primary prophylaxis (P-value < 0.001).

Isoniazid migration into the breast-milk

Garessus et al. [12] explored the safety assessment of maternal isoniazid therapy for infants exposed to isoniazid via breast-milk. These authors applied a physiologically-based pharmacokinetic modelling approach to estimate mother and infant, external and internal, isoniazid exposure non-invasively. Highest isoniazid recommended oral doses to the mother are 300 mg or 900 mg every 3 days. Simulation, of maternal intake of 300 mg, resulted in exposures of 0.58 mg/day (95% confidence interval = 0.42 to 0.69) and 1.49 mg/day (95% confidence interval = 1.22 to 1.50) infants of fast and slow metabolizer mothers, respectively. Infant exposure within the first 24 hours after maternal intake of 900 mg were 1.75 mg/day (95% confidence interval = 1.25 to 2.06) and 4.46 mg/day (95% confidence interval = 4.00 to 4.50), in fast and slow metabolizer mothers, respectively. In infants, maximal isoniazid plasma concentration ranged from 0.04 to 0.78 μg/ml for the two dosing regimens, respectively. These authors concluded that isoniazid exposure to infants via breast-milk, after maternal isoniazid intake of the highest recommend doses is very low. Such an isoniazid low exposure most likely does not cause any clinically significant adverse effects in nursed infants.

Singh et al. [13] documented the isoniazid milk to plasma ratio at steady-state. Isoniazid peak concentrations in plasma and milk were reached within 1 hour and the projected isoniazid exposure to infants is much lower than the prophylactic dose, supporting isoniazid safety during breast feeding. Isoniazid AUC milk to plasma ratio was 0.89 (95% confidence interval = 0.7 to 1.1) and was calculated in 7 women over 24 hours. Isoniazid mean absolute dose was estimated to be 89.9 mg/kg per day in mothers (95% confidence interval = 65.6 to 114) and the relative dose in infants was 1.2% of the body weight adjusted for maternal dose. These results suggest that the maternal isoniazid therapy is safe during breastfeeding.

The percentages of anti-tuberculosis agent doses that potentially may be delivered to the nursing infants ranged from 0.05% to 28% [14]. Currently, isoniazid is used to treat tuberculosis. If the mother chooses to breastfeed her infant, it may be prudent to examine the infant signs and symptoms of toxicity. In infants requiring treatment with anti-tuberculosis agents, it is important to administer anti-tuberculosis drugs at therapeutic doses, since the drug concentrations in the breast-milk are not adequate as effective therapy for treatment or prevention tuberculosis. However, dosing at the lower end of therapeutic range should be prescribed, for example 10 mg/kg per day isoniazid, to decrease the risk of infant toxicity.

Isoniazid treatment, prophylaxis, and prevention, in infants and children with tuberculosis

In 2010, the WHO revised the paediatric dosages of anti-tuberculosis drugs, increasing isoniazid dose to 10 mg/kg. Nansumba et al. [15] assessed treatment outcomes, safety and adherence among children treated with the new recommended dosage. A total of 144 children, aged < 5 years, were treated with isoniazid. Thirty children (22.0%) had moderate to severe malnutrition and 48 (33.3%) children had HIV infection. Treatment outcomes were as follows: 117 (81.35) success, three (2.1%) failures, 4 (2.8%) lost to follow-up, 19 (13.2%) deaths and 1 (0.7%) transferred out. There was no relapse. Severe malnutrition (adjusted hazard ratio = 8.76, 95% confidence interval = 1.59 - 48.25) was the only predictor of death. Two serious adverse events were attributed to treatment: one case (0.7%) had increased ALT values and one with peripheral neuropathy. Mean ALT values at baseline and at weeks 2, 4, and 8, 24 cases (16.7%) (interquartile range = 16 - 39), 26 cases (18.0%) (interquartile range = 18 - 38), and 27 cases (18.7%) (interquartile range = 19 - 38) U/L. Treatment adherence was above 85% on all visits. These authors confirm the good tolerability of, and adherence, to the new treatment recommendation of isoniazid.

The dual epidemic of HIV and tuberculosis is a major cause of sickness and death. Madhi et al. [16] conducted a double-blind, randomized, placebo-controlled trial of isoniazid pre-exposure prophylaxis against tuberculosis in HIV-infected infants and not-HIV-infected infants exposed to isoniazid during the prenatal period. Five hundred and forty-eight HIV-infected and 804 not-HIV-infected were enrolled. Infants were aged 91 to 120 days and were treated with 10 to 20 mg/kg isoniazid or matching placebo for 96 weeks. All infants received Bacille Calmette-Guèrin (BCG) vaccination against tuberculosis within 30 days after birth. HIV-infected infants had access to antiretroviral thereby. The primary outcomes were tuberculosis disease, death in HIV-infected infants, latent tuberculosis infection, and death in not-HIV-infected infants, within 96 to 108 weeks after randomization. Antiretroviral therapy was initiated in 98.9% of HIV-infected infants, protocol-defined tuberculosis or death occurred in 52 infants (19.0%) in the isoniazid group and 53 (19.3%) in the placebo group. Among not-HIV-infected infants, there was no significant difference in the combined incidence of tuberculosis infection, tuberculosis disease or death between the isoniazid group (39 infants, 10.0%) and the placebo group (45 infants, 11.0%). The rate of tuberculosis was 121/1,000 (12.1%) child-years, among HIV-infected children as compared with 41/1,000 (4.1%) child-years among not-HIV-infected infants. There were no significant differences in clinical or severe

laboratory toxic effects, between treatment groups. Primary isoniazid-prophylaxis did not improve tuberculosis-disease-free survival among HIV-infected infants or tuberculosis-infection-free among not-HIV-infected infants immunized with BCG vaccine. Despite access to HIV therapy, the burden of tuberculosis remained high among HIV-infected infants.

Adjobimey et al. [17] assessed the feasibility and results of isoniazid in preventive-therapy in children, aged < 5 years, exposed to tuberculosis as part of the existing routine activities of the National Tuberculosis Programme in Benin, West Africa. From January 2013 to June 2014, 496 children were examined by a doctor and prescribed isoniazid-preventive-therapy for at least 6 months. There were 6 deaths (1.2%) and 3 cases (0.6%) of active tuberculosis among children, during the first 3 months of follow-up. In an Africa country with moderate tuberculosis infection, and the well-functioning National Tuberculosis Program, for children, aged < 5 years, exposed to tuberculosis in the family was feasible based on simple tools associated with the follow-up. The rate of adherence to isoniazid-preventive-therapy was high.

Gomes et al. [18] assessed adherence to isoniazid-preventive-therapy in children exposed to adult pulmonary tuberculosis at home. Children, aged ≤ 5 years or 5 to 15 years, were enrolled for isoniazid-preventive-therapy, and presented a tuberculin skin test induration of ≥ 10 mm. The mean outcome was 6 consecutive months of at least 80% adherence. A total of 2,631 children were identified as contacts of adult cases. Among children identified 1,895 (71.9%) were evaluated for eligibility for isoniazid-preventive-therapy, and 820 children (31.2%) were enrolled in the study: 609 children (23.1%) were aged ≤ 5 years and 211 children (8.0%) were aged 5 to 15 years. A percentage of 79 prescribed doses were taken, with 65% of children taking > 80% of their doses. In all, 51% completed more than 6 consecutive months of isoniazid-preventive-therapy. Overall, the adherence to isoniazid-preventive-therapy was better than previously reported from tuberculosis endemic areas, with 76.0% children completing at least 6 months of treatment, with more than 80% adherence.

Children, in contact with adults having tuberculosis, should receive isoniazid-preventive-therapy. Datiko et al. [19] assessed whether a community-based approach provides isoniazid-preventive-therapy at the household level and improves uptake and adherence in Ethiopia. A total of 6,161 children with pulmonary tuberculosis were identified by health extension workers. In the community, 5,345 children (87%) were visited, identifying 24,267 (454%) children, 7,226 (29.8%) of whom were children, aged < 15 years, 2,949 children (394%) had symptoms of tuberculosis, and 1,336 children (25.5%) were submitted to sputum for examination. Ninety-two (6.9%) had pulmonary tuberculosis and 169 (3.2%) had tuberculosis of all forms. Of 3,027 asymptomatic children, only 1,761 children (58.2%) were offered (and accepted) isoniazid-preventive-therapy. Of these, 1,615 (91.7%) children completed the 6-mounth course. The most frequent reason for discontinuing isoniazid-preventive-therapy was isoniazid shortage. Isoniazid-preventive-therapy-delivery in the community alongside community-based tuberculosis interventions resulted in better acceptance and improved treatment outcome.

