A 43-year-old man presented to our medical center with a 2-day history of increasing left auricular erythema, pain, and swelling. He had been evaluated previously by a physician at an urgent care center elsewhere and was diagnosed as having left auricular cellulitis. A course of moxifloxacin was prescribed, and he was advised to use acetaminophen as needed for analgesia. The patient had not been seen regularly by any physician and, in fact, had been urged by family members to seek evaluation for his ear pain. He denied any history of chronic medical illness. He was a smoker and had an extensive alcohol history, including daily consumption of 8 drinks for more than 25 years.

Within 24 hours of the urgent care consultation, he developed increasing confusion and agitation, and his family brought him to the emergency department at our institution. He continued to complain of pain in the left ear. Laboratory studies yielded the following remarkable results (reference ranges shown parenthetically): hemoglobin, 16.2 g/dL; leukocyte count, 7.2 × 10^9/L; platelet count, 117 × 10^9/L; alkaline phosphatase, 168 U/L; aspartate aminotransferase, greater than 18,000 U/L (12-31 U/L); and alanine aminotransferase, greater than 5000 U/L (10-45 U/L). The total bilirubin level was elevated at 7.0 mg/dL, and the international normalized ratio was 4.0 in the absence of previous warfarin use.

1. Which one of the following is the most likely diagnosis in this patient?
   a. Alcoholic hepatitis
   b. Hepatotoxicity
   c. Acute hepatitis A
   d. Acute hepatitis B
   e. Transient biliary obstruction from a gallstone

Alcoholic hepatitis is commonly misconceived to be a diagnosis of inclusion in patients found to have liver chemistry abnormalities and a history of heavy alcohol consumption. Alcoholic hepatitis rarely causes elevations in transaminase levels in patients with acute alcoholic hepatitis often appear nearly normal, with the clue to diagnosis being a ratio of aspartate aminotransferase to alanine aminotransferase greater than 2:1. Hepatotoxicity is the most likely choice in the differential diagnosis given this patient’s presentation. In fact, only 3 categories of hepatic insult commonly produce a transaminase level greater than 5000 U/L: (1) a toxic event, the prototype of which is acetaminophen toxicity; (2) ischemic hepatopathy; and (3) infection by atypical viruses such as herpes simplex virus. Acute hepatitis A or B, although a cause of transaminits with alanine aminotransferase levels in the thousands, rarely produces levels greater than 5000 U/L. Transient biliary obstruction from a gallstone is unlikely to cause such an increase in transaminase levels and is usually accompanied by abdominal pain, which was absent in our patient.

Further laboratory testing revealed a creatinine level of 3.6 mg/dL (0.9-1.4 mg/dL) and an increased anion gap metabolic acidosis (sodium, 129 mEq/L; chloride, 88 mEq/L; and bicarbonate, 11 mEq/L, giving an anion gap of 30 mmol/L). A spot urinary protein test yielded a concentration of 40 mg/dL with a predicted 24-hour urinary protein value of 600 mg. Microscopic hematuria was noted.

2. Which one of the following is the most likely cause of this patient’s elevated creatinine level?
   a. Chronic renal insufficiency
   b. Acute tubular necrosis
   c. Glomerulonephritis
   d. Ureteral obstruction secondary to ascites
   e. Metabolic acidosis

Our patient had no medical history suggestive of chronic renal insufficiency. Because acetaminophen is purported to cause tubular rather than glomerular damage, acute tubular necrosis is the most likely cause of renal insufficiency in this patient rather than glomerulonephritis. Ascites, per se, does not cause ureteral obstruction and thus is an unlikely cause of renal insufficiency. Metabolic acidosis in this patient is multifactorial, with one of the contributory factors being acute renal insufficiency. The acidosis is a consequence of the metabolic disarray rather than a causative factor of renal insufficiency.

The patient’s condition was remarkable for confusion, agitation, and jaundice. Vital signs revealed tachypnea,
tachycardia with normotension, and no fever. Physical examination disclosed asterixis, a distended abdomen with positive fluid wave, and gross blood on rectal examination. Palpation identified diffuse abdominal tenderness without rigidity. The liver edge was palpable and nonpulsatile. The precordium was hyperdynamic. No focal findings were noted on neurologic examination. Results of the remainder of the physical examination were essentially unremarkable.

3. Which one of the following is the most likely cause of the ascites observed in this patient?
   a. Pancreatitis
   b. Portal hypertension
   c. Heart failure
   d. Exudation
   e. Nephrotic syndrome

   Our patient had no evidence of pancreatitis, and the ascites observed on physical examination is unlikely of pancreatic origin. He did have an extensive history of alcohol use, and chronic exposure to alcohol has deleterious effects on the liver, including progression to cirrhotic liver disease. In the presence of cirrhosis, increased portal venous pressures can lead to ascites, which is the most likely cause in this patient. Heart failure can cause ascites; however, findings on the clinical examination cannot confirm such an etiology. Exudation is an unlikely cause because in portal hypertension, ascites is usually characterized by low rather than high protein levels. Although nephrotic syndrome can cause ascites, our patient’s urinary protein concentration was normal, making this an unlikely etiology. Because of the patient’s declining clinical status and inability to cooperate, ascertaining a diagnosis was imperative in order to institute a rational therapeutic strategy.

