A Fatal Case of Acetaminophen Toxicity: Another Look at the Current Epidemic of Public Ignorance

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ABSTRACT

Despite acetaminophen’s well known association with acute liver failure in the medical community, the approximately 1500 cases/year of acute liver failure that still result from unintentional acetaminophen overdoses illustrate a need to change how both providers and the public view acetaminophen usage. A 31 year old male with a history of chronic low back pain was admitted with and later died of complications due to fulminating liver failure. Further investigation revealed use of multiple medications containing acetaminophen which exceeded the 4-grams/day maximal recommended dosing. The patient was not aware of its potential hepatotoxic effects and his providers were not aware of his dosing habits. A problem that has existed for the past 4-5 decades has only recently been aggressively addressed by the FDA. However, Health Care Providers can also play a larger role in mitigating this nationwide epidemic of public ignorance toward acetaminophen usage.

BACKGROUND INFORMATION

Since its FDA approval in 1955, acetaminophen has developed into the most commonly used analgesic in the U.S. Its ubiquity is evidenced by the wide array of over-the-counter (OTC) and prescription drugs that contain acetaminophen, exceeding 300 brand name products. Acetaminophen has been well known to lead to acute liver failure in acute or chronic overdoses since 1966. With 50,000 ED visits/year for acetaminophen poisoning leading to approximately 500 deaths/year, it has remained the number 1 cause of acute liver failure for the past decade. Despite acetaminophen’s well known association with acute liver failure in the medical community, the approximately 1500 cases/year of acute liver failure that still result from unintentional acetaminophen overdoses illustrate a need to change how both providers and the public view acetaminophen usage.

CASE PRESENTATION

A 31 year-old Caucasian male presented with 3 day history of increasing malaise, fatigue, nausea and poor appetite. He had reportedly recovered from a cold a week prior to presentation. Other review of systems was unremarkable. His past medical history was significant for chronic low back for which he reportedly took hydrocodone/APAP (Lortab®) intermittently, as needed, for the previous year; dosage and frequency were initially unknown. He initially denied use of any other drugs, herbas or OTC medications. He also reported occasional alcohol use, approximating 3 beers on the weekends.

On examination, the patient was afebrile, normotensive, mildly tachycardic at 104 beats/min with 22 respirations/min and normal O2 saturations on room air. Other than exhibiting mild scleral icterus, the rest of his physical exam was unremarkable. Initial laboratory evaluation revealed a WBC count of 28.5 K/μL, lactate of 18.4 mmol/L, bicarbonate of 6 mmol/L, pH of 6.9, AST of 2227 U/L, ALT of 1437 U/L, total bilirubin of 2.7 mg/dl, INR of 3, albumin of 2.7 G/dL, ammonia of 83 mmol/L and normal renal function. With evidence of liver dysfunction, other labs were sent to help narrow the differential. A serum/urine drug screen was positive for opioids and acetaminophen at a level of 12 mg/dl. Serologies for HAV, HBV, HCV, CMV, EBV and HSV were negative. ANA and anti-smooth muscle antibodies were negative. Influenza screen was negative and ceruloplasmin level was within normal limits. A RUQ ultrasound/doppler was also unremarkable, ruling out thrombosis and malignancy.

Initial workup did not reveal any clear etiologies, and albeit his acetaminophen level was well below the toxic threshold, clinical suspicion for acetaminophen induced liver toxicity remained high. More intense questioning and further review of patient’s medical records revealed the patient had been using multiple forms of OTC cold medications for a recent upper respiratory infection (URI) and had multiple prescriptions for hydrocodone/APAP (Lortab®) from multiple providers over a 5 month period. Considering he admitted to taking all of his prescribed medications, the number of prescriptions alone would have amounted to approximately 5-7 grams/day of acetaminophen in addition to the OTC Tylenol®, Nyquil Cold® and Goody’s Powder®, all of which he later admitted to taking for his URI one week prior to admission.

Given his significant metabolic derangements, he was admitted to the MICU and started on an N-acetylcyesteine IV infusion with supportive management. His initial Model End-Stage Liver Disease (MELD) score was 22. Given his severe metabolic acidosis, the patient was intubated for airway protection and promptly transferred to a liver transplant center where he remained clinically stable. Liver transplantation was postponed due to evidence of clinical stability. However, by hospital day 5, he developed cerebral edema with brain stem herniation and subsequently expired. A postmortem liver biopsy revealed marked centrilobular necrosis without inflammation, a nonspecific finding, but often seen in drug/toxin induced acute liver failure.

DISCUSSION

This case illustrates the lack of patient awareness regarding the potential lethality of chronic acetaminophen use and the strong need for increased public awareness as well as provider vigilance in medication reconciliation.

Although some may recognize the potential liver problems acetami-
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(Continued)

Acetaminophen can cause, many may not realize that other brand name drugs (i.e. Nyquil®, Dayquil®, Tylenol®, Excedrin®, Midol®, Goody’s powder®) are potentially hepatotoxic as well, as they all contain the primary offending ingredient, acetaminophen. Acetaminophen is also known as Paracetamol or N-acetyl-p-aminophenol (APAP) and may be prescribed or listed as such in medication bottles, creating confusion. The public ignorance toward acetaminophen usage is highlighted in a 2002 national survey of over 1000 people which revealed 66% of the surveyed population who took an OTC med for their headache could not even identify the active ingredient, 41% felt the OTC meds were too weak to cause problems and 33% took more than directed. Public perception of OTC medications that include acetaminophen is also heavily influenced by marketing which are not subject to the same strict regulations as for prescription drugs.

In response to the growing problem that has existed for the past 4-5 decades, the FDA has gotten involved in recent years. From 1998 to 2008, they set forth recommendations that neither manufacturers nor state boards of pharmacy strictly enforced.1 Only until 2009, such recommendations were enforced with more prominent labeling on packages and strengthening liver-related warnings.7 Other solutions currently being considered by the FDA include 1) reducing the maximum single dose or changing 500mg tablets/capsules to prescription status, 2) establishing package size limits or blister packaging, 3) eliminating combination OTC and/or Rx products containing acetaminophen, and 4) standardizing OTC liquid concentrations.7 Similar options that have not yet been enforced in the U.S. have reduced acetaminophen-related hospitalizations by 10%, deaths by 20% and need for transplants by 56% in the UK.8

Health Care Providers (HCP) can provide education to patients regarding maximum dosage, avoidance of alcohol and being cognizant of combination products. We can limit prescription refills, inquire about other potential prescribers, and assign sole providers for “doctor shopping”. HCP’s must be vigilant with medication reconciliation including herbal and OTC medications.

Hopefully, with improved diligence, there will be mitigation of this nationwide epidemic of public ignorance regarding acetaminophen and its potential toxicities.

REFERENCES
4. Joint Meeting of the Drug Safety and Risk Man-
agement Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee: Meeting Announcement. FDA, June 29-30, 2009 (http://www.fda.gov/advisorycommittees/calendar/acm143083.htm)

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NOTE:
This article highlights Acetaminophen (Tylenol) hepatotoxicity as a growing and serious problem in the United States. It is the leading cause of acute liver failure in the United States. Poison Centers in this country receive over 100,000call per year regarding Tylenol. The West Texas Regional Poison Center is available to assist in efforts to educate both health care professionals and the general public on the risks of liver injury from Tylenol use. The center’s number is: 1-800-222-1222.

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