Zunza et al. [20] summarised the effects of tuberculosis-preventive-treatment versus placebo in HIV-infected children with no known tuberculosis contacts on active tuberculosis, death, and adverse events. These authors included three trials, 991 children, aged < 13 years, from South Africa and Botswana. Children were randomized to isoniazid-prophylaxis or placebo, given daily or three times-weekly. The median length of follow-up ranged from 5.7 to 34 months; some were on antiretroviral therapy. In HIV-infected children who not received antiretroviral therapy, isoniazid-prophylaxis may reduce the risk of active tuberculosis (hazard ratio = 0.31, 95% confidence interval = 0.11 to 0.87; 1 trial, 240 children, low certainty evidence), and death (hazard ratio = 0.46, 95% confidence interval = 0.22 to 0.95; 1 trial, 240 children, low certainty evidence). One trial (182 children) reported the number of children with laboratory adverse events, which was similar between isoniazid-prophylaxis and placebo groups. No clinical adverse events were reported. In HIV-infected children, on antiretroviral therapy, not know isoniazid-prophylaxis reduces the risk of active tuberculosis (risk ratio = 0.76, 95% confidence interval = 0.50 to 1.14; 3 trials, 737 children, very low certainty evidence) or death (risk ratio = 1.45, 95% confidence interval = 0.78 to 2.72; 3 trials, 737 children, very low certainty evidence). Two trials (795 children) reported number of clinical adverse events and 3 trials (795 children) reported the number of clinical adverse events; for both categories, the number of adverse events was similar between isoniazid-prophylaxis and placebo groups. Isoniazid-prophylaxis, given to all children diagnosed with HIV-infection, may reduce the risk of active tuberculosis and death. For children on antiretroviral therapy, no clear benefit was detected.

Isoniazid concentrations in serum or plasma of children

Rangari et al. [21] measured serum isoniazid concentrations in children suffering from tuberculosis, at doses administered under the weight band system of the Revised National Tuberculosis Control Program 2009 of India. Prospective, open label, non-randomized study was conducted in 20 children, aged 5 to 12 years, attending the outpatients, chest clinic of a tertiary care hospital. Children of group 1 (N = 8) received isoniazid at a dose of ≥ 10 mg/kg, and children of group 2 (N = 12) were treated with isoniazid dose ≤ 10 mg/kg. The mean isoniazid serum concentrations were significantly higher in children who received isoniazid dose ≥ 10 mg/kg (group 1) as compared to children who were treated with isoniazid dose ≤ 10 mg/kg (group 2), at all time points, except at 2 hours after dosing (P-value < 0.05). Isoniazid peak concentration was lower in children of group 2 compared to children of group 1 (P-value < 0.002). Lower isoniazid serum concentrations were achieved in children receiving an isoniazid dose ≤ 10 mg/kg. The results are shown in tables 1 and 2.

Table 1: Comparison of isoniazid serum concentrations in children of group 1 and group 2. In group 1 (N = 8) isoniazid dose was ≥ 10 mg/kg, and in group 2 (N = 12) isoniazid dose was ≤ 10 mg/kg. Children were aged 5 to 12 years; the figures are the mean±SEM, by Ringari et al. [21].

	Serum isoniazid concentrations (µg/ml)		
Time (hours)	Group 1	Group 2	P-value
0	00	00	00
1	4.36±0.07	3.82±0.17	0.03
2	6.52±0.14	6.16±0.19	0.12
4	4.06±0.08	3.45±0.12	0.002
6	1.75±0.04	1.45±0.07	0.005
10	0.37±0.01	0.30±0.02	0.021
24	0.18±0.01	0.13±0.07	0.003

Table 2: Comparison of isoniazid pharmacokinetic parameters of children in group 1 and group 2. In children of group 1 (N = 8) isoniazid dose was ≥ 10 mg/kg, and in children of group 2 (N = 12) isoniazid dose was ≤ 10 mg/kg. Children were aged 5 to 12 years; the figures are the mean±SEM, by Rangari et al. [21].

Pharmacokinetic parameters	Group 1	Group 2	95% CI of difference between mean	P-value
Cmax (µg/ml)	6.53±0.15	6.13±0.19	-0.15, 0.695	0.12
Tmax (hours)	2	2	---	---
$AUC_{0\text{-}24\ hours}$ (µg.h/ml)	32.18±0.57	28.01±1.04	1.3, 6.42	0.002
$AUC_{0\text{-}infinite}$(µg.h/ml)	32.32±0.64	28.88±1.07	0.51, 6.45	0.002
Half-life (hours)	4.38±0.055	4.189±0.05	0.01, 0.4	0.023
Elimination rate constant ($hour^{-1}$)	0.16±0.002	0.17±0.002	-0.02, 0	0.021
Distribution volume (L)	42.76±0.49	44.90±2.003	-7.3, 3.1	0.321
Clearance (L/h)	6.77±0.126	7.40±0.275	-1.42, 0.02	0.05

CI = confidence interval.

Mclleron et al. [22] measured isoniazid concentration in 56 hospitalized children with a median age of 3.2 years, (interquartile range = 1.58 to 5.35 years) who received isoniazid dose (median dose, 5.01 mg/kg once-daily [range, 2.94 to 15.58]) as part of the antituberculosis treatment. At 1 and 4 months after treatment initiation, isoniazid concentration was measured at 0.75, 1.5, 3, 4, and 6 hours after dosing. The acetylator genotype, age, sex, and clinical diagnosis were evaluated. Median isoniazid peak concentration in children treated with an isoniazid dose of 4 to 6 mg/kg was 58% lower than that of children receiving isoniazid dose of 6 to 10 mg/kg (mean, 2.39 µg/ml, [interquartile range, 1.59 to 3.40] versus 5.71 µg/ml [interquartile range, 4.74 to 7.62]). Peak isoniazid concentration was < 3 µg/ml in 70% of children treated with isoniazid dose of 4 to 6 mg/kg. Children, who received isoniazid dose of 8 to 12 mg/kg, achieved a peak concentration approximating that in adults treated with 300 mg isoniazid once-daily. Intermediate and fast acetylator genotypes had a reduction of isoniazid peak concentration compared with the slow acetylator genotype. Each 1-mg/kg increase the dose and each year increase of age were associated with an increase isoniazid peak concentration of 21% (95% confidence interval = 16% to 25%) and 6% (95% confidence interval = 3% to 10%), respectively. Younger children require higher isoniazid dose, per kg of body weight, to achieve isoniazid concentration similar to that of adults. A daily isoniazid dose of 8 to 12 mg/kg should be recommended. Table 3 shows the pharmacokinetic assessment at

Table 3: Pharmacokinetic assessment at 1 month after initiation of antituberculosis treatment, according to arylamine N-acetyltransferase-2 (NAT 2) genotype. Children (N = 56) were aged 3 months. The figures are the median and (interquartile range), by Mclleron et al. [22].

		Children with NAT 2 genotype			
Isoniazid measure	[a]All children	Slow acetylators[b]	Intermediate acetylators[c]	Fast acetylators[d]	P-value*
Dose (mg/kg)	5.01 (4.35-9.24)	4.98 (4.12-7.99)	5.26 (4.43-9.37)	4.90 (4.68-7.38)	0.78
Cmax (µg/ml)	3.07 (1.82-5.66)	4.05 (2.72-5.74)	2.63 (1.61-5.26)	1.54 (1.22-4.14)	0.07
Half-life (hours)	1.59 (1.21-2.17)	2.23 (1.80-3.06)	1.36 (1.14-1.75)	1.12 (1.77-6.12)	< 0.001
$AUC_{0\text{-}6\ hours}$ (µg.h/ml)	8.73 (4.55-14.13)	10.60 (8.66-16.4)	6.45 (4.18-13.23)	2.31 (1.77-6.12)	0.014
Concentration at 6 hours (µg/ml)	0.26 (0.12-0.76)	0.76 (0.52-1.86)	0.14 (0.11-0.26)	0.08 (0.05-0.12)	< 0.001

[a]For the dose and Cmax N = 56. For the half-life N = 40. For $AUC_{0\text{-}6\ hours}$ N = 41. For the concentration at 6 hours N = 43. $AUC_{0\text{-}6\ hours}$ and the half-life were not determined for children with missing samples at the 4- or 6-hours time points. For 1 child with a late Cmax measured at 4 hours after the treatment, the dose and the half-life were not estimated. [b]For the dose and Cmax N = 20. For the half-life N = 14. For $AUC_{0\text{-}6\ hours}$ N = 15, for the concentration at 6 hours N = 15, and for the concentration at 6 hours N = 16. [c]For the dose and Cmax N = 24. For the half-life and $AUC_{0\text{-}6\ hours}$ N = 20, and for the concentration at 6 hours and $AUC_{0\text{-}6\ hours}$ N = 21. [c]For the dose and Cmax N = 8. For the half-life and $AUC_{0\text{-}6\ hours}$ and the concentrations at 6 hours N = 4.
*Kruskal-Wallis test to determine the probability of equality between the genotype groups.

1 month after initiation of antituberculosis treatment, according to arylamine N-acetyltransferase-2 (NAT2) genotype.

Suboptimal plasma isoniazid concentrations of antituberualar therapy may lead to delayed treatment response and the emergence of acquired isoniazid resistance. Seth et al. [23] measured the isoniazid plasma concentrations in 41 children, aged 2 to 16 years, who received either isoniazid once-daily or three-times weekly (intermittent treatment). Seventy-seven percent of children had isoniazid peak plasma concentration < 8 μg/ml, and 23% of children had an isoniazid peak concentration > 3 μg/ml. Isoniazid exposure did not differ between daily and intermittent isoniazid regimens on the day of administration. All children had a favourable outcome at the end of therapy.

