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TOXICOLOGY CASE FILE

Case Files from the University of California San Diego Health System Fellowship Coma and Severe Acidosis: Remember to Consider Acetaminophen

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Case Presentation

A 28-year-old man was brought to the Emergency Department (ED) for evaluation of a depressed level of consciousness that developed while in jail. Sixteen hours previously, he had been arrested on charges of murder. The patient's mental status was reported as normal at the time of arrest, and it had remained so during several hours of interrogation and during the booking process at jail. Following interrogation, the patient was placed into a cell with no other inmates. During the jail intake process, the patient had not reported any history of medical problems nor was he prescribed with any medications. Paramedics arrived to find him unresponsive, but maintaining airway reflexes and hemodynamically stable. They measured a blood glucose of 300 mg/dL and noted one episode of blood-tinged emesis during transport to the ED. No seizure activity was witnessed.

On arrival to the ED, vital signs were: heart rate 132/min, blood pressure 129/74 mmHg, temperature 35.3 °C (95.5 °F), respiratory rate 24/min, and 100 % oxygen saturation on 15 l/min of oxygen delivered by non-rebreather face mask. Physical examination was notable for a depressed level of consciousness. His eyes remained closed to pain, he withdrew all extremities equally to pain, and he was non-verbal. He had no signs of trauma, and his pupils were normal in size and reactive. Rapid sequence tracheal intubation was performed for airway protection. An electrocardiogram was normal except for sinus tachycardia at a rate of 111/min. An initial peripherally drawn arterial blood gas obtained immediately after intubation revealed: pH 6.97, pCO_2 40 mmHg, pO_2 215 mmHg. A computed tomography scan of the brain was normal. Initial blood chemistry panel was significant for a serum bicarbonate of 7 mEq/L, glucose of 362 mg/dL, and a normal potassium, blood urea nitrogen (BUN), creatinine, and calcium. The initial serum anion gap was 34 mEq/L. Measured serum osmolality was 320 mOsm/kg, yielding an osmol gap of 9 mOsm/kg (using formula of [2(Na)+BUN/2.8+glucose/18] for calculated serum osmolarity). Initial lactate was 156.5 mg/dL (normal reference range 4.5–19.8 mg/dL) and beta-hydroxybutyrate (βHB) 2.9 mg/dL (normal reference range 0.0–2.8 mg/dL). Initial liver panel included an aspartate aminotransferase (AST) of 64 U/L, alanine aminotransferase (ALT) of 27 U/L, and bilirubin of 0.4 mg/dL. Prothrombin time was 13.1 s (reference range 9.7–12.5), and lipase was normal at 25 U/L. Initial creatinine phosphokinase (CK) was slightly elevated at 373 U/L (0–175). Urinalysis was positive for small ketones and crystals were not present. Measurements of acetone and acetoacetate were not performed. Serum ethanol and salicylate levels were undetectable, and a urine drug of abuse panel by immunoassay was negative for amphetamines as a class, barbiturates as a class, benzodiazepines as a class, benzoylecgonine (cocaine metabolite), methadone, opiates as class, oxycodone, phencyclidine, and tetrahydrocannabinoids. Iron concentration was normal at 87 mcg/dL.

Over the first hour of management, the ED providers administered 3 L of normal saline intravenously. During this

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time period, the patient's blood pressure remained normal and his average heart rate was 115 beats per minute. Repeat vital signs 90 min after presentation included a heart rate of 115/min, blood pressure 134/86 mmHg, rectal temperature 35.8 °C (96.5 °F), and respiratory rate 25/min. The medical toxicology service was consulted for a possible overdose.

Is This Presentation Consistent with Toxic alcohol Poisoning? In Cases Without a Clear History of Ingestion, What Are the Challenges in Making a Definitive Diagnosis of Toxic Alcohol Poisoning?

