

COMA, METABOLIC ACIDOSIS, AND METHEMOGLOBINEMIA IN A PATIENT WITH ACETAMINOPHEN TOXICITY

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ABSTRACT

We present a case of early coma, metabolic acidosis and methemoglobinemia after substantial acetaminophen toxicity in the absence of hepatic failure. A 77-year-old female presented to the emergency department with a decreased level of consciousness. She was found unresponsive by a family member in her bed, and was reported to be acting normally when she was last seen eight hours earlier. Laboratory results on arrival were: pH 7.19, sodium 139 mmol/L, chloride 106 mmol/L, potassium 3.3 mmol/L, CO₂ 8 mmol/L, and an anion gap of 25. Both venous lactate (10.2 mmol/L) and methemoglobin (9.4 %) were elevated. The patient's acetaminophen concentration was markedly elevated at 7138 µmol/L (1078 µg/ml). Hepatic enzymes and coagulation tests were normal [alanine transaminase (ALT) 8 U/L, international normalized ratio (INR) 1.0]. Intravenous N-acetylcysteine (NAC) was initiated at a dose of 150 mg/kg over 15 minutes, followed by 50 mg/kg over the next four hours, followed by 100 mg/kg over the next 16 hours. Twenty-four hours after admission, the anion gap metabolic acidosis had resolved, and the methemoglobin was 2.1%. Aminotransferases peaked at 44 U/L and INR peaked at 1.9. A urine 5-oxoproline assay performed five days after admission was negative, suggesting no evidence of a 5-oxoproline deficiency. We describe the pathophysiology and discuss the literature on acetaminophen-induced coma and metabolic acidosis in the absence of hepatic injury; and propose mechanisms for associated methemoglobinemia.

Key Words: *Acetaminophen, paracetamol, hepatitis, acidosis, methemoglobinemia, poisoning*

The typical course of acute acetaminophen toxicity has been well described in the literature as a four-stage process causing hepatic injury or failure secondary to the accumulation of the toxic metabolite, *N*-acetyl-para-quinone-amine (NAPQI).¹ In rare cases, acute, massive acetaminophen ingestions have been associated with early metabolic acidosis and coma in the absence of hepatic failure.^{2,3} Methemoglobinemia occurs when the normally reduced iron moiety on

hemoglobin becomes oxidized to its ferric form. This becomes clinically important due to the inability of the ferric state to bind oxygen. There are multiple agents that can induce methemoglobinemia, but acetaminophen has not been a well-described cause in humans. We report a case of a patient presenting with severe metabolic acidosis, coma, and methemoglobinemia in the setting of acetaminophen toxicity.

Case Report

A 77-year-old Korean female presented to the emergency department with a decreased level of consciousness. She was found unresponsive by a family member in her bed, and was reported to be acting normally when she was last seen eight hours earlier. There was no antecedent history of feeling unwell, nausea or vomiting. Her past medical history was significant only for previous thyroid cancer treated with surgical removal. The patient's regular medications included levothyroxine, rabeprazole, hydrocortisone cream, betamethasone scalp cream, acetylsalicylic acid, docusate sodium, cromolyn ophthalmic drops, and acetaminophen. Her family reported she had taken 325 mg of acetaminophen twice daily for chronic musculoskeletal neck pain for the past five years. It was later established that she took a supratherapeutic amount within eight hours of presentation to hospital with the intention of self-harm.

The patient was transported by EMS to the emergency department, and was intubated en route secondary to a Glasgow Coma Scale of 3. On arrival in the emergency department, her blood pressure was 77/51 mmHg, heart rate 86 beats/minute, respiratory rate 12 breaths/minute, temperature 35.6 °C, and blood glucose of 26.6 mmol/L. Naloxone was given, with no change in level of consciousness. A computed tomography scan of her head was normal.

Initial chemistry panel showed an anion gap metabolic acidosis (sodium 139 mmol/L, chloride 106 mmol/L, potassium 3.3 mmol/L, CO₂ 8 mmol/L, anion gap 25 mmol/L), and a corresponding venous blood gas (VBG) showed a pH of 7.19, PCO₂ 27 mmHg, PO₂ 134 mmHg [FiO₂ 100%], HCO₃ 10 mmol/L, and O₂ saturation 88%. Both lactate (10.2 mmol/L) and methemoglobin (9.4 %) were also elevated on the VBG. Carboxyhemoglobin was 0% and electrolytes were normal. The patient's acetaminophen concentration was markedly elevated at 7138 µmol/L (1078 µg/ml). Initial hepatic enzymes and coagulation tests were normal [alanine transaminase (ALT) 8 U/L, alkaline phosphatase (ALP) 63 U/L, total bilirubin 20 µmol/L, gamma-glutamyltranspeptidase

(GGT) 11 U/L, international normalized ratio (INR) 1.0], and serum lipase was elevated at 256 U/L. Serum toxicology tests were negative for salicylates, methanol, ethanol, ethylene glycol, isopropyl alcohol, and acetone. A comprehensive urine drug screen by gas chromatography-mass spectrometry performed on a sample taken 2.5 hours after presentation was positive for benzodiazepines (after receiving midazolam for intubation), lidocaine (administered as local anesthetic for central line insertion) and acetaminophen.