Serum isoniazid concentrations was measured in ninety-four children, aged 1 to 13 years, suffering from different types of tuberculosis [24]. Isoniazid peak serum concentration ranged from 4.38 to 8.17 μg/ml, the elimination half-life ranged from 4.0 to 5.0 hours, and $AUC_{0\text{-}7\ hours}$ ranged from 34.1 to 57.5 μg.h/ml. After oral isoniazid administration, Cmax reached 7 to 8 hours after isoniazid dosing and was 30 to 60 time-folds higher than the MIC of the common microorganisms found in children.

Isoniazid plasma concentration were measured in two children aged 12 and 18 mounts [25]. Children were treated with isoniazid dose of 10 mg/kg in three different oral preparations: (1) a crushed tablet was suspended in a household tablespoon of apple sauce, (2) parenteral solution (Nydrazid, Squibb) was mixed with 8 oz of apple juice, and (3) a commercially syrup containing isoniazid (10 mg/ml) and pyridoxine (0.5 mg/ml) was mixed in a methylcellulose vehicle (P-I-N Forte, Lanett). Each child also received an isoniazid intramuscular injection (10 mg/kg) for treating tuberculosis. The respective peak concentration, after the crushed isoniazid tablet suspended in apple sauce ranged from 1.4 to 2.5 μg/ml, and orally administered parenteral solution ranged from 3.3 to 2.5 μg/ml and was much lower than those obtained in syrup which ranged from 6.3 to 11.4 μg/ml. The time required to achieve isoniazid concentration was longer after the cruised tablet and the oral solution (120 min) than after the syrup (45 and 60 min) and intramuscular injection (15 and 30 min). The present results indicate that a crushed isoniazid tablet suspended in the apple sauce is not well absorbed from the gastrointestinal tract. Taken together, these findings indicate that isoniazid tablet suspended in apple sauce has a low absorption rate and may limit the total amount of dose isoniazid absorbed.

Isoniazid treatment optimization in children and adult patients

It has become increasingly clear that antituberculosis regimens need optimization. Information gained using pharmacokinetics-pharmacodynamics methods in hollow fibers and animal model studies, in conjugation with Monte Carlo simulations, can be used to achieve this goal [26]. Pharmacokinetic-pharmacodynamic models of antituberculosis drugs in hollow fibers, and investigations with mice and guinea pigs have been remarkably concordant. Using exposures derived in these models it has been shown that the standard doses of pyrazinamide, rifampin, and ethambutol should be increased for a batter efficacy, while isoniazid doses need to be individualized. In addition, pharmacokinetic-pharmacodynamic driven doses have been proposed for new antituberculosis agents such as moxifloxacin and PA-824.

Aruldhas et al. [27] investigated the isoniazid pharmacokinetics in 41 children, aged 2 to 16 years, to optimize isoniazid treatment. Children were treated with isoniazid for at least 2 months. Isoniazid concentration was measured for 6 hours and analysed by a nonlinear mixed-effect-model. Isoniazid pharmacokinetics were described by a one-compartment disposition model with an absorption model (N = 9). The clearance and the distribution volume were corrected for the body weight to use an allometric function. Simulations with the isoniazid model showed that 84.9% of the population achieved the target isoniazid concentration. The exposure to isoniazid is adequate with the present regimen.

Influence of N-acetyltransferase-2 (NAT2) on isoniazid plasma concentrations and pharmacokinetics in infants and children

The genetically polymorphic arylamine NAT2 gene coding for the hepatic phase II drug-metabolizing enzymes is involved in isoniazid metabolism. Individuals can be classified as homozygous rapid, heterozygous intermediate rapid or homozygous slow acetylators, according to their isoniazid N-acetylation capacity [28]. Rapid acetylators have a shorter isoniazid elimination half-life than that of slow acetylators. In accordance with this, isoniazid plasma concentrations in rapid acetylators are considerably lower than those in intermediate and slow acetylators. Because most isoniazid cannot be acetylated in slow acetylators, it is directly hydrolyzed to hydrazine, which is toxic to the liver. Isoniazid-related liver injury occurred in 78% of slow acetylators receiving conventional isoniazid treatment. These results an increased risk for isoniazid-induced- hepatotoxicity of slow acetylators that is observed in the majority of genotyping studies performed in adults. In children, the incidence of isoniazid-associated hepatotoxicity is lower than in adults. Verhagen et al. [28] studied isoniazid pharmacokinetics in concordance to NAT2 genotype and acetylator phenotype as well as the relationship of both genotype and phenotype of isoniazid pharmacokinetics in 30 Venezuelan children receiving isoniazid as part of their antituberculosis treatment. The results of this study are shown in table 4.

Donald et al. [29] evaluated isoniazid pharmacokinetics associated with optimal early bactericidal activity (EAB), defined as 90% of the maximum early bactericidal activity (EAB_{90}) and the influence of N-acetyltransferase-2 (NAT2) subtype to reach the identified pharmacokinetic values after isoniazid doses ranging from 10 to 12 mg/kg. Isoniazid serum concentrations and NAT2 subtype were determined in four studies of pulmonary tuberculosis children, and in three studies, the early isoniazid bactericidal activity, was

Table 4: Isoniazid pharmacokinetic parameters in 30 Venezuelan children with tuberculosis aged 1 to 15 years. The figures are the mean and (range) by Verhangen et al. [28].

	NAT2 genotype			
Pharmacokinetic parameters	Rapid (N = 5)	Intermediate (N = 13)	Slow (N = 12)	P-value
$AUC_{0\text{-}24\ hours}$ (µg.h/ml)	4.5 (2.6 - 17.1)[a]	7.7 (4.0 - 19.7)	13.3 (2.9 - 31.6)[a]	< 0.01
Cmax (µg/ml)	1.4 (0.7 - 3.5)	1.8 (0.7 - 2.8)	2.3 (0.7 - 5.2)	0.12
N (%) within 3 to 6 µg/ml	17%	0 (0)	4 (33%)	0.069
Tmax (hours)	2.0 (2.0 - 2.0)	2.0 (2.0 - 4.0)	2.0 (2.0 - 4.0)	0.27
Clearance/F (L/h)	15.9 (3.5 - 46.5)[a]	12.7 (3.6 - 27.7)	6.9 (2.7 - 20.7)[a]	0.021
Distribution volume (L)	36.9 (14.0 - 85.6)	34.4 (17.5 - 77.5)	27.0 (13.9 - 79.0)	0.40
Half-life (hours)	1.6 (1.3 - 2.7)[a]	1.9 (1.3 - 3.4)[b]	2.7 (2.0 - 5.6)[a,b]	< 0.01

P-values were calculated by one-way analysis of variance and for the half-life by Kruskal-Wallis test. [a]Apart from the half-life for which median and range was displayed, geometric mean and range shown for all pharmacokinetic parameters. [a,b]Results of pairwise post hoc comparisons. The clearance and the distribution volume were corrected for the bioavailability.

determined. The relationship of early bactericidal activity and the $AUC_{0\text{-}infinite}$ at 2-hours serum concentrations was examined by an exponential regression and fitted curves estimated the $AUC_{0\text{-}infinite}$ and 2-hours serum concentrations at which EBA_{90} was reached. Table 5 shows the influence of NAT2 subtype on the proportion of pulmonary tuberculosis children received different doses and reached an $AUC_{0\text{-}infinite}$ of ≥ 10.52 µg.h/ml. Table 6 shows the influence of the NAT2 subtypes on the proportion of pulmonary tuberculosis children received different doses of isoniazid and reaching 2-hour serum concentrations of ≥ 2.19 µg/ml .

N-acetyltransferase-2 (NAT2) catalyzes the acetylation of isoniazid to acetylisoniazid. NAT2 polymorphism explains 88% of isoniazid clearance variability in adults. Rogers et al. [30] measured the rates of isoniazid elimination and acetylisoniazid production in the blood of 30 children. Since the maturation effects could be non-linear, these authors utilized a pharmacokinetic approach and the artificial intelligence method, multivariate adaptive regression splines, to identify factors predicting NAT2 V_{max} and K_m by examining clinical, genetic, and laboratory factors in toto. Isoniazid concentration predicted both V_{max} and K_m and superseded the contribution of NAT2 genotype. Age non linearly modified NAT2 genotype contributes a maturation at ≥ 5.3 years. Thus, enzyme efficiency was constrained by isoniazid concentration, genes, and age. Multivariate adaptive regression splines output in the form of basic functions and equations and it allows multiscale-

Table 5: Influence of N-acetyltransferase-2 (NAT2) subtype on the proportion of pulmonary tuberculosis, children received different isoniazid doses and reached $AUC_{0\text{-}infinite}$ of ≥ 10.52 µg.h/ml[a], by Donald et al. [29].

	NAT2 subtype								
	Homozygous slow			Heterozygous fast			Homozygous fast		
Dose mg/kg	N	$AUC_{0\text{-}infinite}$ ≥ 10.52 µg/ml	%	N	$AUC_{0\text{-}infinite}$ ≥ 10.52 µg/ml	%	N	$AUC_{0\text{-}infinite}$ ≥ 10.52 µg/ml	%
0.2	1	0	0	2	0	0	0	0	---
1.5	8	2	5	7	1	14.3	1	0	0
3.0	4	4	100	6	2	33.3	3	1	33.3
5.0	21	21	100	27	26	96.3	12	4	33.3
6.0	2	6	100	5	5	100	10	9	90
10 - 12	21	21	100	29	29	100	16	16	100

[a]Children were evaluated following isoniazid doses of both 5 and 10 mg/kg.

