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N-Acetylcysteine and Hemodialysis in Severe Acetaminophen Toxicity in a 15-Year-Old Adolescent: A Case Report

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Study Design A
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Patient: Male, 15-year-old
Final Diagnosis: Acetaminophen toxicity • acute liver injury • metabolic acidosis
Symptoms: Altered mental status • lactic acidosis • nausea
Clinical Procedure: —
Specialty: Critical Care Medicine • Nephrology • Toxicology

Objective: Unusual clinical course

Background: Acetaminophen toxicity is a leading cause of liver injury in adolescents and is usually treated with N-acetylcysteine (NAC). Rarely, adjunctive therapies, including hemodialysis (HD) and fomepizole, are required. This report describes the case of a 15-year-old male adolescent who required 2 hemodialysis sessions greater than 24 hours apart after a massive, intentional ingestion of acetaminophen.

Case Report: A 15-year-old male patient presented to care after a single, intentional ingestion of approximately 195 g of extended-release acetaminophen. He was started on NAC therapy, and due to concern for early mitochondrial failure, he underwent intermittent HD, with reduction of his acetaminophen level. However, over 24 hours later, his transaminases increased and liver synthetic function declined, and he underwent HD a second time. There was no evidence of bezoar formation on computed tomography (CT) scan, suggesting that ongoing absorption was due to the extended-release formulation consumed. After his second HD session, his laboratory values normalized and he was medically cleared for transfer to psychiatry.

Conclusions: The need for a second HD session in acetaminophen toxicity >24 hours after an initial successful HD session is unprecedented. Given an increasing market of extended-release products and the potential for co-ingestions with medications that slow gastrointestinal motility, HD may be more frequently employed going forward, potentially multiple times. While central lines should be removed promptly when no longer needed, we advise caution in removing dialysis catheters within 24 hours of initial HD in these patients, given the need to repeat HD in this case.

Keywords: Acetaminophen • Dialysis • Liver Failure • Toxicology • Case Reports

Abbreviations: **NAC** – N-acetylcysteine; **HD** – hemodialysis; **CT** – computed tomography; **US** – United States; **NAPQI** – N-acetyl-p-benzoquinone imine; **GCS** – Glasgow Coma Scale; **INR** – international normalized ratio; **EXTRIP** – extracorporeal treatments in poisoning

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Introduction

Acetaminophen overdose is the most common cause of overdose-related acute liver failure requiring liver transplantation in the United States [1]. It is also the most commonly identified cause of pediatric acute liver failure, recognizing that approximately 40% of pediatric acute liver failure cases have unidentified causes [2]. Acetaminophen toxicity arises once glucuronidation and sulfation biotransformation pathways become saturated, and glutathione stores become significantly depleted [1]. Rather than renally-excretable nontoxic metabolites, the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) is produced in increased amounts when acetaminophen levels are supratherapeutic via the activity of a pathway involving CYP2E1 [1]. In large quantities, NAPQI can rapidly increase reactive oxygen species and lead to cell death [1,3]. Typically, this manifests as hepatotoxicity and renal injury, which becomes most evident within 1-3 days after ingestion, after typical initial symptoms of nausea, vomiting, and malaise have subsided. To prevent fulminant liver failure, gastric decontamination and early treatment with N-acetylcysteine (NAC) are the mainstays of therapy, as advised by the American College of Medical Toxicology [3]. While NAC therapy is remarkably effective in the vast majority of pediatric acetaminophen overdoses, adjunctive therapies, including hemodialysis (HD) and fomepizole administration, are sometimes employed in patients with massive ingestions, or when patients exhibit signs of mitochondrial failure (eg, altered mental status with lactic acidosis) or acute renal failure (eg, oliguria and rising creatinine) [4,5]. Here, we describe the case of a 15-year-old male patient who received 2 separate intermittent HD sessions greater than 24 hours apart after a massive, intentional ingestion of extended-release acetaminophen.

