Case Files of the University of California, San Francisco Medical Toxicology Fellowship: Seizures and a Persistent Anion Gap Metabolic Acidosis

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Case Presentation

A 17-year-old female was brought into the emergency department (ED) by ambulance after being found unresponsive by her parents at home. She was last seen normal 4 hours previously, and a text message sent to her boyfriend indicated her intention to overdose on ondansetron and loratadine. Upon arrival of emergency medical services, she was administered naloxone without effect, and supportive measures including bag valve mask ventilation were initiated. En route to the ED, she had a witnessed generalized tonic-clonic seizure, and she was treated with midazolam.

In the ED, the patient's vital signs were BP 125/53 mmHg, HR 130/min, RR 18/min, and temperature 33.9 °C (rectal). Her physical exam was notable only for a Glasgow Coma Scale (GCS) of 3 without a gag reflex. Her pupil size was

not commented upon, and she was immediately intubated for airway protection.

What is the Differential Diagnosis for Seizure in the Poisoned Patient? What Diagnostic Testing Should Be Performed?

The differential diagnosis of seizure in a suspected overdose can be overwhelmingly broad. There is no single mechanism that explains all causes of drug-induced seizures; however, there are several common pathways that may help focus the differential diagnosis. Seizures may occur as the result of a loss of the normal inhibitory pathways [1], or conversely, enhancement of excitatory pathways. Gamma-aminobutyric acid (GABA) is the primary neurotransmitter responsible for maintaining inhibitory tone in the central nervous system. A classic example of toxin-induced decrease in GABA activity involves the class of compounds known as hydrazines (e.g., isoniazid and *Gyromitra esculenta*). These agents disrupt the production of GABA, through inhibition of glutamate decarboxylase, decreasing inhibitory tone and consequently causing seizures. Conversely, the accumulation of excitatory neurotransmitters can also result in seizures. Examples include the accumulation of catecholamines such as norepinephrine and dopamine as seen in cocaine use [1], or the accumulation of monoamines such as serotonin following selective serotonin reuptake inhibitor (SSRI) ingestions [1]. Finally, adenosine receptor blockade following methylxanthine ingestion results in increased glutamate release, an important excitatory neurotransmitter, resulting in a decrease in the seizure threshold [1].

Seizures may also occur as a result of withdrawal from medications or substances. The loss of chronic inhibition of GABA receptors in the central nervous system coupled with the upregulation of NMDA receptors, as is seen in alcohol and benzodiazepine withdrawal, is a common mechanism

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resulting seizures [1]. Finally, toxins causing cellular hypoxia such as cyanide result in seizures. This mechanism of seizure production is unclear, but may be the result of extracellular glutamate release following tissue hypoxia [2–4].

Our patient's history did not reveal an obvious cause of her seizure. She had access to loratadine, a second-generation histamine blocker, and ondansetron, a common antiemetic that selectively blocks serotonin (5-HT₃) receptors. Neither of these medications is commonly reported to be associated with seizures in overdose, and the clinician should be suspicious that another as yet unrevealed agent could be involved. Select studies and laboratory testing may help generate a differential diagnosis.

Case Continued

The patient's laboratory studies revealed an initial arterial blood gas (ABG) with a pH of 6.95, PCO₂ of 40 mmHg, a PO₂ of 150 mmHg, and bicarbonate of 8.7 mmol/L with a lactic acid of 9.0 mmol/L. The chemistry panel showed the following: sodium 141 mmol/L, potassium 3.8 mmol/L, chloride 109 mmol/L, bicarbonate 12 mmol/L, blood urea nitrogen (BUN) 13 mg/dL, creatinine 1.11 mg/dL, glucose 204 mg/dL, with an anion gap of 20 mmol/L. A beta-hydroxybutyrate level was 0.5 mg/dL (normal 0.2–2.8 mg/dL). Liver function tests were normal with an AST of 27 U/L and an ALT of 18 U/L. She had no detectable ethanol in her serum, and a urine drug screen was negative. Serum acetaminophen and salicylate levels were undetectable. The patient's EKG was notable only for sinus tachycardia at 116 beats per minute, with normal intervals including a QRS of 88 ms and a QTc of 461 ms. A urine pregnancy test was negative.

What Is Your Interpretation of the Initial Laboratory Results? How Quickly Should Lactate Clear After a Seizure?

