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## **Symptomatic Hypocalcemia During Urinary Alkalinization for Acute Aspirin Toxicity**

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### Abstract

A 16y/o ingested 165 tablets of 325 mg ASA (1000 mg/kg). He presented to an outside facility 8 hours after ingestion alert with stable vital signs and ASA level 78 mg/dL. Initial lab values showed an arterial blood gas (ABG) pH 7.46, pCO<sub>2</sub> 26 mmHg, HCO<sub>3</sub> 18 mmol/L, ionized calcium 1.09 mmol/L, serum calcium 10 mg/dL, albumin 4.5 gm/dL, magnesium 2.1 mg/dL. Urinary alkalization was initiated with a sodium bicarbonate infusion (NaHCO<sub>3</sub>) and he arrived to our facility 12 hours after ingestion with Kussmaul respirations and altered mentation. Repeat ASA 116 mg/dL, ionized calcium 0.88 mmol/L and serum calcium 8.8 mg/dL. He became encephalopathic with marked hyperpnea and diaphoresis. He was not intubated due to the risk of impairing his respiratory drive and lowering his pH. Jaw thrust maneuvers were provided to maintain his airway. A dialysis catheter was placed without sedation and dialysis was initiated. He developed bradycardia, hypotension, ST segment depression, and ventricular dysrhythmias. He required 5 liters of fluid, 3.5 gms calcium chloride, 175 mcg (3.4 mcg/kg) intermittent bolus epinephrine and continuous infusions of dopamine (10 mcg/kg/min), epinephrine (0.12 mcg/kg/min), and norepinephrine (0.05 mcg/kg/min). After 3 hours of dialysis, ASA level 49 mg/dL, vital signs stabilized, ionized calcium normalized, vasopressors were weaned off, and neurological status returned to baseline. To our knowledge, this is the first case report of urinary alkalization leading to low ionized calcium levels with associated hemodynamic instability and dysrhythmias. Altering the serum pH during urinary alkalization can alter the availability of ionized calcium. Urinary calcium loss may be enhanced by the excretion of the sodium load from a NaHCO<sub>3</sub> infusion due to inhibition of calcium reabsorption in the proximal and late distal tubule, contributing to total calcium losses. The degree of insensible losses and volume depletion can be underappreciated in the setting of acute aspirin toxicity. Hypocalcemia in combination with volume depletion and rapid volume shifts seen with initiation of dialysis can lead to significant hemodynamic instability.

### Background

Hypocalcemia during urinary alkalization in acute aspirin (ASA) toxicity is felt to be rare and inconsequential [1]. A search of the literature found only one case report that describes decreased serum calcium in the setting of alkali therapy leading to tetany in a 14 year old male with ASA toxicity [2]. To our knowledge, this is the first case report to describe urinary alkalization leading to low ionized calcium levels with associated hemodynamic instability and dysrhythmias.