Case Report

Our hospital received a transfer request call from a referring hospital for a 15-year-old male who had presented after an intentional ingestion of approximately 300 tablets of extended-release acetaminophen (650 mg each), without reported co-ingestion of other medications. He developed nausea, disclosed his actions to his mother, and presented to the referring facility within 2 hours after ingestion. There, a physical exam was non-contributory without significant tenderness to palpation of his abdomen. He was started on NAC and received oral activated charcoal in consultation with the regional poison control center. Initial laboratory values did not reveal concerning findings beyond an acetaminophen level of 272 mg/L (Table 1, Time A). However, 20 hours after ingestion, his acetaminophen level increased to >400 mg/L (the maximum result of the institution's laboratory), lactate increased to 8.5 mmol/L, and he had an acute change in mental status (Time B). He was

Table 1. Patient laboratory data throughout the inpatient course.

	Time since ingestion						
	4 h A (Admission)	20 h B (Before 1st HD)	30 h C (After 1st HD)	42 h D (After hospital transfer)	68 h E (Before 2nd HD)	96 h F (After 2nd HD)	110 h G (Medically cleared)
Acetaminophen Level (ref 10-30 mg/L)	272	>400	253	193	347	6	<5
ALT (ref ≤40 U/L)	26	27	46	68	5138	5454	4226
AST (ref ≤37 U/L)	30	21	36	34	3595	2218	839
INR (ref 0.9-1.1)	1.1	1.3	1.9	1.8	2.9	1.8	1.3
Glucose (ref 60-100 mg/dL)	166	165	105	117	130	113	184
Lactate (ref 0-2.2 mmol/L)	1.8	8.5	1.0	1.4	3.0	1.0	2.1
HCO3 (ref 21-31 mmol/l)	21	8	23	19	17	24	23
TBili (ref ≤1.2 mg/dL)	0.7	1.8	2.7	2.7	1.5	1.5	1.8
Cr (ref 0.6-1.3 mg/dL)	0.3	0.2	0.2	0.5	0.2	0.3	0.5
Albumin (ref 3.5-5.3 g/dL)	4.1	3.2	3.3	3.5	3.0	3.4	3.6
Ammonia (ref ≤32 mcmol/L)	--	<9	27	30	56	--	48

Ref – laboratory reference range; ALT – alanine aminotransferase; AST – aspartate aminotransferase; INR – international normalized ratio; HCO3 – bicarbonate; Tbili – total bilirubin; Cr – creatinine; HD – hemodialysis; NAC – N-acetylcysteine.

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intubated for airway protection, and, after discussions with a medical toxicologist, the NAC dose was doubled, fomepizole was given, and intermittent HD was urgently initiated (dialysate flow rate 800 mL/min, blood flow rate 200 mL/min). He received 4 hours of HD, after which his acetaminophen level decreased to 253 mcg/dL, and his mental status improved (Time C). The referring facility called our hospital in anticipation of the possible need for liver transplantation.

At our hospital, initial laboratory data showed an acetaminophen level that had continued to downtrend (193 mg/L) on intravenous NAC, no notable transaminase elevation, and minimal acidosis (Time D). Ultrasound imaging of his liver parenchyma and vasculature was reassuring. Clinically, he was alert and oriented x3, with a Glasgow Coma Scale (GCS) of 15, and he had reassuring hemodynamics. He was extubated a few hours after arrival. However, over the next 24 hours, his acetaminophen level markedly increased to 347 mg/L, he developed significant transaminase elevation, and his International Normalized Ratio (INR) rose to 2.9 (Time E). In consultation with medical toxicology, his NAC dose was increased yet again to 25 mg/kg/h (4 times the typical third-bag infusion rate), and fomepizole was re-administered. His GCS remained 15, but he was noted to be less alert. A computed tomography (CT) scan of his abdomen was performed to assess for bezoar formation, with possible endoscopy to follow; however, given no obvious bezoar formation on CT, endoscopy was not pursued. He was ultimately restarted on intermittent HD, which lasted 4 hours (dialysate flow rate 600 mL/min, blood flow rate 300 mL/min), with rapid improvement in acetaminophen levels to 6 mg/L. The transaminase concentrations then began to plateau, his INR normalized, and his NAC was stopped approximately 96 hours after ingestion (Time F). Over the next 24 hours, the transaminase levels decreased, and he was medically cleared for transfer to inpatient psychiatric treatment (Time G).