4. Which one of the following diagnostic tests would be most helpful at this point?
   a. Abdominal ultrasonography
   b. Colonoscopy
   c. Computed tomography of the head
   d. Determination of the acetaminophen level
   e. Coagulation studies

   Ultrasonography can identify abdominal organs as well as the vasculature and may show extensive ascites, but it probably would not lead to a specific diagnosis or direction of therapy. Colonoscopy may be indicated later in this patient’s evaluation but is not an emergent test. Patients presenting with confusion frequently undergo computed tomography of the head. However, given the absence of focal neurologic findings and the presence of clinical evidence of another etiology for confusion in this patient, this test would have a relatively low yield. In view of the initial findings of marked transaminitis, an acetaminophen level should be determined immediately because it may identify a need for specific urgent therapy. Coagulation studies are important in this patient’s evaluation, especially with regard to the need for clotting factors. However, this test would not be the most helpful study at this time because it will guide only supportive therapy rather than definitive therapy that could be administered after a diagnostic test such as measurement of the acetaminophen level.

   Additional history obtained from the family indicated that the patient had indeed taken an unspecified but large amount of acetaminophen to control the pain occurring secondary to his left auricular cellulitis. It was estimated that the patient’s last ingestion occurred 24 hours earlier. The acetaminophen level was determined to be 28 µg/mL, which is in the hepatotoxic range.

5. Which one of the following would not be an appropriate next step in the management of this patient?
   a. Begin intravenous antibiotic therapy
   b. Begin N-acetylcysteine therapy immediately
   c. Insert Foley catheter
   d. Transfer patient to an intensive care unit at a facility with liver transplantation capacity
   e. Arrange for transjugular intrahepatic portosystemic shunt procedure

   Of note, several diagnostic and therapeutic interventions must be initiated concomitantly, and this can be done in an acute care facility. Given the presence of encephalopathy, ascites, lower gastrointestinal tract bleeding, and left auricular source of infection in this patient, intravenous antibiotics were administered. N-acetylcysteine therapy was also initiated, and a Foley catheter was inserted to assess urine output in the presence of renal insufficiency. Patients who present with the manifestations seen in our patient require intensive care and are best managed in an intensive care unit rather than on a general medical ward. In addition, such patients should be treated at an institution with liver transplantation capabilities. A transjugular intrahepatic portosystemic shunt procedure would not be indicated because our patient was confused as a result of fulminant hepatic failure secondary to toxin exposure, and such a procedure could worsen encephalopathy in this situation.

   Our patient was medically stabilized and transferred to a medical intensive care unit with consultation of the liver transplantation service. He was not considered an optimal candidate for liver transplantation because of his ongoing alcohol use. His clinical status continued to decline, culminating in multiorgan failure. After detailed discussion
with the patient’s family, medical support was withdrawn, and the patient died 2 days later.

**DISCUSSION**

Acetaminophen is one of the most commonly used analgesic agents worldwide. Its well-known major adverse effect is massive hepatic necrosis, which can have fatal consequences. Such complications can occur from intentional overdose, but certain predisposing factors can also lead to adverse effects. The pathogenesis of drug- or toxin-induced liver injury usually involves the participation of toxic metabolites that either elicit an immune response or directly affect the biochemistry of the cell. The clinical appearance of hepatitis is a direct consequence of immune-mediated cell death or intracellular stress.1 To appreciate the role of acetaminophen toxicity in the community, physicians should be cognizant of the biochemical processes that lead to toxicity, clinical manifestations of toxicity, and management strategies for patients who present with acetaminophen-induced hepatotoxicity.

In adults, 85% to 90% of acetaminophen is metabolized in the liver, and its metabolism in the liver includes direct sulfation (30%) and glucuronidation (55%) pathways.2 Approximately 5% of an ingested dose is excreted unchanged in the urine, and 5% to 10% is metabolized by cytochrome P-450 (CYP) isozymes, primarily through CYP 2E1 isozymes and CYP 1A2 and CYP 3A4 isoenzymes.2,3 One of the metabolites that is considered likely involved in hepatotoxicity is N-acetyl-p-quinoneimine (NAPQI), which is formed by oxidation of the CYP 2E1 and CYP 3A4 isozymes.3 After therapeutic doses, this metabolite is normally conjugated with glutathione and eventually excreted in the urine as a mercapturic acid metabolite.4 With increased doses, the formation of the NAPQI metabolite exceeds the conjugation capacity of the glutathione system, which leads to toxic effects. The exact mechanism of NAPQI-induced cellular damage is unclear, but among several theories, the most likely explanation is a conglomeration of misdirected biochemical processes. One study suggested that activation of acetaminophen and its metabolites to radical species causes lipid peroxidation and cell death,5 whereas another suggested depletion of cytosolic thiols, which leads indirectly to increased intracellular calcium causing activation of phospholipase and protease and inhibition of intracellular enzyme processes leading to cell death.6