The 21-hour intravenous N-acetylcysteine (NAC) protocol was started at 150 mg/kg over 15 minutes, followed by 50 mg/kg over the next four hours, followed by 100 mg/kg over the next 16 hours. The patient was transferred to the intensive care unit (ICU). The acetaminophen concentration 12 hours after the initial concentration was 1910 µmol/L. The patient was sedated with a propofol infusion for ventilation asynchrony, and required a norepinephrine infusion for less than 48 hours to maintain a systolic blood pressure above 90 mmHg and a mean arterial pressure above 60 mmHg. The patient was never hypoxic nor did O₂ saturations drop below 92%. 24 hours after admission, the acetaminophen concentration had fallen to 705 µmol/L, the anion gap metabolic acidosis had resolved, and the methemoglobin was 2.1%. ALT peaked at 44 U/L (eight hours after presentation), and INR peaked at 1.9 (37 hours after admission). Creatinine remained normal throughout admission. The patient's NAC infusion was discontinued after a period of 65 hours, at which point the acetaminophen concentration had been undetectable for 10 hours. Urine cultures were positive for *Klebsiella ozaenae*, which was treated with ciprofloxacin. Blood cultures were negative. A urine 5-oxoproline assay performed five days after admission was negative, suggesting no evidence of a 5-oxoprolinase deficiency. No methylene blue was administered.

The patient continued to improve over the course of her ICU admission. The patient was coherent and improved rapidly from a neurological perspective and was extubated on post-admission day two, however, was re-

intubated 24 hours later due to hypercapnia secondary to zopiclone administered for sedation.

The patient was extubated 24 hours later, and was discharged from hospital 17 days after admission in stable condition. The patient's hepatic enzymes and coagulation panel normalized prior to ICU discharge (ALT 4 U/L, ALP 49 U/L, total bilirubin 7 μ mol/L, GGT 18 U/L, INR 0.9). The patient's methemoglobin level remained slightly elevated at 1.3% (normal less than 1%). The remaining lab values were normal at discharge.

DISCUSSION

We present a case of massive acetaminophen toxicity with associated coma, metabolic acidosis, and methemoglobinemia without substantial hepatic injury. There have been few reports of early acetaminophen-induced metabolic acidosis resulting in coma in the absence of hepatic injury.^{4,8} In previous reported cases, patients often develop substantial hepatic injury, which may suggest hepatic etiology for the acidosis; however, a few of the reports depict a clinical course with profound acidosis in the absence of any marker of hepatic injury.^{5,6,8}

The mechanism for such impressive metabolic acidosis in the absence of hepatic insult is unclear, but several theories exist. First, animal studies suggest that accumulation of NAPQI can potentially lead to uncoupling of oxidative phosphorylation.⁹ This may explain the development of metabolic acidosis independent of hepatic failure in our patient. NAPQI is also the compound responsible for hepatocellular damage in acetaminophen toxicity. Our patient did not develop hepatic failure; however, this can likely be explained by the early administration of NAC and its continuation until the acetaminophen concentration was undetectable and the coagulopathy had resolved. Second, animal studies have demonstrated that acetaminophen inhibits mitochondrial respiration, and that this inhibition precedes hepatocellular damage in rat models.¹⁰ This direct effect by acetaminophen, independent of NAPQI, could not only explain the development of early and profound metabolic

acidosis in severe toxicity, but also the preservation of hepatic function in our patient. Inhibition of mitochondrial respiration by either mechanism supports the lactic acidosis seen in our patient, given the need for anaerobic metabolism to take place.