The initial impression of the consult team was that a toxic alcohol such as ethylene glycol, methanol, or much less likely propylene glycol could be responsible for this patient's presentation. A major challenge in the diagnosis is the inability to rapidly obtain toxic alcohol concentrations [1, 2]. At most hospitals, including our own, testing for these alcohols is not available on site, and there is often a considerable time delay, particularly for ethylene glycol, in obtaining the results. Definitive testing for ethylene glycol requires a dedicated gas chromatography column that is costly and precludes most laboratories from offering the test [3, 4]. In the USA, poisoning with ethylene glycol is more frequent than methanol [5], but owing to its chemical structure, ethylene glycol is more challenging to analyze [3]. Cases of significant propylene glycol ingestion are very rarely reported [6–9]. At our institution, methanol testing results can be obtained in approximately 6 h and ethylene glycol not for 2 to 3 days. In the absence of a reliable history of ingestion, clinical management decisions prior to laboratory confirmation (or exclusion) are necessary. In a critically ill patient as the one described, empiric treatment should be initiated rapidly. Fortunately, distinguishing between the toxic alcohols is not essential, as the critical steps in management (fomepizole to block alcohol dehydrogenase and hemodialysis to remove the parent compound and metabolites) are identical.

In the Absence of Real-Time Testing for Toxic Alcohols, What Surrogate Markers Might Be Used to Make an Accurate Diagnosis in This Case?

Utilization of clinical and laboratory surrogate markers and an understanding of their limitations in the identification of toxicity with ethylene glycol, methanol, and propylene glycol are essential in managing such cases in the absence of real-time laboratory confirmation. Multiple surrogate markers as they relate to the case are discussed below.

A. Inebriation

The patient was noted to have a normal mental status at the time of his arrest and during subsequent interrogation. Given the available history, it seemed improbable (but not impossible) that he had acquired and ingested one of the toxic alcohols after arrest. Methanol and ethylene glycol themselves, if ingested in high enough quantities, are capable of causing central nervous system effects including inebriation, an effect that may aid in diagnosis [10, 11]. It would appear that this is similarly true for propylene glycol; however, there are only a few reports to base this on [7, 9]. We are not aware of any study that addresses how the absence of inebriation might help exclude the diagnosis of a toxic alcohol. It appears that the absence of initial inebriation would be more likely to occur with methanol rather than ethylene glycol poisoning. Cases of methanol poisoning in which individuals were noted to be "rational and conversing, and …ambulatory" who soon became comatose have been described [12]. Inference from a rat study suggests why inebriation may be less likely with methanol than with ethylene glycol [13]. Wallgren demonstrated that the carbon length of an alcohol is directly associated with its ability to cause inebriation [13]. In our patient, it seemed that if he ingested a toxic alcohol prior to arrest, methanol would be more likely, given his lack of initial inebriation. Since we could not eliminate the possibility of an ingestion subsequent to interrogation, all three of the toxic alcohols were still considered a possibility.

B. Ocular Symptoms and/or Findings

The neurotoxic metabolite of methanol, formic acid, can damage the optic nerve [14–16]. A conscious patient may describe vision changes, and mydriasis with sluggishly responsive or unresponsive pupils may be identified in a patient with methanol toxicity [12]. However, the absence of either findings cannot reliably exclude methanol poisoning, and neither were present in this patient [12]. Blindness, in the setting of a severe acidosis, is also not specific for methanol, as it has been described in both alcoholic ketoacidosis and metformin-associated lactic acidosis (MALA) [17–21].

C. Progressive acidosis without specific intervention

As the metabolism of ethylene glycol and methanol occurs, an anion gap acidosis will progress unless specific intervention is made to block metabolism and/or to remove the toxic metabolites. Similarly, rapid resolution of acidosis without specific interventions may be helpful in excluding a significant ingestion from ethylene glycol and methanol. As mentioned previously, little information exists detailing acute overdoses of propylene glycol. In this case, in which severe acidosis was found at presentation, monitoring for progressive acidosis, or resolution, was not a viable option.