The patient's laboratory studies are most significant for an elevated anion gap metabolic acidosis (AGMA). The differential diagnosis includes a number of important toxicologic and non-toxicologic causes. In this case, the elevated anion gap of 20 mmol/L can be entirely accounted for by the lactate level of 9 mmol/L. While the differential diagnosis of an AGMA due to lactate is broad and can be associated with several specific toxins, in this case, the most likely explanation is seizure. A review of five patients who had lactic acid measurements within an hour of a witnessed generalized tonic-clonic revealed acidosis with pH measurements as low as 6.8, and lactate measurements ranging from 3.8 to 22.5 mmol/L [5]. In this case series, lactate levels fell by as much as 72 % within an hour with supportive care alone [5]. We would expect the patient's lactic acidosis to improve

quickly with intravenous fluid resuscitation and observation alone.

Case Continued

In the intensive care unit (ICU), the patient was noted to have transient hypotension briefly requiring phenylephrine. A bedside electroencephalogram (EEG) was completed that demonstrated no further seizure activity. A serum osmolal gap was calculated and was 12 mOsm/kg, and the creatinine kinase was 125 IU/L. A repeat ABG approximately 3.5 h from the initial ABG demonstrated improved but persistent acidosis, with a pH of 7.35, PCO₂ 30 mmHg, PO₂ 150 mmHg, and bicarbonate of 16 mEq/L. A repeat lactate had fallen to 2.5 mmol/L; however, her serum bicarbonate was 16 mmol/L and a persistently elevated anion gap of 17 mmol/L remained.

This Patient Appears To Have a Persistently Elevated Anion Gap Metabolic Acidosis Despite a Falling Lactate. What Is the Explanation for This Finding? When “MUDPILES” Fails To Determine the Diagnosis, What Should We Consider?

A systematic evaluation is the most prudent approach to the evaluation of a patient with an AGMA. The mnemonic MUDPILES is frequently used and includes the following: Methanol (and Metformin), Uremia, Diabetic ketoacidosis, Paraldehyde, Iron (and Isoniazid), Lactic acidosis, Ethylene glycol, and Salicylates. This is not an exhaustive list and may miss rare causes of persistent AGMA in the poisoned patient.

In applying the MUDPILES mnemonic to our patient, few diagnoses fit the clinical picture. Alcohols such as methanol and ethylene glycol may rarely present with seizure [6, 7]. However, our patient has no clinical history of access to these alcohols, had no evidence of an osmolal gap, and has not developed worsening severe acidosis. There is no laboratory evidence of ketoacidosis or uremia. Isoniazid (INH) is certainly worth considering, as ingestions typically present with seizure, acidosis, and coma [8]. However, this patient's seizures responded well to benzodiazepines, while seizures following INH overdose may be resistant to benzodiazepine therapy and are often recurrent [9]. Finally, her salicylate level was undetectable, excluding this diagnosis.

Table 1 provides a list of toxins known to result in an elevated anion gap acidosis not included in the MUDPILES mnemonic. Our patient's acidosis followed a seizure after an unknown ingestion. While initially explained by an elevated lactate, it is now persistent despite a falling lactate. Therefore, an important consideration is the accumulation of another organic acid.

Table 1 Drugs not included in the MUDPILES mnemonic for AGMA grouped by type of acidosis produced

Lactic acidosis	Organic acids	Lactic acidosis and organic acid	Other
Acetaminophen	Aminocaproic acid	NSAIDs	Inorganic sulfur
Biguanides	Citric acid	Ibuprofen	Methionine
Carbon monoxide	Toluene	Mefenamic acid	Formaldehyde
Catecholamines	Triethylene glycol	Nalidixic acid	
Cyanide	Diethylene glycol		
Didanosine	Polyethylene glycol		
Fluoride	Valproic acid		
Hydrogen sulfide	Nalidixic acid		
Exogenous hyperphosphatemia			
Niacin			
Nitroprusside			
Propofol (prolonged infusion)			
Propylene glycol			
Streptozocin			
Sympathomimetics			
Amphetamines			
Cocaine			
Ephedrine			
Pseudoephedrine			
Theophylline			
Thiamine deficiency			
Zidovudine			

Adapted from [10]

Few agents are associated with AGMA not attributable to lactate and also associated with seizure in overdose (Table 1). Aminocaproic acid is an antifibrinolytic often used during cardiothoracic surgery [11, 12]. It has been reported to produce an anion gap metabolic acidosis, especially in patients with impaired renal function [11]. It has also been uncommonly associated with seizure [12]. The acidosis is likely the result of the accumulation of aminocaproic acid and its metabolite adipic acid [11]. However, it was unlikely to have been available to this patient.

