Convulsive Seizures with a Therapeutic Dose of Isoniazid

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Abstract

An 86-year-old woman who had been treated for tuberculous peritonitis and pulmonary tuberculosis, exhibited a disturbance of consciousness and tonic-clonic convulsions seven days after the administration of the antituberculous drug isoniazid. As her serum vitamin B6 level was remarkably low, she was diagnosed with convulsive seizures due to vitamin B6 deficiency associated with isoniazid treatment. Seizures refractory to standard anticonvulsant therapy were controlled with the administration of pyridoxine. Most reported cases of isoniazid-induced convulsive seizures occurred as a result of an overdose due to attempted suicide. This report presents a case of convulsive seizures that occurred in association with the short-term administration of a therapeutic dose of isoniazid.

Key words: isoniazid, seizure, pyridoxine, tuberculosis

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Introduction

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 (1). 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 (2). Major adverse events include hepatitis and peripheral neurotoxicity, which is uncommon at conventional doses (3). Central nervous system effects, such as dysarthria, irritability, seizures and the inability to concentrate, have been reported; however, the specific incidences remain unclear (1). Most reported INH-induced seizures occurred as a result of an overdose in suicide attempts (4-7). 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 (8).

The occurrence of seizures at conventional doses has rarely been reported (9). This report presents a case of convulsive seizures that occurred in association with the administration of a short-term therapeutic dose of INH.

Case Report

An 86-year-old woman whose medical history included pleuritis, hypertension and diabetes mellitus complained of abdominal distension two months prior to admission. An abdominal computed tomography (CT) scan revealed a large quantity of ascitic fluid and peritoneal thickening. A characteristic of the ascites was an exudative pleural effusion with lymphocyte predominance and a high level (80.1 U/L) of adenosine deaminase (ADA). Neither bacteria nor tumor cells were detectable in the ascites. However, the patient had experienced pleuritis of the right lung at 20 years of age, and chest radiography showed pleural thickening with calcification. The QuantiFERON®-TB Gold In-Tube (QFT-GIT Cellestis Limited, Carnegie, Victoria, Australia) test, an interferon-γ release assay used to diagnose tuberculosis with high sensitivity and specificity (10), was positive, and Mycobacterium tuberculosis was detected in the sputum cultures. Consequently, tuberculous peritonitis and pulmonary tuber-
cution were diagnosed. The patient’s weight was 45 kg. She did not have a history of excessive alcohol consumption. Her liver function and renal function tests were normal (aspartate aminotransferase: 23 IU/L, alanine aminotransferase: 8 IU/L, blood urea nitrogen: 14.4 mg/dL, creatinine: 0.83 mg/dL). After ascitic drainage was performed, antituberculous drugs were administered, including INH at a dose of 4.4 mg/kg/day (200 mg daily), rifampicin at a dose of 10 mg/kg/day (450 mg daily) and ethambutol at a dose of 16.6 mg/kg/day (750 mg daily). Vitamin B₆ should have been administered taking into consideration the patient’s age and history of diabetes mellitus. However, vitamin B₆ was not prescribed in order to reduce the risk of noncompliance due to the large number of tablets.

On day 5, the patient complained of visual and auditory hallucinations; however, no abnormalities were apparent on a head CT scan. Two days later, the patient developed a disturbance of consciousness and tonic-clonic convulsions. On an examination, her blood pressure was 180/92 mmHg, her temperature was 36.3°C, her heart rate was 107 beats/min, her respiratory rate was 26 breaths/min and her oxygen saturation was 97% on room air. The findings of a systemic physical examination were normal. She was unconscious and moved all four extremities equally upon receiving a deep painful stimulus. Her limbs exhibited tonic-clonic convulsions. Chest radiography showed no definite interval changes. No abnormal findings were detected on head CT or magnetic resonance imaging (MRI) scans (Fig. 1). The findings of a cerebrospinal fluid examination were normal, and both acid-fast bacteria stains and culture tests were negative. Even after conducting other tests, including electroencephalography, the cause of the convulsions was not identified. The usual laboratory findings for causes of convulsions were absent, except for the important finding that the patient’s serum vitamin B₆ level was remarkably low (pyridoxamine: PAM <0.2 ng/mL, normal range <0.6 ng/mL), pyridoxal: PAL <2.0 ng/mL (4.0-19.0 ng/mL), pyridoxine: PIN <3.0 ng/mL (<3.0 ng/mL)). No other medicines that cause vitamin B₆ deficiency were administered. This led us to diagnose the patient with convulsive seizures due to vitamin B₆ deficiency associated with INH treatment. The patient did not complain of peripheral neuropathy.

