Massive acetaminophen ingestion with early metabolic acidosis and coma: treatment with IV NAC and continuous venovenous hemodiafiltration

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Context. We report the extraction of acetaminophen by continuous venovenous hemodiafiltration (CVVHD) during treatment of an acute ingestion of 200 g with a peak recorded serum acetaminophen level of 1,614 mg/L (10,652 μmol/L).

Case details. The patient presented with early onset of coma, metabolic acidosis, and hypotension in the absence of significant hepatic injury. In addition to N-acetylcysteine (NAC) therapy, CVVHD was performed to manage the acid–base disturbance. Flow rate, effluent volume, and serum and effluent drug concentrations were obtained at hourly intervals. During 16 h of CVVHD the acetaminophen level dropped from 1,212 to 247 mg/L.

Discussion. The average clearance of acetaminophen by CVVHD was 2.53 L/h, with removal of 24 g of acetaminophen over 16 h. As NAC is effective in preventing hepatic injury after acute acetaminophen overdose, the role of dialysis or CVVHD is limited.

Keywords. Acetaminophen; Acid–base disorders; N-Acetylcysteine; Hemodialysis; Coma

Introduction

Acetaminophen overdose is usually characterized by mild initial gastrointestinal upset shortly after ingestion, followed 24–48 h later by hepatic injury because of the generation of a toxic intermediate (N-acetyl-para-quinone imine, NAPQI) during hepatic P450 metabolism. Coma and lactic acidosis, if they occur, are usually a result of fulminant hepatic failure and develop after 2–3 days. Massive acetaminophen ingestion, however, has been reported to cause severe metabolic acidosis and coma early after ingestion, even in the absence of hepatic failure.1

Although N-acetylcysteine (NAC) is the definitive antidote for preventing acetaminophen-induced liver toxicity, more aggressive supportive care measures, including extracorporeal elimination, may be indicated in rare cases of massive overdose to facilitate correction of the acidosis. This might hasten removal of the drug, but there is no data in the literature regarding the effects of continuous venovenous hemodialfiltration (CVVHD) on acetaminophen kinetics.

Case report

A 23-year-old woman was brought to the Emergency Department (ED) by ambulance with altered mental status. The evening before admission, she had eloped from the inpatient unit of a local mental health facility. At 8:20 am she was found lying supine on a park bench. In her belongings was a receipt from a local pharmacy for four bottles each containing 100 Tylenol Extra Strength™ tablets (a total of 200 g of acetaminophen). The receipt was dated the morning of admission at 7:01 am (approximately 1 h and 20 min before she was found). No other medication bottles were found on or near the patient. According to paramedics she was difficult to arouse and answered questions slowly but was oriented to person and place. While being transported to the hospital, she became less responsive and on arrival at the ED 20 min later she was confused and oriented only to person. By 9:30 am she was unresponsive to voice or touch and was intubated for airway protection. A single dose of 50 g of activated charcoal was given after intubation. Gastric lavage was not performed.

Initial vital signs included a core temperature of 34.2°C, blood pressure 116/54 mmHg, pulse 95/min, respiratory rate 13/min, and oxygen saturation 97% while intubated on 48% inspired oxygen. Pupils were 7 mm and non-reactive. Eye movements had a slow left-to-right repetitive movement,
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resembling nystagmus, and were occasionally disconjugate. Bowel sounds were decreased.

Initial laboratory data included serum sodium 140 mEq/L, potassium 3.4 mEq/L, chloride 97 mEq/L, bicarbonate 12 mEq/L, blood urea nitrogen 10 mg/dL, creatinine 0.5 mg/dL, glucose 226 mg/dL, white blood count 17,800, hemoglobin 14.3 g/dL, hematocrit 40.8%, platelets 429,000, aspartate aminotransferase (AST) 39 IU/L, alanine transaminase (ALT) 22 IU/L, international normalized ratio (INR) 1.2, and total bilirubin 0.8 mg/dL. Arterial blood gases while receiving 100% oxygen: pH = 7.17, pCO2 = 20.7 mmHg, and pO2 = 260 mmHg. The urine toxicology screen was negative for alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, and opiates. Serum salicylate was less than 10 mg/dL. The serum acetaminophen level was 816 mg/L.

During the first several hours after admission the patient developed worsening acidosis, with a blood pH as low as 6.91 and a serum lactate level of 25.1 mmol/L. She had hypotension with systolic blood pressures as low as 75 mmHg despite treatment with dopamine, phenylephrine, and norepinephrine. The acetaminophen level continued to rise, with the highest recorded level of 1,614 mg/L obtained 9 h after presentation (Fig. 1).

