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Massive acetyaminophen overdose: effect of hemodialysis on acetyaminophen and acetylcysteine kinetics

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ABSTRACT

Context: Early onset acidosis from mitochondrial toxicity can be observed in massive acetyaminophen poisoning prior to the development of hepatotoxicity. In this context, the efficacy of acetylcysteine to reverse mitochondrial toxicity remains unclear and hemodialysis may offer prompt correction of acidosis. Unfortunately, toxicokinetics of acetyaminophen and acetylcysteine during extracorporeal treatments hemodialysis have seldom been described.

Case details: An 18-year-old woman presented to the emergency department 60 minutes after ingestion of 100g of acetyaminophen, and unknown amounts of ibuprofen and ethanol. Initial assessment revealed an agitated patient. Her mental status worsened and she required intubation for airway protection. Investigations showed metabolic acidosis with lactate peaking at 8.6 mmol/L. Liver and coagulation profiles remained normal. Acetyaminophen concentration peaked at 981 µg/ml (6496 µmol/L).

Pending hemodialysis, the patient received 100 g of activated charcoal and an acetylcysteine infusion at 150 mg/kg over 1 hour, followed by 12.5 mg/kg/h for 4 hours. During hemodialysis, the infusion was maintained at 12.5 mg/kg/h to compensate for expected removal before it was decreased to 6.25 mg/kg for 20 hours after hemodialysis. The patient rapidly improved during hemodialysis and was discharged 48 hours post-admission.

Toxicokinetics: The acetyaminophen elimination half-life was 5.2 hours prior to hemodialysis, 1.9 hours during hemodialysis and 3.6 hours post hemodialysis. The acetyaminophen and acetylcysteine clearances by A-V gradient during hemodialysis were 160.4 ml/min and 190.3 ml/min, respectively. Hemodialysis removed a total of 20.6 g of acetyaminophen and 17.9 g of acetylcysteine.

Conclusion: This study confirms the high dialyzability of both acetyaminophen and acetylcysteine. Hemodialysis appears to be a beneficial therapeutic option in cases of massive acetyaminophen ingestion with coma and lactic acidosis. Additionally, these results suggest that the infusion rate of acetylcysteine must be more than double during hemodialysis to compensate for its ongoing removal and provide similar plasma concentrations to the usual acetylcysteine regimen.

Introduction

Acetaminophen is a widely available over-the-counter medication that ranks amongst the most common drug overdoses overdose in the United States.[1] Early onset acidosis can be observed in the setting of massive acetaminophen ingestion (> 500 mg/Kg) with peak plasma acetaminophen concentrations exceeding 750 µg/ml (> 5000 µmol/L).[2–4] Various mechanisms have been implicated as potential causes of lactic acidosis in massive acetaminophen overdose,[2,4] including (1) depletion of liver glutathione stores leading to 5-oxoprolinemia; (2) N-acetyl-p-benzoquinone-imine induced inhibition of mitochondrial respiration causing uncoupling of oxidative phosphorylation; (3) covalent bonding of acetaminophen to mitochondrial aldehyde-dehydrogenase causing direct mitochondrial toxicity.

Acetylcysteine is used to prevent and treat acetaminophen-induced hepatotoxicity.[2,3,5] Acetylcysteine, however, has undetermined efficacy in correcting mitochondrial toxicity that may follow massive overdose.[6] In addition, it is unclear if the intravenous dose of acetylcysteine is sufficient to account for the amount of NAPQI formed.[7] Hemodialysis has been used in several reports to correct the acidosis induced by early acetaminophen exposure and to facilitate the removal of acetaminophen due to its favorable molecular characteristics (Table 1). Unfortunately, hemodialysis may also remove acetylcysteine, although there are few reports quantifying this.[2,8] We present a case of massive acetaminophen overdose illustrating the kinetics of both acetaminophen and acetylcysteine during hemodialysis.

Case details

An 18-year-old woman, weighing 80 kg, presented to the emergency department 60 minutes after an intentional...
ingestion of 100g of acetaminophen, a handful of ibuprofen tablets and an unknown amount of ethanol.