Discussion

This case report demonstrates the critical role that extracorporeal removal of acetaminophen plays in massive ingestion, while also showing the hazard of stopping dialysis too early when the risk of delayed absorption is high, as with extended-release products. The risk of future cases like this one is hardly negligible: among all medication poisonings, acetaminophen causes the most hospital admissions among pediatric patients in the United States, with >1 child admitted every hour due to acetaminophen ingestion [6]. Unfortunately, it is a growing problem. Data from US poison control centers indicates that while around 10 000 intentional overdoses of acetaminophen among youths took place in each of the pre-COVID pandemic years of 2016-18, that number jumped to greater than 15 000 in 2020 and to approximately 20 000 in 2021 and in 2022 [7].

Our patient was a teenage boy who intentionally ingested approximately 200 g of acetaminophen. He was appropriately started on gastric decontamination and NAC therapy once he presented to care, which was quite soon after ingestion. As expected, he did not show signs of liver injury in this immediate post-ingestion period, but did experience the typical clinical symptom of nausea. However, within hours after ingestion, he exhibited signs of mitochondrial failure, with metabolic acidosis and altered mental status before any demonstrable liver injury. This phenomenon is thought to be due to both acetaminophen itself and reactive oxygen species resulting from NAPQI interfering with energy production. Extracorporeal removal of acetaminophen is indicated in this clinical scenario according to the Extracorporeal Treatments in Poisoning (EXTRIP) guidelines, a publication written by a working group of international toxicologists, nephrologists, and other experts advising the appropriate use of extracorporeal therapies for specific toxin removal [8]. These guidelines recommend the use of intermittent HD over continuous renal replacement in acetaminophen toxicity given the superior drug clearance of the former technique. Given modern HD membranes and acetaminophen's low molecular weight (151 Da) and low protein binding (<25%), dialysis has been shown to very effectively remove the drug [8]. Nevertheless, continuous renal replacement has also been shown to be successful in acetaminophen toxicity in pediatric patients, with 1 report describing its use in a toddler who had high transaminases and concern for cerebral edema, attempting to limit fluid shifts typical of intermittent HD that might worsen cerebral edema [4].

Our patient also underwent treatment with fomepizole, which prevents formation of toxic metabolites by inhibiting CYP2E149]. In the last decade, there have been a small number of case reports on use of both fomepizole and renal replacement therapy in acetaminophen toxicity [5,10-13]. While intermittent HD was the initial choice for renal replacement in these cases, those without a drop in acetaminophen level with initial HD were switched to continuous renal replacement therapy [12,13]. In most of these, NAC dosing was empirically increased, as it was in this case, given some evidence it is dialyzable [5,10,11,13].

Thus, while there have been rare cases requiring repeated intermittent HD sessions and/or trials of continuous renal replacement therapy, none of these had initial improvement and then required re-initiation of extracorporeal toxin removal >24 hours later. However, in this case, the patient's acetaminophen level began to climb again more than 24 hours after the initial session of hemodialysis was performed, which suggests that ongoing absorption complicated our patient's clinical course. Given the efficiency with which intermittent HD clears acetaminophen, we concluded that the patient's drug absorption continued after the first HD session. With a negative CT scan, a bezoar does not appear to have played a role in slowing the

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transit of the large quantity of ingested drug, instead suggesting that the continued absorption was caused by ingesting an extended-release product.

Conclusions

Given the growing number of extended-release formulations of acetaminophen on the market, and the possibility of co-ingestions of medications that slow gastric motility (eg, antihistamines such as diphenhydramine, with which acetaminophen is often combined in a single pill), we anticipate that the need for subsequent HD sessions may be required 24 hours or more after the initial session. As such, we recommend close vigilance of both drug levels and markers of liver function for at least 24 hours before removal of dialysis catheters, as subsequent dialysis may be warranted.

Acknowledgements

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Patient Consent

Both the patient and patient's parents consented to the publication of this case report.

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