A loading dose of NAC of 140 mg/kg was given via nasogastric tube in the ED. The route of administration was later changed to intravenous because of concern for poor gastrointestinal absorption in the setting of the patient’s hypotension. Intravenous NAC was continued throughout the patient’s course.

The patient remained severely acidic despite repeated doses of intravenous bicarbonate, and nephrology was consulted regarding dialysis to facilitate the correction of the acidosis. CVVHD was performed, because of concern that the initiation of conventional hemodialysis might cause a further drop in the blood pressure. CVVHD was performed for 16 h, during which time the acetaminophen level dropped from 1,212 to 247 mg/L (see Fig. 1). By the time CVVHD was discontinued, the metabolic acidosis had resolved.

A total of 24 g of acetaminophen was removed in the CVVHD effluent. The average clearance of acetaminophen during CVVHD was 2.53 L/h (42.1 mL/min), calculated using the equation

\[ CL_{\text{CVVHD}} = \frac{UV}{P} \]

where \( U \) is the concentration of acetaminophen in the effluent, \( V \) is the flow rate of the effluent, and \( P \) is the serum acetaminophen concentration. This represents 66% of the total body clearance of acetaminophen during the same time, which was estimated to be 3.82 L/h using the equation

\[ CL_{\text{Total}} = 0.693 \times \frac{V_d}{\text{Half-life}} \]

where the volume of distribution was assumed to be 40 L (0.9 L/kg).

The patient did not develop severe liver injury. Serum transaminase levels peaked on the third day of hospitalization with an AST of 420 U/L and ALT 262 U/L. The INR rose transiently to 3.3 on the second day but normalized without any use of vitamin K or blood products. She became more alert on the third day of hospitalization and eventually fully recovered.

Discussion

The early onset of acidosis in this patient contrasts with the typical course of acetaminophen intoxication. Lactic acidosis associated with massive acetaminophen ingestion may occur at two distinct time frames.2 Late-onset acidosis is associated with the damaged liver’s inability to clear lactic acid, whereas early-onset acidosis occurs well before any apparent liver injury. Although the exact mechanism remains uncertain, there are several potential mechanisms for the early-onset acidosis.

Acetaminophen can cause transient 5-oxoprolinuria associated with depletion of liver glutathione stores. This may even occur with therapeutic dosing of acetaminophen in individuals with various conditions resulting in glutathione deficiency (inborn error of metabolism, malnutrition).3 Transient 5-oxoprolinuria has been reported even in mild overdose and the treatment is to replenish glutathione stores through standard therapy with NAC.1,3,4

Animal studies have implicated NAPQI as a strong inhibitor of mitochondrial respiration, with uncoupling of oxidative phosphorylation.5,6 There is also evidence that acetaminophen

![Fig. 1. Series of patient’s acetaminophen concentrations (mg/L) over time (h).](image-url)
itself, in high concentrations, can act as a direct mitochondrial toxin by coupling covalently to mitochondrial aldehyde dehydrogenase.  

Historically, reports regarding extracorporeal removal techniques for acetaminophen refer to use of charcoal hemoperfusion. Charcoal hemoperfusion is now rarely used because high flux dialysis equipment provides clearances similar to, or better than, charcoal hemoperfusion. Also, hemoperfusion cartridges are not stocked in most centers and most nephrologists are not familiar with this technique.

Several reports demonstrate that acetaminophen can be removed by hemodialysis. However, there are few case reports describing the use of hemodialysis for acute acetaminophen overdose. Pond described a patient who presented late after an estimated 58 g acetaminophen ingestion. The initial acetaminophen level obtained at 22 h was 485 mg/L. A half-life and apparent half-lives of 14 h and longer have been reported. It would have been reasonable to predict primary to help correct acid–base and fluid abnormalities, and any increase in the removal of acetaminophen was considered a secondary benefit.

Conclusion

Coma and metabolic acidosis preceding hepatic injury in acetaminophen intoxication is rare, but can occur after massive overdose. Treatment for acetaminophen toxicity should emphasize early treatment with NAC. Hemodialysis or CVVHD may be of use in restoring acid–base balance in patients with refractory or severe acidosis because of massive acetaminophen ingestion. Extracorporeal removal of acetaminophen might also shorten the duration of coma and hypotension if these complications are because of direct inhibition of mitochondrial respiration by high levels of acetaminophen or NAPQI. However, the clinical benefit because of more rapid removal of acetaminophen remains unclear.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References