Although diazepam (10 mg), phenobarbital (500 mg) and phenytoin (500 mg) were administered intravenously as needed and phenytoin (200 mg) was taken daily, the clonic convulsive seizures did not stop. The antituberculous drugs were discontinued and pyridoxal phosphate hydrate (60 mg per day) was administered, after which the number of convulsive seizures gradually decreased; The seizures then ceased altogether three days after pyridoxal phosphate hydrate was first administered. The serum vitamin B₆ level normalized eight days after the start of treatment (PAM <0.2 ng/mL, PAL 50.3 ng/mL, PIN <3.0 ng/mL). Phenytoin (200 mg) and pyridoxine (60 mg) were administered daily starting on day 7. Because the patient’s condition was complicated by intensive care unit delirium, the visual and auditory hallucinations were prolonged. After the central nervous symptoms disappeared, she resumed taking ethambutol (500 mg daily) starting on day 38 in addition to rifampicin (450 mg daily) and INH (200 mg daily); however, neither the convulsive seizures nor liver function abnormalities recurred. The serum vitamin B₆ level was stable seven days after resuming the INH therapy (PAM <0.2 ng/mL, PAL 62.1 ng/mL, PIN <3.0 ng/mL). The patient was able to continue taking these medicines until the end of treatment (Fig. 2).

**Discussion**

INH can cause various adverse events. Central nervous system effects, such as headaches, dysarthria, irritability, seizures, dysphoria and restlessness, have been reported (2). Central nervous system effects occur due to vitamin B₆ deficiency. In the present case, a deficiency of vitamin B₆ was regarded to be the cause of the patient’s convulsive seizures because the serum vitamin B₆ level on admission was low. Similar to that observed in previously reported cases, the seizures in our case were refractory to anticonvulsant therapy (11). The rate of production of GABA is influenced by the level of pyridoxal 5’ phosphate. The administration of anticonvulsants, such diazepam and phenytoin, alone is not
effective; however, when combined with vitamin B₆, these medications offer complete protection from seizures. In this case, treatment with pyridoxal phosphate hydrate was effective, although the improvement was slow because the patient was given only a small amount of pyridoxine.

It has been suggested that the concurrent administration of vitamin B₆ protects against the development of INH peripheral neuropathy (12). However, it is not necessary to routinely prescribe vitamin B₆ supplements for patients taking a standard dose of INH for the following reasons: 1) peripheral neuropathy occurs infrequently and is easily reversible upon the institution of high-dose vitamin B₆ therapy; 2) supplementation of vitamin B₆ raises the cost of treatment; and 3) patient compliance with therapy may be adversely affected by an increase in the number of tablets prescribed (13).

In the present case, we gave priority to the internal use compliance of the patient, who had no medical history of seizures. Neither pyridoxine nor pyridoxal phosphate hydrate were administered, as vitamin B₆ is generally sufficiently provided in the daily diet. The patient suffered from central nervous system effects. An acute overdose of INH can cause severe toxicity, as the level of toxicity is closely correlated with the dose of INH. However, the development of convulsive seizures associated with the short-term ingestion of a therapeutic dose of INH is rare.

There are three factors influencing the risk of INH-induced neuropathy. The first is the dose of INH used. The incidence of peripheral neuropathy has been shown to be dose-related, with a large dose resulting in a high rate of adverse effects. The second factor is the patient’s nutritional status. Money reported that the incidence of peripheral neuropathy is increased in malnourished patients (14). The third factor is the INH acetylation rate. Patients who acetylate INH slowly are at an increased risk of developing neuropathy.

In the present case, mild central nervous symptoms developed five days after the start of therapy, and the convulsions developed on the seventh day. The signs and symptoms of INH-induced neurologic syndrome tend to appear much later in patients who take low doses of INH than in those taking high doses (12). In the present case, the blood level of INH did not suddenly increase; however, the vitamin B₆ deficiency gradually developed, suggesting that the patient’s nutritional status most affected the development of convulsions. The patient did not consume a diet adequately rich in vitamin B₆ due to peritonitis.

This case is unique because the short-term ingestion of a therapeutic dose of INH resulted in the development of convulsive seizures. The supplementation of vitamin B₆ is recommended in patients with other conditions indicative of subclinical vitamin B₆ deficiency to help prevent central nervous system effects.

The authors state that they have no Conflict of Interest (COI).

References
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