Scientific Research Publishing

Case Reports in Clinical Medicine, 2025, 14(7), 368-374
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Occult Life-Threatening Acetaminophen Toxicity in an Elderly Patient Presenting with Confusion: A Case Report

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How to cite this paper: Devleesschauwer, L., Sabbe, M. and Govindan, T. (2025) Occult Life-Threatening Acetaminophen Toxicity in an Elderly Patient Presenting with Confusion: A Case Report. *Case Reports in Clinical Medicine*, **14**, 368-374.
https://doi.org/10.4236/crcm.2025.147049

Received: June 24, 2025
Accepted: July 15, 2025
Published: July 18, 2025

Abstract

Acetaminophen overdose is a common and potentially life-threatening cause of acute liver injury. While intentional overdoses are widely acknowledged, occult overdoses often remain overlooked, especially in vulnerable populations such as older adults. This can be associated with a significant risk of clinical deterioration due to delayed diagnosis and timely delivery of antidote treatment. We present the case of a 68-year-old man who unknowingly consumed supra-therapeutic doses of acetaminophen, unaware of the drug's potential for harm. This led to a high anion gap metabolic acidosis, multiple organ failure, including encephalopathy and severe hepatotoxicity. This case emphasizes the critical need to consider acetaminophen toxicity in patients with altered mental status and highlights the importance of early recognition, timely initiation of N-acetylcysteine therapy, and increased vigilance in elderly patients and patients who present with altered mental status or unexplained high anion gap metabolic acidosis.

Keywords

Acetaminophen Toxicity, Screening, Altered Consciousness, Emergency Medicine

1. Introduction

Acetaminophen toxicity is a leading cause of drug-induced liver injury and a major contributor to acute liver failure worldwide, especially in regions where it is widely available over the counter [1].

Toxicity occurs when excessive acetaminophen overwhelms the liver's metabolic

capacity. Under normal conditions, acetaminophen is metabolized in the liver into non-toxic metabolites. However, in overdose situations, this process is overwhelmed, leading to the accumulation of the toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI). NAPQI binds to liver cell proteins, causing oxidative stress and mitochondrial dysfunction. This disrupts the electron transport chain and impairs ATP production, forcing cells to shift toward anaerobic glycolysis, resulting in lactate accumulation and early high-anion gap metabolic acidosis. The systemic acidosis contributes to hepatic encephalopathy by promoting increased cerebral ammonia uptake and impairing neuronal metabolism. If untreated, these processes can lead to acute liver failure, kidney injury, and death [2] [3].

Early symptoms, such as nausea, vomiting, general malaise or reduced consciousness, are often nonspecific and can be delayed for up to 24 hours. This delay in symptom onset complicates early diagnosis. Therefore, screening for acetaminophen toxicity is essential for timely diagnosis and intervention. Within 24 to 72 hours, signs of liver damage become evident, including elevated liver enzymes, jaundice, and, in severe cases, hepatic encephalopathy, leading to fulminant hepatic failure. Early administration of the antidote N-acetylcysteine (NAC) is critical, as it replenishes glutathione and can prevent irreversible liver damage. It is most effective when administered within 8 hours following ingestion, highlighting the importance of early identification [4].

Routine screening of serum acetaminophen levels in patients presenting with collapse or altered consciousness has been discussed in previous studies, as acetaminophen poisoning can often be occult [5] [6]. In previous data, nearly half of the patients who developed severe liver damage due to acetaminophen toxicity did not intentionally overdose, but rather took the medication for therapeutic purposes, often exceeding the safe recommended daily dose [4].

Between 1989 and 2004, 26% of patients referred to the Victorian Liver Transplant Unit for acetaminophen-induced acute liver failure had experienced accidental poisoning [7].

This highlights the risk of inadvertent overdose, especially when individuals take multiple over-the-counter medications containing acetaminophen or are unaware of the cumulative dose consumed. Additional risk factors include prolonged fasting, excessive alcohol consumption, advanced age, and the concurrent use of drugs that induce cytochrome P450 (CYP450) [7]. Elderly patients are particularly vulnerable due to polypharmacy, cognitive impairment leading to dosing errors, age-related declines in hepatic function and glutathione reserves, alcohol use that increases toxic metabolite formation, comorbidities such as malnutrition and renal dysfunction, and often delayed clinical presentation caused by atypical or unrecognized symptoms [8].

