INH-Associated Hepatotoxicity

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Case Summary

A 13 year-old boy presents to the emergency department with four days of jaundice, upper abdominal pain, nausea, vomiting, and headache. He had a positive tuberculin skin test two months prior, and had been taking INH (isonicotinylhydrazine, isoniazid). The patient has no other pertinent past medical history and uses no other medications. He had visited his primary care physician four days prior for nausea and vomiting. Although the INH was discontinued at that time, he developed progressive jaundice and abdominal pain.

On physical examination, he is alert and oriented with the following vital signs: blood pressure, 113/62 mmHg; heart rate 88 beats/minute; respiratory rate 14 breaths/minute; 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 pertinent laboratory results include: AST >2600 IU/L; ALT >2600 IU/L; total bilirubin >20 mg/dL; INR 3.7; acetaminophen concentration < 10 mcg/mL.

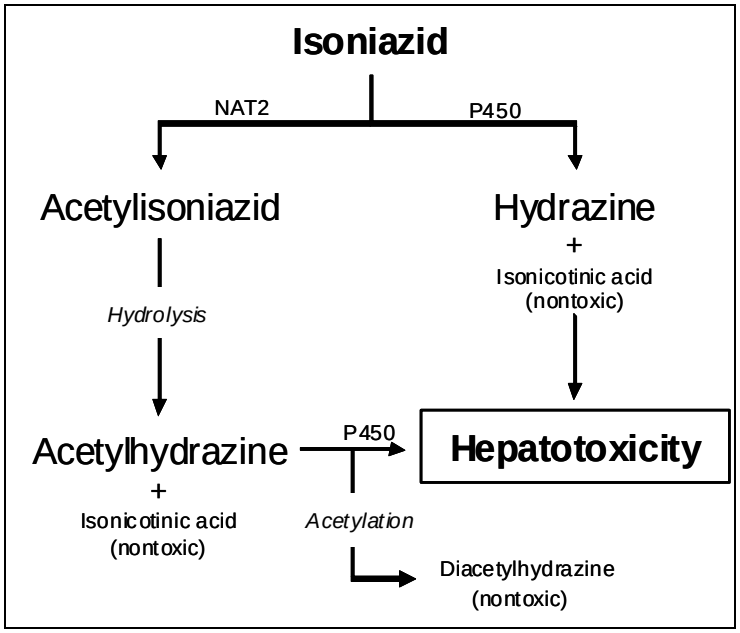
What is the mechanism by which INH treats tuberculosis?

INH interferes with synthesis of mycolic acids, which are 70 to 90 carbon fatty acids that are a key component of the mycobacterial cell wall. INH is a prodrug that enters mycobacterium by passive diffusion, where it is metabolized by intracellular catalase-reductase, katG, to its active form (INH-NAD). This active form irreversibly inhibits InhA, an enzyme required for the synthesis of mycolic acids that requires NADH as a cofactor. Without mycolic acids the cell wall cannot be properly developed and the mycobacterium dies. (Vilcheze 2007)

How does INH cause hepatotoxicity?

The primary means for INH metabolism in humans is through acetylation by N-acetyltransferase (NAT-2) in the liver generating acetylisoniazid. Acetylisoniazid can undergo hydrolysis to form acetylhydrazine (and nontoxic isonicotinic acid). Polymorphisms of NAT-2 have been identified in the population that relegates humans to be either “rapid” or “slow” acetylators. [See figure below] Slow acetylators shunt some INH to a secondary metabolic pathway of oxidation via Cytochrome P450, producing hydrazine (and nontoxic isonicotinic acid also). It appears that both acetylhydrazine and hydrazine, generated by the rapid and slow acetylators respectively, are capable of participating in reactions that generate oxidative stress (e.g., free radicals). Hydrazine

may induce Cytochrome P 450 (specifically CYP2E1), increasing production of additional toxic metabolite. Thus, hepatotoxicity may occur in both rapid and slow acetylators, though for slightly different reasons. (Gurumurthy 1984)



What is the frequency of hepatotoxicity in patients taking isoniazid?