D. Lactate

A significantly elevated lactate may occur following the ingestion of ethylene glycol, methanol, and propylene glycol, but in each case for different reasons. Glycolic acid is the principle metabolite responsible for the metabolic acidosis in ethylene glycol poisoning and has a similar molecular structure to lactate [22]. In many analyzers, glycolic acid will cause interference and result in a false elevation in lactate, a finding that has been increasingly recognized in cases of ethylene glycol poisoning [23–30]. The technique performed in our laboratory to measure lactate is known to cross-react with glycolic acid. A true lactic acidosis, although to a lesser degree and not universally present, may also occur with ethylene glycol metabolism and has been attributed to an increased nicotinamide adenine dinucleotide (NADH)/NAD^+ ratio that favors the formation of lactate from pyruvate [22, 31, 32]. Formic acid is the principle metabolite responsible for the acidosis present in methanol poisoning [33, 34]. A lactic acidosis has been described, albeit rarely in methanol cases, and has been attributed to inhibition of oxidative phosphorylation by formic acid [35–37]. Both isomers (D- and L-) of lactic acid are metabolites of propylene glycol, and lactic acidosis has been described in poisoning [6, 9, 38]. However, if D-lactate predominates, as has been described in some cases, an elevated lactate may not be detected, depending on the analytical method used [9]. The presence of an elevated lactate, as described in this case, could not exclude toxicity from any of the three toxic alcohols.

E. Osmol Gap

The patient had a serum osmol gap of nine, which is not highly elevated. A large osmol gap can be helpful in suggesting the presence of an unmetabolized toxic alcohol. However, the absence of a significantly elevated osmol gap, as in this patient, cannot exclude toxicity from one of the toxic alcohols [39]. As time progresses, much of the "parent" toxic alcohol that can cause an osmol gap may have been metabolized away. Further, even if a clinically significant quantity of "parent" compound is present, it may not necessarily cause a large osmol gap. This could occur when a patient has a baseline osmol gap in the negative range [40]. Owing to the large molecular weight of ethylene glycol, toxic concentrations of the "parent" compound can exist with minimal contribution to the measured serum osmolality [39] Lastly, multiple equations exist to calculate the estimated serum osmolarity, and the degree of osmol gap will vary depending on which one is used [40]. In this case, the osmol gap was not helpful in excluding a toxic alcohol as the etiology.

F. Hypocalcemia, Calcium Oxalate Crystalluria, and Progressive Acute Kidney Injury

Calcium oxalate crystalluria, hypocalcemia, and progressive acute kidney injury are three other laboratory surrogate markers that can potentially be used to help diagnose ethylene glycol poisoning. Some of ethylene glycol are metabolized to oxalic acid, which can bind to calcium and generate the renally toxic calcium oxalate [41, 42]. Certainly, the presence of significant calcium oxalate crystalluria in the appropriate clinical setting is quite specific for ethylene glycol poisoning [41]. However, time is required for the formation of calcium oxalate, its subsequent excretion, and resultant kidney injury [43]. Therefore, the absence of hypocalcemia, calcium oxalate crystalluria, and acute kidney injury in this case did not exclude ethylene glycol as the etiology. Similar to the potential diagnostic benefit of monitoring for progressive acidosis, serial evaluation for hypocalcemia, calcium oxalate crystalluria, and acute kidney injury was not an ideal option in this case nor is it likely to be in most cases in which ethylene glycol is being considered. Fluorescein is often added to ethylene glycol to aid in the detection of radiator leaks. The identification of urinary fluorescence has been well studied as another potential surrogate marker and has been found to be unreliable [44–46].

Given that toxic alcohol poisoning could not be excluded, and the degree of metabolic acidosis precluded observation without intervention, fomepizole was administered and preparations for hemodialysis were made as other potential etiologies were entertained.

Could This Be Metformin-Associated Lactic Acidosis?

