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CASE STUDIES IN TOXICOLOGY

Series Editor: **Lewis S. Nelson, MD**

INH-Associated Hepatoxicity

A teenage boy who has been undergoing isoniazid (INH) treatment for latent tuberculosis presents to the ED with signs and symptoms of hepatotoxicity. The mechanism of action of INH, the drug's role in causing hepatotoxicity, and current management recommendations are discussed.

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Case

A 13-year-old boy presents to the ED with a 4-day history of jaundice, upper abdominal pain, nausea, vomiting, and headache. He had a positive result on a tuberculin skin test 2 months ago and has been taking isoniazid (isonicotinylhydrazine; INH) for treatment of latent tuberculosis. The patient has no other pertinent medical history and uses no other medications. He visited his primary care physician 4 days earlier for nausea and vomiting. Although the INH was discontinued at that time, he developed progressive jaundice and abdominal pain.

On physical examination, the patient is alert and oriented with the following vital signs: blood pressure, 113/62 mm Hg; heart rate, 88 beats/min; respiratory rate, 14 breaths/min; pulse oximetry, 100% on room air; temperature, 37.1°C. His skin is jaundiced, but without ecchymoses or petechiae. Eye examination reveals scleral icterus. Cardiovascular and pulmonary findings are unremarkable. His abdomen is soft but diffusely tender to palpation, without any organomegaly, rebound, guarding, or rigidity. Initial laboratory test results include an aspartate aminotransferase (AST) level greater than 2,600 U/L; alanine aminotransferase (ALT) level greater than 2,600 U/L; total bilirubin level greater than 20 mg/dL; international normalized ratio (INR) of 3.7; and acetaminophen concentration less than 10 µg/mL.

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What is the mechanism by which INH treats tuberculosis?

INH interferes with synthesis of mycolic acids, long-chain fatty acids containing 70 to 90 carbons that are a key component of the mycobacterial cell wall. INH is a prodrug that enters mycobacteria by passive diffusion, where it is metabolized by KatG, an intracellular catalase-peroxidase, to its active form, INH-NAD (INH–nicotinamide adenine dinucleotide), in which INH forms a covalent adduct with NAD. This active form irreversibly inhibits InhA, an enzyme needed for the biosynthesis of mycolic acids that requires reduced NAD, or NADH, as a cofactor. Without mycolic acids, the cell wall cannot develop properly, and the mycobacterium dies.[1]

How does INH cause hepatotoxicity?

The primary means for INH metabolism in humans is through acetylation by N-acetyltransferase 2 (NAT-2) in the liver, a reaction that generates acetylisoniazid. Acetylisoniazid can undergo hydrolysis to form the toxic metabolite acetylhydrazine (and nontoxic isonicotinic acid). Polymorphisms of NAT-2 identified in humans determine whether an individual has the "rapid-" or "slow-acetylator" phenotype. Those with the slow phenotype shunt some INH to a secondary metabolic pathway of oxidation via cytochrome P-450 enzymes, producing hydrazine as well as nontoxic isonicotinic acid (Figure). It appears that both acetylhydrazine and hydrazine, generated by rapid and slow acetylators, respectively, are capable of participating in reactions that generate oxidative stress (eg, free radicals). Hydrazine may induce cytochrome P-450 enzymes (specifically CYP2E1), increasing production of additional toxic metabolites. Thus, hepatotoxicity may occur in both rapid and

slow acetylators, albeit for slightly different reasons.[2]

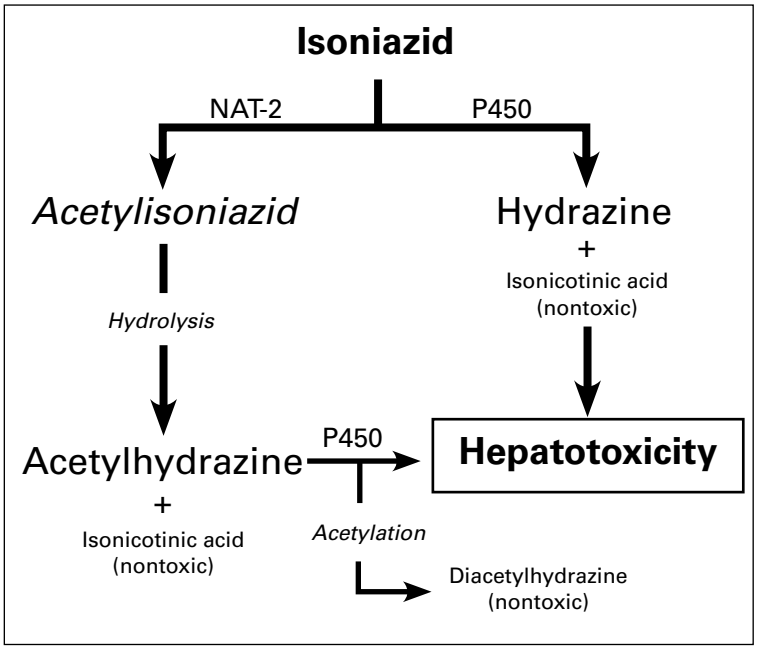
What is the frequency of hepatotoxicity in patients taking INH?

