

# A Therapeutic Dose of Isoniazid Induced Seizure Episode

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## ABSTRACT

Seizures are a common complication of drug intoxication, and up to 9% of cases are caused by a drug or poison. Most drug-induced seizures are self-limited. It occurs generally as a result of inadequate inhibitory influences (e.g., gamma amino butyric acid, GABA) or excessive excitatory stimulation (e.g. glutamate) although many other neurotransmitters play a role. To minimize the risk of adverse events, the dose must be adjusted for the patient's age and medical history. Adverse events associated with INH are dose-related, with approximately 1-2% occurring during conventional low-dose therapy. Seizures refractory to standard anticonvulsant therapy were controlled with the administration of pyridoxine. Benzodiazepines are the first-line treatment for drug-induced seizures, with addition of pyridoxine if isoniazid or other hydrazine toxicity is suspected. This is a case report of 29-year-old female patient admitted to the hospital for the complaints of severe breathlessness. She was diagnosed for pulmonary tuberculosis for which CAT 1 ATT regimen was initiated on her sixth day of admission. One hour later after the administration of first dose of ATT drug an episode of seizure was developed which lasted for 5 min. The drug was then stopped,

and she was given vitamin B6 tablet of 40 mg. Re-challenging of each ATT drugs were carried out one by one. Patient did not develop any further episode of seizure even after continuing the drugs. She restarted anti-tubercular regimen and continued along with pyridoxine. This reports a case of seizure induced on a therapeutic dose of isoniazid.

**Key words:** CAT ATT, Seizure, Re-challenge, Isoniazid, Therapeutic dose. Isoniazid should be closely monitored since it may cause seizure even with a single therapeutic dose.

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## INTRODUCTION

DOTS (directly observed treatment, short course) are the internationally recommended control strategy for TB.<sup>1</sup> Isoniazid (INH) is a first-line agent in the treatment of tuberculosis and is also used in preventive therapy. The recommended dose of INH for treatment in adults is 5 mg/kg with a maximum of 300 mg daily or 15 mg/kg with a maximum of 900 mg once, twice or three times per week.<sup>2</sup> Most reported INH-induced seizures occurred as a result of an overdose in suicide attempts.<sup>3</sup> The acute ingestion of INH at a dose above 30 mg/kg typically causes seizures, and INH ingestion of more than 80 mg/kg can rapidly cause death.<sup>4</sup> Isoniazid intoxication produces a characteristic clinical syndrome including seizures, metabolic acidosis, and in severe cases, respiratory depression and coma.<sup>5</sup>

The occurrence of seizures at conventional doses has rarely been reported.<sup>6</sup> This case report presents an incidence of a seizure episode after administering the first therapeutic dose of isoniazid.

## CASE REPORT

A 29-year-old female patient was admitted to the general medicine for the complaints of breathlessness for the past three months. She had history of cough with expectoration which was mucoid in consistency. Sputum had yellowish color and did not foul smell. She had evening rise of temperature, loss of appetite and loss of weight. Also, history of easy fatigability and sneezing was reported. Her past medical and medication history showed no illness or details of any drugs. General examination revealed she was anemic, febrile and dyspnoeic. Her systemic examination showed no abnormalities except respiratory system with bilateral crept. On the first day of admission her blood pressure level was 100/70 mm hg, pulse rate 86 beats per min, respiratory rate 20 breaths per min and temperature was normal. Laboratory investigation showed: WBC  $10.1 \times 10^9/L$  ( $4-10 \times 10^9/L$  %), Lymphocytes 8.3 (0.8-4.0), Monocytes 0.3 (0.1-8.5), Granulocytes 9.0 (2.0-7.0), RBC  $4.67 \times 10^{12}/L$  ( $3.5-5.5 \times 10^{12}/L$ ), Hemoglobin 12.09 g/dl (12-16 g/dl), Platelet  $273 \times 10^9/L$

