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CASE REPORT

Side effects of isoniazid: case report

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Abstract

Treatment of latent tuberculosis infection (LTBI) is an important preventive measure and deserves international interest. Although other LTBI treatment regimens exists, the use of isoniazid is established. The present case report is of a 9-year-old boy with asthma and epilepsy who presented adverse reactions to the use of isoniazid prescribed as a therapy for ILTB. After withdrawing the drug that was replaced by rifampicin, the patient showed clinical improvement.

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INTRODUCTION

The WHO estimated that one million new cases of tuberculosis (TB) involving children aged less than 14 years occurred in 2017, with most cases and deaths by the disease affecting individuals below the age of five years[1,2].

TB prevention is based on the immunization of newborns with the BCG vaccine, the treatment of patients with the bacillus, and the treatment of individuals with latent TB infection (LTBI). LTBI is characterized as having contact with an adult with TB, showing no clinical or imaging signs of the disease, and having a positive tuberculin skin test[3].

Diagnosis involves analyzing instances of close contact between the child and an adult with TB considered the index case.[4] The child, if asymptomatic and with normal X-ray images and an induration greater than 5 mm, is diagnosed with LTBI[5].

Treatment of LTBI is required to control TB, since it may prevent future cases and consequently decrease the transmission of the disease. Treatment is offered to individuals diagnosed with LTBI and subjects belonging to groups at risk of developing active TB.

Two drug protocols are prescribed in Brazil to individuals with LTBI: six to nine months of isoniazid (INH) and four months of rifampicin (RMP). A reporting system for LTBI treatment was recently implemented to monitor, assess, and follow cases and potential adverse effects[6].

INH has been used in the treatment of LTBI since 1952. The compound features a simple structure, made with a pyridine ring and a hydrazide group, with a minimum inhibitory concentration (MIC) for *Mycobacterium tuberculosis* of 0.02-0.20 µg/mL[7].

It works as a bactericide against bacilli with high rates of multiplication but is not as effective against slow growth bacilli (usually intracellular) and bacilli with intermittent multiplication rates (generally extracellular). It is highly soluble in water, with greater stability at a pH of 6.6. It can be delivered through all fluids and tissues of the body, including the central nervous system. The most significant adverse effects described in the literature originate in the nervous system and the liver, both rare in children. Serum levels of the drug in children and adults depend on the acetylation rate (rapid, intermediate or slow), determined by the different N-acetyltransferase 2 genotypes of each ethnicity. INH is used in prophylaxis against TB at a dose of 10 mg/kg per day up to a maximum of 300 mg[8,9].

Severe adverse reactions to INH may require replacement with another drug. The most severe adverse reactions include[6]:

a) Psychosis, seizures, mental confusion, and coma: These are less frequent, more severe complications, often hard to diagnose. Differential diagnosis must consider tuberculous meningitis and hepatic encephalopathy. Suicide attempts have been reported in patients on isoniazid.

b) Hematologic disorders or vasculitis: These are rare events that occur due to hypersensitivity.

c) Peripheral neuropathy: It occurs in about 20% of the cases. It is a dose-dependent condition that is uncommon in patients given 5 mg/kg a day of medication. Frequency increases with doses greater than 300 mg/day. The risk of polyneuritis increases in the presence of other factors such as advanced age, diabetes mellitus, alcohol drinking, nutritional deficiency, slow acetylation phenotype, HIV infection, kidney failure, pregnancy, and breastfeeding. Prophylactic care is performed with pyridoxine 25-50 mg/day. Appearance of polyneuritis calls for the administration of 100-200 mg/day of the vitamin.

d) Clinical hepatitis: Recent studies showed that the incidence of clinical hepatitis is lower than previously thought. The incidence of hepatitis was 0.6% in a meta-analysis that combined six studies looking into the use of isoniazid alone. When combined with rifampicin, incidence increased to 2.7%. When isoniazid is prescribed alone, risk increases with age. Clinical hepatitis is rarely seen in individuals aged less than 20 years, while 2% of the patients aged 50-64 years will develop the disease. Risk also increases in individuals with a history of liver disease, persons who drink alcohol daily and heavy drinkers, and females in the immediate postpartum. Fatal cases of hepatitis are extremely rare, with death reported in less than 0.023% of the cases. Treatment must be suspended and the causing drug identified in cases of therapy schemes with multiple drugs.

e) Lupus-like: Patients may develop antinuclear antibodies while on isoniazid. Less than 1% develop systemic lupus erythematosus. Incidence is equal in either of the sexes. Isoniazid may deteriorate the condition of patients with preexisting lupus.

This article describes the case of a patient with LTBI and epilepsy on anticonvulsants who developed an adverse reaction when given INH.

CASE REPORT

A nine-year-old boy with epilepsy and asthma on a prescription of beclomethasone dipropionate nasal spray and salbutamol spray 300mcg/dose in case of asthma attacks, in addition to carbamazepine, valproic acid, phenobarbital, and topiramate.

The patient was prescribed pulse steroid therapy with prednisolone for presenting difficult-to-manage seizures which required frequent hospitalization. X-ray images of the chest taken previously were normal and the patient had a positive

tuberculin skin test with a 6 mm induration. His guardian said he had not been in contact with anyone with tuberculosis. The patient was treated for LTBI and started on INH (200 mg/day).

When the patient was taken to an appointment 45 days after the start of treatment, his aunt said that he began to experience more focal seizures and increased hypoactivity 15 days after he was prescribed INH. The patient did not have signs of infection. INH was replaced with RMP (10 mg/kg/day). The patient was taken to an appointment 15 days after he was prescribed RMP and his guardian said that he had improved from the seizures and that he now interacted more actively with the environment around him.

The patient progressed well, without other complaints, and was advised to take the medication until the end of the four months of treatment as stipulated in Brazilian standards of care[6].

DISCUSSION

The patient described in this report had been previously diagnosed with asthma and epilepsy. Since he was started on pulse steroid therapy, considered an immunosuppressive therapy, and had a positive skin tuberculin test, the choice was made to start treatment for LTBI with INH.

Concurrent use of immunosuppressive therapy, immunobiologicals, and antineoplastic drugs also require the prescription of preventive therapy against TB to asymptomatic individuals with normal chest X-ray images and positive skin tuberculin tests, despite the absence of recent contact with someone with TB[6,10].

The patient described in this report had epilepsy and asthma, which placed him at risk of adverse events if he was prescribed INH. Isoniazid produced severe side effects and increased the occurrence of focal seizures in our patient, which only subsided after INH was changed for RMP.

Children are usually fast acetylators. Slow acetylators develop more adverse effects[6]. In clinical practice, one cannot determine whether a patient is a slow or fast acetylator.

Even though this has not been described in the literature, one cannot rule out the possibility that our patient suffered from drug interactions between INH and prescribed anticonvulsants.

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