Letters

Acetaminophen as a cause of "non-acetaminophen-related acute liver failure"

Jawad and colleagues[1] report on an 18-year-old patient who developed acute liver failure after infection with hepatitis A virus (HAV) and norovirus. Presenting symptoms included "a 4-day history of fever (self-reported 38.5°C), chills, abdominal pain, anorexia, and 2 days of emesis." The authors stated that the patient had taken 4 g acetaminophen each day over the previous 4 days. Subsequent tests showed an elevated alanine transaminase (ALT) level (> 7000 U/L) and an international normalized ratio that increased up to 2.1 within the first 24 hours of presentation. He was categorized as having grade II hepatic encephalopathy.

In the discussion of this case, the authors did not address whether the multiple doses of acetaminophen could have acted synergistically with the viral infection to induce liver failure. Although this patient did not exceed the recommended dose for this drug, one might question how often a therapeutic dose can induce liver failure. Animal and human studies have suggested that acute viral infections can enhance the hepatotoxicity of acetaminophen,[2] including in patients with acute HAV infection. Rezende and colleagues[3] evaluated 40 patients with acute HAV infection who had acetaminophen intake quantified. In comparison to no use, those who used acetaminophen had significantly higher ALT and bilirubin levels, and a higher risk of encephalopathy — even though acetaminophen intake was low and within recommended doses. Yaghi and colleagues[4] conducted a prospective study involving 37 consecutive patients hospitalized for acute viral hepatitis (22/37 with HAV infection). Although no patient exceeded the recommended daily dosage, those with higher acetaminophen serum levels were more likely to have greater markers of acute hepatitis severity, with 2 deaths due to hepatic encephalopathy seen in those with the highest acetaminophen serum levels. The authors concluded that "acetaminophen might be toxic even when used at therapeutic dosages in the patients with acute viral hepatitis, in particular acute hepatitis A."[4]

One might argue that acetaminophen is a widely used drug and liver failure is rare; however, this was the same argument used to disregard the association between acetylsalicylic acid (ASA) and Reye syndrome[5] — a rare complication after acute viral infections. Targeted studies compared rates of Reye syndrome among patients who took ASA and those who did not, which uncovered why this safe drug was not so safe in children; however, unlike in ASA and Reye syndrome, there are no epidemiologic studies to show that acute hepatitis, whether after acute infection or with indeterminate or other cause, is more likely after use of acetaminophen (within the therapeutic range), and thus its safety in this regard is unsubstantiated. In the case of acute HAV infection, acetaminophen is not an innocent bystander, but may aggravate the severity of liver injury and should be avoided whenever possible.

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