

Pitfalls in the Management of Aspirin Poisoning

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A 17-year-old girl was brought to the emergency department after a brief, generalized tonic-clonic seizure. She had no significant medical history and stated that she took no medications or dietary supplements, did not smoke, and used no illicit drugs. She was in good health until immediately prior to presentation, when she was found repeatedly vomiting. The seizure occurred en route to the emergency department.

On arrival she was alert, oriented, and extremely agitated. Vital signs were: heart rate, 155; blood pressure, 105/34; temperature, 99.6°F; respirations, 30; oxygen saturation, 98% on room air. Her blood glucose level was 112 mg/dl. She was flushed and diaphoretic, with no signs of trauma. The patient's pupils were 4 mm and reactive bilaterally, her extraocular movements were intact, and no nystagmus was present. The rest of the physical exam was normal. Cardiac monitoring and supplemental oxygen therapy were initiated, and the patient was given an intravenous (IV) bolus of normal saline. She received 5 mg of haloperidol and 2 mg of lorazepam for behavioral control. The lorazepam doubled as a seizure prophylactic. Electrocardiography revealed a narrow complex sinus tachycardia with normal axis and intervals. Chest radiographs were normal.

Venous blood gas analysis showed: pH, 7.41; pCO₂, 26 mm Hg; bicarbonate, 16 mmol/L; lactate, 4 mmol/L. Serum electrolyte concentrations were: sodium, 146 mEq/L; potassium, 3.6 mEq/L; chloride, 108 mEq/L; bicarbonate, 15 mmol/L; calcium, 8.6 mg/dl; blood glucose level,

120 mg/dl; blood urea nitrogen, 14 mg/dl; creatinine, 1 mg/dl. Her complete blood count, transaminases, and coagulation profile were all normal. Ethanol and beta-human chorionic gonadotropin were undetectable. Trace ketones were present in her urine.

Likely Suspects

This patient has altered mental status, tachypnea, and tachycardia in the setting of a severe elevated anion gap metabolic acidosis with concomitant primary respiratory alkalosis. In order to narrow the otherwise broad differential diagnosis for elevated anion gap metabolic acidosis, it is important to first consider the type of unmeasured anions that may be present and then seek out a reason for them. To help locate this source, we used the mnemonic **KULTS: Ketones, Uremia, Lactate, Toxic alcohols, Salicylates**. The presence of ketones, lactate, and salicylates can be rapidly determined in most hospitals. The unmeasured anions that accumulate in uremia are mostly phosphate and sulfate and can be inferred if renal failure is present. Although the toxic alcohols, ethylene glycol and methanol, do not increase the anion gap, their metabolites do. Since laboratory confirmation of toxic alcohol exposure is often not readily available, poisoning should be suspected in patients with persistent, unexplained elevated anion gap metabolic acidosis after negative tests for ketones, renal failure, lactate, ethanol, and salicylates.

Case continuation

On reexamination the patient was sedate. Her speech was unintelligible, but she was able to follow simple motor commands. Her blood pressure had increased to 116/50 mm Hg, heart rate decreased to 140 beats per minute, and respirations remained at 30 per minute. A serum salicylate concentration returned at 80 mg/dl.

Manifestations of salicylate toxicity

Aspirin is toxic to multiple organ systems, but early dysfunction and death is primarily due to neurotoxicity. Early clinical manifestations of acute salicylate toxicity include nausea, vomiting, diaphoresis, and tinnitus. Salicylates stimulate the respiratory functions of the brainstem causing hyperpnea and tachypnea and leading to respiratory alkalosis. Neurological effects include agitation, hyperactivity, and delirium. Depressed mental status and seizures may develop as the severity progresses. Other serious complications of salicylate toxicity include acute lung injury, coagulopathy, renal tubular damage, and central nervous system hypoglycemia.

Salicylates are mitochondrial toxins that cause the uncoupling of oxidative phosphorylation, resulting in cellular energy failure. Potential energy from the electron transport chain cannot be incorporated into ATP (adenosine triphosphate) production and is released as heat. Mild hyperthermia is common, but in severe cases the temperature elevations can be marked. Paratonia (muscle rigidity) and rhabdomyolysis may also occur in these situations. Uncoupling of oxidative phosphorylation leads to an increased concentration of lactic acid in the serum, while impaired energy utilization increases fatty acid metabolism and generates ketone bodies. An elevated anion gap metabolic acidosis is a result of the accumulation of lactate and ketoacids, as well as salicylic acid and its derivatives. In this clinical setting, the finding of a primary respiratory alkalosis with a primary metabolic acidosis is nearly pathognomonic for consequential salicylate poisoning.

Managing salicylate toxicity

The management of salicylate toxicity consists of decontaminating the gastrointestinal tract, restoring the patient's fluids, alkalizing both the serum and the urine, and, in select cases, extracorporeal elimination measures. Patients with signs and symptoms of salicylate toxicity

should be treated as confirmed cases until serum analysis says otherwise. Consultation with a regional poison control center can be helpful in determining the best course of treatment for your individual patient. Gastric emptying may be warranted in patients who present soon after large salicylate ingestions; however, vomiting is generally prominent, which limits the benefits of this procedure. Multiple doses of activated charcoal may mitigate ongoing absorption of large amounts of salicylate, especially if concretions have formed.

