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BRIEF REPORT

Seizures in an Immunocompetent Adult From Treatment of Latent Tuberculosis Infection: Is Isoniazid to Blame?

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Isoniazid-induced seizures are a rare adverse reaction especially in immunocompetent adults. We report a case of a healthy man with seizures shortly after ingestion of his first therapeutic dose of isoniazid with rifapentine therapy for treatment of latent tuberculosis infection. Only 6 other similar cases are reported in the literature.

Keywords. isoniazid; latent tuberculosis; pyridoxine; seizures; tuberculosis.

Latent tuberculosis infection (LTBI) is defined as *Mycobacterium tuberculosis* (TB) bacteria infecting an asymptomatic person who does not have risk of transmission to others. Worldwide, approximately 25% of the population has LTBI. According to the US National TB Surveillance System (2011–2015), an estimated 8.9 million persons (3.1%) have LTBI [1]. The Centers for Disease Control and Prevention (CDC) and American Thoracic Society strongly recommend testing and treating LTBI to avoid development of active TB disease. Treatment regimens for LTBI include isoniazid (INH), INH plus rifapentine (RPT), or rifampin (RIF) based therapy. A randomized controlled trial (RCT) published in 2011 demonstrated a once-weekly INH and RPT regimen for 12-weeks (3HP) to be as effective as 9 months of daily INH therapy for treatment of LTBI. Treatment completion rate in the directly observed once-weekly 3HP group was higher (82%) compared with the group receiving self-administered daily INH (69%) ($P < .001$) [2]. Increased adherence was attributed to directly observed and shorter duration of therapy. According to the recent guidelines published by the National Tuberculosis Controllers Association and CDC, INH is now considered as an alternative LTBI regimen due to long duration of therapy, hepatotoxicity, and potential low treatment completion rate [3]. Currently, the CDC recommends the 3HP regimen in persons that are 2 years or older, including those with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), as the preferred treatment of choice for LTBI [4].

Adverse effects of the 3HP regimen in the RCT indicated a higher number of cases that discontinued the 3HP regimen due to an adverse event (4.9%) compared with those on INH (3.7%) ($P = .0009$) [2]. However, there was no difference in serious adverse events or risk of death in either treatment group; moreover, the risk for hepatitis was lower with 3HP. A follow-up postmarketing observational study of 3288 US clinic-based patients who successfully completed the 3HP regimen reported adverse drug reaction in 35.7% of the patients [5]. The most common adverse reactions included nausea (15%), fatigue (12%), myalgias (8%), other systemic complaints (8%), and headaches (7%). Approximately 6% of patients complained of fever/chills, dizziness, or abdominal pain. Approximately 5% or less had rash/hives, appetite loss, neuropathy, diarrhea, or jaundice as reported reactions. No serious adverse reactions (including seizures) were reported. Despite the adverse reactions, 79% of the patients successfully completed LTBI treatment. Thus, the 3HP regimen is recognized as an effective, safe treatment with high treatment completion rates and potential to further decrease TB disease in the United States. In this study, we report the first case of seizures after the first dose of the 3HP regimen in an immunocompetent adult.

CASE

A 28-year-old man, originally from Pakistan, presented to the Employee Health for a pre-employment health screening. His QuantiFERON-TB Gold test was positive. Subsequent evaluation was negative for any signs or symptoms of active TB. Chest radiograph was negative for any pulmonary disease. Laboratory screening test was negative for HIV antigen/antibody with normal renal and hepatic function test. Diagnosis of LTBI was established. The patient had no other comorbidities, and he denied history of seizures. He did not have previous or active history of alcohol consumption or illicit drug use. He was not taking any medications or herbals at that time. He was initiated on the 3HP regimen (oral INH 900 mg with RPT 900 mg once weekly for 12 weeks). After ingestion of his first dose of 3HP, he returned to work. Approximately 1–2 hours postingestion, he had a medical doctor-witnessed generalized tonic-clonic (GTC) seizure lasting approximately 2 minutes. No tongue-biting,

