Metabolic Acidosis in Acetaminophen Overdose without Concurrent Liver Toxicity

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Introduction

Metabolic acidosis and coma are common complications of acetaminophen overdose. These affects are usually attributed to massive hepatic necrosis caused by *N*-acetyl-*p*-benzoquinoneimine (NAPQI), a toxic metabolite of acetaminophen. We describe an unusual case of lactic acidosis and coma in a patient with acetaminophen toxicity without associated hepatocellular damage as the identifiable cause.

Case Report

A 47-year-old female in otherwise good health, presented after a suicide attempt involving the ingestion of 213 extra strength (500 mg) acetaminophen gel capsules. She was taken to the nearest emergency department, where her serum acetaminophen level was determined to be 810 mcg/ml. Her toxin screen was otherwise negative. Intravenous N-acetylcysteine (NAC) was initiated approximately 90 minutes after the ingestion of the capsules. Charcoal and sorbitol were administered via nasogastric tube, and the patient was transferred to our university hospital for further evaluation.

Upon arrival to our facility, she was obtunded with a Glasgow coma score of 7 (opens eyes to painful stimuli, made no verbal noises, and withdrew to painful stimuli). She was afebrile with a respiratory rate of 28 bpm, heart rate 115 bpm, blood pressure 134/87 mmHg, with peripheral oxygen saturation of 97% while on 6 liters of oxygen by nasal canula. Her physical exam was remarkable for obesity and diminished mental status. Her pupillary reflexes were intact. The patient had very diminished cough and gag reflexes. Her examination was otherwise unremarkable. She was endotracheally intubated due to concerns relating to airway protection.

Admission laboratory results were not suggestive of significant hepatocellular damage. The liver panel showed normal aspartate aminotransferase (AST: 22 u/L; normal range 5-34), alanine aminotransferase (ALT: 20 u/L; normal range 10-4), and alkaline phosphatase (ALP: 81 u/L; normal range 38-126). Her prothrombin time was 15.2 seconds (normal range 12.5-15.5). Arterial blood gases showed a pH of 7.14 (normal range 7.35-7.45), pC02 of 33 mm Hg (normal range 32-48), and p02 of 180 mm Hg (normal range 83-108) on 6 liters of oxygen by nasal canula (prior to endotracheal intubation), with serum bicarbonate and lactic acid levels of 12 mmol/L (normal range 21-31) and 7.2 mg/dL (normal range 5-20), respectively. The calculated anion gap was 18 (normal range 3-12). An extensive evaluation was conducted to identify possible

etiologies of her lactic acidosis, including evaluation for infections consisting of chest and abdominal imaging, blood and urine cultures, and a lumbar puncture. Urine toxicology screening was negative, and serum toxicology screening was only notable for acetaminophen. All other laboratory results were within normal limits.

Clinical course. The patient's acidosis resolved and her acetaminophen level decreased to an undetectable level within 36 hours. The results of relevant laboratory studies are summarized in Table 1, demonstrating no signs of liver damage or impaired synthetic function at any time. The NAC was discontinued after 48 hours and she was liberated from ventilator support on hospital day three, at which time her mental status was completely normal.

Table 1. Serial blood chemistry measurements during hospital stay.

	Admit	12 hours	24 hours	36 hours	48 hours
Apap (mcg/mL)	810	600	106	>10	>10
pH	7.14	7.23	7.24	7.48	7.43
Anion Gap	18	13	11	6	7
Lactate (mmol/L)	7.2	4.5	1.9	1.4	1.1
Protime (sec)	15.2	13.8	13.2	12.8	13
AST (u/L)	22	16	17	17	15
ALT (u/L)	20	16	19	19	20
Alk Phos (u/L)	81	62	64	61	59

Apap - Acetaminophen; Protime - Prothrombin Time; AST - aspartate aminotransferase; ALT - alanine aminotransferase; Alk Phos - alkaline phosphatase.

Discussion

Overdose with acetaminophen is a common cause of ICU admission and is the leading cause of acute fulminant liver failure in the United States.[1] Morbidity and mortality frequently occur during acetaminophen toxicity due to overwhelming liver failure caused by NAPQI, a toxic metabolite. NAPQI rapidly binds to and depletes glutathione stores.

Glutathione is essential for detoxifying peroxides, and its absence leads to hepatic damage from oxidative stress.[2] Chronic alcoholism, hepatitis, low protein diets, malnutrition, and smoking have been associated with lower baseline glutathione levels[3,4] and patients with these risk factors may be at increased risk for ill effects of NAPQI. Once glutathione is no longer available to bind NAPQI, this metabolite covalently bonds to sulfhydryl-containing proteins causing further damage to hepatocytes,[1,5] culminating in loss of hepatic function, massive acidosis, organ failure, and in approximately 500 cases per year, death.[6]

In addition to hepatotoxicity, NAPQI inhibits mitochondrial respiration by blocking electron transport between the cytochrome B/C complex and the cytochrome oxidase complex within the electron transport chain.[7] Early administration of NAC maintains stores of glutathione, which conjugates NAPQI thereby alleviating its toxic effect. While NAC serves as an effective antidote to a toxic metabolite of acetaminophen, it has no effect on the intact drug.[8]