Table 6: Influence of N-acethyltrabsferase-2 (NAT2) subtype on the proportion of pulmonary tuberculosis, children received different isoniazid doses and reached 2-hours serum concentration of ≥ 2.19 µg/ml[a], Donald et al. [29].

	NAT2 subtype								
	Homozygous slow			Heterozygous fast			Homozygous fast		
Dose mg/kg	N	2 hours ≥ 2.19 µg/ml	%	N	2 hours ≥ 2.19 µg/ml	%	N	2 hours ≥ 2.19 µg/ml	%
0.2	1	0	00	2	0	0.0	0	0	---
1.5	8	1	12.5	7	0	0.0	1	0	0.0
3.0	4	4	100	6	2	33.3	3	1	33.3
5.0	21	21	100	27	26	96.3	12	3	25.0
6.0	6	6	100	5	5	100	10	8	80.0
10 – 12	21	21	100	29	29	100	16	16	100

[a]Children were evaluated following isoniazid doses of both 5 and 10 mg/kg.

system-modelling from the level of cellular chemical reactions to the whole body physiological parameters, by an automatic selection of significant predictors by the algorithm.

Metabolic clearance of isoniazid may be up to 10 times faster in individuals who are rapid acetylators compared with slow acetylators. Keller et al. [31] evaluated the genotype and phenotype of NAT2 in an Argentinean paediatric population. Almost half of children (46.02%) possessed wild-type haplotype, with 17.5% of children had fully functional alleles, 57.95% children had fully functional allele and 25.0% children with no fully functional allele. According to phenotype, most children (96.59%) were classified as fast acetylators, whereas 1.14% children were intermediate and 2.27% children were slow acetylators. There was a positive association between age and metabolic ratio ($r = 0.52985$, P-value < 0.000001) with a significant metabolic ratio difference between age categories (P-value < 0.001). These authors found higher proportion of rapid acetylators compared with other populations. Acetylator phenotype showed a positive correlation with age, with a significant change around the 4th year of life.

The roles of NAT2 genotype and enzyme maturation on isoniazid pharmacokinetics were studied in South Africa infants with prenatal HIV exposure enrolled in a randomized, double-blind, controlled isoniazid trial for the prevention of tuberculosis disease and latent infection [32]. Plasma concentration-time measurements of isoniazid from 151 infants (starting at 3 to 4 months of age) receiving single oral isoniazid doses 10 to 20 mg/kg per day during the course of 24-month study were incorporated in the population analysis along with NAT2 genotype, body weight, age, and sex. These results showed different NAT2 enzyme maturation profile for each of 3 acetylation groups, with 70-kg body weight-normalized typical apparent clearance for the fast and intermediate acetylators increasing from 14.25 L/kg to 10.88 L/kg at 3 months of age to 22.84 L/h and 15.88 L/h at 24 months of age, respectively, with no significant change in the apparent clearance of the slow group during this period. A hypothesis is proposed to explain the genotype-dependent enzyme maturation processes for the NAT2 enzyme.

Isoniazid toxic effects in children

Leeb et al. [33] assessed the prevalence of elevated hepatic transaminase activities in children undergoing isoniazid-prophylactic-treatment for tuberculosis infection. Of 277 children who were treated with isoniazid, 113 children (40.8%) had elevated hepatic transaminase activities. Of these, 97 children (35.0%) had levels that were less than three times the upper limit of range and 16 (5.8%) had levels that were more than three times the normal range. Four children had to discontinue isoniazid treatment and were successfully switched to rifampicin. In 17 children (6.1%), the highest transaminase peak did not occur after 6 months of treatment. Elevated hepatic transaminase activities were significantly more common in children aged below 9 years (62.0%) than in those aged 10 to 18 years (28.0%). Hepatic transaminase activities were elevated in 44.0% of all boys and 36.0% of all girls. Elevated transaminase activities were common in children receiving isoniazid-prophylactic-treatment for tuberculosis and started at different points throughout the treatment period. Younger children faced an increased risk. Regular blood tests are recommended through treatment.

Acute isoniazid poisoning is uncommon in children [34]. Isoniazid is increasingly being used to control the speared of tuberculosis, and physicians should know its potential fatal effects. Isoniazid overdose is known to result in rapid onset of seizures, metabolic acidosis, and prolonged obtundation secondary to isoniazid overdose that was immediately reversed by pyridoxine. Parenteral pyridoxine administration is an effective method in isoniazid intoxication. The intravenous form of pyridoxine must be available in the emergency care units, and must be administered if isoniazid toxicity is suspected in any child with refractory seizures and metabolic acidosis.

Treatment with isoniazid induced vitamin B6 deficiency which is reportedly not common in adults but rare in children. Thirty-eight children had low serum levels of vitamin B6 tested while receiving therapy with isoniazid [35]. A biologic assay using the protozoan Tetrahymena thermophila determined deficiency of vitamin B6 status after 2 to 18 months of isoniazid therapy. Five children (13.1%) were vitamin B6 deficient. None had definitive clinical symptoms or sign consistent with vitamin B6 deficiency. Three children (7.9%) had normal nerve conduction velocity. Children receiving an isoniazid dose > 10 mg/kg daily had a higher incidence of efficiency. The present recommendations, for withholding vitamin B6 prophylaxis in children receiving isoniazid therapy, must be reconsidered in the light of these findings, particularly in those children who are debilitated or have a poor nutritional history with a known pyridoxine deficit prior to therapy with isoniazid.

Berg et al. [36] examined isoniazid side effects and non-specific-somatic complaints on medication adherence in 96 Latino adolescents participating in a controlled trial designed to increase isoniazid adherence. These children (who received usual medical care) were interviewed monthly for over 9 months. Children were questioned regarding medication taking, the frequency of 15 isoniazid-related-side-effects from the Physician's Desk Reference, and 21 non-specific somatic complaints. Of children, aged 12 to 19 years, 53.1% were male, 66.7% were born in Mexico, 73.0% had no health insurance, and 52.5% were classified as bicultural. Approximately 70% children experienced at least one side effect during the trial. Side effects that occurred while taking isoniazid were not significantly related to the total number of pills taken; somatic complaints that occurred during 9 months of isoniazid treatment in these children were significantly negatively related to cumulative adherence. Females reported significantly more somatic complaints at baseline than males.

Concomitant administration of isoniazid and rifampin induces hepatotoxicity in children

The incidence and degree of liver injury was prospectively evaluated in 44 children, aged 4 months to 14 years (mean,

4.5), and treated with isoniazid (15 to 20 mg/kg daily) and rifampin (15 mg/kg daily) for tuberculosis [37]. None of the children had hepatic dysfunction before treatment. Elevation of the serum alanine aminotransferase (ALT) concentration (> 100 units) occurred in 36 children (82.0%). Fifteen of 36 children (41.7%) developed clinical hepatitis with jaundice. In 7 children (9.1%) liver enlargement and prolongation of the prothrombin time were also observed. In all, but not in one child, liver dysfunction was recognized 6 to 30 days (mean, 14) after start of treatment. Biochemical signs of hepatic injury were observed in 35 (79.5%) children and they regressed completely without alteration of the isoniazid-rifampin treatment in 22 children (48.9%). These results suggest the possibility that hepatocellular damage may be due to the effect of tubercle bacilli products liberated in the liver after their destruction by isoniazid and rifampin treatment. The high rate of hepatotoxic reactions warms that isoniazid dose should not exceeded 10 mg/kg per day when co-administered with rifampin.

Linna and Uhari [38] determined the hepatotoxicity of isoniazid co-administered with rifampin in 18 children. Fifteen children (83.8%) had a rise in ASAT values > 29 U/L. Seven children (38.9%) had ASAT values between 40 and 100 U/L and were treated without any changes in isoniazid-rifampin regimen and transaminases normalized later in the treatment. Six children (33.3%) with ASAT values > 100 U/L were allowed a three-week pause in isoniazid-rifampin treatment and in one child (5.5%) the treatment was discontinued entirely. The therapy was discontinued in 3 children (16.7%) because of a second high rise in the transaminase values. Follow-up tests are necessary when isoniazid is co-administered with rifampin.

Isoniazid penetration into the cerebrospinal fluid in children

Isoniazid cerebrospinal fluid and plasma concentrations were determined on 96 occasions in 38 children affected by tuberculosis, with a mean age of 1.5 years, treated with isoniazid doses of 10 or 20 mg/kg [39]. Maximum isoniazid cerebrospinal fluid concentration was reached 2 to 4 hours after dosing. Isoniazid cerebrospinal fluid concentration was 4.6±2.4 μg/ml following an isoniazid dose of 10 mg/kg and was significantly lower (P-value < 0.0001) following an isoniazid dose of 20 mg/kg (11.6±2.7 μg/ml). Isoniazid cerebrospinal fluid concentration was 3.2±1.1 μg/ml in faster acetylators, after an isoniazid dose of 10 mg/kg, and was significantly higher (7.7±1.3 μg/ml) (P-value < 0.0001) in slow acetylators. After an isoniazid dose of 20 mg/kg, isoniazid cerebrospinal concentration was 10.5±2.5 μg/ml in faster acetylators compared with 14.1±1.4 μg/ml in slower acetylators (P-value < 0.0001). Following isoniazid doses of both 10 and 20 mg/kg, isoniazid cerebrospinal fluid concentrations of the MIC for Mycobacterium tuberculosis and persisted 12 to 14 hours later.

