

## Potential of Epileptogenic Effect of Isoniazid By Ethanol Consumption

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### Abstract

Tuberculosis is highly prevalent in India with the incidence being highest among individuals of low socio-economic status owing to their unhygienic living conditions and poor nutrition. The antitubercular drugs are thus, easily accessible to the general population, isoniazid being an integral part of all the regimes. Apart from the other neurological manifestations, isoniazid may precipitate convulsions in patients with seizure disorders and rarely in patients with no history of seizure disorder. Alcohol intake is seen to augment the epileptogenic effect of isoniazid. Here we report a case of status epilepticus following consumption of isoniazid and ethanol.

**Keywords:** Tuberculosis; Isoniazid; Ethanol; Seizure; Neurological manifestations

### Introduction

The incidence of adverse reaction to isoniazid was estimated to be 3.4% in a study done in more than 3000 patients treated with this drug. The most common adverse effect being rash (2%), fever (1.2%), jaundice (0.6%) and peripheral neuritis (0.6%). If pyridoxine is not given concurrently, the incidence of peripheral neuritis (most commonly parasthesias of hands and feet) is the most common adverse reaction to isoniazid and occurs in about 2% of patients receiving 5 mg/kg. Higher doses may result in peripheral neuropathy in around 10-20% of the patients.

The prophylactic administration of pyridoxine prevents the development not only of peripheral neuritis, but also of other neurological adverse effects. Muscle twitching, dizziness, ataxia, parasthesias, stupor and toxic encephalopathy are other manifestations of the neurotoxicity of isoniazid.

Isoniazid may precipitate convulsions in patients with seizure disorders and, rarely in patients with no history of seizures. Isoniazid binds to pyridoxal-5-phosphate, the active form of pyridoxine (vitamin B6), to form INH-pyridoxalhydrazones. Pyridoxal-5-phosphate is a cofactor for glutamic acid decarboxylase and GABA transaminase in the GABA synthetic pathway. Isoniazid overdose results in decreased pyridoxal-5-phosphate, decreased GABA synthesis, increased cerebral excitability, and seizures. Co-ingestion of ethanol potentiates toxicity by enhancing degradation of phosphorylated pyridoxine [1,2].

The drug readily diffuses to all body fluids and tissues, with the largest concentration in the liver. The plasma half-life in patients with normal renal and hepatic function is 1 to 4 hours; the plasma half-life may be prolonged in acute overdose [3]. Blood levels are not helpful in managing an acute isoniazid overdose.

If the amount of isoniazid ingested is unknown, 70 mg/kg pyridoxine (up to 5 g) should be administered. If the amount is known, the first dose should match the isoniazid dose ingested (up to 5 g). Pyridoxine is administered over a 5-15 minute period via an intravenous line separate from the one being used for administration of other anticonvulsants. If the seizures are refractory, diazepam should be infused after adequate airway control is established. The simultaneous administration of pyridoxine with benzodiazepine has a synergistic effect in terminating seizures. In severe cases with refractory seizures urgent hemodialysis leads to rapid improvement [4].

### Case Report

A 24 year old male weighing 50 kgs was brought to the emergency department of Gaba Hospital, Yamuna Nagar, India after ingesting 10 tablets of isoniazid (300 mg) which were prescribed to him for the treatment of pulmonary tuberculosis along with ingestion of 800 ml of illicit country liquor. Patient was a known alcoholic with no prior history of any seizure disorder. After 2 hours of the above mentioned intoxication, patient developed generalized tonic clonic seizures. At the time of presentation (7 hours after the intoxication) patient was in status epilepticus. At that time patient's blood pressure was 140/90 mm of Hg, pulse rate was 90/min, respiratory rate was 20/min, Random blood glucose was 223 mg% and SpO<sub>2</sub> was 92%. On examination patient was comatose with seizure activity, mid dilated pupils with sluggish response to light and deep tendon reflexes were diminished. Patient was administered intravenous diazepam for seizure control along 5 gram of pyridoxine by separate intravenous lines. Patient was intubated to protect the airway and gastric decontamination was done. Seizures were controlled.

Patient's serum potassium was 2.9 mEq/L, SGOT was 77 IU/ml, SGPT was 129 IU/ml, Total Leucocyte Count was 23,200/mm<sup>3</sup>, Differential Leucocyte Count was Polymorphs 91% Lymphocytes 8% Eosinophils 1%, Serum creatinine was 1.46 mg%. Patient's Arterial Blood gas analysis, Prothrombin time, activated partial thromboplastin time and serum sodium levels were within normal limits. On next day after stabilization of the patient Electroencephalogram and Magnetic Resonance Imaging were carried out both of which were normal. Serum Isoniazid and pyridoxine levels could not be done because of lack of facilities. On day four all laboratory parameters returned to normal and patient was discharged with full recovery on anxiolytics, antidepressants, pyridoxine and anti tubercular therapy.

### Discussion

We report a case of isoniazid poisoning along with ethanol intoxication that presented as status epilepticus. Brzeski and Kuczyński

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reported a case of isoniazid poisoning potentiated by ethanol intoxication [1]. Along with anti epileptics, high dose of pyridoxine was used as an antidote with good response, as reported earlier.

Ingestion of more than 80 mg/kg body weight has been reported to produce severe central nervous system symptoms and a dose of 125 mg/kg to be potentially lethal if not promptly treated [5]. Our patient had consumed 60 mg/kg isoniazid well below 80 mg/kg threshold but presented in status epilepticus demonstrating the potentiation of isoniazid by ethanol.

Similarly Tai et al. [5] had reported one case in which the recovery was uneventful after isoniazid toxicity. Sood et al. [6] reported isoniazid toxicity in a young girl in which the generalized tonic clonic seizures were successfully treated with high intravenous doses of pyridoxine [6]. Patients exposed to an overdose of isoniazid may become symptomatic within 30 to 45 minutes of ingestion, or as in our patient symptoms may be delayed for up to 2 hours, when blood levels peak. Our patient was on isoniazid for the management of pulmonary tuberculosis, and he presented with a minimal increase in liver enzyme levels. Although chronic use of Isoniazid at therapeutic doses has been associated with hepatotoxicity and peripheral neuritis, severe isoniazid overdoses are characterized by neurotoxic effects.

## Conclusions

With high prevalence of tuberculosis and widespread use of isoniazid, there is high risk of over dosage. This is especially true for poor, illiterate subjects in whom there is also high incidence of ethanol intoxication. Emergency department physicians should be aware of the potential manifestations of isoniazid and ethanol overdose so that can intervene timely to save lives.

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