Cases similar to this one have been reported previously.[9-13] However, careful documentation of the timing of acetaminophen levels with recovery from acidosis and coma, such as reported herein, was lacking. In all reported cases, the common finding

was high levels of unmetabolized acetaminophen. Mechanistically, the acidosis and coma could be explained by inhibition of mitochondria respiration by unmetabolized acetaminophen. In this regard, *in vitro* studies demonstrated dose-dependent inhibition of mitochondrial electron transport and ATP formation by acetaminophen.[14]

Animal studies reported accelerated rates of glycolysis in response to acetaminophen overdose, even when hepatocellular injury was prevented with NAC, presumably related to inhibition of aerobic (mitochondrial) respiration. Namely, acetaminophen toxicity in animal models was associated with inhibition of electron transport via NADH dehydrogenase (Complex I)[7] and depletion of cytochrome b (a Complex III subunit) in vital organs.[14] Consequent reductions in aerobic respiration increases reliance on ATP production through glycolysis.[15]

Compared to mitochondria-mediated aerobic respiration, glycolysis is much less efficient, producing a fraction of the ATP for each molecule of glucose consumed. Hence, more glucose is needed to maintain adequate ATP formation during anaerobic metabolism. Moreover, ongoing glycolysis in the absence of mitochondrial respiration leads to the build-up of pyruvate (see Figure 1) which, in turn, is reduced to lactate.[16]

The accumulation of lactate leads to an anion gap acidosis, as was observed in our patient. Furthermore, the relatively low levels of ATP produced as a result of impaired mitochondrial respiration and increased reliance on glycolysis, likely contributes to diminished organ function, particularly in tissues with high basal metabolic rates, such as the brain. In this regard, acetaminophen also has been shown to cross the blood brain barrier and reach significant levels in cerebral spinal fluid.[17] Although a direct link remains to be established, it is reasonable to speculate that acetaminophen could inhibit the function of central nervous system mitochondria and contribute to the neurologic impairment seen in patients with acetaminophen overdose.

The direct effects of elevated serum lactate on mental status in humans is unclear,[11] however, animal models suggest that elevated local lactate concentrations could undermine cognitive functions. Intrathecal injection of DL-lactate in calves results in more dramatic alterations of behavior and mentation than does a treatment with hydrochloric acid to achieve the same pH. It was reasoned that d-lactate, and to a lesser extent L-lactate, block neuronal glucose metabolism and alter the membrane potential in neurons.[18] Thus, direct neurological effects of lactate represent another potential mechanism by which acetaminophen overdose compromises cognition.

Despite efforts to intervene as early as possible with NAC treatment, most individuals presenting with acetaminophen overdose experience some degree of hepatocellular insult, ranging from mild elevation in transaminases to complete loss of synthetic function and hepatic failure.[1,6] This hepatic damage typically is associated with overt clinical manifestations, including encephalopathy, metabolic acidosis, and altered synthetic function (e.g., coagulopathy). It is likely that most patients being treated for acetaminophen-induced liver failure also experience a "type B" lactic acidosis (i.e., relating to interference with mitochondrial function).

This notion is supported by the documentation of metabolic acidosis prior to the onset of overt hepatocellular injury in a series of patients presenting with acetaminophen toxicity.[11,19] A two-stage acidosis sequence is proposed, initially related to inhibition of mitochondrial respiration by unmetabolized acetaminophen followed by a second phase of acidosis

