Salicylate (Aspirin) Ingestion
California Poison Control 1-800-876-4766

Background
1. The prevalence of aspirin-containing analgesic products makes these agents, found in virtually every household, common sources of both accidental and suicidal ingestion
2. Aspirin or aspirin-equivalent preparations (in milligrams):
   a. Children’s aspirin (80-mg tablets with 36 tablets per bottle)
   b. Adult aspirin (325-mg tablets)
   c. Methyl salicylate (e.g., oil of wintergreen) (98% salicylate)
   d. Pepto-Bismol (236 mg of nonaspirin salicylate per 15 mL)

Pathophysiology
1. Salicylates directly or indirectly affect most organ systems in the body by uncoupling oxidative phosphorylation, inhibiting Krebs cycle enzymes, and inhibiting amino acid synthesis

Acid-Base Status
1. Salicylates stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis
2. Salicylates also interfere with the Krebs cycle, limit production of ATP, and increase lactate production, leading to ketosis and a wide anion-gap metabolic acidosis
3. Adult patients who are acutely poisoned usually present with a mixed respiratory alkalosis and metabolic acidosis
4. Respiratory alkalosis may be transient in children so that metabolic acidosis may occur early in the course
5. Patients with mixed acid-base disturbances have been found to have normal anion-gap metabolic acidosis; therefore, normal anion-gap acidosis does not exclude salicylate

Respiratory System Effects
1. A salicylate level of 35 mg/dL or higher causes increases in both rate (tachypnea) and depth (hyperpnea)
2. Salicylate poisoning may cause noncardiogenic pulmonary edema
3. Although the exact etiology is not known, hypoxia is considered a major factor

Glucose Metabolism
1. Increased cellular metabolic activity due to uncoupling of oxidative phosphorylation may produce clinical hypoglycemia, even though the serum glucose levels are within reference range
2. As intracellular glucose is depleted, the salicylate may produce discordance between levels of plasma and cerebrospinal fluid (CSF) glucose

Fluid and Electrolyte Effects
1. Salicylate poisoning may result in dehydration because of increased gastrointestinal tract losses (vomiting) and insensible fluid losses (hyperpnea and hyperthermia)
2. All patients with serious poisoning are more than 5-10% dehydrated
3. Renal clearance of salicylate is decreased by dehydration
4. Hypokalemia and hypocalcemia can occur as a result of primary respiratory alkalosis

Central Nervous System Effects
1. Salicylates are neurotoxic, which is manifested as tinnitus, and ingestion can lead to hearing loss at doses of 20-45 mg/dL or higher
2. CNS toxicity is related to the amount of drug bound to CNS tissue
3. Other signs and symptoms include nausea, vomiting, hyperpnea, and lethargy, which can progress to disorientation, seizures, cerebral edema, hyperthermia, coma, and, eventually, death

Gastrointestinal Tract Effects
1. Nausea and vomiting are the most common effects
2. Pylorospasm and decreased GI tract motility can occur with large doses

Hepatic Effects
1. Hepatitis can occur in children ingesting doses at or above 30.9 mg/dL
2. Reye syndrome is another form of pediatric salicylate-induced hepatic disease characterized by nausea, vomiting, hypoglycemia, elevated levels of liver enzymes, fatty infiltration of liver, and coma

Hematologic Effects
1. Hypoprothrombinemia and platelet dysfunction are the most common effects
2. Bleeding also may be promoted either by inhibition of vitamin K–dependent enzymes or by the formation of thromboxane A$_2$

Musculoskeletal effects
1. Rhabdomyolysis can occur because of dissipation of heat and energy resulting from oxidative phosphorylation uncoupling
2. Rhabdomyolysis- the destruction or degeneration of skeletal muscle tissue that is accompanied by the release of muscle cell contents (as myoglobin and potassium) into the bloodstream resulting in hypovolemia, hyperkalemia, and sometimes acute renal failure

