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Correspondence

Isoniazid-induced liver disorder in the treatment of tuberculosis

Dear Editor,

Liver damage occurs in 18–20% of patients taking isoniazid; however, in most cases, a slight increase in serum glutamic oxaloacetate transaminase (SGOT) occurs when the medication is continued.[1] Notwithstanding, in around 1% of patients, isoniazid causes hepatitis.[2–4] There are currently no methods for determining whether a patient with a marginally increased SGOT will develop hepatitis upon continuing isoniazid.[5] Clinical highlights are widely variable, ranging from gastrointestinal indications, a virus-like disease, or tricky jaundice to extreme touchiness such as fever, rash, and eosinophilia.[6]

The general conclusions were that liver sickness can occur in patients on isoniazid preventive treatment. Age is a prevalent factor that appears to increase the risk of liver damage among subjects accepting isoniazid.[7] This dynamic liver harm occurs infrequently in patients <20 years old, up to 0.3% in patients aged 20–34 years, up to 1.2% in patients aged 35–49 years, and up to 2.3% in patients aged ≥50 years.[8] Daily liquor consumption may likewise increase the risk. The recurrence may differ among places and times and contingent on unknown factors. The liver sickness that develops is not an after-effect of a specific assembling procedure or contaminant.[9] The improvement of the liver malady is not surprising in any individual patient. The morphological pathology of isoniazid liver infection, as directly comprehended, does not allow its prepared separation from viral hepatitis.[10] Routine checking by lab tests such as SGOT or serum glutamic pyruvate transaminase (SGPT) is not valuable for foreseeing hepatic maladies in patients taking isoniazid. Here we report on isoniazid-induced liver disorder in the treatment of tuberculosis.

Case 1 is a 40-year-old man who was admitted to the casualty medical ward in a tertiary care hospital complaining of fever, abdominal pain, persisting vomiting, breathlessness, and decreased sleep and appetite. He was diagnosed with sputum-positive pulmonary tuberculosis 2 months prior with positive radiological findings on a chest X-ray and started on category one anti-tubercular therapy (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1.5 gm/day, ethambutol 800 mg/day, and pyridoxine 20 mg/day). The patient's medical record showed indinavir use and subsequent treatment with a tenofovir + lamivudine + nevirapine (TLN) regimen. There was no past personal or family history of liver disorder. The patient weighed 65.0 kg; his blood pressure and pulse rate at admission were 100/70 mmHg and 84 beats/min, respectively. The clinical examination revealed that all body systems were within normal limits except for liver function as evidenced by elevated bilirubin and liver enzymes. Within a few days after starting category one anti-tubercular therapy, signs of liver dysfunction were observed, the patient was treated symptomatically by the withdrawal of the anti-tubercular therapy and cured. The anti-tubercular therapy was restarted and he developed the same signs of liver dysfunction.

The patient's signs of liver dysfunction were treated by withdrawal of the anti-tubercular therapy and symptomatic treatment with paracetamol, ondansetron, dicyclomine, and pantoprazole. The patient's condition improved over the next 3 days; he was then discharged with modified anti-tubercular therapy without isoniazid. On review, his condition improved without any signs of liver dysfunction. The Naranjo Reverse Drug Reaction Probability Scale and World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria were applied to determine the cause of the suspected adverse drug reaction (ADR). The causality assessment with both scales revealed that the ADR being due to

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isoniazid in this case was "probable" (Naranjo overall score, 6); on the modified Hartwig and Siegel scale, it was categorized as a moderate 4(b) reaction.

Case 2 is a 60-year-old man who was admitted to the casualty medical ward in a tertiary care hospital with complaints of fever, abdominal discomfort, and generalized weakness. He was diagnosed with sputum-positive pulmonary tuberculosis with positive radiological findings on chest X-ray and started on category one anti-tubercular therapy (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1.5 g/day, ethambutol 800 mg/day, and pyridoxine 20 mg/day). His medical record revealed a history of indinavir use and subsequent TLN regimen treatment. There was no past personal or family history of liver disorders. The patient weighed 75 kg and the blood pressure and pulse rate at admission were 110/70 mmHg and 86 beats/min, respectively. The clinical examination revealed that all body systems were within normal limits except for liver function, i.e., elevated bilirubin and liver enzyme levels.

The patient was diagnosed with positive pulmonary tuberculosis and started on category one anti-tubercular therapy. Within a few days, the patient had developed signs of liver dysfunction, which were treated by the withdrawal of anti-tubercular therapy and symptomatic treatment with ursodeoxycholic acid, paracetamol, ondansetron, streptomycin, levofloxacin, and pantoprazole. The patient's condition improved over the next 3 days. He was then discharged with modified anti-tubercular therapy without isoniazid. On review, his condition improved without any signs of liver dysfunction. The causality of the ADR was assessed using the Naranjo and WHO-UMC criteria. Both scales revealed that the ADR being due to isoniazid in this case was "probable" (Naranjo overall score, 6); on the modified Hartwig and Siegel scale, it was categorized as a moderate 4(b) reaction.