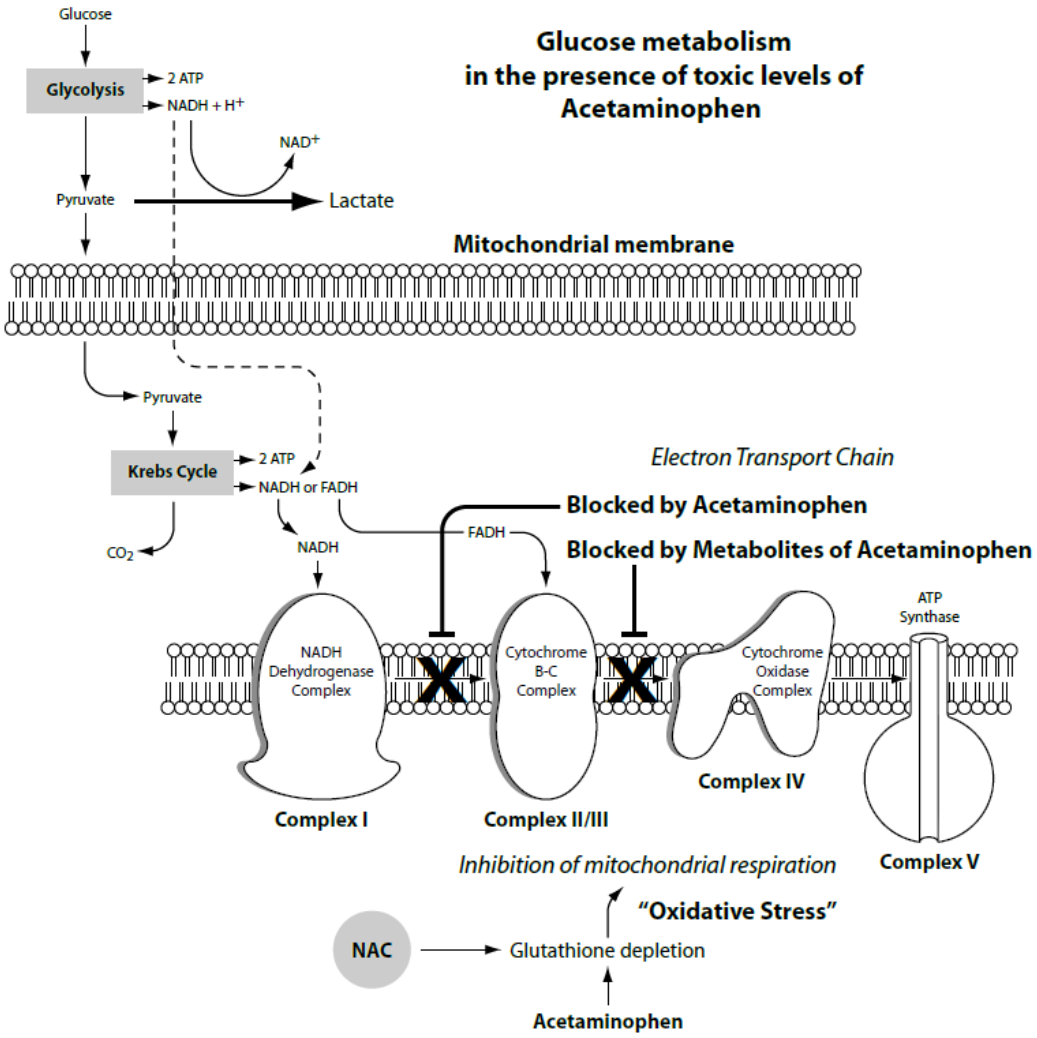

Figure 1. The breakdown of glucose and how it is inhibited by acetaminophen and its metabolites.

caused by overt hepatocellular necrosis, resulting in impaired lactate clearance and, presumably, ongoing mitochondrial inhibition. This scenario is substantiated by *in vitro* studies wherein exposure of hepatocytes to toxic doses of acetaminophen resulted in an inhibition of mitochondrial respiration 3-4 hours prior to the onset of detectable hepatocellular damage.[20]

Another rare cause of anion gap acidosis in the setting of acetaminophen overdose is accumulation of 5-oxoproline.[21] Excessive levels of 5-oxoproline can occur in the presence of acetaminophen overdose due to depletion of glutathione. This mechanism was unlikely to contribute to our patient's anion gap acidosis, as rapid administration of NAC would have prevented depletion of hepatic glutathione, and there would have been signs of hepatocellular injury. In this regard, glutathione levels need to drop by 80% in hepatocytes before significant accumulation of 5-oxoproline can occur.[22] 5-oxoproline is more likely to cause gap acidosis in acetaminophen toxicity from chronic use and is not believed to contribute to the sudden onset lactic acidosis seen in acute overdose.[21]

Our patient provided an unusual opportunity to observe the metabolic manifestations of massive acetaminophen overdose (977 mg/kg) in the absence of hepatocellular damage. It is evident from this case that acetaminophen can cause acute lactic acidosis and coma which resolve as the drug levels normalize, presumably relating to acute, reversible mitochondrial inhibition. Given the critical role of mitochondria and ATP as determinants of cell viability,[23] particularly in the context of acetaminophen toxicity,[24] it is reasonable to postulate that acetaminophen-induced mitochondrial inhibition predisposes to subsequent hepatocellular damage (e.g., relating to glutathione depletion).

Lactic acidosis is seen commonly in patients with sepsis, shock, renal failure, and inter-abdominal ischemia. Even in the presence of acetaminophen overdose, these clinical signs should be considered before ascribing the metabolic abnormality to acetaminophen.

While a comprehensive review of the management of lactic acidosis is beyond the scope of this article, several excellent reviews on the subject exist.[25-26] As discussed in these reviews, every effort was undertaken to consider alternative explanations and to prevent lactic acidosis, including optimization of hemodynamic variable, exclusion of severe infection, and appropriate supportive care.

Since our patient's renal and hepatic functions were preserved, she was able to clear the excess lactate soon after the acetaminophen levels normalized. While this case emphasizes the utility of timely NAC administration, it also identifies the early manifestations of acetaminophen toxicity, and leads us to consider opportunities to avoid further hepatocellular injury through avoidance of mitochondrial toxins (e.g., antimicrobial agents) commonly administered in the hospital setting.[27]

Acknowledgments. The authors would like to thank Timothy Eubank, Ph.D. for his assistance in creating the figure for this article.

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Key Words: acidosis, acetaminophen, overdose, coma, lactic acid