( $100-300 \times 10^9/L$ ), RDW CV 12.0% (11-16%), RDW SD 36.7 fl (35-56 fl), ESR 14 mm/hr (up to 20 mm/hr), PCT 0.199% (0.108-0.282%), MCV 81.3 fl (80-100 fl), MCH 25.6 Pg (27-34 Pg), MPV 7.3 fl (6.5-12 fl), RBS 120 mg/dl (80-120 mg/dl), B. Urea 22 mg/dl (10-50 mg/dl) and S. Creatinine 0.8 mg/dl (0.7-1.4 mg/dl). Urine analysis reported pale yellow, acidic urine. Albumin was found in trace amounts while sugar was absent. Pus cells were 6-8/HPF, epithelial cells were 4-5 cells/HPF, and RBC cells were 5-8. Electrocardiogram was taken on the same day. Its report showed right atrial enlargement, poor R wave progression, and tachycardia. In chest X- ray, bilateral infiltration was found. Sputum AFB test was conducted to confirm tuberculosis that revealed positive outcome. Thus, patient was diagnosed to have pulmonary tuberculosis.

She had already started intravenous antibiotic empirical therapy (cefazolin) for the first five days along with intravenous deriphyllin, dexamethasone and oral medications included montelukast, acetaminophen and syrup brozedex. On sixth day of admission she was advised to start CAT 1 ATT drugs under DOTS therapy which included isoniazid, rifampicin, pyrazinamide and ethambutol. She had one dose of all them in the morning. After completing an hour, she developed an episode of seizure. There was no personal or family history of epilepsy or history of head injury. CT scan of head was normal and there was no history of any alcohol abuse. So, ATT drugs were withheld.

Rechallenge of ATT drugs was done one by one in consecutive days to check the drug reaction. But then patient did not show any signs of seizure. On tenth day, CAT 1 ATT drugs were restarted since the patient showed no intolerance. Thereafter, Vitamin B6 of dose 40 mg was also continued to administer along with these drugs to avoid seizure episodes.

## DISCUSSION

Drug-induced seizures can occur as a direct result of altering neural pathways and specific excitatory or inhibitory transmitters and receptors within those pathways. Many drugs and toxins can also cause seizures as

a result of indirect effects on brain perfusion, oxygenation or metabolic disturbances.<sup>7</sup> Patients with active disease are put on a regimen of INH combined with other anti-tubercular medications. It is a very safe anti-tubercular drug that has been used as a first-line agent for treatment of tuberculosis since 1952 yet is known to cause varied adverse effects. Central nervous system effects, such as headaches, dysarthria, irritability, seizures, dysphoria and restlessness, have been reported.<sup>8</sup> Convulsions are reported in patients being treated with isoniazid, with no prior history of seizure, however few patients have developed seizures with a single conventional doses of isoniazid.<sup>9</sup>

In this case report patient developed seizure episode with no family history or no medical background. Other possibilities of seizure were ruled out through clinical examinations as well as relevant examinations. Most of the case report studies say that isoniazid has the higher chance of causing neurological related adverse effects even when administered in their therapeutic dose. The adverse effects due to Isoniazid are divided into toxic, idiosyncratic and hypersensitivity reactions. Neurologic syndrome is dose-related, and seizures are attributed to over dosage.<sup>10</sup> The presumed etiology of isoniazid induced seizure involves a decrease in the availability of gamma-amino butyric acid (GABA). Isoniazid metabolites, such as isoniazid hydrazones, inhibit pyridoxine phosphokinase. This enzyme converts pyridoxine (vitamin B-6) to its active form, pyridoxal-5-phosphate. Pyridoxal 5 phosphate, a co-factor for glutamic acid decarboxylase enzyme required for the synthesis of GABA, which is the major inhibitory neurotransmitter in the central nervous system. The consequent reduction in GABA increases the susceptibility to seizures. Thus, neurologic effects of isoniazid are specifically countered by administration of pyridoxine.<sup>11</sup>

In our case, as seizures occurred with single dose of isoniazid, pyridoxine deficiency could not be the cause of seizures. Prolonged use of isoniazid might lead to pyridoxine deficiency and seizures, which respond to pyridoxine administration. There are three factors influencing the risk of INH induced neuropathy. The first is the dose of INH used. The second factor is the patient's nutritional status. The third factor is the INH acetylation rate. Patients who acetylate INH slowly are at an increased risk of developing neuropathy.

## CONCLUSION

In conclusion, physicians should be aware of possible isoniazid induced seizure even with therapeutic doses. Neurologic effects of isoniazid are specifically countered by administration of pyridoxine

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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