SEIZURES WITH SINGLE THERAPEUTIC DOSE OF ISONIAZID

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Summary: Isoniazid (INH) is an integral component of treatment of tuberculosis. An acute overdose is potentially fatal and is characterised by the clinical triad of repetitive seizures unresponsive to the usual anticonvulsants, metabolic acidosis with a high anion gap and coma. A case of isoniazid induced seizures after therapeutic dose of 600 mg, as a part of CAT I thrice weekly intermittent anti-tuberculosis regimen for pulmonary tuberculosis is reported. The frequency of the usage of Isoniazid as antituberculosis therapy requires that physicians be aware of such toxicity. [Indian J Tuberc 2012;59: 100-102]

Key words: INH, Seizures, Isoniazid, INH Toxicity

INTRODUCTION

Isoniazid is an effective and widely used drug in the treatment of tuberculosis. The administration of toxic amounts of isoniazid (INH) causes recurrent seizures, profound metabolic acidosis, coma and even death but therapeutic dose of isoniazid rarely causes seizures. Presented is a case of 65-year-old male who developed isoniazid induced seizures after first therapeutic dose as a part of CAT I thrice weekly intermittent anti-tuberculosis regimen with isoniazid 600 mg, rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg.

CASE REPORT

Mr S K, a 65-year-old non-smoker male, was admitted in emergency ward with history of seizure after administration of first dose of anti-tuberculosis chemotherapy for pulmonary tuberculosis. He was apparently well six months’ ago when he developed cough and expectoration. He was diagnosed as a case of sputum smear positive pulmonary tuberculosis. He was advised CAT I intermittent anti-tuberculosis regimen with isoniazid 600 mg, rifampicin 450mg, ethambutol 1200 mg and pyrazinamide 1500 mg thrice weekly. On the very first day of anti-tuberculosis therapy, he developed convulsions after one hour. He was admitted in the nearest health facility and was administered oxygen therapy and injection phenytoin intravenously and was referred to our institute after six hours. Patient’s wife told that he developed seizure one hour after taking two tablets of Isoniazid 300 mg and one capsule Rifampicin 450 mg. On admission, he was conscious, pulse rate was 82 per minute, blood pressure 120/80 mm of Hg and oxygen saturation of 95% at room air. Thorough nervous system examination revealed no abnormality. Routine blood examination revealed: haemoglobin 11.2 gm %, total leucocyte count 12400 cells / cu mm with polymorphs 94%, and lymphocytes 6%, blood urea 25mg% (normal 10-50mg%), serum creatinine 0.58 mg/dl (normal 0.20-1.20 mg%), serum sodium 140 mmol/1(normal 133-145 mmol /L), serum potassium 5.6mmol /L (normal 3.8-5.56mmol /L), fasting blood sugar 100mg% (normal 70-110 mg%). Platelet count was 150,000/ cu mm and routine urine analysis was normal. There was no personal or family history of epilepsy or history of head injury; CT scan head was normal. There was no history of alcohol abuse. After admission, there was no seizure for two days, anti-tuberculosis chemotherapy with rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg was administered orally. Isoniazid was withheld. He tolerated these drugs without any
adverse event. Isoniazid is an integral component of treatment of tuberculosis, so it was decided to add isoniazid 600 mg in the next dose along with rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg under supervision. After forty-five minutes of this treatment, he complained of dizziness and his body became stiff and head turned to one side followed by rhythmic tonic and clonic convulsions of both upper limbs. There was frothing at mouth. He was given injection 200 mg phenytoin intravenously stat and infusion of 600 mg phenytoin without any control over seizures. After 15 minutes, his attack was controlled with intravenous administration of 5 mg of diazepam. Later on, tablet pyridoxine 100 mg twice a day was given. Isoniazid was thus proved as the offending drug. Subsequently, his sputum culture sensitivity test revealed *Mycobacterium tuberculosis* resistant to Isoniazid and sensitive to rifampicin, pyrazinamide and ethambutol. His follow-up period was uneventful with daily regimen consisting of rifampicin 450 mg, ethambutol 800 mg and pyrazinamide 1500 mg, with which he is improving well.

**DISCUSSION**

Isoniazid is an antimicrobial that has been used as a first-line agent for treatment of tuberculosis since 1952. Patients with active disease are put on a regimen of INH combined with other antituberculous medications. It is a very safe antitubercular drug, yet is known to cause varied adverse effects. A minority of patients receiving INH experience neurological side effects, including peripheral neuritis, dizziness, and insomnia. INH may precipitate convulsions in patients with seizure disorder, and rarely, in patients with no history of seizure. 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. In our case, there was no previous personal or family history of epilepsy. All other possible causes of seizures were ruled out by thorough clinical examination and relevant investigations. Our patient developed severe acute isoniazid neurotoxicity with single therapeutic dose in the absence of overdose or any underlying conditions that would predispose him to such a severe adverse reaction. Remission and recurrence of seizures when isoniazid was stopped and reintroduced proved it to be an offending drug to induced seizures.

The adverse effects due to Isoniazid are divided into toxic, idiosyncratic and hypersensitivity reactions. In patients receiving conventional low dose INH therapy, symptoms usually do not appear until six months. With high doses of INH, symptoms often appear within three to five weeks. The earliest known and most widely recognized untoward effects of INH are the peripheral neuropathies. Pyridoxine, 50 mg daily, can prevent the occurrence of peripheral neuropathy in the high susceptibility groups. Neurologic syndrome is dose-related and seizures are attributed to overdosage. The susceptibility of adverse effects is the highest in individuals with liver disease, impaired renal function, epilepsy, psychosis, alcoholism, malnutrition and pyridoxine deficiency. None of these factors was present in our cases. Acute ingestion of as little as 1.5 g of INH can cause mild toxicity in adults. Doses larger than 30 mg per kg often produce seizures that are usually refractory to anticonvulsant therapy. Ingestion of the drug in amounts greater than 80 to 150 mg per kg can rapidly lead to death.

The presumed etiology of isoniazid-induced seizure involves a decrease in the availability of gamma-aminobutyric 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. Five grams of IV pyridoxine given over 5-10 minutes is sufficient to abolish the neurologic effects of isoniazid in
most cases. In case of INH toxicity, pyridoxine should be administered in a dose equivalent to the suspected amount of isoniazid ingested (i.e., gram-per-gram replacement). If amount of INH ingested is unknown, 5 gm of pyridoxine should be given intravenously. Repeat dosing may be required for persistent seizure activity. Prolonged use of isoniazid might lead to pyridoxine deficiency and seizures, which respond to pyridoxine administration. Pyridoxine administration did not help in the seizures with single conventional dose of INH. In our case, as seizures occurred with single dose of isoniazid, pyridoxine deficiency could not be the cause of seizures. In conclusion, physicians should be aware of possible isoniazid induced seizure even with therapeutic doses.

REFERENCES