2. Case Description

A 68-year-old male with a medical history of type 2 diabetes, arterial hypertension, rheumatoid arthritis, and chronic back pain presented to the Emergency Depart-

ment (ED) at the Royal Adelaide Hospital (Australia) following sudden onset of lethargy and dizziness. He complained of lower back pain. He was transported by ambulance, during which paramedics administered 1 gram of intravenous paracetamol for pain relief.

On arrival, the patient reported back and hip pain, exhibited confusion, and was unable to follow commands or provide coherent responses. He was hemodynamically stable with a Glasgow Coma Scale (GCS) score of 13/15 (E3M6V4), euglycemic, and afebrile. There were no meningeal signs or focal neurological deficits. The ECG was within normal limits. Initial venous blood gas (VBG) analysis revealed a high anion gap metabolic acidosis (HAGMA): pH 7.24, bicarbonate 16 mmol/L, sodium 132 mmol/L, potassium 5 mmol/L, partial pressure of carbon dioxide (pCO_2) 38 mmHg, base excess (BE) –10.9, and lactate 3.3 mmol/L. The anion gap was 23.

Due to the patient's lethargy and confusion, the clinical history was unreliable, prompting a broad panel of tests, including a serum acetaminophen level, to identify the cause of the HAGMA. Given a qSOFA score of 2/3, broad-spectrum antibiotics were initiated for suspected sepsis.

Laboratory results showed no leukocytosis but revealed an unexpected serum acetaminophen level of 1276 μmol/L. Considering the recent administration (30 minutes to 1 hour prior to arrival) of intravenous acetaminophen during transport, the test was repeated. A second measurement, taken three hours after ED arrival, showed a serum acetaminophen level of 1819 μmol/L. The patient's liver function tests were normal at that time. His estimated weight was 70 kg.

After consulting the local toxicology team, the patient was administered 200 mg/kg of N-acetylcysteine (NAC) over a span of 4 hours, succeeded by 300 mg/kg over the course of 16 hours, an additional 300 mg/kg over another 16-hour period, and ultimately 100 mg/kg over the final 16 hours. This dosing strategy was based on local toxicology guidelines, which recommend adjusting the NAC dose to the serum acetaminophen level in massive overdose [9]. NAC therapy was continued as there was persistent elevation in liver transaminases and detectable serum acetaminophen levels, showing insufficient metabolic clearance, which made the SNAP protocol unsuitable for our case [9].

Comprehensive investigations, including chest X-ray, urine analysis, blood cultures, nasopharyngeal swab, and computed tomography (CT) of the abdomen, pelvis, and brain, were unremarkable.

The patient received three days of NAC infusion until lactate levels and serum acetaminophen concentrations normalized, as per local guideline. The highest acetaminophen level was 2422 μmol/L. Upon arrival, liver function tests (LFTs) were within normal limits. However, during the course of the patient's admission, the LFTs became markedly deranged, with alanine transaminase (ALT) levels reaching 1187 U/L and aspartate transaminase (AST) levels rising to 752 U/L. The INR level peaked at 1.8. LFTs gradually returned to normal after 14 days, and the encephalopathy subsequently resolved. The patient denied intentional overdosing. Determining the precise amount and pattern of acetaminophen ingested remained challenging, as

the patient had limited recollection of the events leading up to his presentation. The patient made a full recovery.

3. Discussion

3.1. Broadening the Screening Criteria for Acetaminophen Toxicity

The importance of screening for acetaminophen levels in patients presenting with altered consciousness and metabolic acidosis cannot be overstated. While most publications primarily focus on accidental overdoses in high-risk patient groups, such as patients with alcohol dependence or substance use disorder, or on intentional overdoses, this case presents a rather rare scenario of discovery of acetaminophen toxicity by careful consideration of broad differentials associated with unexplained HAGMA in a patient who presented in altered mental status. This highlights the potential need for broader screening protocols, as acetaminophen poisoning can occur in individuals without the typical risk factors [5] [6].

As previously stated, measuring plasma acetaminophen concentrations in patients who present with altered consciousness and unexplained HAGMA would significantly impact clinical management of occult acetaminophen toxicity and could potentially improve outcomes [5] [6]. This aligns with the recommendations for routine screening of acetaminophen levels in these patients, even when the history of overdose is not immediately clear. The delay in diagnosis can lead to worsened outcomes, emphasizing the need for early intervention based on acetaminophen concentration testing.

