Toxin-Induced Hepatic Injury

Annette M. Lopez, MD[a,b,*], Robert G. Hendrickson, MD[a,b,c]

KEYWORDS

• Toxin • Liver injury • Management • Acetaminophen • Valproic acid • Amanita • Ethanol • Statins

KEY POINTS

- Toxins such as pharmaceuticals, herbals, foods, and supplements may lead to hepatic damage that presents as nonspecific symptoms in the setting of liver test abnormalities.
- Most cases of toxin-induced damage are caused by acetaminophen, which is treated with *N*-acetylcysteine.
- The most important step in the patient evaluation is to gather an extensive history that includes toxin exposure and excludes common causes of liver dysfunction.
- Patients with acute liver failure benefit from transfer to a transplant service for further management.
- The mainstay in management for most exposures is cessation of the offending agent.

EPIDEMIOLOGY

Nature and Scope of the Problem

Toxin-induced hepatic injury may be defined as damage to the liver caused by a xenobiotic or toxin that leads to abnormalities of liver-related blood tests or liver function.[1,2] Toxin-induced hepatic injury may range from a mild increase in aminotransferase concentrations to fulminant liver failure and may manifest as acute hepatic necrosis, cholestasis, steatosis, cirrhosis, or asymptomatic increased aminotransferase concentration. Hepatic injury is a common diagnostic and treatment dilemma for the emergency physician, and a comprehensive understanding of the causes, evaluation, and treatment are essential.

Disclosures: None.

[a] Department of Emergency Medicine, Oregon Health and Science University, 3181 South West, Sam Jackson Park Road, CSB-550, Portland, OR 97239, USA; [b] Medical Toxicology, Oregon Health and Science University, 3181 South West Sam Jackson Park Road, CSB-550, Portland, OR 97239, USA; [c] Oregon Poison Center, 3181 South West, Sam Jackson Park Road, CSB 550, Portland, OR 97239, USA

* Corresponding author. Department of Emergency Medicine, Oregon Health and Science University, 3181 South West, Sam Jackson Park Road, CSB-550, Portland, OR 97239.
E-mail address: lopezan@ohsu.edu

Emerg Med Clin N Am 32 (2014) 103–125
http://dx.doi.org/10.1016/j.emc.2013.09.005 **emed.theclinics.com**
0733-8627/14/$ – see front matter

Incidence

It is difficult to assess the true frequency and incidence of toxin-induced hepatic injury because of difficulties establishing the cause, the retrospective nature of studies, and the intrinsic selection bias of many studies performed in liver transplant centers.[1] To date, one prospective study was restricted to pharmaceuticals and demonstrated an incidence of drug-induced liver injury of 14 cases per 100,000 inhabitants.[1–3] Retrospective studies in Sweden and the United Kingdom have noted incidences of 2 to 3 cases per 1000,000 inhabitants; in Spain, the annual incidence is reported at 1 per 100,000 inhabitants.[1,3] With regard to nonpharmaceutical herbs and dietary supplements, there are few studies available. In one study, 10 of the 20 patients with acute liver failure who were referred for liver transplantation had used an herb or dietary supplement with potential hepatotoxicity.[4,5] The incidence of toxin-mediated hepatic injury may be dynamic, particularly with the increasing use of pharmaceuticals, supplements, and herbals.[6]

Overdose of acetaminophen is common, due to its ready availability over the counter and in prescribed combination products in the United States and the developed world. Acetaminophen has an estimated annual incidence of 21 overdoses per 100,000 people in the United States.[7] In 2011, there were 85,069 intentional and unintentional exposures to acetaminophen reported to US poison centers.[8]

Other drugs such as antibacterials, nonsteroidal antiinflammatory agents, and anticonvulsants accounted for 4% to 10% of cases of jaundice admitted to inpatient hospitals.[3,9,10] Of those drugs, amoxicillin/clavulanic acid is the most common compound leading to hepatic injury. Hepatotoxin incidence may also vary by region. In western countries, herbals account for less than 10% of reported cases of toxicity; however in Asia, these agents account for a much higher proportion.[10]

An individual's risk of hepatotoxicity may also vary based on identified factors that are independently associated with worse prognosis, including advanced age, female sex, and increased aspartate aminotransferase (AST) concentrations.[3,10] Both chronic disease (diabetes, hepatitis B and C, psoriasis, obesity) and xenobiotic dose have been associated with higher risk of toxin-induced heptatotoxicity.[2,3,11] Several risk factors have been identified for specific types of hepatotoxicity as well:[10]

- African Americans are at an increased risk of anticonvulsant hepatotoxicity.
- Younger patients are at increased risk for hepatotoxicity from valproic acid and salicylates.
- Younger patients are also more likely to develop drug-induced hepatocellular injury.
- Older age increases the risk of developing cholestatic injury.
- Females may be at higher risk of drug-induced hepatotoxicity, particularly autoimmune hepatic injuries.
- Alcohol (ethanol) use may increase toxicity in patients with repeated supratherapeutic ingestion of acetaminophen, methotrexate overdose, and toxicity from antituberculosis medications.

Morbidity

The morbidity of toxin-related hepatic injury varies widely from patients with asymptomatic increased aminotransferase concentrations to those with acute liver failure. The short-term morbidity of patients with asymptomatic increased aminotransferase concentrations in the emergency department (ED) is likely low. Most of these ED patients have mild transient increases in aminotransferase concentrations and many have chronic increased aminotransferase concentrations from repeated ethanol use. However, care must be taken to avoid missing cases with reversible causes