### Case Presentation

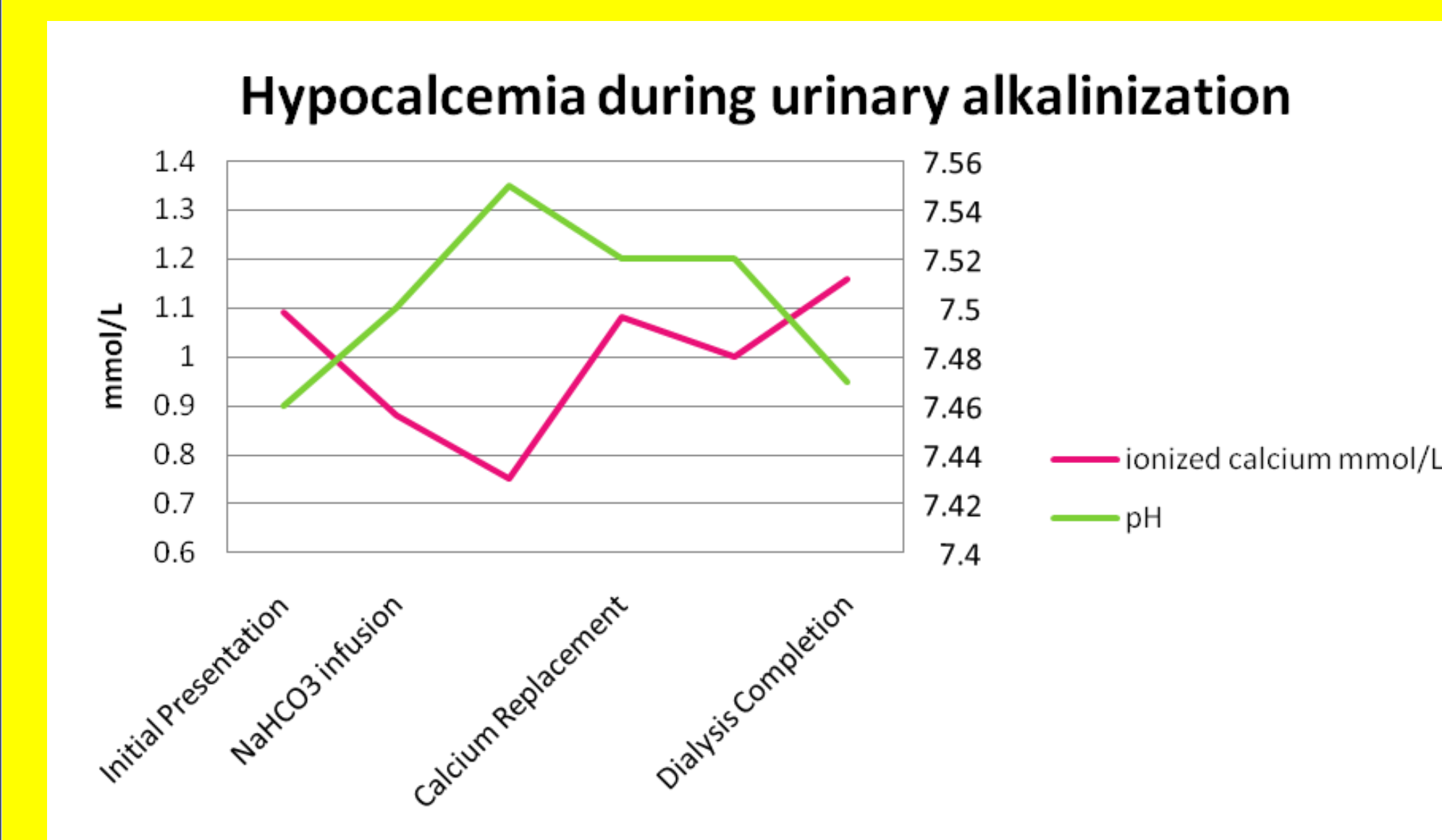
HPI: A 16yo previously healthy male presented to a referring facility approximately 8 hours following ingestion of 165 tablets of 325mg ASA (1000mg/kg). He had stable vital signs, and an ASA level of 78 mg/dL with complaints of nausea, vomiting, and tinnitus. He was noted to have a normal physical exam without labored breathing, normal mentation, and was cooperative with an appropriate affect. Initial laboratory values showed an ABG with a pH of 7.46, pCO<sub>2</sub> 26 mmHg, HCO<sub>3</sub> 18 mmol/L, ionized calcium 1.09 mmol/L, serum calcium 10 mg/dL, albumin 4.5 gm/dL, and magnesium 2.1 mg/dL. Urinary alkalization was

initiated with a NaHCO<sub>3</sub> continuous infusion. He arrived to our facility 12 hours after ingestion with Kussmaul respirations and altered mentation. Repeat laboratory values on arrival showed an ASA level of 116 mg/dL, ABG with a pH of 7.5, pCO<sub>2</sub> 20 mmHg, HCO<sub>3</sub> 15 mmol/L, serum calcium 8.8 mg/dL and ionized calcium that had decreased to 0.88 mmol/L [Graph 1]. Intravenous calcium replacement was not given initially due to concern for causing precipitant formation with the concurrent NaHCO<sub>3</sub> infusion.

