Case Report

Salicylate Toxicity from Ingestion and Continued Dermal Absorption

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INTRODUCTION

Salicylates are commonly used for their analgesic, antipyretic, anti-inflammatory and antiplatelet properties. Acute salicylate poisoning is a common overdose resulting in high morbidity and mortality. Insidious cases of salicylate intoxication may also occur, caused by either ingestion or topical absorption, most often in elderly patients with associated medical illnesses. We present a fatal case of acute methyl salicylate toxicity from both ingestion and dermal absorption of oil of wintergreen. This case highlights the point that topical absorption of salicylates, particularly in patients with renal failure, can result in severe intoxication.

CASE REPORT

An 80-year-old man with end-stage renal disease had oil of wintergreen (containing 35% mg/ml methyl salicylate) rubbed regularly on his lower extremities by a live-in attendant. He applied it to the patient's legs and left the bottle on the nightstand. The patient mistakenly drank a mouthful when he mistook it for a beverage. The attendant said the patient vomited the oil of wintergreen immediately. Two hours later, the man was found seizing. When paramedics arrived the patient remained unresponsive and apneic with a wide QRS complex on the cardiac monitor.

The patient's medical history included diabetes mellitus, diabetic nephropathy requiring hemodialysis three times per week, and severe coronary artery disease. He had a coronary artery bypass graft and a pacemaker. He was dialyzed one day prior to presentation and had otherwise been in his usual health.

Upon presentation to the Emergency Department, the patient was unresponsive and apneic. He had a blood pressure of 146/66 mm Hg, a palpable pulse at 55 beats per minute, and depressed respirations requiring assisted ventilation by bag valve mask. External cardiac monitoring revealed a wide QRS rhythm. The patient smelled of oil of wintergreen. Head and neck exam was normal. His lungs were clear and his heart without murmurs. Abdominal and rectal exam were unremarkable. His lower extremities demonstrated acrocyanosis and were cool to touch. Diminished pulses were noted, and no reflexes were elicited. His bilateral forearm shunts appeared intact.

Resuscitation in the Emergency Department consisted of oral endotracheal intubation, followed by gastric lavage and administration of activated charcoal. The patient initial arterial blood gas on FiO2 100% was pH 6.95, pCO2 34 mmHg, pO2 400 mmHg, and the patient was given intravenous sodium bicarbonate. The serum potassium level was 8.6 mmol/L and the patient was given 1 gm of calcium gluconate intravenously. His electrocardiogram showed a wide complex QRS with pacemaker depolarizations at 80 spikes per minute. The patient also developed several runs of ventricular tachycardia, which responded to 1mg/kg (75 mg) lidocaine.

The patient's chest radiograph demonstrated cardiomegaly with no evidence of pulmonary edema. The endotracheal tube was in good position above the carina. Serum chemistries revealed the following values: sodium 134 mmol/L, potassium 8.6 mmol/L, chloride 97 mmol/L, bicarbonate 6 mmol/L, urea nitrogen 62 mmol/L, creatinine 6.9 mmol/L. He had an anion gap of 31 (normal < 14). His salicylate level was 74.8 mg/dl.

Immediate hemodialysis was initiated upon transfer to the Intensive Care Unit. Repeat arterial blood gas after 1 1/2 hrs of dialysis demonstrated a pH of 7.37, PaCO2 34 mmHg, and PaO2

147 mmHg. Repeat potassium was 4.3 mmol/L.

Approximately nine hours after admission, the patient had another generalized tonic-clonic seizure, which responded to diazepam. However, because the patient desired no heroic measures, no resuscitative efforts were performed when he continued to deteriorate.

An autopsy revealed a postmortem salicylate level of 82.6 mg/dl; 7.8 mg/dl higher than his pre-dialysis level, and the cause of death was determined to be acute salicylate intoxication. It was concluded that the cause of salicylate toxicity in this patient was due to continued dermal absorption of oil of wintergreen in this patient with chronic renal failure.

DISCUSSION

Salicylate intoxication can produce serious morbidity and mortality after accidental or intentional acute ingestion, or chronic over-medication. Percutaneous absorption of salicylates may also result in toxicity, especially in patients with renal failure.

Prior to antibiotics, topical salicylates were widely used to treat scabies and impetigo, and toxicity associated with dermal absorption was common. One case series reported 13 deaths, 10 of them in children, substantiating the severe potential for toxicity associated with this route.[1] A review of the literature of topical salicylates reported 17 documented cases of toxicity associated with underlying illnesses, days to diagnosis, and serum salicylate.[2] Psoriasis is the main entity still treated with topical salicylates, and there are numerous case reports documenting toxicity.[1,2] Another route of application is with sports creams used in massage therapy for muscle pain. Local skin necrosis and interstitial nephritis have also been associated with these creams.[2]

Our patient experienced seizures with a salicylate level of 74.8 mg/dl and was hemodialyzed immediately upon presentation, which should have lowered his serum salicylate level. However, his subsequent serum level was 82.6 mg/dl. Despite aggressive treatment with intubation, gastric lavage, charcoal, bicarbonate, and dialysis, his salicylate level continued to increase. It is likely that percutaneous penetration of salicylate contributed to his rising level. No efforts were made to decontaminate his skin because it was thought to be insignificant at that time.