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bowel, or bladder incontinence was observed. He was transferred to the emergency department (ED) in a postictal state. In the ED, vital signs were stable with blood pressure of 136/82 mmHg, pulse 106/minute, temperature 98.3°F, respiratory rate of 18/minute, oxygen saturation of 97% on room air, and weight of 70.8 kg. Physical examination was normal with the exception of altered mentation. While in the ED, he experienced another episode of GTC seizure lasting approximately 1minute. Point-of-care laboratory tests showed a blood glucose level of 143 mg/dL and normal serum electrolytes. Urine drug screen was not performed. He received 2 mg of lorazepam and was given 1 gram of levetiracetam. Due to concerns for potential INH toxicity, initially 250 mg of vitamin B6 was administered. Subsequently, toxicology was consulted and he received a loading dose of 4750 mg of vitamin B6. Serum vitamin B6 level was not collected before loading. All diagnostic tests per neurology recommendation were negative including computed tomography of the head, magnetic resonance imaging of the brain, and electroencephalography. Infectious diseases (ID) experts recommended withholding further LTBI treatment during hospitalization. He had no further seizures during the 24-hour observation period and was discharged home when mentation was back to baseline. He was seen in the outpatient ID clinic 10 days after the event. He denied any history of prior TB including close contact with persons with active TB, prior treatments for TB, or any further seizure activity since discharge. He had self-initiated oral vitamin B6 postdischarge with intermittent adherence, and the subsequent serum B6 level was 78 mcg/L (normal value 5–50 mcg/L). Due to concern for INH-induced seizures, he was initiated on RIF 600 mg oral daily regimen for 4 months. He successfully completed LTBI treatment with RIF without any reported adverse events.

DISCUSSION

Seizures are a rare but serious adverse reaction related to medication ingestion. Up to 6% of new-onset seizures are associated with drug toxicity [6]. Exposure to medications, including but not limited to opiods, antidepressants, antibiotics, stimulants, and immunosuppressants, can increase excitatory or reduce inhibitory neuronal activity inducing seizures. Most events are self-limited without serious consequences.

Among medications used to treat LTBI, there are currently no reports of RPT or RIF causing seizures in the adult population. The most common adverse reaction secondary to INH is elevation of serum transaminases, and the most severe and at times fatal reaction is hepatitis. Isoniazid diffuses readily across all body fluids including the cerebrospinal fluid (CSF) [7]. Isoniazid is associated with adverse reactions involving central nervous system (CNS), such as paresthesia, peripheral neuropathy, psychosis, and seizure, with undefined frequency. Usually, overdose or ingestion of a toxic dose of INH has been associated with these CNS reactions. A dose over 30 mg/kg may be associated with hallucinations, recurrent seizures, metabolic acidosis, hypotension, and coma. Death may occur at doses of over 80 mg/kg [8]. Isoniazid mainly acts by inhibiting pyridoxal-5-phosphate or pyridoxine phosphokinase enzyme, thus reducing gamma amino butyric acid (GABA) levels, an inhibitory neurotransmitter, and thus precipitating seizure activity. Pyridoxine is a cofactor in GABA synthesis and its deficiency can further enhance INH-induced seizures. Pyridoxine deficiency can be present in patients with underlying medical conditions such as pregnancy, cancer, uremia, alcoholism, chronic liver disease, and advanced age. In patients at high risk for peripheral neuropathy and other INH toxicities, concomitant supplementation of oral pyridoxine (25–50 mg daily) with INH is recommended [9]. Pyridoxine causes immediate cessation of seizures by rapidly binding to INH and restoring GABA production. The recommended pyridoxine treatment dose for an unknown INH overdose is a maximum of 5 grams intravenously to an adult or child [8]. Alternatively, in cases of the known ingested dose, a pyridoxine dose equivalent to the amount of INH ingested (gram for gram) is recommended.