Initial assessment revealed a healthy but agitated patient. Triage vital signs included: BP – 101/39 mmHg, HR – 109 bpm, RR – 16-breaths/min, temperature – 37.2°C, and Glasgow Coma Scale 14. The electrocardiogram showed sinus tachycardia with normal QRS and QT intervals. The patient was monitored in the emergency department. Three hours post-ingestion the patient became somnolent and required intubation for airway protection. A 50-gram dose of activated charcoal was given via nasogastric tube immediately after intubation.

The venous blood gas sampled on arrival indicated metabolic acidosis (pH – 7.19, PCO₂ – 27.7 mmHg, HCO₃⁻ – 10 mmol/L). Three hours post-ingestion, serum lactate was 8.6 mmol/L. Electrolytes were normal except for hypokalemia. Hepatic enzymes and coagulation tests were normal throughout the patient’s stay. Serum salicylates and toxic alcohols were undetectable. Urine immunoassay screening was negative for common drugs of abuse. The initial acetaminophen concentration sampled at 90 minutes post-ingestion was 981 μg/ml (6496 μmol/L), ethanol concentration was 18 mg/18mg/dL (3.9 mmol/L). Ibuprofen concentration was not measured. The acetaminophen concentration at the beginning of hemodialysis was 500.9 μg/ml (3315.7 μmol/L) with a pH of 7.20 and a lactate concentration of 4.3 mmol/L.

Approximately 2 hours post ingestion a loading dose (150 mg/kg) of intravenous acetylcysteine was administered over one-hour, followed by 4 hours infusion at 12.5 mg/kg/h. During hemodialysis, the acetylcysteine infusion rate was kept at 12.5 mg/kg/h to compensate for the predicted losses in the dialysate. Hemodialysis was performed via a double lumen temporary dialysis catheter in the right jugular vein, with a Fresenius Optiflux F200 dialyzer (surface area = 2.0 m²), with a blood flow = 400 mL/min and a dialysate flow = 1000 mL/min. No net ultrafiltration was prescribed. Hemodialysis was continued for a duration of 6.5 hours, at which time the acetaminophen concentration returned to 58 μg/ml (384 μmol/L) (Figure 1).

Following hemodialysis, acetylcysteine infusion was decreased to 6.25 mg/kg/h until the acetaminophen concentration was undetectable. At 24 hours post-ingestion, the patient was extubated and remained asymptomatic until her hospital discharge 48 hours post-ingestion. The patient’s creatinine, INR and transaminases remained within normal values. Table 2 shows the calculations used to determine pharmacokinetics of acetaminophen and acetylcysteine during hemodialysis.

### Toxicokinetics

Apparent acetaminophen elimination half-life prior, during, and after hemodialysis was 5.2, 1.9, and 3.6 hours, respectively. The half-life of acetylcysteine was not calculated since a constant infusion was administered during hemodialysis. Despite doubling the infusion rate during hemodialysis, serum acetylcysteine concentrations decreased steadily to only 20% of its initial concentration at the onset of dialysis. The acetaminophen and acetylcysteine extraction ratios were 57% and 69%, respectively, and remained constant during dialysis. The clearance of acetaminophen and acetylcysteine during hemodialysis, calculated by A-V difference, were 160.4 and 190.3 mL/min, respectively. Hemodialysis removed 20.6 g of acetaminophen, representing 51% of the estimated total body content at the onset of hemodialysis. Hemodialysis also removed 17.9 g of acetylcysteine out of the total of 22.1 g that was administered from admission to the end of hemodialysis.

### Limitations

The half-life measurements are limited by the possibility of ongoing absorption. We were also unable to measure potential co-ingestants such as ibuprofen or other analytes of interest in the assessment of the metabolic acidosis such as 5-oxoprolinuria. The contribution of ibuprofen to the metabolic acidosis cannot be assessed.

### Discussion

This case report demonstrates the toxicokinetics of acetaminophen and acetylcysteine during hemodialysis. Hemodialysis was initiated in this patient because of altered mental status, metabolic acidosis and high acetaminophen concentrations. Hemodialysis reversed metabolic acidosis and improved the patient’s mental status. Despite the fact that acetaminophen concentrations decreased significantly before hemodialysis, and some would question the decision to perform dialysis at these concentrations, results were unavailable to us when hemodialysis was initiated; the procedure was effective at decreasing total body burden of acetaminophen. The apparent half-life decreased during dialysis and a large percent of the total body burden was removed. It is unknown how much more could have been removed had hemodialysis been initiated earlier when the serum acetaminophen concentrations were higher.