Metformin-associated lactic acidosis (MALA) was considered a possibility. The patient had not provided a history of diabetes when he was arrested. However, we considered that his initial hyperglycemia may reflect that he had diabetes and therefore he could potentially be on metformin. In one case of acute metformin overdose, significant hyperglycemia was described; however, in that case, it was profound and progressive [47]. An acute overdose of metformin can cause a severe lactic acidosis [48–51]. In such cases, a depressed level of consciousness may occur following several hours of lucidity, although typically it is in the setting of cardiovascular instability [47, 52–56]. Hypothermia, as observed in our patient, has also been well described in acute metformin overdoses [47, 54, 57–60]. Similar to ethylene glycol, at most institutions including our own, metformin measurements are send out tests, with results

being available days after empiric clinical management decisions are necessary. Although we felt MALA was unlikely, we could not exclude it. Fortunately, one of the critical interventions beyond supportive care for severe MALA appears to be hemodialysis [61], which we were preparing to do already for potential toxic alcohol poisoning.

Could This Be Cyanide Poisoning?

Cyanide poisoning characteristically manifests with a rapid onset of a depressed level of consciousness, apnea, lactic acidosis, and potentially cardiovascular collapse [62, 63]. It was not clear how rapid the patient had developed coma at jail as he was not observed continuously in his cell. It seemed plausible that the patient, who was aware of his impending arrest, could have concealed cyanide on him and ingested it later in custody. Also possible would be the ingestion prior to arrest of an agent such as acetonitrile that is metabolized to cyanide and characteristically manifests with a delayed onset in toxicity [64–67]. Similar to the toxic alcohols and metformin, cyanide measurements are generally not immediately available, including at our institution, mandating clinical decisions based on clinical manifestations and surrogate clinical and laboratory markers alone [62].

Wouldn't Cyanide Poisoning Associated with Severe Metabolic Acidosis (pH 6.97) Also Cause Hypotension?

As with most disease processes, a spectrum of clinical manifestations may occur with cyanide poisoning. Many patients poisoned with cyanide do not manifest hypotension despite having a depressed level of consciousness or coma [63, 68–76]. However, hypotension generally occurs in more severely poisoned patients and appears to correlate with a lower serum pH [64–66, 70, 74–79]. In a series of patients poisoned with cyanide, Baud et al. detailed that plasma lactate concentrations correlated positively with blood cyanide concentrations and inversely with systolic blood pressure and arterial pH [75]. In Baud's study, hypotension was present in multiple patients even though none had a pH less than 7.10 [75]. Hypotension typically appears in cases where the pH is less than 7.1 and/or the serum bicarbonate is less than 10 [64–66, 70, 74–79]. Although we have found several cases where significant acidosis in cyanide poisoning occurred in the absence of hypotension, we have not been able to identify a case in which the pH was less than 7.00 [68, 69, 71, 74, 80]. Therefore, our impression that hypotension would be expected if cyanide was the etiology in our case appears to be accurate. Whether the absence of hypotension despite a coincident pH of 6.97 could exclude cyanide as the etiology, we were hesitant to conclude.

Beyond the Presence of Lactic Acidosis, What Other Laboratory Surrogate Marker Could Be Used to Help Make the Diagnosis of Cyanide Poisoning?

By inhibition of oxidative phosphorylation, cyanide prevents cellular oxygen utilization and increases venous oxygen content, often referred to as "arteriolization" [81, 82]. In multiple case reports, the presence of an elevated venous oxygen content, either from centrally or peripherally drawn blood and often done simultaneously with analysis of arterial blood oxygen content, has been used as a surrogate marker for cyanide poisoning [63, 74, 79, 80, 82–87]. Serial measurement of venous oxygenation has also been described to monitor the need for additional antidotal treatment [87], and analysis of venous oxygen content has been used in animal studies evaluating the efficacy of cyanide antidotes [88].