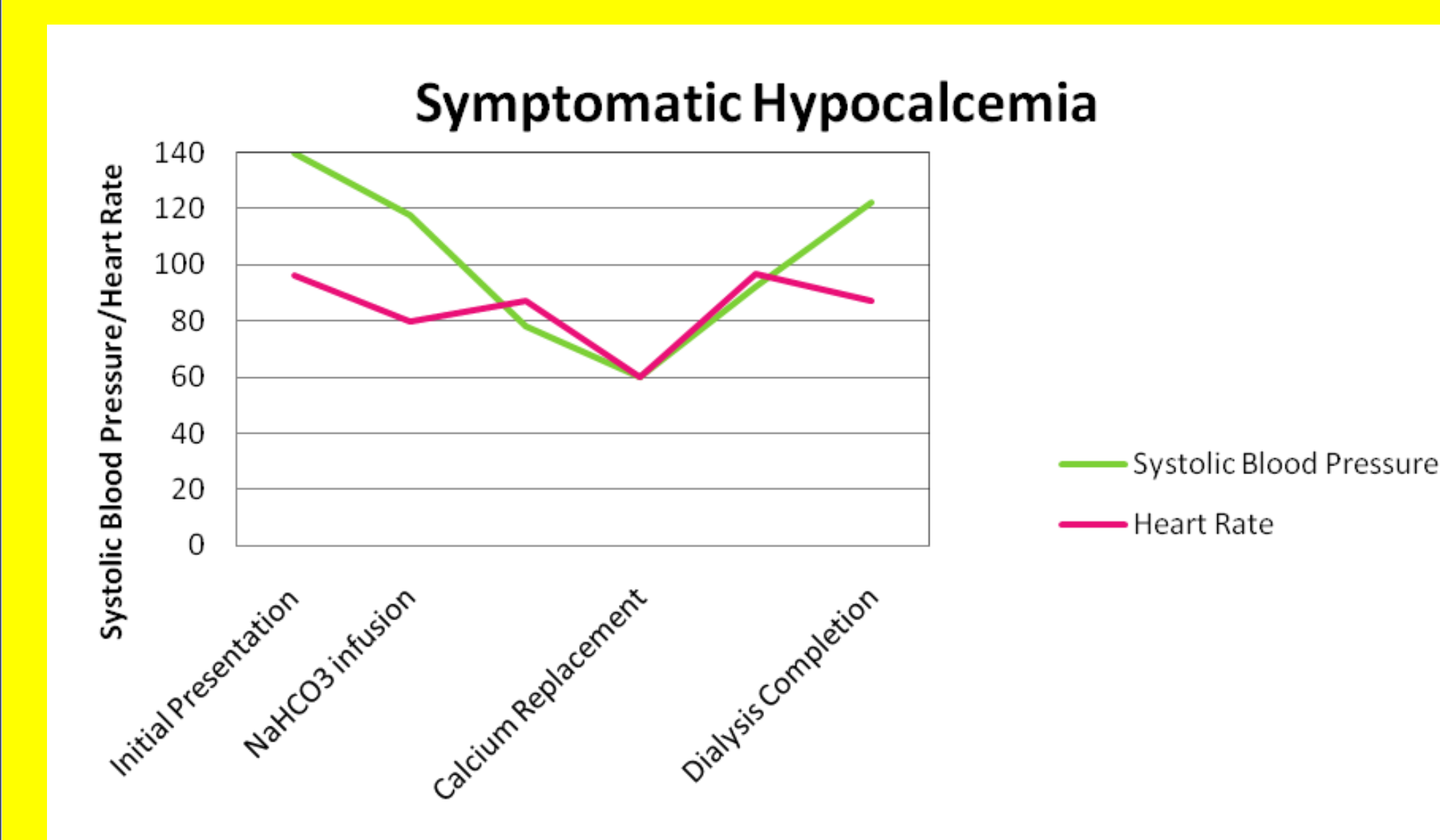
Four hours following admission, he became encephalopathic with marked hyperpnea and diaphoresis. He was not intubated due to the risk of impairing his respiratory drive and decreasing his serum pH. Jaw thrust maneuvers were provided and a nasal trumpet was placed to maintain his airway. A dialysis catheter was placed using only local anesthesia and hemodialysis was initiated.

