



# Isoniazid and Adverse Events

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Submission: 📅 August 28, 2017; Published: 📅 November 13, 2017

## Introduction

Isoniazid is one first line antituberculosis essential for tuberculosis treatment in paediatric population.

Since many years a lot of articles were published on adverse events due to Isoniazid. According to WHO and several publication liver injuries is a most important adverse event of Isoniazid. This is a review of literature on side effect induced by INH.

## Method

Review of literature from 1978 to 2010

### Selection criteria

A. All reports publications articles on INH induced liver toxicity.

B. Search strategy: pubmed/medline, Google scholar, WHO site, Embase.

C. Pediatric population from 0 day to 18 years old.

### Exclusion criteria

a. Adult population.

b. Articles or reports do not allow differentiating the pediatric population than adults.

c. Articles inability to differentiate side effects of isoniazid from that of other TB

Table 1: Isoniazid adverse events.

Study	Children N° Treated by INH	Age (y)	INH Range	Abnormal Hepatitis Enzyme >5 Times and Symptoms	Mild Enzyme Elevated
Vincent Palusci et al. [1]	318	0.6- 18	10-15mg(maxi :300mg)	1	2
Nakajo et al. [2]	564	0.25-18	5mg/kg/d	1	NA
Col Richard et al.	63	0-19	NA	0	NA
Dash et al.	644	<15	NA	1	4
ROBERT S.Rapp	116	0-10	10-15mg/kg/d	0	5
Iris F et al.	178	Dec-16	300 mg	Na	Na
P SPYRIDIS et al.	239	Sep-14	NA	2	39
Richard j et al.	118	ND	NA	ND	ND
CDC (SAE INH 2004-2008)	NA(17SAE included 2 children)	<15	10-15mg(maxi :300mg)	2	0
Elisabeth A et al. (New York INH toxicity 01/1993-09/1993)	NA	14-21	10 mg/kg/ j(maxi:300mg)	ND	ND
Ajmad Khan. Rittesh Agarwal	695	NA	5-10mg/kg(maxi.300 mg)	8	4
Total	2935			15	54
Percentage				0.56%	2.68%

## Results

Nine of eleven reports and articles in Table 1 have been analyzed (9 and 10 excluded). Of the 2935 children treated by IINH, the percentage of patients with symptomatic liver enzymes 5 times the normal is: 0.56%. We found 54 cases of moderate elevated hepatic enzyme: 2.68%.

## Discussion

### INH-associated liver injury

It is estimated at 1 per 1000 patients (CDC report march 5, 2010). In this report only two of 7 patients were children. Symptoms such as nausea, abdominal pain, fatigue and jaundice was the key of diagnosis before laboratories analysis. In hour Table 1, we have the same results; all patients with liver injury developed the same symptomatology [1-2]. In a meta-analysis of 6 studies the incidence was 0.6% in case of use of isoniazid alone and 1.6% in combination with other TB drugs; the risk was higher at 2.7% in combination with Rifampicine in 19 reported cases. In The 2003 CDC report of 11.141 children receiving IHN incidence was estimated between 0.1- 0.15%. E J Forget et al estimated the adjusted incidence to 0.8/1000 [3,4].

In a study of risks in tuberculosis induces liver toxicity in Japanese children [5] Katushito and Col. 117 patients aged 0-16 were included, 8 were eligible for liver toxicity criteria, none for the IHN only. After a multiple logistic regression analysis, age and pyrazinamide was associated with increased risk of hepatotoxicity [6]. The mechanism of hepatotoxicity remains unclear, a recent theory has suggested the conversion of INH to acetylisoniazid, and then to a toxic metabolite, the acetyl hydrazine, which covalently binds to macromolecules of adipose tissue [7]. In an experimental study in mice exposed to INH [7] it was found an increase in liver enzyme activity that is the bilirubin glucuronyl transferase. 95 % of INH is absorbed from gastrointestinal tract after ingestion, the peak concentration of IHN in children is 6 to 20µg/ml (with the dose of 10-15 mg/kg/d); with the heterogeneity IHN rate acetylating. Some study in adults has suggested INH related AE and acetylation but there is not a clear relation between both [8,9].

Several authors have discussed the influence of acetylators in the susceptibility to develop side effects. In an article published in 2001 Rey and neck [10,11]. Studied the PK of Children by the phenotype of acetylation: the plasma clearance was lower, the volume of distribution higher and half life longer in the group of slow acetylators. McIleron Helen and colleagues [12] have studied in South Africa the PK and the NAT2 genotype in a cohort of 56 children at a dose of 4-6mg/kg/j. One month after initiating treatment with isoniazid; Cmax were below reference dose in 70% of children regardless the type of acetylators (p = 0.67). Meanwhile children who received a daily dose of isoniazid 8-12mg/kg/j reach the peak concentration comparable to adult with the IHN 300 mg daily regardless of the influence of NAT2 genotype [13,14].

In a study of 64 children under 3 years Schaaf et al. [15] highlights the considerable difference in exposure to INH between

slow and fast metabolisers, the cmax at 2 hours is double and AUC multiplied by three (10mg/kg/j dosage used) in Fast compare to slow acetylators. Other side effects have been identified [16].

### Peripheral neuropathy

(polyneuritis characterized, among others, paresthesia, muscle weakness and decreased tendon reflexes) is estimated at less than 1 to 2% of the general population has been observed in some patient groups, including adolescents, pregnant women and breastfeeding women, the elderly, the "slow acetylators" alcoholics, diabetics, people with HIV, as well as those suffering from malnutrition, renal failure or seizures. Several authors and the American Thoracic Society suggest the administration of pyridoxine (vitamin B6) in addition to the IHN if predisposition [1,6].

Central nervous system: effects such as slurred speech, irritability, seizures, dysphoria, and inability to concentrate were reported but were not quantified [1]. Isoniazid can reduce the excretion of phenytoin or increase its effects. It is recommended to avoid phenytoin intoxication, one must adjust the dosage appropriately this anticonvulsant [6]. Side effects such as hypersensitivity/allergy, gastrointestinal symptoms and neurological changes in the adult literature of 0.1 to 3%.

### Conclusion

Tuberculosis (TB) is one of the most serious infectious diseases worldwide and a leading cause of death for nearly 3 million deaths annually. In 2013, an estimated 9.0 million people were infected with tuberculosis, and 1.5 million died from this diseases. Isoniazid, also known as isonicotinylhydrazide (INH), is one of a combined drug of tuberculosis treatment [17]. Most common adverse effects of isoniazid described in literature are peripheral neuritis and hepatitis. In our literature review; hepatotoxic see to be the most common side effect but it remain low in children [18].

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