Case continued:

Simultaneously drawn peripheral arterial and venous blood gases were performed 1 h after arrival on our patient, with the patient receiving 50 % FiO_2. The arterial blood gas revealed: pH 7.14, pCO_2 28 mmHg, pO_2 189 mmHg, oxygen saturation 99.0 %. The concurrent venous blood gas revealed: pH 7.12, pCO_2 30 mmHg, pO_2 77 mmHg, oxygen saturation 92.1 %.

How High Should Venous Oxygen Content Be to Help Make the Diagnosis of Cyanide Poisoning?

In a case report of cyanide poisoning, Johnson and Mellors detail a patient with an elevated peripherally drawn venous oxygen content [82]. They provide supporting evidence that a central venous oxygen saturation greater than 90 % is abnormal and likely indicates inhibition of oxygen utilization [82]. They suggest that when using the venous blood as a surrogate for cyanide poisoning, it should ideally be drawn from central blood, but as in their case, peripherally drawn blood may potentially be helpful [82]. Multiple subsequent case reports have detailed central venous oxygen saturations greater than 90 % in cyanide poisoning [74, 79, 83–85, 87].

How Sensitive and Specific Is a Central Venous Oxygen Saturation Greater Than 90 % for Cyanide Poisoning?

We are not aware of any study that addresses this question. Based on the mechanism of cyanide poisoning, the degree to

which central venous oxygen content is increased should correlate with the degree of toxicity. Therefore, one would expect that, at lesser degrees of toxicity, a central venous oxygen content could be less than 90 %, and at least one case report of cyanide poisoning details this finding [73]. One would also expect other toxins that inhibit oxidative phosphorylation, such as hydrogen sulfide, could also produce central venous oxygen saturations above 90 %. In the absence of toxicity from such agents, central venous oxygen saturations greater than 90 % are certainly not common, but have been described. Sepsis and resuscitation from cardiac arrest are two situations in which central venous oxygen saturations greater than 90 % have been described [89–93]. In both situations, mitochondrial dysfunction and the resulting diminished inability to extract oxygen may be responsible [94].

What Is the Significance of Peripherally Drawn Venous Oxygen Saturation Greater Than 90 %, As in Our Case?

Although studies have established what normal central venous oxygen content is and how it varies in many clinical situations, there appears to be very little corresponding information on peripheral venous oxygen content [89, 92, 93, 95, 96]. An elevated peripheral venous oxygen content has been reported in multiple case reports of cyanide poisoning [63, 80, 82]. However, it appears that using peripherally drawn blood for analysis of elevated venous oxygen content is not ideal. Studies have detailed how things such as nerve blocks and contraction of the forearm muscles can lead to venous oxygen saturations above 90 % in peripherally drawn blood from the forearm [97, 98].

How Might the Empiric Administration of the Cyanide Antidote Hydroxocobalamin Potentially Complicate the Management of This Case?

Hydroxocobalamin has a bright red color and administration leads to reddish discoloration of plasma that is well described to interfere with many colorimetric laboratory tests [99]. The resulting reddish plasma can also interfere with hemodialysis, as some hemodialysis machines interpret the discoloration as a blood leak across the dialysis membrane. This has complicated similar cases in which hemodialysis was attempted for a potential toxic alcohol poisoning and hydroxocobalamin had been administered for possible cyanide poisoning [79, 100].

Case continued:

The clinical laboratory now reported that the serum acetaminophen concentration drawn soon after arrival was 616 μg/mL. This test had been ordered simply as part of routine screening in a patient suspected of having attempted self-harm with another agent. Intravenous *N*-acetylcysteine (NAC) administration was then initiated (150 mg/kg over the first hour, 50 mg/kg over the next 4 h, followed by 100 mg/kg every subsequent 16 h).

Does an Isolated Massive Acetaminophen Overdose Explain the Clinical Picture?