Methyl salicylate (oil of wintergreen) contains more salicylate than other salicylates; 5 ml methyl salicylate is equivalent to five aspirin tablets (325 mg each).

The primary effects of salicylate toxicity are complex and include direct stimulation of the CNS respiratory center leading to a respiratory alkalosis. Salicylates also uncouple oxidative phosphorylation at a cellular level, producing an increased metabolic rate. This results in increasing oxygen consumption, glucose utilization, and heat production.[4] Salicylates inhibit the Krebs cycle and alter lipid metabolism and amino acid metabolism, producing lactic acid and ketones with resultant metabolic acidosis.[4] They also interfere with hemostasis by damaging hepatocytes and interfering with prostaglandin synthesis.

These effects cause hyperpnea, tachypnea, tachycardia, fever, hemorrhage, and hypoglycemia, all of which can subsequently progress to altered mental status and seizures.[4,5]

Factors that affect the rate of percutaneous absorption of salicylate include: the effect of salicylic acid on the epidermis, the pathologic state of the skin, the degree of hydration of the stratum corneum, and the solvents used.[1] Strakosch studied the histological changes of the skin caused by the application of salicylate in concentrations ranging from 1% to 15%.[5] His studies were conducted on the normal skin of volunteers. Depending on the concentration of the salicylate and on the ointment base used, the salicylate ointments caused injury to the epidermis within two to 14 days. On histological examination, the findings included swelling and exfoliation of the stratum corneum. He also showed that the addition of 3% or 6% sulfur to 3% salicylate accelerated the onset of swelling and exfoliation of the stratum corneum.[6]

It is likely that compromised epidermis, by exposing viable cells, is a significant factor in the percutaneous penetration of salicylates.[7] In both animal models and human subjects, the rate of percutaneous penetration of salicylate in various ointment bases was determined by measuring the serum concentration and urinary output of salicylates.[8,9] Both studies demonstrated significant absorption of salicylate, especially in hydrophilic ointment base.

The severity of toxicity can generally be predicted from the amount of drug absorbed. Ingestion of less than 150 mg/kg is usually not associated with systemic toxicity; 150-300 mg/kg may produce mild to moderate symptoms of hyperpnea and neurologic disturbances (lethargy and/or excitability). A dose of greater than 500 mg/kg of salicylate can result in severe hyperpnea, coma, and occasionally seizures.[10]

About 20% of the salicylate is oxidized in the tissues and 70% is excreted by the kidneys.[3] Because the hepatic enzymatic metabolism becomes saturated as salicylate levels increase, renal excretion becomes increasingly important as a means of elimination.[2,11,12] Therefore, renal insufficiency or renal failure contributes to further accumulation of salicylate.

The treatment of acute salicylate intoxication consists of decreasing further absorption of salicylates, enhancing drug elimination, and correcting for acid-base, fluid, and electrolyte imbalances. Gastric lavage has not demonstrated to be better than charcoal alone at reducing toxicity in an evidence-based review.[13] Extra doses of activated charcoal may be needed to achieve the desired ration of 10:1 activated charcoal to salicylates. Repeated doses of activated charcoal may enhance elimination through enteroenteric recirculation.[14]

Prompt correction of systemic acidosis with sodium bicarbonate is critical to prevent further transfer of unbound salicylate into the CNS. Alkalization of the urine with sodium bicarbonate (2-3 mEq/kg loading dose intravenously, and 2 mEq/kg every 3-4 hours thereafter to maintain a urine pH above 8) will enhance urinary excretion of salicylate and reduce serum half-life.[7,11] Overly vigorous fluid administration can lead to pulmonary edema or cerebral edema. Fluid or osmotic diuresis

does not increase renal salicylate excretion more than urinary alkalization.[12]

Hemodialysis is the most efficient method of removing salicylates from the blood. Dialysis is the treatment of choice in salicylate-intoxicated patients who have severe renal, hepatic, or cardiovascular disorders, uncorrectable acidosis, comatose, seizing, or are unresponsive to other methods of treatment.

SUMMARY

Salicylate toxicity from percutaneous absorption can occur, especially with methyl salicylate. Renal dialysis patients are at increased risk for salicylism because salicylates are primarily excreted by the kidneys. Physicians should be aware of the potential risks of salicylate dermal absorption and toxicity.

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