Given these findings, we advocate for routine screening for acetaminophen levels in all patients with altered consciousness or suspected drug overdose. This approach not only aids in early diagnosis but also facilitates prompt treatment, potentially reducing morbidity and mortality associated with acetaminophen toxicity.

3.2. Evolving Treatment Landscape in Acetaminophen Overdose

The management of acetaminophen overdose is undergoing significant changes. The adoption of the SNAP regimen, a 12-hour N-acetylcysteine (NAC) protocol, has replaced the traditional 21-hour regimen, offering comparable efficacy with fewer adverse effects in low-risk ingestions [10]. This shift has enabled more patient-friendly treatment pathways and laid the foundation for ongoing innovation. The HiSNAP trial is evaluating the safety and efficacy of higher NAC doses to enhance detoxification [11].

However, NAC's effectiveness declines markedly when administered more than eight hours after ingestion, leaving late-presenting patients with limited options aside from hemodialysis or liver transplantation. One study of patients presenting with massive overdose demonstrated a failure rate of 9% despite NAC administration [12]. NAC fails in a manner dependent on paracetamol concentration [13]. While NAC supports detoxification of the ultimate hepatotoxin, NAPQI, it does not address the intrinsic mitochondrial toxicity of paracetamol, the mechanism of

NAPQI generation or the downstream cellular pathways of hepatotoxicity [14]. This unmet need has prompted several novel therapeutic investigations.

Recent interest has emerged in fomepizole as a potential adjunct in the treatment of severe or late-presenting acetaminophen poisoning. Traditionally used as an alcohol dehydrogenase inhibitor in toxic alcohol ingestions, fomepizole also inhibits CYP2E1, the key enzyme responsible for converting acetaminophen to its toxic metabolite, NAPQI. In doing so, it not only reduces NAPQI formation but also prevents activation of harmful intracellular pathways such as c-JNK, thereby mitigating mitochondrial injury and downstream hepatocellular damage. Unlike NAC, which primarily supports detoxification after NAPQI has already formed, fomepizole targets upstream mechanisms and may offer additional protection in massive overdoses or in patients with mitochondrial dysfunction, metabolic acidosis, or very high paracetamol concentrations (>600 - 900 mg/L). Preliminary case series and experimental models suggest that fomepizole may improve outcomes even when administered late, and its safety profile appears favourable. While randomized controlled trials are still lacking, fomepizole represents a promising therapeutic addition for high-risk acetaminophen-poisoned patients where NAC alone may be insufficient [14].

In parallel, several innovative approaches are under investigation that aim to further improve outcomes in acetaminophen toxicity. The MAIL trial explores macrophage cell therapy to promote liver regeneration in acute liver injury [15]. The ALBATROSS trial will assess Aladote®, a new compound designed to mitigate liver damage when NAC is no longer effective [16].

Together, these developments reflect a broader evolution in the treatment paradigm, from focusing solely on NAC dosage adjustments to incorporating adjunctive and alternative strategies aimed at improving outcomes, especially for high-risk and late-presenting patients.

4. Conclusions

This case highlights the importance of increased awareness and advocates for routine screening for acetaminophen toxicity in patients presenting with altered consciousness, even in the absence of a clear history of overdose. Accidental repeated supratherapeutic ingestion of acetaminophen remains an underrecognized but significant cause of acute liver injury, particularly in elderly patients and those without traditional risk factors. The patient's unexpected and life-threatening toxicity underscores the need for broader screening protocols to facilitate early diagnosis and timely intervention.

While N-acetylcysteine remains the cornerstone of treatment, its efficacy is time-dependent, and alternative strategies are required for late-presenting patients. Emerging therapies, including high-dose NAC regimens, fomepizole, macrophage cell therapy, and novel hepatoprotective drugs such as Aladote®, offer promising avenues for improving patient outcomes. Additionally, the development of rapid point-of-care diagnostics, such as the POC-DILI test, may enable earlier identification of liver

injury and enhance treatment precision.

Ultimately, increasing awareness, improving screening protocols, and advancing treatment modalities are crucial steps in mitigating the morbidity and mortality associated with acetaminophen toxicity. However, as with any case report, the conclusion should be interpreted within the context of a single patient's experience and is not necessarily applicable to all clinical scenarios.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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