The EXTRIP workgroup recently published recommendations and a systematic review, and recommendations on the use of extracorporeal treatment in patients with massive acetaminophen overdose.[2] They advocate for a useful role for extracorporeal treatment in patients with large acetaminophen overdose suggestive of mitochondrial failure, who present with metabolic acidosis, altered mental status, elevated lactate, and acetaminophen concentration above 900 μg/ml (5960 μmol/L) (1D) or more than 800 μg/ml (5300 μmol/L) (2D). Our patient met these criteria at the time of decision-making.

The benefit of acetaminophen removal during extracorporeal treatment is compounded by the removal of acetylcysteine. Acetylcysteine appears extensively dialyzable based on its physicochemical properties (Table 1). Despite a doubling of the acetylcysteine infusion (to 12.5 mg/kg/h) during hemodialysis as suggested by previous reports,[2] acetylcysteine associations were undetectable. At 24 hours post-ingestion, the patient was extubated and remained asymptomatic until her hospital discharge 48 hours post-ingestion. The patient’s creatinine, INR and transaminases remained within normal values. Table 2 shows the calculations used to determine pharmacokinetics of acetaminophen and acetylcysteine during hemodialysis.
concentrations fell quickly during dialysis. Usual dosing protocols for intravenous acetylcysteine infusion (150 mg/kg over 60 min followed by 12.5 mg/kg over 4 hours, then 6.25 mg/kg for the next 16 h) resulted in mean steady state plasma acetylcysteine concentrations of 35 l g/ml (232 l mol/L) and 33.4 l g/ml (221 l mol/L).

This, in addition to the risk associated with obtaining central venous access and the fact that the majority of acetaminophen poisoning cases are efficiently managed with acetylcysteine alone,[11] justifies the use of hemodialysis only for patients presenting with evidence of mitochondrial failure. This clinical scenario is suggested by metabolic acidosis and altered mental status when endogenous clearance of acetaminophen is reduced and N-acetyl-p-benzoquinone-imine production is likely in excess of what can be detoxified by the standard acetylcysteine dosing regimen of (300 mg/kg).[8]

Table 2. Calculations for acetaminophen and acetylcysteine toxicokinetics.

1) The apparent elimination half-life (T1/2) was calculated as:

\[ T_{1/2} = \frac{0.693}{Ke} \]

where Ke is the elimination rate constant and represents the slope from the equation derived by best fit using a linear regression log transformed graph. The half-life of acetylcysteine was not calculated because of ongoing administration.

2) The extraction ratio (ER) was calculated as:

\[ ER = \frac{(C_A - C_V)}{C_A} \]

where CA is the arterial (pre-filter) concentration and CV is the venous (post-filter) concentration, measured simultaneously.

3) Extracorporeal clearance (CLECTR) by A-V difference was calculated as:

\[ C_{\text{LECTR}} = Q_P \times ER = \frac{Q_B}{(1 - Hct)} \times ER \]

where QP is the plasma flow, QB is the blood flow, and Hct is the hematocrit.

4) The amount removed (A) during dialysis over 2 sample points was calculated as:

\[ A = C_A \times Q_B \times T \]

C0 is the average concentration in the dialysate and T is the time during this collection.

The total amount recovered represents the sum of all the amounts removed during dialysis.

5) The total body content (TBC) of acetaminophen at the onset of hemodialysis was calculated as:

\[ TBC = V_D \times \text{Weight} \times C_S \]

VD is the volume of distribution of acetaminophen (1L/Kg) and CS is the serum concentration of acetaminophen.

This case report demonstrates the favorable clinical evolution of a patient presenting with massive acetaminophen overdose treated with hemodialysis. While hemodialysis is effective in enhancing acetaminophen and acetylcysteine elimination, its use in the patient described in this report also reversed metabolic acidosis and improved mental status, which are commonly present in such overdose.[12,13] Our pharmacokinetic data imply that acetylcysteine dosage must be more than double during hemodialysis to compensate for its loss via the dialysate.

Disclosure statement

None of the authors have any conflicts of interest to declare.

References


