Acetaminophen Dose Considerations in Frail and Malnourished Elderly Patients: A Case Report of Hepatotoxicity with Therapeutic Doses

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Can J Hosp Pharm. 2023;76(4):337-9 https://doi.org/10.4212/cjhp.3415

INTRODUCTION

Acetaminophen is a medication commonly used for older adults.[1] It is used not only to treat fever but also as a first-line analgesic for mild to moderate pain. Although it is generally well tolerated, the main concern with acetaminophen use is drug-induced liver injury. Indeed, acetaminophen is the most frequent cause of drug-induced hepatotoxicity. Hepatotoxicity occurs when supratherapeutic doses of acetaminophen are ingested voluntarily or inadvertently. The results of liver function tests (LFTs) can also be mildly elevated when therapeutic doses are used, but such elevations are usually transient and asymptomatic, and they resolve without lasting effect in healthy individuals.[2] Frail elderly people are at increased risk of acetaminophen-induced hepatotoxicity because they have diminished acetaminophen clearance, diminished glucuronidation, and diminished glutathione reserves and synthesis.[3] All of these factors create challenges for optimal dosing to prevent acetaminophen hepatotoxicity in frail elderly patients. Here, we present a case of acute liver injury associated with therapeutic acetaminophen use in a frail elderly patient.

CASE REPORT

A 69-year-old woman was admitted to the hospital for fracture of the eighth and ninth thoracic vertebrae after a fall.* Her home medications consisted of aripiprazole, citalopram, pantoprazole, vitamin D, vitamin B_{12}, and magnesium. She had a history of falls, intellectual disability, untreated diabetes, severe chronic malnourishment, hypothyroidism, anemia, chronic hyponatremia, bipolar disorder, hiatal hernia, and polyneuropathy. At 30.1 kg and 130 cm, she presented severe cachexia and sarcopenia. The patient reported drinking 2 or 3 beers daily, although her consumption was likely higher than stated, according to her social worker.

*The patient provided written informed consent for publication of her clinical details.

On admission, acetaminophen 650 mg PO 4 times daily was prescribed for pain, and a diazepam protocol was initiated for alcohol withdrawal syndrome. The patient presented with hypoglycemia upon admission (glucose 3.3 mmol/L), and her glycated hemoglobin (HbA1c) was 0.039 or 3.9%. No LFTs were done at the time of admission. However, her aspartate aminotransferase level had been within normal limits 2 months before the hospitalization (38 U/L; normal range 13–39 U/L).

The patient had a second episode of hypoglycemia on day 5 of admission, and LFTs were performed on day 6; the results showed liver injury (Table 1) with acute kidney injury. The differential diagnosis included acetaminophen toxicity, and upon testing at 90 minutes after her last dose, the acetaminophen level was found to be 388 µmol/L (58.7 mg/L; therapeutic serum concentration 66–132 µmol/L).

Abdominal and pelvic ultrasonography showed moderate diffuse liver steatosis without signs of cirrhosis, focal lesions, or biliary tract obstruction. Screening for viral hepatitis yielded negative results. On the same day, the patient became very drowsy with altered state of mind, despite having received no diazepam. She had no abdominal pain, nausea, or asterixis.

Following a gastroenterology consultation, acute liver injury caused by chronic acetaminophen intoxication was diagnosed, as no other causes could be identified. Acetaminophen was discontinued, and *N*-acetylcysteine (NAC) was given. Her LFT results started to improve (Table 1). However, on day 7, she started desaturating, and aspiration pneumonia was diagnosed. Her condition worsened rapidly, and she died of respiratory failure on day 8 of the admission.

DISCUSSION

Acetaminophen hepatotoxicity at therapeutic doses of 4 g/day has been reported in patients with risk factors such as advanced age, lower weight, and chronic alcohol use,[4,5] but not in frail older patients with severe malnutrition. The dose

TABLE 1. Results of Liver Function Tests 2 Months before and during Incident of Acetaminophen-Induced Hepatotoxicity

Timing	AST (U/L)	ALT (U/L)	Total Bilirubin (μmol/L)	INR
Normal range	13–39	8–31	7–23	0.9–1.2
2 months before	38	Not done	Not done	Not done
Day 6				
At 0645	3383	2231	Not done	Not done
At noon		Last dose of acetaminophen given: 650 mg PO		
At 1330	2472	2158	71	1.4
At 1815		21-h perfusion of NAC started		
Day 7	808	1359	75	1.4

ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, NAC = *N*-acetylcysteine.

of acetaminophen given to this patient had been adjusted for her age (2.6 g/day or 21.6 mg/kg per dose). Nonetheless, hepatotoxicity occurred after 6 days of treatment, with the patient's acetaminophen concentration reaching more than 2.5 times the upper limit of normal. The patient had multiple risk factors for hepatotoxicity, including her age, low weight, severe malnutrition (low glutathione production and reserves), and alcohol use (which would have induced the cytochrome P450 2E1 isozyme).

Some guidelines now recommend a maximum dose lower than 4 g/day for long-term use (i.e., more than 7–14 days), but they do not necessarily recommend any adjustment for short-term use, even for elderly patients.[6-8] However, local guidelines recommend a dosage of 15 mg/kg per dose 4 times daily in patients weighing less than 50 kg, regardless of the duration of use.[8] Given that this patient was at high risk for acetaminophen hepatotoxicity, it is unclear whether a weight-based dose adjustment or a dose of 2 g/day might have been sufficient to prevent the liver injury. The causality of the adverse drug reaction was estimated as "probable" on the Naranjo scale.[9]

There are limits to what we can infer from this case. We excluded the main causes of liver injury but could not formally exclude all possible causes of hepatitis. No LFTs were done upon admission, and it is therefore possible that a liver injury was already present, before any acetaminophen intake. Measurement of acetaminophen level was not repeated. A second level would have allowed us to calculate the half-life of elimination, which would in turn have permitted an evaluation of acetaminophen metabolism. Also, it was unknown whether the patient was already taking acetaminophen at home. Nonetheless, even if acetaminophen was not the main cause of her liver injury, it was a contributing factor, given the improvement in her LFT results after acetaminophen was stopped and NAC was given.

CONCLUSION

This case report suggests that for frail elderly patients at high risk of hepatotoxicity, a weight-based dosing strategy for acetaminophen (e.g., 15 mg/kg per dose qid), with monitoring by LFTs, should be applied or an alternative analgesic should be considered. If the decision is made to initiate acetaminophen, LFTs should be performed before initiating the drug and within the first week of treatment.

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Competing interests: None declared.

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Funding: None received.