Upon initiation of dialysis, he developed significant hemodynamic instability with bradycardia, hypotension, ST segment depression, and ventricular dysrhythmias. He required 5 liters of fluid resuscitation, 3.5 grams of calcium chloride, 175mcg (3.4mcg/kg) of intermittent bolus epinephrine and continuous infusions of dopamine (10mcg/kg/min), epinephrine (0.12mcg/kg/min), and norepinephrine (0.05mcg/kg/min). Following 3 hours of dialysis, his ASA level was 49 mg/dL, vital signs stabilized, and his neurological status returned to baseline. Once his ionized calcium normalized with bolus calcium chloride, his vasopressor therapy was weaned off and his dysrhythmias resolved [Graph 2]. He continued on NaHCO<sub>3</sub> infusion until ASA levels were <30 mg/dL with aggressive calcium replacement.

Graph 1



Graph 2

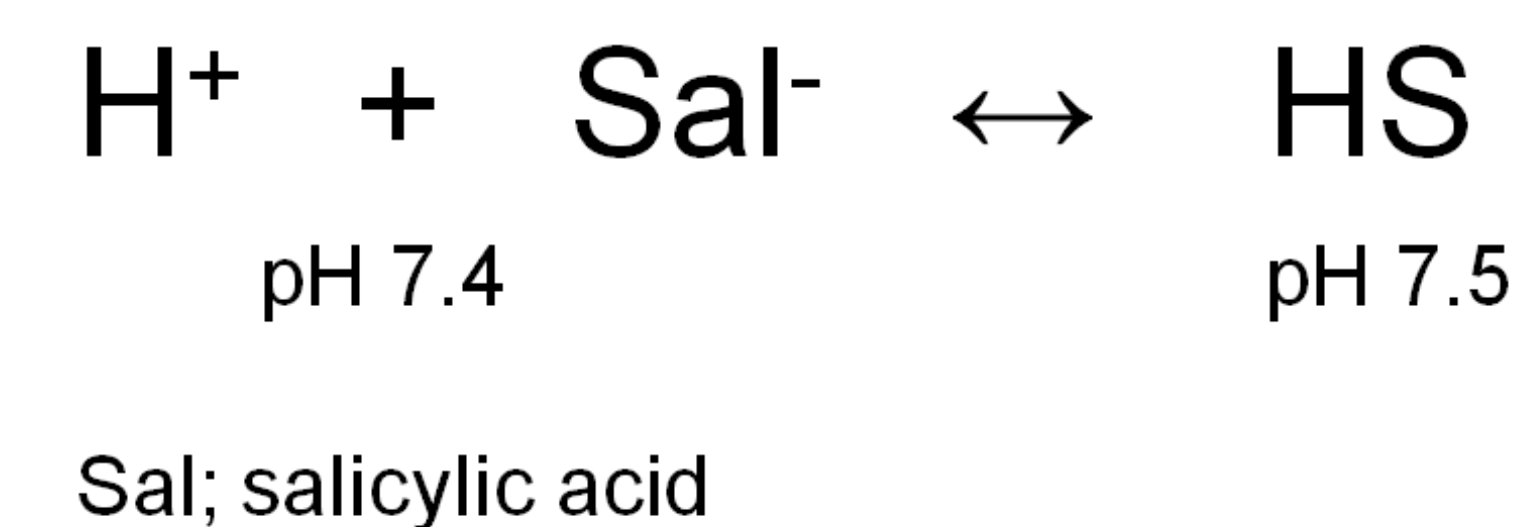


### Discussion

The pathophysiologic effects of ASA toxicity are complex but important to understand when managing a patient with an acute ingestion. The primary effects of ASA intoxication include direct stimulation of the respiratory center of the brain, uncoupling of oxidative phosphorylation, inhibition of the Krebs cycle, stimulation of gluconeogenesis with increased tissue glycolysis, and alterations of lipid and amino acid metabolism [3]. These effects lead to respiratory alkalosis, metabolic acidosis, and impaired glucose metabolism with increased insensible water and electrolyte losses.