Case 3 is a 60-year-old woman who was admitted to the casualty medical ward in a tertiary care hospital with complaints of loss of appetite and vomiting. She was diagnosed with sputum-positive pulmonary tuberculosis with positive radiological findings on a chest X-ray and started on category one anti-tubercular therapy (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1.5 g/day, ethambutol 800 mg/day, and pyridoxine 20 mg/day). There was no past personal or family history of liver disorder. The patient weighed 75 kg and had an admission blood pressure and pulse rate of 120/90 mmHg and 86 beats/min, respectively. The clinical examination revealed that all body systems were within normal limits except liver function (elevated bilirubin and liver enzyme levels; total bilirubin, 4.3 mg/dl; SGPT, 263 U/L; SGOT, 143 U/L; total protein, 6.2 mg/dl; albumin, 2.4 mg/dl). The patient was diagnosed with positive pulmonary tuberculosis and started on category one anti-tubercular therapy. Within a few days, the patient developed signs of liver dysfunction. The patient was symptomatically treated by the withdrawal of the category one anti-tubercular therapy and then restarted on the same therapy; soon thereafter, she developed the same signs of liver dysfunction.

The anti-tubercular therapy was withdrawn again and the patient was treated symptomatically with ursodeoxycholic acid, pantoprazole, and ondansetron. The patient's condition improved over the next 3 days. She was then discharged with modified anti-tubercular therapy without isoniazid. On review, her condition improved without any signs of liver dysfunction. The causality assessment on both scales revealed that the ADR being due to isoniazid was "probable" (Naranjo overall score, 6); on the modified Hartwig and Siegel scale, it was categorized as a moderate 4(b) reaction.

Isoniazid is metabolized via an acetylation process by *N*-acetyltransferase (NAT-2) in the liver, where it is converted to acetyl isoniazid. The *N*-acetyl isoniazid undergoes hydrolysis to form acetyl hydrazine (AcHz).[2] The polymorphisms of NAT-2 cause people to be either "quick" or "moderate" acetylate metabolizers. Slow acetylate metabolizers shunt some isoniazid to an optional metabolic pathway of oxidation via cytochrome P450, delivering hydrazine (Hz). This suggests that both AcHz and Hz, produced separately by the quick and moderate acetylate metabolizers, participate in responses that create oxidative pressure (e.g., free radicals). Hz may instigate cytochrome P450 (specifically CYP2E1), expanding the generation of an extra-harmful metabolite. Subsequently, hepatotoxicity may occur in both fast and moderate acetylate metabolizers, however for somewhat extraordinary reasons.[3] Isoniazid acetylation forms ac-isoniazid via the *N*-acetyltransferase (NAT) enzyme, while hydrolysis delivers isonicotinic acid and Hz via amidase. Acisoniazid can likewise be hydrolyzed to form isonicotinic acid and AcHz. Moreover, Hz can be acetylated to AcHz and diacetyl Hz. Hz and AcHz are believed to be additionally oxidized to responsive metabolites and engaged with isoniazid hepatotoxicity, which was proposed to be intervened by microsomal P450, particularly CYP2E56.[5]

Once a drug-induced liver disorder develops, all conceivably hepatotoxic medications must be discontinued until the clinical and biochemical determination of the hepatotoxicity causation is made. In the meantime, no fewer than three non-hepatotoxic medications (e.g., ethambutol, streptomycin, and quinolones;

or levofloxacin, ofloxacin, or ciprofloxacin) can be utilized after suitable assessment of the patient's renal capacity and visual acuity.[6] After the thorough determination of transaminases, most anti-tubercular medications can be carefully restarted. The British Thoracic Society suggested that primary anti-tubercular medications can be reintroduced sequentially in the order of isoniazid, rifampicin, and pyrazinamide with regular observation of the patient's biological condition and liver capacity. Isoniazid should be started at a dosage of 50 mg/day and gradually increased to 300 mg/day, more than a few days in the event that it is all around endured and preceded thereafter.[7] A few days later, rifampicin can be started at a dosage of 75 mg/day and gradually increased to 300 mg/day. Thereafter, it can be increased to 450 mg (<50 kg) or 600 mg (>50 kg) according to the patient's weight. On the off chance that this medication is not well-tolerated, it is discontinued. And finally, pyrazinamide can be started at 250 mg/day, gradually increased to 1000 mg/day, and then increased to 1500 mg (<50 kg) or 2000 mg (>50 kg) according to the patient's body weight. On the off chance that these medications are not well-tolerated, they can be discontinued.

Tuberculosis is more pervasive in developing nations like India. Subsequently, physicians must know about the medication danger profiles of anti-tubercular drugs like isoniazid. The mental complexities can enormously affect the patients' personal satisfaction and a physician's state of mind about using isoniazid; thus, effective control of these inconveniences is critical. These case reports explain the features of isoniazid-induced liver disorders.

Conflict of interest

Authors do not have any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdtm.2018.11.003.

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