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Need to rethink before prescribing acetaminophen in malnourished patients? Acetaminophen-induced liver injury in a malnourished cancer patient in palliative care department

Abstract

Acetaminophen toxicity is one of the major causes of acute liver failure worldwide. Due to wide availability and perception regarding safety, it also remains the most common drug used in cancer pain settings. Incidental detection of acute liver failure during the hospital course may be observed in cachexia cancer patients. N-acetyl cysteine (NAC) can be used as a rescue drug in case of liver injury as manifested clinically or from altered lab values. There are only a few cases reported of acetaminophen toxicity in malnourished subjects. This case report can provide insight into the importance of reducing of dosage of acetaminophen in cachectic patients.

A 47-year-old female patient with no known comorbidities was diagnosed with locally advanced squamous cell carcinoma mid-oesophagus. She was advised best supportive care and was referred to the palliative medicine department where she presented with complaints of central chest pain and absolute dysphagia. General examination revealed a body weight of around 30 kg, Body Mass Index (BMI) of 14.5, and performance status of 4. Her analgesics included an injection of tramadol 50 mg twice daily and an injection of paracetamol 1 g thrice daily. During her stay in the hospital routine examinations revealed an acute rise in the liver enzymes, aspartate transaminase (AST) was 1526 U/L, and alanine transaminase (ALT) was 1880 U/L, compared to the previous day's values (on admission to the department the AST and ALT values were 38 and 40 U/L, respectively). Acute liver injury due to paracetamol overdose was suspected. N-acetyl cysteine was initiated according to the 21-hour protocol. Later liver enzymes declined and the patient improved clinically and was discharged home in a stable condition.

This case report underlines the importance of cautious dose reduction of acetaminophen in chronic pain patients with less than 50 kg to not more than 2 g per day for the prevention of acute liver failure.

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Keywords: acetaminophen, N-acetyl-para-benzo quinonimine, N-acetyl cysteine, hepatotoxicity, malnourished, alanine aminotransferase, aspartate aminotransferase

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Introduction

Acetaminophen toxicity is one of the most prevalent causes of liver failure [1]. The hepatotoxicity associated with acetaminophen is due to its metabolite N-acetyl-para-benzoquinone imine (NAPQI) which may cause hepatocyte damage [2]. Chronic malnutrition is considered to be one of the important reported risk factors for hepatotoxicity development [3]. Traditionally, severe hepatoxicity in acetaminophen overdose is defined as an elevation of ALT to more than 1000 U/L [4]. There are only a few cases reported to date on hepatotoxicity, due to acetaminophen administration in therapeutic range dosage, in malnourished subjects. This case report aims to highlight the lower threshold of acetaminophen to cause hepatotoxicity in malnourished subjects.

Case presentation

A 47-year-old female patient, a resident of Haryana with no known comorbidities was diagnosed with locally advanced squamous cell carcinoma mid-oesophagus. She was oncology treatment-naive and was advised the best supportive care given her poor performance status and progressive disease and was referred to the palliative medicine department.

She had presented with central chest pain which is non-radiating for 1 week with a numerical rating scale score of 6/10 and dull aching in nature. She also had progressive dysphagia for solids and liquids for the past 3 months with absolute dysphagia for the last 10 to 12 days. The patient also had altered mental status in the form of irrelevant talk for 1 day. On general examination, she was anicteric, and cachectic with a body weight of around 30 kg, body mass index (BMI) of 14.5, and had a performance status of 4.

Her routine investigations in the ward revealed hypernatremia (sodium 159 mmol/L) for which correction was initiated in the form of intravenous 5% dextrose at 60 mL/h. A nasogastric tube was inserted and nasogastric feeds were started at 100 mL every 2 h and slowly up-titrated after dietician review. For central chest pain, she was given an injection of tramadol 50 mg twice daily, an injection of paracetamol 1 g thrice daily along with injection of pantoprazole once daily.

On admission to ward her baseline AST and ALT values were 38 and 40 U/L, respectively. During her stay in the hospital, the fifth day's routine examinations revealed an acute rise in the liver enzymes AST and ALT. AST was 1526 U/L and ALT was 1880 U/L compared to previous day values of 191 U/L and 130 U/L respectively (Table 1). The albumin value was 2.6 g/dL compared to the previous day's value of 3.9 g/dL. The patient had negative viral markers. Liver metastasis was excluded from her imaging reports.