Isoniazid concentration in the cerebrospinal fluid, 3 hours after isoniazid administration, was 3.78 μg/ml. Isoniazid cerebrospinal fluid concentration was well above the MIC for Mycobacterium tuberculosis, but declined below the MIC at later times [40]. Isoniazid cerebrospinal fluid concentration is about 20% of that in serum. In 8 children, who received isoniazid in combination with steroids, the mean isoniazid cerebrospinal fluid and serum concentrations, as well as the isoniazid cerebrospinal fluid to serum isoniazid concentration ratio was not statistically significant from 8 children who did not receive steroids.

Pouplin et al. [41] described isoniazid pharmacokinetics in plasma and in cerebrospinal fluid of children with tuberculous meningitis. These authors performed a prospective observational study of 100 consecutively treated children aged ≤ 15 years. Isoniazid dose of 5 mg/kg was administered for 8 months. Isoniazid concentration was measured in plasma at day 14 and in the cerebrospinal fluid at 1 month after treatment. A naive-pooled non-compartmental data analysis was used to describe isoniazid pharmacokinetic properties in children aged ≤ 4 years or > 4 years. Isoniazid cerebrospinal fluid concentration was comparable to that in plasma in both age groups. There is an age-dependent-variation in the plasma and cerebrospinal fluid of isoniazid pharmacokinetic parameters.

Isoniazid drug interactions

Some isoniazid-drug interactions via inhibition and induction of CYPs are described by Gumbo [2] and are listed in table 7.

Isoniazid pharmacokinetics in infants and children

Rey et al. [42] studied the isoniazid pharmacokinetics in 34 children according to acetylator phenotype. Two children, aged 0 to 1 month, 17 children, aged 2.4 to 19 months, and 15 children, aged 1.1 to 8.2 years, were enrolled. Antituberculosis-drugs were administered 24 hours after isoniazid treatment. None of

Table 7: Some isoniazid-drug interactions via inhibition and induction of CYPs, by Gumbo [2].

Co-administered drugs	CYP isoform	Adverse effects
Acetaminophen	CYP2E1 induction	Hepatotoxicity
Carbamazepine	CYP3A inhibition	Neurological toxicity
Diazepam	CYP3A and CYP2C19	Sedation and respiratory depression
Ethosuximide	CYP3A inhibition	Psychotic behaviours
Isoflurane and enflurane	CYP2E1 induction	Decreased effectiveness
Phenytoin and fosphenytoin	CYP2E1 induction	Neurological toxicity
Theophyline	CYP2C19 inhibition	Seizures, palpitation, nausea
Vincristine	CYP3A inhibition	Limb weakness and tingling
Warfarin	CYP2C9 inhibition	Possibility of increased bleeding (higher risk with isoniazid dose > 300 mg per day)

children had any gastrointestinal or hepatic dysfunctions. An isoniazid powder was suspended in water and a single oral dose of 10 mg/kg isoniazid was administered to fasting children. Blood samples (1 ml) were collected before and 1, 2, 3, 6, and 12 hours after isoniazid dosing. Plasma was separated from blood and used for isoniazid concentration determination. In slower acetylator children, the molar metabolic ratio, Tmax, Cmax, clearance, distribution volume and the half-life were 0.28±0.10, 1.66±1.29 hours, 6.32±2.28 µg/ml, 0.30±0.09 L/h/kg, 1.56±0.65 L/kg, and 3.88±1.89 hours, respectively. The clearance and the distribution volume were corrected for the body weight. Tmax, Cmax, and acetylisoniazid half-life were 3.57±1.45 hours, 1.89±0.48 µg/ml, and 6.47±2.84 hours, respectively. In faster acetylator children, the molar metabolic ratio, Tmax, Cmax, clearance, distribution volume and the half-life were 2.40±2.18, 1.26±0.61 hours, 7.44±2.01 µg/ml, 0.53±0.23 L/h/kg, 1.06±0.45 L/kg, and 1.64±1.10 hours, respectively. The clearance and distribution volume were corrected for the body weight. In slower acetylator children, Tmax, Cmax, and acetylisoniazid half-life were 1.64±1.10 hours, 6.28±2.05 µg/ml, and 3.36±0.92 hours, respectively. The oral clearance was significantly lower (P-value < 0.05) in the slower than in faster acetylator children. The distribution volume was significantly higher (P-value < 0.05) in slower than in faster acetylator children. The half-life was significantly longer (P-value < 0.05) in slower than in faster acetylator children. Acetylisoniazid Cmax was significantly lower (P-value < 0.05) in slower than in faster acetylator children, and acetylisoniazid half-life was significantly longer (P-value < 0.05) in slower than in faster acetylator children. Isoniazid half-life significantly (P-value < 0.05) decreased with age.

Schaaf et al. [43] investigated isoniazid pharmacokinetics in 64 children, aged < 13 years, with primary respiratory tuberculosis. An isoniazid oral dose of 10 mg/kg was administered by nasogastric tube to overnight fasting children. A light breakfast was permitted 60 to 90 min later. Four blood samples (1 to 1.5 ml) were collected 2, 3, 4, and 5 hours post-dose. Serum was separated from blood and used for isoniazid concentration determination. A further single 3 ml blood sample was collected for DNA analysis. Table 8 shows isoniazid pharmacokinetics and table 9 shows the significance of isoniazid straight line regression concentrations, based on age, with common slope for genotype.

Seifart et al. [44] explored isoniazid pharmacokinetics in 13 children, aged 0.8 to 7.6 years (mean, 2.3), treated with 20 mg/kg isoniazid, 20 mg/kg rifampicin, 30 mg/kg pyrazinamide, and 20 mg/kg ethionamide. All antimicrobial agents were given in a single oral dose. Blood samples were collected at 2.0, 2.75, 3.5, 4.25, and 5.0 after dosing. Plasma was separated from blood and used for isoniazid concentration determination. Blood samples were obtained before initiation of treatment (group 1) and after 6 months of treatment (group 2). Isoniazid plasma concentrations were 20.17±7.20 µg/ml (group 1) and 18.5±5.71 µg/ml (group 2), P-value was > 0.05. The apparent first-order isoniazid elimination rate constant was 0.38±0.16 h^{-1} (group 1) and 0.39±0.17 h^{-1} (group 2), P-value was > 0.05. Isoniazid elimination half-lives were 2.14±3.95 hours (group 1) and 2.16±1.08 hours (group 2), P-value was > 0.05.

Mcllleron et al. [22] studied isoniazid pharmacokinetics in 56 hospitalized children, aged 3 months to 13 years (mean, 3.2), and the interquartile range was 1.58 to 5.38 years. Isoniazid single oral dose ranged from 2.94 to 15.58 mg/kg (mean, 5.01). Children were treated with isoniazid and rifampin for 6 months and with pyrazinamide or pyrazinamide and ethambutol for the first 2 months. Isoniazid single oral dose

Table 8: Mean first order elimination rate constant (K, h^{-1}), $AUC_{2\text{-}5\ hours}$ (µg.h/ml), and isoniazid mean serum concentrations (µg/ml) in 64 children, aged < 13 years, at 2, 3, 4 and 5 hours after isoniazid dosing of 10 mg/kg. The figures are the mean±SD, by Schaaf et al. [43].

			Mean±SD isoniazid concentrations (µg/ml)			
Genotype (N)	K (h^{-1})	$AUC_{2\text{-}5\ hours}$ (µg.h/ml)	2 hours after dosing	3 hours after dosing	4 hours after dosing	5 hours after dosing
SS (25)	0.254±0.046	18.36±4.69	8.60±1.86	6.58±1.61	5.10±1.35	4.01±1.18
FS (24)	0.513±0.074	8.25±3.35	5.13±1.86	3.17±1.29	1.95±0.88	1.19±0.56
FF (15)	0.653±0.117	3.37±3.08	3.94±1.75	2.04±1.06	1.25±0.65	0.64±0.43
F	88.92±2.61	58.42±2.55	33.39±2.59	61.94±2.61	84.91±2.61	0.64±2.57
P-value	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.0005

SS = Homozygous slow acetylators. FS = Heterozygous fast acetylators. FF = Homozygous fast acetylators. F = bioavailability.

Table 9: Significance of a straight line regression of isoniazid concentrations on age with a common slope for genotype, by Schaaf et al. [43].