Patients are typically hypovolemic due to vomiting, diaphoresis, tachypnea, and hyperthermia, and fluid and electrolyte balances should be aggressively restored. Excretion of the drug is enhanced most effectively by increasing urinary pH. Increasing urinary volume by providing excess fluids has no proven benefit.

Salicylic acid is a weak acid with a pK_a of 3.5. At physiologic pH it exists primarily in its unprotonated, charged form. As the environment becomes more acidic, some of this ionized salicylate picks up a proton, losing its charge. This electrically neutral form crosses biologic membranes more readily than the ionized molecule, leading to increased tissue burden of the drug.

Bicarbonate therapy creates an increasingly alkaline pH gradient between the tissues, serum, and urine, promoting movement of the nonionized species from tissue to serum to urine. In alkaline urine, dissociated salicylate cannot undergo passive reabsorption; it is “trapped” and eliminated. Alkalinization is accomplished with an IV bolus dose of 1 to 2 mEq/kg of 8.4% sodium bicarbonate. This is followed by an infusion of 150 ml of 8.4% sodium bicarbonate in 1 L dextrose 5% in water at double the maintenance dose. The goal here is to achieve a urine pH of 8 and serum pH of between 7.45 and 7.55. Potassium supplementation may be required since

hypokalemia promotes acidic urine. Alkalinization is indicated in patients with signs and symptoms of salicylate toxicity or a serum salicylate concentration greater than 40 mg/dl. Arterial or venous blood gas, electrolyte, and salicylate concentrations should be monitored hourly until the clinical status stabilizes. Similarly, bicarbonate infusion should be continued until metabolic acidosis has resolved and serum salicylate falls under 40 mg/dl.

Indications for emergent hemodialysis include renal failure, an inability to tolerate bicarbonate therapy (i.e., congestive heart failure), evidence of end-organ toxicity (e.g. acute lung injury, hepatic injury, or neurological disturbance), progressive clinical deterioration despite treatment, or a serum salicylate concentration above 100 mg/dl, even without ominous clinical signs.

Case continuation

An intravenous bicarbonate infusion was started at 250 ml/hr. Two hours later her serum salicylate concentration had risen to 125 mg/dl. While her vital signs and physical exam were unchanged, the patient became increasingly agitated. Nephrology was consulted to begin immediate dialysis. In order to facilitate her management the decision was made to sedate and endotracheally intubate the patient.

Risks of intubation

Patients who are intubated often develop a transient respiratory acidosis as they are sedated in preparation for endotracheal tube placement. This is normally not a concern, but may be in the setting of severe salicylate poisoning. Additionally, ventilator settings are usually based on weight initially. These are substantially below the minute volume requirements of a salicylate-poisoned individual. This results in a relative hypoventilation [I don't think a doctor is going to

be confused by this term] and a relative respiratory acidosis. Even a small decrease in serum pH will increase the amount of nonionized salicylate molecules in the body, facilitating movement of the drug into tissue. All efforts should be made to put the patient in an alkalemic state. In fact, in this setting a “normal” pH is relatively acidic and is cause for alarm. Efficient airway management, intravenous sodium bicarbonate, and aggressive postintubation ventilator management are essential. A strategy of high tidal volumes, high respiratory rates, and frequent blood gas analyses should be used to maximize minute volume while avoiding barotrauma.

Case continuation

A 2 mEq/kg IV bolus of sodium bicarbonate was given just prior to rapid sequence intubation, and the patient was placed on the ventilator with a tidal volume of 7 ml/kg and a respiratory rate of 20 breaths per minute. Approximately 15 minutes later several premature ventricular contractions were noted. An arterial blood gas was drawn at that time and revealed a pH of 7.2 with a pCO₂ of 60 mm Hg. Her serum lactate was 11 mmol/L and salicylate levels had increased again to 130 mg/dl. The patient’s cardiac rhythm progressed to atrioventricular dissociation, followed by asystole. Advanced cardiac life support was performed, but the patient could not be resuscitated. Rapid rigor mortis and hyperthermia were noted perimortem.

Conclusions

Salicylate toxicity can be fatal and prompt initiation of treatment is critical to survival. Patients with clinical manifestations suggestive of salicylate toxicity should be volume resuscitated and receive alkalization therapy pending determination of serum salicylate concentration.

Symptomatic patients who cannot tolerate or who worsen despite bicarbonate therapy, have evidence of end-organ toxicity, or have serum concentrations greater than 100 mg/dl should be

dialyzed regardless of symptoms. Clinicians should be aware that even a small decrease in serum pH below 7.4 may have profound effects on the tissue burden of the drug. Care must be taken to preserve minute volume in these patients, since the development of respiratory acidosis may be a preterminal event. For this reason, any sedation or intubation of patients with severe salicylate toxicity must be approached with caution and monitored aggressively.