It was previously suggested that approximately 10% of all patients treated with INH will have a twofold to threefold increase in ALT over baseline levels and that 10% of these patients (1% overall) will develop clinical hepatitis (nausea, vomiting, jaundice, or abdominal pain).[3] Furthermore, it was reported that 10% of those with hepatitis (0.1% overall) can be expected to develop fulminant hepatic failure with an outcome of liver transplantation or death. However, this pessimistic prediction was subsequently refuted by studies that excluded high-risk patients (eg, those older than 35 years with unknown tuberculin purified protein derivative [PPD] converter status); these studies also employed a more aggressive approach to surveillance for early signs of hepatotoxicity. A prospective 7-year survey study conducted in a public health clinic followed a population of more than 11,000 patients for the duration of treatment for latent tuberculosis with INH.[4] Hepatitis was diagnosed clinically in 11 patients, all of whom demonstrated improvement when the drug was discontinued. Not only did the investigators demonstrate a reduced incidence of hepatotoxicity in therapeutic INH use (0.1%[4] vs the previously reported 1%[3]); they also confirmed the earlier finding[3] that increasing age is a risk factor for hepatotoxicity. In another study, the reported incidence of hepatotoxicity (defined as AST >5 times the upper limit of normal [ULN]) was 0.6% (19/3,377 patients), although only 1 of the 19 patients had clinical symptoms.[5] The higher frequency observed in this study may be due to the inclusion of older patients, as 55% of the study cohort was older than 35 years. Indeed, the subgroup data analysis showed that risk factors for developing hepatotoxicity were age greater than 50 years and a baseline AST concentration greater than the ULN.

What is the currently recommended regimen for INH use in patients with latent tuberculosis?

Recognizing the trade-off between treating latent tuberculosis and the slightly increased risk of INH-induced hepatotoxicity in individuals older than 35 years, the current guidelines recommend treatment of all known tuberculin PPD converters, regardless of age.[6,7] Pregnant women, who have an increased risk of hepatotoxicity, should not receive INH prophylaxis unless the risk of developing tuberculosis is high. If possible, delaying therapy for 2 to 3 months after delivery is recommended; however, INH is not teratogenic. Breastfeeding is not a contraindication.

FIGURE. INH Metabolism and Hepatotoxicity



INH = isoniazid; NAT-2 = N-acetyltransferase 2; P450 = cytochrome P-450.

What are the current recommendations for INH hepatotoxicity surveillance?

The current recommendations for surveillance in patients using INH are complex and allow the physician discretion in choosing whom to monitor. The American Thoracic Society recommends the following: (1) Baseline blood tests are generally not recommended for healthy patients treated with INH or rifampin; (2) baseline and follow-up measurement of serum ALT and bilirubin is recommended for patients with a possible liver disorder (ie, those with a history of chronic liver disease [hepatitis B or C, alcoholic cirrhosis] or chronic alcohol use), HIV patients receiving HAART (highly active antiretroviral therapy), pregnant women, and women up to 3 months postpartum; (3) baseline testing should be considered for those with

chronic medical conditions; (4) baseline and follow-up measurement of ALT is recommended for patients older than 35 years; tests can be performed monthly, bimonthly, or at 1, 3, and 6 months, depending on perceived risk and ALT stability; (5) measurement of ALT is the preferred method of detecting and tracking hepatotoxicity.[8]

How should INH-induced hepatotoxicity be managed?

The mainstay of treatment for INH-induced hepatotoxicity is discontinuation of the medication. A CDC report states that seven out of eight patients undergoing evaluation for liver transplantation eligibility due to severe INH-induced hepatotoxicity continued to take INH after they had developed clinical hepatotoxicity; five of these patients underwent transplantation and three died waiting for a donor.[9] The American Thoracic Society recommends the following interventions for hepatotoxicity: (1) INH should be withheld if the ALT level is at least three times the ULN when jaundice and/or hepatitis symptoms are reported or if the ALT level is five times the ULN in the absence of symptoms; (2) rapid increases in ALT (even if below the ULN) may signal the need for more frequent monitoring; (3) if the baseline ALT level is more than three times the ULN, an increase of twofold to threefold is an indication to halt treatment, even in the absence of symptoms.[8]

Additionally, N-acetylcysteine prevents liver toxicity in rats receiving hepatotoxic doses of INH.[10] Although studies of N-acetylcysteine treatment in humans in this setting are lacking, the benign nature of this intervention and its general utility in other hepatotoxic syndromes should prompt its use in most cases.

Conclusion

The case patient was transferred for evaluation by a liver transplantation team. His vital signs remained stable throughout his hospitalization. He received IV saline at a maintenance rate and oral vitamin K supplementation daily. N-acetylcysteine treatment was recommended but was not initiated. The patient developed grade II encephalopathy, and his liver function abnormalities peaked shortly after transfer: AST, 3,490 U/L; ALT, 3,366 U/L; total bilirubin, 30.5 mg/dL; and INR, 5.0. Although his AST and ALT levels began to decline slowly, his hyperbilirubinemia and coagulopathy persisted, suggesting liver failure. He underwent heterotopic liver transplantation on hospital day 10, after which his coagulopathy and hyperbilirubinemia resolved. He was stable for hospital discharge on day 16. □

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