Time after isoniazid dosing (hours)	Ordinates at mean age				
	SS	FS	FF	Slope	P-value*
2	8.622	5.078	3.882	0.278	< 0.0005
3	6.650	3.128	2.001	0.214	< 0.0005
4	5.150	1.924	1.092	0.166	< 0.0005
5	4.048	1.129	0.604	0.136	< 0.0005

SS = homozygous slow acetylators. FS = heterozygous fast acetylators. FF = homozygous fast acetylators. *Significance of the slope coefficient.

of 300 mg was administered to children (6 mg/kg in children weighing 50 kg). Isoniazid peak concentration was < 3 µg/ml in 70% of children receiving an isoniazid doses of 4 to 6 mg/kg, and was 58% lower in children treated with isoniazid oral doses of 8 to 10 mg/kg (2.39 µg/ml [interquartile range, 1.59 to 3.4 µg/ml] versus 5.71 µg/ml [interquartile range, 4.74 to 7.62 µg/ml]). Intermediate or fast acetylator genotypes independently predicted a 38% reduction of peak isoniazid concentrations (95% confidence interval = 21% to 51%), compared with the slow acetylator genotype. Each 1-mg/kg increase in the dose and each year increase in age were associated with an increase of isoniazid peak concentrations of 21% (95% confidence interval = 16% to 25%) and 6% (95% confidence interval = 3% to 10%), respectively. Younger children require higher isoniazid dose, per kg body weight, to achieve isoniazid concentrations similar to that of adults. An isoniazid daily dose of 8 to 12 mg/kg is recommended. Table 9 shows the pharmacokinetic assessment at 1 month after initiation of antituberculosis treatment, according to arylamine N-acetyltransferase-2 (NAT 2) genotype.

Bacterial resistance to isoniazid in infants and children

Marais et al. [45] described the genotype diversity in children with culture-confirmed-tuberculosis and investigated the relationship between genotype and drug-resistance. All children, aged < 13 years, were diagnosed with culture-confirmed-tuberculosis. Genotype analysis and phenotypic drug-susceptibility-testing were performed on the first culture-positive isolate from each child. Spoligotyping was successfully performed on isolates from 391 of 399 (98.0%) children diagnosed with culture-confirmed-tuberculosis. Drug-susceptibility-testing was also performed on 391 isolates; 49 (12.5%) of these isolates were resistant to isoniazid, and 20 (5.1%) of these isolates were resistant to both isoniazid and rifampin. Beijing was the most common genotype family identified in 130 of 391 (33.2%) cases. The presence of both Beijing and Haarlem genotype families were significantly associated with drug-resistance (26 of 49 [53.1%] versus 113/432 [33.0%]; odds ratio = 1.7; 95% confidence interval = 1.0 to 2.9). The high prevalence of Beijing and LAM in children with culture-confirmed-tuberculosis reflects considerably transmission of these genotype families within the community. The overrepresentation of Beijing and Haarlem genotype families in children with drug-resistant-tuberculosis demonstrates their contribution to transmitted drug-resistance and their potential importance in the emergent drug-resistant-tuberculosis epidemic.

Isoniazid-resistance is an obstacle to the treatment of tuberculosis disease and latent tuberculosis infection in children [46]. Yuen et al. [46] summarized the literature describing the risk of isoniazid-resistant-tuberculosis among children with tuberculosis disease. These investigators identified 3,403 citations, of which 95 studies (2.8%) met inclusion criteria. The studies evaluated 8,351 children with tuberculosis disease for resistance to isoniazid. The median proportion of children found to have isoniazid-resistant strains was 8%; the distribution was right-skewed (25th percentile = 0% and 75th percentile = 18%). High proportions of isoniazid-resistance among children with tuberculosis have been reported in many settings suggesting that diagnostics detecting only rifampin resistance are insufficient to guide appropriate treatment in children. Many children are likely receiving substandard tuberculosis treatment with empirical isoniazid-base regimens, and treating latent tuberculosis infection with isoniazid may not be effective in large numbers of children. Work is urgently needed to identify effective regimens for the treatment of sick children exposed to isoniazid-resistant-tuberculosis.

Resistance to isoniazid threatens the efficacy of treatment of tuberculosis disease and infection. Yuen et al. [47] sought to estimate both the proportion of child tuberculosis cases with isoniazid-resistance and the number of incident isoniazid-resistant-tuberculosis cases in children, by region. A percentage of 12.1 (95% confidence interval = 9.8% to 14.8%) of children with tuberculosis had isoniazid-resistant disease, representing 120,872 (95% confidence interval = 96,628 to 149,059) incidence cases of isoniazid-resistant-tuberculosis in children in 2010. The majority of these occurred in the Western Pacific and Southeast Asia regions; the European region had the highest proportion of children with tuberculosis having isoniazid resistance, 26.1% (95% confidence interval = 20.0% to 33.6%). The burden of isoniazid-resistant-tuberculosis in children is substantial, and the risk varies considerably by setting. A large number of children have signals of extensive ongoing transmission from adults with isoniazid-resistant-tuberculosis. The risk of isoniazid-resistance must be considered when evaluating treatment options for children with tuberculosis or latent tuberculosis infection to avoid inadequate treatment and consequent poor outcomes.

Isoniazid-resistant-tuberculosis may be a risk factor for poor outcomes, but has been poorly described in children. Garcia-Prats et al. [48] characterised the clinical presentation, treatment, clinical, and microbiological outcomes among children with culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis. Of 72 children included in the study with a median age of 50.1 months (interquartile range = 21.5 to 102.5), 42% were male. Forty-four children (61.1%) had a positional source case; only 13 (29.5%) were culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis**.** Of 66 children, 12 children (18.2%) were HIV-infected, and 36 children (60.0%) had pulmonary tuberculosis and severe diseases. Seventy children (97.2%) had treatment data: the median total treatment duration was 11.3 months (interquartile range = 9 to 12.3); 25 children (34.7%) initiated treatment with a three-drug intensive phase; 52 children (72.2%) received a fluoroquinolone. Of 63 children with known outcomes, 55 (87.3%) had a favourable outcome, 1 child died and 3 (4.8%) had treatment failure. Ten children (15.9%) had positive follow-up tuberculosis (P-value = 0.023) and severe pulmonary tuberculosis at ≥ 2 months after starting treatment. Children, with older age, had previous antituberculosis treatment (P-value = 0.023) and severe pulmonary tuberculosis (P-value = 0.018). These children had a failure to culture-convert at ≥ 2 months. Although overall outcomes were good, prolonged

culture positivity, and cases of treatment failure emphasise the need for additional attention to the management of children with isoniazid-resistant and rifampin-susceptible tuberculosis.

A total of 312 sputum samples from paediatric patients presumptive of multidrug-resistant-tuberculosis were tested for the detection of drug-resistance using the GenoTypeDrplus assay [49]. A total of 193 children (61.8%) were smear positive and 119 children (38.1%) were smearing negative by the Ziehl-Neelsen staining. Line probe assay was performed for 208 (66.7%) samples tested for culture (193 cultures [61.8%] were smear positive samples and 15 cultures [4.8%] were smear negative samples). Valid results were obtained in 198 tests (63.5%). Of these, 125 of 198 tests (63.1%) were rifampicin and isoniazid sensitive. Of these, 73 of 198 tests (36.9%) were resistant to isoniazid and rifampicin, multidrug-resistance. Children with tuberculosis are often infected by someone close to them, so strengthening of contact may help in early diagnosis to identify additional cases within the household. There is a need to sough newer diagnostic assays which have a high sensitivity in the case of smear negative samples, additional samples, other than sputum, among young children not able to expectorate, should be available.

Paediatric tuberculosis is a marker for actively transmitted disease in the community, Arora et al. [50] investigated drug-resistance-patterns of 97 Mycobacterium tuberculosis complex strains isolated from children and explored their phylogenetic associations. The sputum of 111 children was analyzed for drug-susceptibility. Drug-susceptibility-testing and spoligotyping were performed on cultures positive for Mycobacterium tuberculosis complex. Drug-susceptibility-testing against four first-line drugs showed that 31 of 97 (31.9%) strains were pan-susceptible, while 66 of 97 (68.0%) were resistant to at least one drug, including 55 of 97 (55.7%) that were resistant to at least isoniazid and rifampicin, multidrug-resistance. The majority of isolates (81 of 90, 90.0%) belonged to the principal genetic strains, the most predominant spoligotyping clusters being spoligotyping international type (SIT)/Beijing (n = 28), SIT26/CAS1-Delhi (N = 27) and SIT53/T1 (N = 6). The involvement of Beijing and CAS1-Delhi clades play a major role in ongoing active transmission in children with tuberculosis.

Lapphra et al. [51] evaluated the rate, clinical features, and risk of drug-resistant-tuberculosis in children. Observational prospective study was conducted in children diagnosed with tuberculosis at a tertiary care center in Bangkok. Of 230 children with tuberculosis, with a median age 6.5 years, 63% had identified adult source cases, and only 7% had received prior isoniazid treatment for latent tuberculosis infection in 195 (84.7%) specimens submitted, 57 (24.8%) were positive using culture or PCR. Fifth-three (23.0%) were positive using culture or PCR. Of 53 positive specimens available for drug-susceptibility-testing, 18 (34.0%) had any resistance, 13 (24.5%) were mono-resistant, 2 (3.8%) were polyresistant and 3 (5.7%) were multidrug-resistant. In multivariate analysis, prior tuberculosis treatment (P-value < 0.001), presence of atelectasis (P-value = 0.039) or lobar consolidation (P-value = 0.012) on chest X-ray were associated with drug-resistant-tuberculosis. Drug-resistant-tuberculosis requires longer treatment but there were no differences in cure rates, treatment completion, or death. The high rate of drug-resistant-tuberculosis underscores the importance of routine drug-susceptible-testing. History of treatment and drug-susceptibility in source cases was useful in guiding initial treatment in children.