In addition to the above proposed etiologies of metabolic acidosis, patients shown to have early acetaminophen-induced acidosis have been reported to have higher urinary levels of 5-oxoproline, suggesting that an alternative pathway may be responsible for the metabolic derangements.^{11,12} Elevated 5-oxoproline concentrations have been suggested as a cause of acidosis in previous case reports.¹³ 5-oxoproline is an intermediate in the γ -glutamyl cycle, which is integral in the uptake of amino acids, production of glutathione, and inactivation of free radicals. Inherited as well as acquired processes have been demonstrated to result in an accumulation of 5-oxoproline. Specifically, deficiencies in either glutathione synthetase or 5-oxoprolinase may result in an accumulation of 5-oxoproline and subsequent acidosis. In addition to inherited deficiencies leading to the accumulation of this metabolite, it has been suggested that there may be an acquired pathway enhanced by the ingestion of acetaminophen that may produce a similar biochemical and clinical picture.¹⁴ Interestingly, the accumulation of 5-oxoproline in this scenario is not typically the result of large intentional acetaminophen ingestion but the product of chronic ingestion of what would be considered therapeutic doses, which was a known historical feature in this case. It has been postulated that repeated acetaminophen ingestion may lead to relative hepatic glutathione deficiency resulting in an accumulation of 5-oxoproline.¹⁵ A review of patients presenting with anion gap metabolic acidosis as the result of 5-oxoprolinuria by Fenves et al. described that malnourished women consuming chronic acetaminophen were particularly susceptible.¹⁶ As a result of acquired glutathione deficiency, it has been proposed that NAC, having shown to work with some success in inherited glutathione synthetase deficiency, may be an effective therapy for patients presenting

with acidosis secondary to chronic acetaminophen ingestion and 5-oxoprolinuria.¹⁷

Methemoglobinemia occurs when the ferrous (Fe^{2+}) iron moieties on hemoglobin become oxidized to their ferric (Fe^{3+}) state. This becomes important in the context of oxygen transport and delivery for two reasons: first, the ferric state is unable to bind oxygen, and second, the remaining reduced hemoglobin has a higher affinity for oxygen molecules (i.e. the oxy-hemoglobin desaturation curve is left-shifted). The most common causes of methemoglobinemia are acquired secondary to the ingestion of medications with oxidizing potential. Examples of common methemoglobin-inducers include local anesthetics, dapsone, and nitrites. Acetaminophen-induced methemoglobinemia in humans has not been described in detail. A single reported case from 1968 describes the presence of methemoglobinemia without quantifying the methemoglobin concentration.¹⁸ Methemoglobinemia in conjunction with acetaminophen use has been described previously when acetaminophen was administered in conjunction with sulfasalazine and sodium nitrate.^{19,20} In addition, acetaminophen-induced methemoglobinemia in both dogs and cats has been demonstrated in several reports and may be related to increased NADPH glutathione reductase activity as seen in feline acetaminophen toxicity models.²¹⁻²³ It is unclear whether increased activity of this enzyme occurs in humans under similar conditions.

The reason for the development of methemoglobinemia in our patient remains unclear. First, the role of acetaminophen metabolites such as NAPQI in the development of methemoglobinemia remains speculative and should be investigated in future research. Second, her hypotension secondary to her urinary tract infection (despite a negative blood culture) could have contributed to her methemoglobinemia. Finally, the possibility of a false positive methemoglobin exists. We ruled out the possibility of sulfhemoglobinemia by confirming with the manufacturer of the spectrometer that methemoglobin and sulfhemoglobin are read individually. We also determined that the

absorbance spectrum of acetaminophen and methemoglobin do not overlap, and it is unlikely that there was interference with the reading by acetaminophen.

Our case report has limitations. First, we recognize that the patient's toxicology screen was positive for lidocaine, which is a known methemoglobin inducer. However, we were able to confirm that lidocaine was not administered by the paramedics prior to intubation and ruled out any other exposure to lidocaine prior to obtaining the methemoglobin level on the blood gas. We have concluded the source of the lidocaine on the urine toxicology screen was from the local injection during the placement of the central line. Secondly, the possibility of hypotension secondary to her urinary tract infection (despite a negative blood culture) could also have contributed to her altered mental status, metabolic acidosis, and methemoglobinemia. Lastly, we cannot entirely rule out the possibility of interference between the extremely high acetaminophen concentration in the blood and the spectrometer reading of methemoglobin. However, we feel it is unlikely that there is any interference given that the maximum absorbance spectrum of acetaminophen (243 nm)²⁴ is outside the measuring range of our blood gas analyzer, the Radiometer ABL 725 (478-672 nm). Furthermore, onboard instrument software algorithms allow for the detection and correction of interfering substances.

In conclusion, although acetaminophen toxicity has been classically described as a four-stage process culminating in hepatic failure, a unique presentation of coma and metabolic acidosis following massive acetaminophen ingestion may also occur. The coma and metabolic acidosis may be accompanied by methemoglobinemia, the mechanism of which remains unclear.

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