Toluene is rarely associated with seizures [13–16]. While we typically think of toluene as causing a distal renal tubular acidosis, an elevated anion gap metabolic acidosis unexplained by ketones or lactate has also been described [17]. It has been suggested that the acidosis is the result of the oxidation of toluene to benzoic and hippuric acid [17]. There was no history of hydrocarbon abuse in our patient, and this solvent was not discovered in her home.

Nalidixic acid was the first quinolone antibiotic available, introduced in the USA in 1964 [18]. It is rarely used in the USA today; however, reports of overdose include altered mental status, seizure, coma, and metabolic acidosis [19, 20]. The mechanism of toxicity in producing both seizures and acidosis is unclear. Nalidixic acid itself has been implicated, though the reported plasma concentrations measured after overdose would

be unlikely able to account for the observed acidosis [19]. The metabolite hydroxy-nalidixic acid may be found in the plasma following ingestion, although its contribution to a metabolic acidosis is unclear [19].

Diethylene glycol, triethylene glycol, and low molecular weight polyethylene glycol are also found in household products that result in AMGA in ingestion. Diethylene glycol (DEG) is found in several products including brake fluid, fog machine fluid, and cooking fuel and has been implicated in several mass poisonings throughout history [21, 22]. Ingestion of DEG results in the characteristic development of intoxication with an associated AGMA and gastrointestinal irritation, followed by a worsening metabolic acidosis with renal and hepatotoxicity [21]. Patients who survive initial toxicity may develop peripheral neuropathies, particularly of cranial nerve VII [21]. The exact cause of the metabolic acidosis and end-organ toxicity associated with DEG is unclear, but may be the result of accumulation of the DEG metabolites 2-hydroxyethoxyacetic acid and diglycolic acid [21–23]. Triethylene glycol (TEG) may also be found in brake fluid, though ingestions are rare. Triethylene glycol ingestion has been associated with coma and significant anion gap metabolic acidosis likely secondary to the accumulation of organic acid metabolites including diacid and hydroxy acids [24]. Low-molecular weight polyethylene glycol (PEG) is another

rare ingestion. A single case report of an ingestion of lava lamp fluid containing polyethylene glycol (200 MW), kerosene, chlorinated paraffin, and microcrystalline wax by a 65-year-old male resulted in a non-anion gap metabolic acidosis as well as progressive renal failure and altered mental status [25]. While DEG, TEG, and PEG may result in an AGMA, none has been reported to be associated with seizure.

Citric acid is a familiar food additive, but is also used industrially as a component of detergent or as a cleaning product, and there are few reports of ingestion. DeMars et al. described a patient who ingested an unknown amount of an industrial cleaner containing ethanol, citric acid, and a blue dye. The patient presented to the ED with hypotension, AGMA, hyperkalemia, and hypocalcaemia [26]. The exact cause of this patient's hypokalemia and hypocalcaemia is unclear and may be related to the patient's acidosis and the additional dye [26]; however, the AGMA in this case was attributed to the parent compound citric acid, which is itself an organic acid.

Valproic acid (VPA) is a familiar antiepileptic and mood stabilizer with multiple complications in overdose including CNS depression, hepatotoxicity, hyperammonemia, and AGMA [27]. The pathophysiology of the AGMA associated with VPA overdose is speculated to be the result of a high concentration of the parent drug itself [28]. Seizure is not a common feature of VPA overdose.

Non-steroidal anti-inflammatory drug (NSAID) ingestion is another important consideration in this patient. Several NSAIDs, including ibuprofen and mefenamic acid, have been associated with seizure in overdose [29–38]. Outside of the USA, mefenamic acid is one of the most common causes of seizure in isolated overdose [37]. It is rarely prescribed or used given its side effect profile and so is less likely the cause of this patient's symptoms. In contrast, ibuprofen is widely available, found in many homes, and may be purchased easily over-the-counter. Massive ingestions are associated with metabolic acidosis [29–33, 39, 40] and have also been associated with the development of coma and seizure [29–33, 35, 39–41].