Tuberculosis meningitis is associated with delayed diagnosis and poor outcome in children. Seddon et al. [52] investigated the impact of drug-resistance on clinical outcome in children with tuberculosis meningitis. One hundred and twenty-three children, aged 0 to 13 years, were treated with isoniazid, rifampin, pyrazinamide, and ethionamide according to South Africa guidelines. Of 123 children, 6 (4.9%) had any form of drug-resistance and 5 children (4.1%) had multidrug-resistant-tuberculosis. Time from start of symptoms to appropriate treatment was longer in children with any drug-resistance (median age, 31 days versus 9 years, P-value = 0.001). Multidrug-resistant-tuberculosis (adjusted odds ratio = 12.4 [95% confidence interval = 1.17 to 123.3] P-value = 0.037]) remained risk factors for unfavourable outcome, and multidrug-resistant-tuberculosis remained a risk for death (adjusted odds ratio = 63.9 [95% confidence interval = 4.84 to 843.2], P-value = 0.002). These authors did not detected any difference in outcome between those with isolate-resistant to only isoniazid and those with fully susceptible strains (adjusted odds ratio = 0.22 [confidence interval = 0.03 to 1.87]; P-value = 0.17). Multidrug-resistant-tuberculosis meningitis in children has poor clinical outcome and is associated with death. No difference in outcomes between children with isoniazid mono-resistant tuberculous meningitis and those with drug-susceptible tuberculous meningitis was observed.

An emergence of drug-resistant-tuberculosis in settings affected by HIV and tuberculosis has been observed. Hesseling et al. [53] investigated the prevalence of drug-resistant-tuberculosis in P1041, a multicentered, randomised, double-blind trial which compared the treatment with isoniazid to placebo, in HIV-infected, not-HIV-infected, and African infants in the absence of any documented tuberculosis exposure. The prevalence of drug-resistant-tuberculosis was 22.2% (95% confidence interval = 8.5 to 45.8) and isoniazid monoresistance 5.6% (95% confidence interval = 0.1 to 27.6) among culture-confirmed cases, with all multidrug-resistant-tuberculosis occurring in a single site. There was no association between isoniazid treatment and placebo group, or between HIV status, and drug-resistant-tuberculosis prevalence. There was a high prevalence of drug-resistant-tuberculosis among HIV-exposed and -unexposed children. Surveillance of multidrug-resistant-tuberculosis among children in high-burden tuberculosis settings should be routinely assessed.

Schaaf et al. [54] assessed the prevalence of drug-resistant-antituberculosis among children with tuberculosis in South Africa. Drug-susceptibility-testing for isoniazid and rifampin was prospectively done in March 2005 through

February 2007. These authors found that 291 children who had culture-confirmed-tuberculosis. Resistance to isoniazid or rifampin was increased from 21 of 306 (6.9%) from 41 of 319 (12.8%) and from 43 of 285 (15.1%) in the first to third surveys (P-value = 0.005) and multidrug-resistance from 7 of 306 (2.3%) from 18 of 319 (5.6%) and from 19 of 285 (6.7%); P-value = 0.033). Although previously treated children had significantly more drug-resistance than did new tuberculosis cases (19 of 66 [28.8%] versus 24 of 255 [10.7%]; odds ratio = 3.39; 95% confidence interval = 1.67 to 7.05), evidence suggests transmission rather than acquisition of resistance. HIV infection was not significantly associated with drug-resistance. These results indicate a high and rising prevalence of antituberculosis-drug-resistance among children in the Western Cape, South Africa, which suggests ongoing transmission of drug-resistant-strains within the community. Improved control of tuberculosis in adults, including early identification and treatment of drug-resistant cases, is necessary to reduce transmission to children.

Sneag et al. [55] performed a retrospective review of medical records of 5 children residing in the Western Cape, South Africa, who developed multidrug-resistant-tuberculosis receiving conventional chemoprophylaxis with either isoniazid or a combination of isoniazid, rifampin, and pyrazinamide. Adult multidrug-resistant-tuberculosis source cases were identified for children aged 4.8 months. Four HIV-uninfected infants had tuberculosis-related-symptoms several months after being given chemoprophylaxis. Stigmata of tuberculosis were cough > 3 weeks in 4 children, weight loss, or a history of failing to thrive in 3 infants, fever in 2 infants, and reported night sweats in 1 infant. Chest radiographs at diagnosis revealed lymphadenopathy, lobar opacification, and airway narrowing. All infants were treated for varying time periods at a tuberculosis referral institution in the Western Cape, South Africa. Standard, first-line antituberculosis agents were inadequate to prevent multidrug-resistant-tuberculosis in infants exposed to multidrug-resistant-tuberculosis contacts.

Schaaf et al. [56] determined the MIC of isoniazid for strains of isoniazid-resistant or multidrug-resistant Mycobacterium tuberculosis isolated from children in the Western Cape, South Africa. During the period March 2003 to October 2005, 45 isoniazid-resistant-Mycobacterium-tuberculosis isolated, were observed, 21 children, aged < 13 years, were also rifampicin-resistant. Drug-susceptibility-testing by the radiometric BACTEC 460 method found 11 isolates which were isoniazid-resistant at 0.1 µg/ml, 27 isolates were isoniazid-resistant at 0.2 µg/ml, and 7 isolates were isoniazid-resistant at ≥ 5 µg/ml. Thus, isoniazid MIC concentration for more than 80% of isoniazid-resistant strains isolated from children was relatively low as could be exceeded by high-dose (15 to 20 mg/kg) isoniazid regimens.

Jiao et al. [57] studied 440 children including 90 children (20.40%), aged < 15 years, 159 (36.1%) were adolescences, aged 15 to 18 years, and 191 (43.4%) were adults, aged > 18 years, residing in 25 provinces across China were subjected to spoligotyping and drug-susceptibility-testing. As a result, Beijing family strains were shown to remain predominant in China (86.5%, 81.1%, and 75.4% in three above groups, respectively), especially among new children cases (91.0% versus 69.6% in previously treated cases (P-value = 0.03). The prevalence of the Beijing genotype was higher in northern and central China in the total collection (85.1% in northern and 83.9% in central versus 61.6% in southern China (P-value < 0.001) and a similar trend was seen in all three groups (P-value = 0.708, < 0.001, and 0.025, respectively). In adolescents, the frequency of isoniazid-resistant and ethambutol-resistant isolates were significantly higher among Beijing genotype strains compared to non-Beijing genotype strains (P-value = 0.028 for isoniazid and P-value = 0.027 for ethambutol). Furthermore, strong association was observed between resistance to rifampicin, streptomycin, and multidrug-resistance, among Beijing compared to non-Beijing strains in previously treated cases of children (P-value = 0.01, 0.01, and 0.025, respectively). Beijing family was more prevalent in northern and central China compared to southern China and these strains were predominant in all age groups. The genetic diversity of Mycobacterium tuberculosis isolates from children was similar to that found in adolescences and adults. Beijing genotype was associated with rifampicin, streptomycin, and multidrug-resistance in previously treated children.

An outbreak of isoniazid-resistant-tuberculosis occurred in a large second level school. Shannon et al. [58] investigated 1,160 teenage children that were at risk. Nineteen cases (1.6%) of tuberculosis were diagnosed, 15 (1.3%) were children, 251 children (21.6%) were non-vaccinated, and 6 children (0.66%) among 909 were vaccinated. Two cases of miliary tuberculosis, one of them had also tuberculosis meningitis, occurred in the non-vaccinated group. The number of children with Heaf grade +3 or +4 was significantly greater among children who had been given Bacille Calmette-Guérin vaccination (8.0% versus 4.4%). This suggests a boosting effect on the response in vaccinated children. The protective effect of neonatal Bacille Calmette-Guérin vaccination in these children suggests that it provides significant protection against tuberculosis.