Salicylic acid, the ingredient in ASA, is a weak acid that exists in both an ionized and non-ionized state. Non-ionized, lipid soluble molecules move easily across the blood brain barrier and is enhanced in an acidic pH [Figure]. A metabolic acidosis thus drives the reaction to the non-ionized state potentiating CNS toxicity. An alkalotic pH favors the ionized, water soluble molecule which moves from intracellular sites to the plasma and urine. Based on this physiology, urinary alkalization has been the recommended therapy for acute aspirin toxicity to enhance the renal excretion of ASA.

Figure



Hypocalcemia in the setting of urinary alkalization has been documented as a known side effect, but is felt to be rare and usually asymptomatic [1]. Our patient initially presented with a normal serum and ionized calcium that precipitously dropped following the initiation of NaHCO<sub>3</sub>. Hypotension and ventricular dysrhythmias ensued at the initiation of hemodialysis in the setting of low ionized calcium levels. The blood pressure and dysrhythmias responded well to calcium chloride boluses and completely resolved once the ionized calcium level normalized. There are likely three mechanisms for low ionized calcium in the setting of urinary alkalization. 1) Altering the serum pH to a more alkalotic state alters the availability of ionized calcium 2) alkalotic urine may interfere with the renal tubules ability to resorb calcium complexes 3) urinary calcium loss is enhanced by the increased excretion of the sodium load from the NaHCO<sub>3</sub> infusion due to inhibition of calcium reabsorption in the proximal and late distal tubule [4]. In combination, these mechanisms decrease the total body calcium and total bioavailable calcium.

There are other important factors that should be considered while caring for a patient with ASA toxicity. There are case reports of adult patients with acute aspirin toxicity who developed a sudden decrease in the serum pH during the intubation process and died shortly thereafter with the presumed mechanism of allowing salicylic acid to convert to the non ionized

molecule and readily cross the blood-brain barrier[5,6]. This highlights the importance of allowing patients to maintain their respiratory drive to allow for preservation of an alkalotic pH or match the patient's minute ventilation with mechanical ventilation if intubation is unavoidable. The most common side effect noted in urinary alkalization is hypokalemia by shifting potassium to the intracellular space in exchange for hydrogen ions. Hypokalemia makes urinary alkalization difficult as the distal tubule will secrete hydrogen ions in exchange for potassium in an attempt to increase serum potassium [1,3]. This stresses the importance of replacing potassium and maintaining a normal serum potassium level during urinary alkalization therapy.

Insensible water losses are easily underestimated in the setting of ASA toxicity. Increased water losses from hyperpnea, tachypnea, fever, and diaphoresis are common. Dehydration can be further perpetuated by the diuretic effect of the NaHCO<sub>3</sub> infusion and the renal tubules attempt to excrete the excess sodium. It is important to provide adequate fluid therapy during urinary alkalization and especially when considering dialysis as a therapeutic intervention. The combination of hypocalcemia with volume depletion and rapid volume shifts seen during the initiation of hemodialysis can lead to significant hemodynamic instability.

### Conclusions

#### Conclusions:

1. Urinary alkalization for acute ASA toxicity can lead to electrolyte imbalances, specifically hypocalcemia
2. Maintaining a patient's minute ventilation and alkalotic pH is imperative in preventing CNS toxicity in acute ASA intoxication
3. Hypokalemia prohibits the ability to alkalize the urine with NaHCO<sub>3</sub>
4. Insensible water losses are easily underestimated in acute ASA ingestion
5. Hypocalcemia in combination with volume depletion and rapid volume shifts seen with hemodialysis can lead to significant hemodynamic instability

### References

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