In our case, the patient was immunocompetent with no known underlying risk factors to precipitate pyridoxine deficiency, and he did not consume a toxic dose of INH. Even though current literature reviews indicate that most cases of INH-induced seizures have been reported secondary to overdose or toxicity, it is worth noting that our patient received a dose 3 times higher than the usual daily dosing but consistent with intermittent dosing regimen per guidelines. He developed seizures 1–2 hours after INH and RPT ingestion. Plasma levels of INH usually peak 0.75 to 2 hours after dosing; meanwhile, CNS peak concentration occurs approximately 4 hours after ingestion [10, 11]. Peak plasma concentration of RPT occurs approximately 5 hours after ingestion, and overall CSF penetration is estimated to be low (lipophilic and plasma protein binding of 80%) [10, 12, 13]. These findings favor INH as the most likely culprit given its shorter peak time and good CSF penetration. To further determine causality, the Naranjo adverse drug reaction probability scale was applied and validated INH as probable cause for the seizures (score = 6) [14]. Due to concern for INH-induced seizures, th patient received the maximum dose of pyridoxine, which possibly prevented further seizures.

To our knowledge, only 6 case reports are published on INH-induced seizures after receiving a therapeutic INH dose (Table 1). Of the 6 reports, 67% cases were receiving INH treatment for active TB [15–18]. Of the 2 LTBI cases, 1 was an elderly patient with end-stage renal disease and 1 was an adult with HIV infection [19, 20]. All 6 reported cases had underlying medical conditions, except for 1 elderly man receiving treatment for pulmonary TB. Pyridoxine treatment was successful in achieving cessation of refractory seizures in two thirds of the reported cases. One did not respond to any treatments and died. One did not receive pyridoxine, but TB treatment was stopped.

Table 1. Literature Review of Six Case Reports on INH-Induced Seizures

Cases	Age (years)	Sex	Underlying Illness	Diagnosis	Ongoing Treatment	Time to Seizure	Type of Seizure	Seizure Response	Outcome
1	67	M	Hypertension, Chronic kidney disease	Disseminated TB	INH 200 mg daily, pyridoxine 25 mg daily, Streptomycin 250 mg daily	13 days	GTC	No response to phenytoin, pyridoxine 500 mg, diazepam, phenobarbital	Died
2	35	M	Alcohol and tobacco abuse	Pulmonary TB	INH 600 mg+RIF 450 mg+PZ 1500 mg+ETM 1200 mg (thrice weekly)	Within 24 hrs	GTC	Response to cessation of TB treatment	Survived
3	65	M	None	Pulmonary TB	INH 600 mg+RIF 450 mg+ETM 1200 mg+PZ 1500 mg (thrice weekly regimen)	1 hour after first dose	GTC	Unresponsive to phenytoin, diazepam. Response to pyridoxine 100 mg bid	Survived
4	86	F	Hypertension, Pleuritis, Diabetes mellitus	Disseminated TB	INH 200 mg+RIF 450 mg+ETM 750 mg daily	7 days	GTC	No response to diazepam, phenobarbital, phenytoin. Response to pyridoxal phosphate 60 mg/day	Survived
5	66	F	End-stage renal disease on peritoneal dialysis	LTBI	INH 300 mg daily	24 hours–2 days	Focal	Response to pyridoxine 50 mg	Survived
6	44	F	HIV	LTBI	INH 300 mg daily	2 months	GTC, Status epilepticus	No response to lorazepam, phenytoin, Response to pyridoxine 5 g	Survived

Abbreviations: ETM, ethambutol; F, female; g, gram; GTC, generalized tonic-clonic; HIV, human immunodeficiency virus; INH, isoniazid; LTBI, latent tuberculosis infection; M, male; PZ, pyrazinamide; RIF, rifampin/rifampicin; RPT, rifapentine; TB, tuberculosis.

CONCLUSIONS

Our case is unique and illustrates the possibility of risk of seizures while treating an immunocompetent adult with therapeutic doses of INH. Our patient did not have comorbidities or evidence of malnutrition. Healthcare providers should be cognizant of this uncommon but potentially severe adverse reaction and consider concomitant therapy with vitamin B6 during INH treatment and administering appropriate pyridoxine dosing if a seizure occurs.

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