Discussion

Isoniazid (isonicotinic acid hydrazide) is used, with pyrazinamide or rifampin, in the primary treatment and re-treatment of tuberculosis. Tuberculosis is still the most important infectious killer of humans. Isoniazid is bacteriastatic, and at high concentrations, is bactericidal against Mycobacterium tuberculosis. This antibiotic should be co-administered, with at least another antibiotic, to improve antituberculosis effects and to prevent bacteria-resistance to isoniazid. Co-administration of isoniazid and rifampin has been recommended, and such antibiotic combination reduces the treatment period to 3 to 4 months, whereas isoniazid monotherapy requires a treatment period of 9 months. Isoniazid therapy is safe in children [10] but isoniazid therapy increases the hepatic transaminase activities [33] and the excretion of vitamin B6 [36]. Isoniazid doses are 5 mg/kg for neonatal

prophylaxis, 10 mg/kg for treating neonatal tuberculosis latent infection [1], and 10 to 20 mg/kg in children [2]. This drug is mainly excreted in the urine mostly as acetylisoniazid and isoninicotinic acid [7]. Isoniazid enters bacilli by passive diffusion and is not toxic to the bacillus but must be activated to isoniazid toxic form with the bacillus by KatG, multifunctional catalyses-peroxidise [2]. Isoniazid is metabolized to acetylisoniazid by hepatic arylamine N-acetyltransferase-2 (NAT2) encoded by a variety of NAT2* alleles. This enzyme is polymorphic, and individuals are classified as fast and slow acetylators. Genotypes are: homozygous and heterozygous fast acetylators and homozygous slow acetylator, and phenotypes are: fast homozygous and intermediate and slow acetylators [6]. Acetylisoniazid formation rate is higher in faster than slower acetylators. In accordance with this, isoniazid plasma concentration is lower in rapid and intermediate acetylators than slower acetylators and this has therapeutic implications: isoniazid half-life is longer in slower than fast acetylators [6, 8]. Because most isoniazid cannot be acetylated in slow acetylators, it is hydrolyzed to hydrazine, which is toxic to the liver. Isoniazid-related liver injury occurred in 78% of slow acetylators [27]. Rapid acetylators have reduced microbial cure, increased relapse, and increased acquired resistance [9]. Isoniazid migration into breast-milk is poor [12-14]. Isoniazid infant exposition is greater in slower than faster mothers [12]. Isoniazid breast-milk concentration is not enough for tuberculosis prevention and prophylaxis and infants tuberculous-infected require an appropriate antituberculosis chemotherapy [14]. Isoniazid treatment, prophylaxis and prevention have been described by various authors [15-20] in infants and children. After isoniazid conventional treatment doses, 81.35%, 2.1%, and 0.7% children had treatment success, failure, and death, respectively. Primary isoniazid-prophylaxis does not improve tuberculosis-disease, and 19% infants died [16]. Isoniazid preventive-therapy in children caused 1.2% and 0.6% dead and had active tuberculous infection, respectively [17]. Isoniazid-preventive-therapy had 80% children with adherence to isoniazid protocol [18]. Isoniazid-preventive-therapy yielded 6.9% children who had pulmonary tuberculosis and 3.2% children had tuberculosis of all forms [19]. Isoniazid-preventive-therapy resulted in better acceptance and improved treatment outcome. Isoniazid-prophylaxis, given to children diagnosed with HIV-infection, may reduce the risk of active tuberculosis and death [20]. Isoniazid concentration in serum, or plasma, of children was measured by several authors [21-25]. Isoniazid serum concentrations depended by isoniazid dose [21, 22]. Suboptimal isoniazid plasma concentration may lead to the emergence of acquired isoniazid-resistance [23]. After conventional isoniazid oral dose, MIC values were 30 to 60 time-folds higher against the common microorganisms found in children. Plasma concentrations depend by the type of oral preparation [25]. Isoniazid treatment needs optimization to provide appropriate therapy [26, 27]. This antibiotic is safe in children [11], however isoniazid therapy causes increases of hepatic transaminase activities [33] and excretion of vitamin B6 [35]. Isoniazid overdose causes seizures, metabolic acidosis, and prolonged obtundation and requires immediate treatment with pyridoxine [34]. About 70% of children had at least one side-effect [36]. Concomitant administration of isoniazid and rifampin induces hepatotoxicity in children [37, 38]. Isoniazid penetration into the cerebrospinal fluid is poor [39-41]. Following isoniazid doses of 10 or 20 mg/kg, isoniazid concentrations in the cerebrospinal fluid were 4.6±2.4 and 11.6±2.7 μg/ml, respectively (P-value < 0.0001). Isoniazid cerebrospinal fluid concentration was higher in slower than higher acetylators [39]. Cerebrospinal fluid to serum ratio of isoniazid is about 20% [40]. Flowing isoniazid treatment of 5 mg/kg for 8 months, isoniazid concentration in cerebrospinal fluid was comparable to that in plasma [42]. Isoniazid pharmacokinetics were extensively studied in infants and children by several authors [22, 42-44]. After an isoniazid single oral dose of 10 mg/kg to children, plasma Cmax and half-life were 6.32±2.28 μg/ml and 3.88±1.89 hours, respectively, in slower acetylators, these values were 7.44±2.01 μg/ml and 1.64±1.10 hours, respectively, in faster acetylators [42]. Following isoniazid dose of 10 mg/kg to children, $AUC_{2\text{-}5\ hours}$ values were 18.36±4.69, 8.25±3.35, and 3.37±3.08 μg.h/ml in homozygous slow acetylators, heterozygous fast acetylators, and homozygous fast acetylators, respectively. The $AUC_{2\text{-}5\ hours}$ values were significantly different (P-value < 0.0005) in three acetylators groups studied [43]. Children were treated with 20 mg/kg isoniazid, 20 mg/kg rifampicin, and 30 mg/kg pyrazinamide before initiation of therapy and after 6 months of therapy. Isoniazid plasma concentration, apparent first-order isoniazid elimination rate constant, and the half-life were not different in two groups studied [44]. Following a mean isoniazid dose of 5.01 mg/kg to children, the median Cmax, half-life and $AUC_{0\text{-}6\ hours}$ were 4.05 μg/ml, 2.2 hours and 10.60 μg.h/ml, respectively, in slow acetylators, 2.63 μg/ml, 1.36 hours, and 6.45 μg.h/ml, respectively in intermediate, and 1.54 μg/ml, 1.12 hours, and 2.31 μg.h/ml, respectively, in fast acetylators. The half-life and $AUC_{0\text{-}6\ hours}$ were different in the three groups of acetylators [22]. Bacteria-resistance to isoniazid was reported by several authors [45-58]. Gumbo [2] described the isoniazid mechanisms of resistance. The prevalence of isoniazid-resistant mutants is about 1 in 10^6 bacilli. Because tuberculosis cavities may contain as many as 10^7 to 10^9 microorganisms, pre-existent resistance can be expected in pulmonary tuberculosis cavities of untreated patients. These spontaneous mutants can be selected and amplified by isoniazid monotherapy. Thus, two or more agents are usually needed. Because mutations resulting in drug resistance are independent events, the probability of resistance to two antimicrobial agents is small, about 1 in 10^{12} ($1 \times 10^6 \times 10^6$), a low probability considering the number of bacilli involved. Resistance to isoniazid is associated with mutation or deletion of KatG, overexpression of the genes for InhA (confers low-level resistance to isoniazid and some cross-resistance to ethionamide), and *ahp*C and mutations in the kasA and katG genes. KatG mutants exhibit a high level of resistance to isoniazid. The most common mechanism of isoniazid-resistance in clinical isolates is due to single point

mutations in the heme-binding catalytic domain of KatG, especially a serine-to-asparagine change at position 315. Although isolates with this mutation completely loss the ability to form nicotinoyl-NAD^+/$NADP^+$ adducts, they retain good catalase activity and maintain good bioftness. Compensatory mutations in the *ahp*C promoter occur and increase survival of katG mutant strains under oxidative stress. Efflux pump induction by isoniazid has been demonstrated, and it also confers resistance to ethambutol [59]. In an in-vitro pharmacodynamic model, efflux pump-induced resistance developed within 3 days and was followed by develop of katG mutations [60].

Conclusion

In conclusion, isoniazid (isonicotinic acid hydrazide) is used, with pyrazinamide or rifampin, in the primary treatment and re-treatment of tuberculosis. Tuberculosis is still the most important infectious killer of humans. Isoniazid is bacteriastatic and bactericidal at high concentrations, against Mycobacterium tuberculosis. This antibiotic enters bacilli by passive diffusion, and is activated to its toxic form with the bacillus by KatG, multifunctional catalyses-peroxidise. In infants, isoniazid doses are 5 mg/kg, for treatment of neonatal prophylaxis, 10 mg/kg for the treatment of latent tuberculosis infection, and 10 to 20 mg/kg in children. Isoniazid half-lives are 2 to 5 hours in infants and 1.5 to 2.5 hours in children. This antibiotic is metabolized to acetylisoniazid by N-acetylteansferase-2, which is polymorphic. Acetylisoniazid formation rate is higher in faster than slower acetylators and isoniazid plasma concentration is lower in faster than slower acetylators, this has therapeutic implications: isoniazid half-life is shorter in faster than slower acetylators. Because most isoniazid cannot be acetylated in slow acetylators, it is hydrolyzed to hydrazine, which toxic to the liver, and isoniazid-related liver injury occurs in 78% of slow acetylators. Isoniazid is safe in children; however, increase of hepatic transaminase activities and excretion of vitamin B6 have been reported. Isoniazid penetration into the cerebrospinal fluid is poor; however, isoniazid concentration is well above the MIC for Mycobacterium tuberculosis. Isoniazid migration into breast-milk is poor and isoniazid concentration in breast-milk is not enough for tuberculosis prevention and prophylaxis. Infants, who have tuberculous-infection, should require appropriate antituberculosis chemotherapy. Concomitant administration of isoniazid and rifampin induces hepatotoxicity in children. Isoniazid pharmacokinetics have been extensively studied in infants and children. Several bacteria my become resistant to isoniazid and consequent isoniazid-resistance is an obstacle to the treatment of tuberculosis disease and latent tuberculosis infection.

Conflict of Interests

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This article is a review and drugs have not been administered to men or animals.

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