Acute liver injury likely caused by paracetamol overdose was suspected. Paracetamol injections were stopped. On the same day, the patient developed nausea, vomiting, and irritability. There were no new findings on examination. N-acetyl cysteine (NAC) was initiated according to the 21-hour protocol. A loading dose of 4500 mg was administered over 15 to 60 min (150 mg/kg) followed by 1500 mg over 4 h (50 mg/kg). Finally, a dose of 3000 mg was administered in the remaining 16 h (100 mg/kg). The next day her routine investigations were repeated, and AST and ALT were in a declining trend. Renal function test had also started to become elevated the next day

Table 1. Investigations

Investigations	Day 1	Day 3	Day 5	Day 6	Day 7
Total bilirubin	1.2	3.2	1.8	0.9	0.6
Direct bilirubin	0.5	1.5	1.3	0.7	0.39
Indirect bilirubin	0.7	1.7	0.5	0.2	0.26
ALT	40	130	1880	765	479
AST	38	191	1526	289	169
Total protein	7.2	6.6	4.7	3.9	4.1
Albumin	4.3	3.9	2.04	1.8	2.4
PT	–	–	–	13.9	11.4
INR	–	–	–	1.2	1.05
Urea	107	68.5	96	181	116
Creatinine	1.2	1.06	1.2	1.8	0.9

ALT — alanine aminotransferase; ALP — alkaline phosphatase; AST — aspartate aminotransferase; INR — international normalised ratio; PT — prothrombin time

with urea of 181 mg/dL and creatinine of 1.8 mg/dL (on admission her urea was 102 and creatinine was 1.2 mg/dL). She was hydrated and her lab parameters were monitored. The patient became clinically better in the coming days and liver enzymes further declined with AST 169 U/L and ALT of 479 U/L (Table 1) and the renal functions improved. The patient was discharged home in a stable condition. Possible contributors to paracetamol toxicity may be oesophageal obstruction leading to cachexia, absolute dysphagia leading to a recent fasting state, and frail condition.

Discussion

Acetaminophen is one of the most common analgesics used globally. However, overdose can be highly hepatotoxic as the therapeutic window is narrow but considered safe at therapeutic doses [5]. The mechanism of action is not clearly understood but seems to inhibit brain cyclooxygenase selectively and also inhibits central nervous system prostaglandin synthesis [6].

Almost 90% of paracetamol is metabolized to non-harmful substances via glucuronidation and sulfidation and finally excreted through kidneys at blood therapeutic levels. But in overdose, these pathways can be saturated causing conversion of paracetamol in huge amounts into NAPQI, its toxic metabolite, by cytochrome P450 enzyme. Once glutathione conjugation occurs, NAPQI is rendered into non-toxic metabolites. In malnourished patients, the risk of acetaminophen-induced hepatotoxicity is higher as there are depleted glutathione stores in them and so the conjugation of NAPQI species may not take place which may predispose to liver damage [7]. Additionally, in malnourished or fasting states glycogen levels may be inadequate resulting in less availability of glucose. This results in decreased formation of uridine diphosphate glucuronic acid thus affecting the step of glucuronidation in the metabolism of paracetamol [8].

The mainstay of treatment of acetaminophen overdose is NAC administration which replenishes glutathione stores thus acting as an antidote for acetaminophen-induced hepatotoxicity [9]. NAC produces cysteine which can act as a glutathione precursor thereby protecting from liver damage, especially in early acetaminophen toxicities. NAC also supplies thiol groups additionally to bind with reactive metabolites thus scavenging NAPQI [10]. NAC was found to prevent glutathione depletion against a placebo in 24 healthy subjects who were given acetaminophen (1 g four times daily for 4 days) in a randomized control trial [11].

Therefore, malnourished patients with a weight less than 50 kg can present a greater risk of toxic hepatic injury, a cautious reduction of dose to 2 g or less per 24 h is recommended for regular usage for cancer pain [8]. As reported by Kunce et al. [12] malnourished patients have a lower threshold for paracetamol toxicity owing to their lower stores of glutathione resulting in their limited metabolic clearance. This in turn can cause amplified paracetamol levels with the intake of normal doses of paracetamol. Kurtovic et al. [13] in their case report also suggest that in severely malnourished patients the daily dose of acetaminophen should be restricted to at least 2 g, especially when patients have been fasting recently. Also, the hepatotoxicity caused within the recommended dose may be dose-dependent, especially with malnourished or recently fasting patients [13]. Claridge et al. [14] in their case report also emphasize the same as they mention that the potential for hepatotoxicity may be higher if more than 4 g of paracetamol is administered per day in patients with lower body weights and malnourishment. Also, they recommend the maximum dose of paracetamol be limited to less than 3 g for patients with chronic malnutrition.

Conclusions

In this case scenario, if the patient presents with a pain crisis again during the next visit, a fixed-dose combination of tramadol and paracetamol where paracetamol will be present in a smaller dose can be used. Also, a higher step 3 opioids according to the World Health Organization (WHO) pain ladder may be considered.

Article information and declaration

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NSA — drafting the work; SM, SB — critical revision.

Conflict of interest
None.

Ethics statement
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for results of her investigations and clinical information to be reported in the journal. The patient understands that her name will not be published and due efforts will be made to conceal her identity.

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