It was previously suggested that approximately 10% of all patients treated with INH will have 2-3 fold increase in baseline alanine aminotransferase (ALT), and that 10% of those patients (1% overall) develop clinical hepatitis (nausea, vomiting, jaundice, or abdominal pain). (Kopanoff, et al) Furthermore, 10% of this latter group (0.1% overall) developed fulminant hepatic failure and required liver transplantation or died. However, this pessimistic data was subsequently refuted based on the exclusion of high risk patients (e.g., those over 35 year of age with unknown PPD converter status) and a more aggressive approach to surveillance for early signs of hepatotoxicity. A prospective 7 year long study in a public health clinic followed a population of over 11,000 patients for the duration of treatment for latent tuberculosis with INH. (Nolan, et al) Eleven patients were identified as having clinical hepatitis, all of whom improved when the drug was discontinued. Not only did the investigators demonstrate a reduced incidence of hepatotoxicity in therapeutic INH use (0.1% vs 1%), they also identified that increasing age is a risk factor for developing hepatotoxicity. Another study reported the incidence of hepatotoxicity (defined as aspartate aminotransferase (AST) > 5x the ULN) as 0.6% (19/3377 patients), although only 1 of the 19 had clinical symptoms. The higher frequency may be due to an older patient population, as 55% of the study cohort was over the age of 35. Indeed, the subgroup data analysis showed that risk factors for developing hepatotoxicity were age >50 years old and a baseline AST concentration greater than the ULN. (Fountain 2005)

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

Recognizing the trade off between importance of treating latent tuberculosis and the slight increased risk of INH-induced hepatotoxicity in individuals older than 35 year of age, the current guidelines recommend treatment of all known PPD converters, regardless of age. (ATS 2000, Munsiff 2005) Pregnant woman, who have an increased risk of hepatotoxicity, should not be treated with INH prophylaxis unless the risk of developing tuberculosis is high. If possible, delaying therapy for 2-3 months after delivery is recommended, and breastfeeding is not a contraindication.. INH is not teratogenic.

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 has the following recommendations (Saukkonen 2005):

1. Baseline blood tests are generally not recommended for healthy patients treated with INH or rifampin
2. Baseline and follow up serum ALT and bilirubin are recommended for patients with a possible liver disorder: history of chronic liver disease (Hepatitis B or C, alcoholic cirrhosis), chronic alcohol use, HIV patients receiving HAART, pregnant women, and women up to 3 months post-partum.
3. Baseline testing should be considered for those with chronic medical conditions
4. Baseline and follow up ALT concentrations for patients > 35 years old; can be monthly, bi-monthly, or at 1, 3, and 6 months, depending on perceived risk and ALT stability
5. ALT is the preferred lab test for detecting and tracking hepatotoxicity

What is the management of INH induced hepatotoxicity?

The mainstay of treatment for INH induced hepatotoxicity is discontinuation of the medication. In one study, seven out of eight patients receiving INH-related liver transplantations had continued to take INH following the development of clinical hepatotoxicity (Halpern 1993). The American Thoracic Society recommends the following interventions for hepatotoxicity (Saukkonen 2006):

1. INH should be withheld if ALT is at least three times the upper limit of normal (ULN) when jaundice and/or hepatitis symptoms are reported, or ALT is five times the ULN in the absence of symptoms
2. Rapid increases in ALT (even if below the ULN) may indicate need for more frequent monitoring
3. If baseline ALT is more than three times the ULN, an increase of two- to three-fold is an indication to halt treatment, even in the absence of symptoms

Additionally, N-acetylcysteine prevents liver toxicity in rats receiving hepatotoxic doses of INH. (Attri 2000) Although there are no human studies regarding NAC treatment in this setting, the benign nature of this intervention and general utility in other hepatotoxic syndromes should prompt its use in most cases.

Case Conclusion

The patient was transferred for evaluation by a liver transplantation team. His vital signs remained stable throughout his admission. He received intravenous saline at a maintenance rate and oral vitamin K supplementation daily. N-acetylcysteine was recommended, but was not initiated by the healthcare team. He developed grade II encephalopathy, and his liver function abnormalities peaked shortly after transfer: AST 3490 IU/L; ALT 3366 IU/L; total bilirubin 30.5 mg/dL; and INR 5.0. Although his AST and ALT began to decline slowly, his bilirubin and coagulopathy persisted, suggesting liver failure. He subsequently underwent heterotopic liver transplantation on hospital day #10, after which his coagulopathy and hyperbilirubinemia corrected. He was stable for hospital discharge on day #16.

References:

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