Clinical and Laboratory Manifestations
1. Phase 1
   a. Hyperventilation resulting from direct respiratory center stimulation, leading to respiratory alkalosis and compensatory alkaluria
   b. Both potassium and sodium bicarbonate are excreted in the urine
   c. May last as long as 12 hours
2. Phase 2
   a. Paradoxic aciduria in the presence of continued respiratory alkalosis occurs when sufficient potassium has been lost from the kidneys
   b. May begin within hours and may last 12-24 hours
3. Phase 3
a. Dehydration, hypokalemia, and progressive metabolic acidosis
b. May begin 4-6 hours after ingestion in a young infant or 24 hours or more after ingestion in an adolescent
4. Nausea, vomiting, diaphoresis, and tinnitus are the earliest signs and symptoms of salicylate toxicity
5. Other early effects include vertigo, hyperventilation, hyperactivity, agitation, delirium, hallucination, convulsion, lethargy, and stupor
6. Hyperthermia is an indication of severe toxicity

Lab Studies
1. Bedside ferric chloride testing
   a. Qualitative determination for the presence of salicylates can be performed rapidly in the emergency department by adding a few drops of 10% FeCl$_3$ to 1 mL of urine
   b. If salicylates are present, the solution changes to a brown-purple color
2. Arterial blood gas (ABG)
   a. ABG should be obtained for the evaluation of mixed acid-base disturbance
   b. Primary respiratory alkalosis may occur, followed by concomitant primary metabolic acidosis resulting from production of lactic acid, metabolites, and other organic acids
3. Salicylate concentration
   a. Initial and serial salicylate levels are important in the evaluation of salicylate toxicity
   b. The absolute level should not detract from the importance of careful and repeated clinical evaluation
   c. Therapeutic range of salicylate is 15-30 mg/dL
   d. Patients often are symptomatic at salicylate concentrations higher than 40-50 mg/dL
   e. Patients with salicylate concentrations approaching or exceeding 100 mg/dL usually have serious or life-threatening toxicity
   f. Caution: Always confirm the units of measurement with the laboratory
      i. Traditional units are milligrams per deciliter; however, many laboratories report salicylate concentrations in milligrams per liter or micrograms per milliliter, both of which differ by a factor of 10 from the traditional units
      ii. A concentration of 100 mg/L is equal to a concentration of 10 mg/dL
   g. In overdoses, the peak serum concentration may not occur for 4-6 hours
   h. Toxicity of salicylates correlates poorly with serum levels, and the levels are less helpful in patients with long-term exposure
4. Other lab studies
Medical Care
1. California Poison Control 1-800-876-4766
2. Principles of treatment include limiting absorption, enhancing elimination, correcting metabolic abnormalities, and providing supportive care
3. No specific antidote is available for salicylates
4. Gastrointestinal tract decontamination
   a. Initial treatment should include the use of oral activated charcoal, especially if the patient presents within 1 hour of ingestion
   b. Activated charcoal can limit further gut absorption by binding to the available salicylates
   c. Recommended initial dose of activated charcoal is 1-2 g/kg
   d. Some authorities may recommend performing gastric lavage in all symptomatic patients regardless of time of ingestion
5. Urinary alkalization
   a. Renal excretion of salicylic acid depends on urinary pH
   b. Increasing the urine pH to 7.5 prevents reabsorption of salicylic acid from the urine
   c. Since acidosis facilitates transfer of salicylate into tissues, especially in the brain, it must be treated aggressively by raising blood pH higher than brain pH, thereby shifting the equilibrium from the tissues to the plasma
   d. Concomitant alkalinization of blood and urine keeps salicylates away from brain tissue and in the blood, in addition to enhancing urinary excretion
   e. When the urine pH increases to 8 from 5, renal clearance of salicylate increases 10-20 times
   f. Hypokalemia and dehydration limit the effectiveness of urine alkalization
   g. Urinary alkalization should be continued at least until serum salicylate levels decrease into the therapeutic range (<30 mg/dL)
6. Hemodialysis
   a. Rapid salicylate elimination is required if the patient is very ill with salicylate poisoning, has a very high salicylate level (eg, >90-100 mg/dL after acute overdose or >40-50 mg/dL in long-term toxicity), has severe fluid or electrolyte disturbances, or is unable to eliminate the salicylate
   b. Although hemoperfusion has a slightly higher rate of drug clearance than hemodialysis, dialysis is recommended
because of its ability both to correct for fluid and electrolyte disorders and to remove salicylates
c. Peritoneal dialysis is only 10-25% as efficient as hemoperfusion or hemodialysis and not even as efficient as renal excretion