**Abstract**—Acetaminophen is one of the most frequently used medications in the United States. While usual dosing of acetaminophen is considered harmless, both acute and chronic overdoses can be fatal. The majority of reported cases of chronic acetaminophen toxicity in adults occur in chronic alcohol abusers, patients taking P450-inducing medications, or following massive dosing. We describe a case of toxic hepatitis free of the aforementioned risk factors associated with chronic ingestion of moderately excessive doses of acetaminophen. Our patient ingested approximately 5.0 to 6.5 g of acetaminophen daily for 6 to 8 weeks via multiple medications. The inclusion of acetaminophen in numerous medications combined with the frequency of use of acetaminophen necessitates an increased concern for not only acute but also chronic acetaminophen toxicity.

**Keywords**—acetaminophen toxicity; poisoning; chronic; hepatotoxicity

**INTRODUCTION**

Acetaminophen (N-acetyl-p-aminophenol [APAP]) is one of the most frequently used medications in the United States. Its analgesic and antipyretic properties and presumed safety in recommended doses reflects its wide use alone and in combination preparations. Acute APAP toxicity is commonly diagnosed in an Emergency Department (ED); however, chronic APAP toxicity is not so apparent.

Hepatotoxicity resulting from chronic APAP therapeutic misadventures in adults has been previously reported. The overwhelming majority of these cases occur with chronic ethanol use or chronic use of P450-inducing medications (1-7). Additionally, an association between chronic APAP use with short-term fasting and hepatotoxicity has been described (8,9). We present a patient who developed significant hepatotoxicity from excessive chronic APAP use without the aforementioned risk factors.

**CASE REPORT**

A 54-year-old woman was admitted to our ED with altered mental status, decreased appetite, and a questionable history of loss of consciousness. The patient was lethargic and poorly responsive to interview; however, she complained of lower abdominal pain, weakness, and drowsiness for 1 week’s duration. She denied headache, chest pain, shortness of breath, vomiting, or diarrhea.

Medical and surgical history was significant for hypercholesterolemia, depression, rheumatoid arthritis, gastric bypass, and cervical spine fusion. She took the following medications as directed: carisoprodol, citalopram, fexofenadine, celecoxib, estradiol, and gabapentin. She was allergic to penicillin and non-steroidal anti-inflammatory agents. The patient denied the use of alcohol (confirmed by family members) and did not smoke. She denied fasting...
the month before admission. She denied a history of hepatitis, blood transfusions, or illicit drug use. Family history was significant for colon cancer and uterine cancer.

Physical examination revealed a well-developed and well-nourished lethargic woman in acute distress (Glasgow Coma Scale 13). Vital signs included the following: blood pressure 97/56 mm Hg; pulse 93 beats/min; respirations 16 breaths/min; temperature 37.3°C. She had scleral icterus with mild jaundice of the skin. Cardiac and pulmonary examinations were normal. Neurologic examination revealed cranial nerves II through XII to be intact with normal deep tendon reflexes and Babinski sign. The abdomen was tender to palpation in the lower quadrants without rebound tenderness or guarding. Asterixis was present with extension of the arms.

Laboratory analysis on admission revealed hyponatremia, acidosis, renal insufficiency, and hepatic damage:

- Sodium 122 mEq/L; Potassium 4.7 mEq/L; Chloride 88 mEq/L; CO₂ 25 mm Hg; pO₂ 115 mm Hg; bicarbonate 13 mmol/L; base excess –1 mmol/L; oxygen saturation 98%; FiO₂ 21%. Lactic acid was elevated at 5.4 (normal 0.5-2.2 mEq/L). A complete blood count with differential was normal. Urinalysis showed large blood, protein 100, and trace ketones, and microscopic urinalysis revealed RBC 20-50; WBC 0-2; hyaline casts, course granular crystals, and amorphous crystals. Urine electrolytes were within normal limits.
- Serum salicylates and ethanol were undetected. An acetaminophen level was elevated at 66 μg/mL (normal 0-20 μg/mL). A comprehensive urine drug screen and analysis for volatiles (methanol, ethanol, acetone, isopropanol) were negative.

Hepatitis profile was negative, including hepatitis B surface antigen and antibody, hepatitis core antibody, hepatitis A IgM antibody, and hepatitis C antibody. Thyroid profile (TSH, T₄, T₃ uptake) was normal.

Electrocardiogram revealed normal sinus rhythm with left axis deviation and increased QT intervals (QT/QTc 444/566 ms). Cardiac enzymes were within normal limits. Chest radiograph was normal. Blood and urine cultures were obtained and showed no growth of bacteria or fungal elements.

Therapy for acetaminophen toxicity was implemented and included N-acetylcysteine (NAC) 140 mg/kg for one dose followed by 70 mg/kg orally for 17 additional doses every four hours. Oxygen and intravenous fluid (normal saline with 5% dextrose and bicarbonate) were started and subcutaneous (SC) vitamin K was given. She was given lactulose 30 mL every 6 h. The patient was transferred to the intensive care unit for continued treatment and observation. Liver enzymes, serum electrolytes, and acetaminophen levels all corrected during the hospital course (Table 1). Her mental status returned to normal and both her scleral icterus and cutaneous jaundice disappeared. She was discharged home on hospital Day 8 and followed routinely as an outpatient.