Although the elevated acetaminophen concentration surprised us, we were familiar with cases of massive acetaminophen overdoses presenting with coma and severe lactic acidosis in the absence of hepatic dysfunction [101–116]. Analysis of the previously reported cases revealed that hyperglycemia and hypothermia have also been described [103, 105–107, 111, 112, 116]. The exact time of coma onset was not clear in this patient, but appeared to have been delayed by a minimum of 3 to 4 h following ingestion, given the available history. In many of the published cases of massive acetaminophen ingestion causing coma and lactic acidosis, a clear time of ingestion is not detailed. When the time between ingestion and coma onset is described, it is typically within 3–4 h [102, 103]. We found one case in which there was a documented delay of 7 h between ingestion and coma [116]. It was ultimately determined that the initial acetaminophen concentration of 616 μg/mL in this patient was drawn at least 16 h following ingestion, and therefore, a massive acetaminophen overdose adequately explained the clinical presentation.

Could Acetaminophen Toxicity Explain the Patient's Elevated Peripherally Drawn Venous Oxygen Saturation?

A massive overdose of acetaminophen would appear to be a situation that could, similarly to cyanide, produce an elevated venous oxygen content. Multiple animal studies have demonstrated that very high concentrations of acetaminophen and its metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) can inhibit mitochondrial oxidative phosphorylation [117–124]. This mechanism results in diminished oxygen utilization and is likely responsible for both the coma and lactic acidosis that manifest in massive acetaminophen overdoses. One previous case report of a massive acetaminophen overdose detailed venous oxygen saturation. In this case, which was also complicated by 9.4 % methemoglobinemia, the venous oxygen saturation (not specified if was drawn centrally or peripherally) was 88 % [115].

Should Hemodialysis Be Performed on This Patient?

Although acetaminophen is amenable to removal by hemodialysis, the vast majority of overdoses are effectively treated with the antidote NAC alone. In massive overdoses, however, the standard dosing of NAC may be insufficient to address the mitochondrial dysfunction induced by both acetaminophen and the metabolite NAPQI [125]. Removal of acetaminophen by hemodialysis in such cases may address this problem. A 2014 article by the Extracorporeal Treatments in Poisoning workgroup recommends hemodialysis for acetaminophen removal in cases of early mitochondrial failure (coma, lactic acidosis) when the APAP concentration is above 900 μg/mL [125]. They gave this a level 1D (strong, with very low level of evidence) recommendation [125]. It is possible that if the patient had presented earlier with a higher serum acetaminophen level, he may have fit these recommended criteria for hemodialysis. We ultimately opted not to perform hemodialysis.

Case Conclusion

The patient was continued on intravenous NAC, and serial acetaminophen concentrations revealed the initial level to be the highest concentration measures. His depressed level of consciousness progressively improved, as did his metabolic acidosis, and he was extubated approximately 30 h after hospital arrival. When interviewed, the patient described having ingested a very large quantity of acetaminophen prior to his arrest and denied having ingesting any other agents. His acetaminophen concentration became undetectable by 45 h after ED presentation, at which point NAC administration was discontinued. His peak AST was 67 U/L, and peak prothrombin time was 15.4 s. His creatinine remained within normal limits, and his peak CK was 424 U/L. His initial hyperglycemia resolved without intervention beyond intravenous fluids. He had no gastrointestinal bleeding during his hospital course. Methanol and ethylene glycol concentrations, drawn approximately 90 min after ED arrival, were undetectable. Propylene glycol and metformin levels were not tested. Cyanide was below detection limits (<5 μg/dL) and thiocyanate was within normal limits at 3 μg/mL (reference range 1–4 μg/mL for nonsmoker). Qualitative comprehensive urine and serum drug screening by immunoassay, gas chromatography–mass spectrometry, and liquid chromatography-tandem mass spectrometry revealed only acetaminophen and caffeine. Urine screening for organic acids revealed elevated concentrations of acetaminophen, lactic acid, and pyruvic acid. The excretion of 5-oxoproline (pyroglutamic acid) was reported as mildly above 400 mmol/mol creatinine, the upper limit of the normal reference range.

Conflict of Interest The authors (Janna Villano, Charles O'Connell, Binh Ly, and Aaron Schneir) have no conflicts of interest to disclose.

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