Case Continued

Additional history became available that two empty bottles of ibuprofen were found near the patient. Pill counts revealed a possible ingestion of up to 66 grams.

What Is the Typical Clinical Presentation of an Acute Overdose of Ibuprofen? Are Seizures and Coma Common Presenting Features of an Acute Overdose of Ibuprofen?

Ibuprofen is perhaps the most familiar of the NSAID class and is one of the most popular over-the-counter analgesics available. Overdoses are generally well tolerated; however,

significant adverse effects including seizure, coma, metabolic acidosis, renal failure, gastrointestinal (GI) bleeding, and fatalities have been described [29–33, 35, 39–42]. In one retrospective review of 126 single drug exposures to ibuprofen, only 19 % of patients developed any symptoms [29]. Mild central nervous system depression occurred in 11 patients and GI upset in eight. There were two patients who developed seizure and one death.

A prospective study by the same authors [30] reviewed 45 cases of isolated ibuprofen overdose. Seven patients were noted to have adverse reactions including GI upset and mild CNS depression. One child was noted to develop a metabolic acidosis, lethargy, and apnea after an ingestion of 666 mg/kg. A subsequent retrospective review of 329 cases [43] reported that 42 % of patients developed GI upset as the primary adverse event, with 30 % of patients exhibiting CNS depression with only one of these patients experiencing severe symptoms attributable to ibuprofen. Fatalities following ibuprofen overdose often are associated with significant hypotension [31, 44], metabolic acidosis [31, 44], oliguria [30], coma [31, 44], and multiple organ system failure [31].

What Is the Etiology of Neurotoxicity and Acidosis Seen in Ibuprofen Overdose?

Central nervous system side effects have been seen with many of the NSAIDs and include aseptic meningitis, seizure, and possible neuronal degeneration [35]. Seizures have been described with ibuprofen, mefenamic acid, meclofenamate, diclofenac, indomethacin, and phenylbutazone [35]. The association of seizure with mefenamic acid is well described [36, 37] and remains one of the most common causes of seizure in drug overdose worldwide. The mechanism of seizure associated with NSAIDs in general is unclear, although it has been postulated that seizure threshold may be decreased with decreased prostaglandin production [35].

The exact cause of the anion gap metabolic acidosis associated with massive ibuprofen overdoses is likely multifactorial. Lactic acidosis as a result of decreased tissue perfusion [45] in the setting of massive ibuprofen overdose has been postulated as one contributing etiology. It has also been suggested that the accumulation of ibuprofen metabolites 2-carboxyibuprofen and 2-hydroxyibuprofen that are themselves acids and even ibuprofen which is a weak acid likely contributes to the development of an AGMA [39, 45].

What Is the Treatment of Ibuprofen Overdose?

The mainstay of therapy in ibuprofen ingestion is supportive care [29, 45]. No specific antidote is available. Gastrointestinal decontamination with activated charcoal is an important

consideration in patients who are able to swallow and have an adequately protected airway [29, 45]. Whole bowel irrigation using large molecular weight PEG via nasogastric tube is another reasonable option. Aggressive fluid resuscitation is advised, and intravenous proton pump inhibitors may be helpful in patients presenting with evidence of gastritis or upper gastrointestinal bleeding [45]. Hemodialysis will correct electrolyte abnormalities including persistent acidosis or renal failure but will not remove a significant amount of ibuprofen due largely to protein binding [32].

Case Conclusion

The patient's serum from arrival was sent to the clinical chemistry laboratory and was found to contain 6-monoacetylmorphine (6-MAM), midazolam, alpha-hydroxymidazolam, naloxone, loratadine, and ibuprofen. Hospital records indicate the patient had been treated with midazolam and naloxone. The patient's serum ibuprofen concentration on arrival to the hospital was quantified at 641.5 µg/mL. Maximum therapeutic serum concentrations of ibuprofen are reported from 6.1 to 47.7 µg/mL with peak levels 1–3 h after ingestion, depending upon formulation [46].

The patient improved quickly and was extubated on hospital day 2, at which time she admitted to ingesting ondansetron, loratadine, and ibuprofen in a suicide attempt. The patient's acidosis resolved with intravenous fluid resuscitation on hospital day 3, and the patient was discharged home with her parents following a psychiatric evaluation.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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