Subsequent discussion with the patient revealed that for 6 to 8 weeks she had taken one acetaminophen 500 mg gelcap every 3 to 4 h around the clock, and Lortab 10 (an analgesic containing 500 mg acetaminophen) 4 to 5 times a day. This approximates a daily dose of 5.0 to 6.5 g of APAP (recommended maximal daily dose is 4 g for adults). Her last dose of APAP was taken approximately 10 h prior to arrival at our ED. She had taken both the Tylenol and Lortab for persistent leg, back, and neck pain.

### DISCUSSION

Acetaminophen is the most commonly used analgesic-antipyretic and is responsible for more hospitalizations after overdose than any other common medication (10). While acute APAP toxicity has been well described, chronic APAP toxicity is less common (3,11,12). The availability of APAP both alone and in combination preparations sets the stage for unintentional overdose.
Susceptibility to the hepatotoxic effects of acetaminophen is, therefore, dependent upon many factors, some of which have interindividual variability (e.g., the dose taken, genetically determined P-450 activity, GSH [reduced glutathione] availability, capacity for glucuronidation and sulfation, and regeneration capacity) (10). Our patient consumed 5.0 to 6.5 g/day over a 6 to 8 week period and did not develop signs of toxicity until 1 week before her presentation to a medical facility. We know from animal experiments that exposure of hepatocytes to APAP results in a time and dose-dependent depletion of cellular GSH and that hepatic toxicity is evident only when hepatic GSH is \( \leq 30\% \) (14,15). A human study demonstrated that the hepatic supply of reduced glutathione began to be depleted over the range of 0.5 to 3.0 g of acetaminophen (16). Despite these data, the ability to predict the dose taken and the length of time taking that dose required for the development of toxicity is very difficult given the interindividual variability of acetaminophen metabolism.

Acetaminophen toxicity manifests as hepatic necrosis characteristically appearing in zone 3 of the hepatic lobule. This appears to be secondary to an active electrophilic metabolite \([\text{N-acetyl-p-benzoquinoneimine (NAPQI)}]\) that binds covalently to tissue macromolecules (1). Under normal circumstances, a therapeutic dose of APAP results in the production of a small fraction (5%) of NAPQI after metabolism by cytochrome P450 enzymes (13). The majority of APAP is excreted as conjugates of glucuronide and sulfate. The small amount of NAPQI that is produced is rapidly detoxified in a reaction with glutathione to form mercapturic acid or cysteine conjugates and is excreted, resulting in no hepatic damage (1). Hepatic necrosis occurs only when the amount of NAPQI produced exceeds the binding capacity of the liver’s store of GSH. The excessive NAPQI combines covalently with hepatocyte membrane proteins. It is the binding to mitochondrial proteins that appear to be the key lesions for necrosis (1).

Most reported cases of APAP hepatotoxicity as a therapeutic misadventure involve the use of alcohol (1,13). Johnston and Pelletier reported 53 cases of acetaminophen hepatotoxicity associated with alcohol use (13). Alcohol lowers hepatic glutathione levels, which decreases the available amount of GSH for detoxification of NAPQI. In addition, alcohol induces several liver cytochromes that increase the amount of NAPQI produced (13). The combination of increased NAPQI (the toxic metabolite) and decreased GSH lends itself to increased hepatic necrosis with a lower dose of acetaminophen.

Acetaminophen hepatotoxicity also has been associated with concomitant use of other medications, specifically cytochrome P450-inducers. Examples include isoniazid, rifampin, and anticonvulsants (e.g., phenobarbital, phenytoin) (6,7,17-20). Short-term fasting and malnutrition also have been associated with increased risk of hepatotoxicity in patients taking excessive chronic doses of APAP, as well as in patients with certain underlying diseases (8,9,21).

Outside of these “high risk” groups, the incidence of serious chronic APAP toxicity appears to be rare (10). It has been proposed that an asymptomatic patient without risk factors taking repeated doses of APAP in any 24 h period does not require laboratory evaluation unless the dose exceeds 7.5 g, and possibly as high as 10 to 12 g (22).

N-acetylcysteine has been traditionally utilized as a glutathione precursor to prevent the development of hepatotoxicity following a significant overdose of APAP (23). Recent evidence has shown the benefit of delayed treatment with NAC in patients with acetaminophen-related hepatic failure (24).

Our case is unique in that no associated risk factor known to increase the patient’s susceptibility to APAP toxicity was found. Two medications that our patient was taking for 2 to 3 months, celecoxib and estradiol, have been described in a few case reports to potentially cause an elevation of liver function tests from therapeutic use (25). Also, a third medication that she was taking, carisoprodol, is metabolized to meprobamate, an anxiolytic that has been shown to affect various hepatoenzymatic activities in rats, and theoretically could have altered her acetaminophen metabolism (26). We believe that our patient’s hepatotoxicity was secondary to her excessive chronic APAP use; however, we cannot rule out hepatotoxicity from her other medications. NAC may have been beneficial in treating her hepatotoxicity. We propose that there is a need for increased awareness of APAP-containing medications. Healthcare providers should educate patients on the risk of acetaminophen toxicity with use of these medications on a routine basis.

REFERENCES

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