The dose of acetaminophen that causes hepatotoxicity varies, but most authorities contend that doses of less than 6 g/d are nontoxic and that recommended daily cumulative doses should not exceed 4 g/d.7 In patients with long-term excessive alcohol exposure, the theoretical consequence of up-regulation of the CYP 2E1 system is increased production of NAPQI and hence increased hepatocellular damage. Whether normal doses of acetaminophen increase the risk of massive hepatic necrosis in patients with long-term excessive alcohol exposure is controversial. Some studies contend that hepatic injury in alcoholic patients occurs with acetaminophen doses otherwise considered therapeutic.7 In contradistinction, a randomized, double-blind, placebo-controlled trial reported that repeated administration of the maximum recommended daily doses of acetaminophen (4 g/d) to patients with chronic alcoholism was not associated with evidence of liver injury.8 Given the well-known dangers of acetaminophen toxicity, current recommendations include a maximum daily dose of 4 g/d for individuals with no predisposing factors for liver damage and 2 g/d for those with long-term excessive alcohol exposure or hepatic dysfunction due to other causes.7

Clinically, acetaminophen toxicity has been postulated to manifest in 3 phases.9 Within the first 24 hours, patients may complain of gastrointestinal symptoms such as nausea, vomiting, anorexia, and abdominal pain. During the next 24 to 48 hours, the gastrointestinal symptoms tend to subside, which can lead to underestimation of the severity of the underlying illness. At this time, the biochemical parameters of hepatic injury begin to manifest. Serum aminotransferase levels can reach 20,000 U/L or higher, the bilirubin concentration may increase, and coagulopathy may develop. The third phase usually occurs within 3 to 5 days after ingestion and is marked by a clinical course that culminates in fulminating hepatic failure with jaundice, encephalopathy, and coagulopathy. Acetaminophen can also cause renal failure. Although the exact pathogenesis of acetaminophen-induced renal failure remains unclear, animal models suggest direct proximal tubular damage.10

As is the case with acetaminophen-induced hepatic necrosis, acetaminophen-induced renal dysfunction is accentuated in the presence of chronic alcoholism. Predictors of acute renal failure in the presence of acetaminophen toxicity include severe acute hepatic damage, chronic hepatic disease, male sex and advanced age, concurrent stimulation of CYP enzymes, chronic renal failure, and other concurrent acute renal injuries such as hypotensive injury or rhabdomyolysis.8

As in the evaluation of all medical illnesses, elicitation of a thorough history, careful attention to physical examination findings, and a high index of suspicion will lead to a correct diagnosis. In particular, evidence of chronic liver disease must be sought, and potential drug exposures must be explored. Such patients are critically ill, and their care is best afforded by expeditious transfer to an intensive care setting where multiple organ system function can be monitored carefully. Because hepatotoxicity can result in fulmi-
nant hepatic failure, such patients should be treated at an institution with the resources to evaluate for and perform liver transplantation. Initial tests should be performed with the aim of making a definitive diagnosis and predicting prognosis. Liver chemistries and laboratory tests measuring hepatic synthetic function should be assessed. Measurement of serum electrolytes and arterial blood gases is important to establish the presence of any acid-base disorders. Currently, acetaminophen-induced hepatotoxicity is managed with early gastric decontamination with activated charcoal and concomitant administration of N-acetylcysteine, which substitutes for glutathione. Care is often supportive, and those who continue to have decompensated liver failure and are deemed to be suitable candidates may benefit from transplantation.

The King’s College criteria are the best known and most widely used prognosticator for determining the need for liver transplantation in patients with fulminant hepatic failure secondary to acetaminophen exposure. These criteria include either an arterial pH of less than 7.30 after adequate fluid resuscitation or a combination of an international normalized ratio greater than 6.5, a creatinine level greater than 3.4 mg/dL, and grade III/IV encephalopathy. Although the King’s College criteria are widely accepted, not all patients who eventually require liver transplantation meet these criteria. In one meta-analysis, the King’s College criteria had moderate sensitivity (69%; range, 55%-100%) and high specificity (92%; range, 43%-100%), which indicates that these criteria may fail to identify some patients requiring transplantation. Again, clinical vigilance and individual patient assessment constitute the foremost approach to selecting patients who are candidates for liver transplantation, with systems such as the King’s College criteria used as guides to a patient’s short-term prognosis.

CONCLUSION

Acetaminophen is a medication used commonly worldwide, and its overuse, especially in combination with alcohol, can have serious clinical implications. In the primary care setting, physicians should be cognizant about the use of acetaminophen or acetaminophen combination preparations by their patients and of any predisposing factors, such as long-term alcohol use, that may increase their risk for toxicity. Above all, a high index of suspicion in the correct clinical context and the expeditious mobilization of resources will lead to the best clinical outcomes when treating patients who have had intentional or accidental acetaminophen overdose.

REFERENCES


Correct answers: 1, b, 2, b, 3, b, 4, d, 5, e