Nonsteroidal Anti-inflammatory Drug and Salicylate Poisoning

Ellie E. Rakovchik, MD,* Daniel M. Fein, MD*
**Albert Einstein College of Medicine/Children's Hospital at Montefiore, Bronx, NY.*

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Nonsteroidal-anti-inflammatory-drugs (NSAIDs) and salicylates are commonly found in over-the-counter (OTC) analgesics that are available for purchase in large quantities at relatively little cost in the United States. Consequently, they are ubiquitous in households, often in quantities that, if ingested, can cause toxicity. Analgesics (including NSAIDs, salicylates, and acetaminophen) are the most common substance class involved in all human ingestions and the second most common in children younger than 6 years of age, after cosmetics.

NSAIDs function by reversibly inhibiting the enzyme cyclooxygenase (COX), thereby preventing the formation of prostaglandins, prostacyclins, and thromboxane A_2 from arachidonic acid. This ultimately results in antipyretic, analgesic, and anti-inflammatory effects. There are two isoforms of COX: COX-1, which is present in all tissues, and COX-2, which is produced locally during the inflammatory response. Common OTC NSAID formulations of ibuprofen and naproxen inhibit COX-1 more than COX-2, while newer prescription NSAIDs such as celecoxib have a greater affinity for COX-2. Most NSAID ingestions in the United States involve ibuprofen.

Symptoms of NSAID overdose manifest within 4 to 6 hours of ingestion. Most NSAID ingestions are asymptomatic or are associated with only minimal gastrointestinal (GI) symptoms, such as nausea, emesis, abdominal pain, and GI bleeding. Hepatic injury resulting in increased liver enzymes and liver failure can occur. Neurologic symptoms that frequently occur in the setting of NSAID ingestion are tinnitus, headache, drowsiness, lethargy, and dizziness. Cardiovascular symptoms are predominantly mild tachycardia and hypotension.

Although the vast majority of NSAID ingestions do not result in significant injury, ingestions of greater than 400 mg/kg are associated with a higher risk of coma, seizures, hepatotoxicity, and clinically important cardiovascular effects such as significant hypotension and bradycardia or other dysrhythmias. Acute renal failure may be associated with a substantial overdose, but nephrotoxicity is more characteristic of chronic NSAID use. Of note, several COX-2 inhibitors, such as rofecoxib and valdecoxib, have been removed from the market by their manufacturers because of increased risk of thrombotic cardiovascular events.

The diagnosis of an NSAID overdose is based on the history and physical examination because laboratory tests that can rapidly determine plasma NSAID levels are rarely available. Significant toxicity can result in an elevated anion-gap metabolic acidosis and electrolyte abnormalities such as hypo- or hyperkalemia, hypophosphatemia, and hyponatremia. Thrombocytopenia and disseminated intravascular coagulation may also occur with significant overdoses.

Management of NSAID toxicity begins with rapid assessment of the airway, breathing, and circulation (ABCs). Activated charcoal should be administered to the

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patient who has a history of a substantial ingestion if the patient is not at risk for aspiration. Further management is limited to symptomatic and supportive care.

Although salicylates are technically NSAIDs and achieve their therapeutic effect via COX inhibition, salicylism represents a distinct clinical entity with significant morbidity and mortality. Common commercially available oral salicylates are aspirin (acetylsalicylic acid [ASA]) and bismuth subsalicylate. Topical salicylates include salicylic acid (keratolytic skin care products) and methyl salicylate (topical muscular analgesics). Small volumes (as little as 5 mL) of a pure methyl salicylate preparation such as oil of wintergreen may be lethal to a toddler. Salicylates are also found in mixed preparation drugs.

Salicylates are weak acids (pKa: 3.0) that are rapidly absorbed from the stomach. Dermal absorption of salicylates is relatively slow, although enteric absorption of ingested topical salicylates is rapid and can lead to significant morbidity and mortality. The half-life of salicylates in therapeutic doses is 2 to 4 hours but may be as long as 20 hours in an overdose because the rate of elimination is changed from first- to zero-order kinetics.

The classic acid-base disturbance in salicylism is a mixed respiratory alkalosis and metabolic acidosis. Initially, tachypnea and hyperpnea from stimulation of the medullary respiratory center cause alkalosis. Metabolic acidosis, which develops 4 to 6 hours after ingestion (may be delayed as long as 24 hours in adolescents), is the result of multiple factors: uncoupling of oxidative phosphorylation, Krebs cycle enzyme interference, renal impairment, and promotion of ketoacidosis. Younger children tend not to develop marked hyperpnea; they primarily develop an increased anion-gap metabolic acidosis with only a limited respiratory component.

Salicylism presents with a spectrum of disease severity affecting multiple organ systems. Neurologic manifestations range from confusion and agitation to convulsions, cerebral edema, and coma. Tinnitus is one of the most common symptoms of salicylism and may progress to hearing loss. Nausea and vomiting are the most common GI symptoms; hemorrhagic gastritis, pylorospasm, and concretion formation may also occur. Pulmonary complications include hypoxia, pulmonary edema, and acute lung injury. Hyperthermia and diaphoresis frequently occur and may be mistaken as originating from an infection when, in fact, they result from the uncoupling of oxidative phosphorylation. Dehydration can follow vomiting, diaphoresis, increased insensible losses with tachypnea, and an osmotic diuresis. The resultant prerenal azotemia and nephrotoxicity lead to decreased elimination of salicylates and increased accumulation of organic and inorganic acids. Although not the effect of an overdose, Reye syndrome may occur with ASA use in the setting of a viral syndrome (classically varicella) and manifests with GI symptoms, fatty liver with hepatitis, and altered mental status.

Among the common electrolyte derangements in salicylism are hypoglycemia from impaired hepatic ability to regulate glucose metabolism and hypokalemia from potassium losses in the urine and intracellular shifts with the initial alkalosis. Rhabdomyolysis, leukocytosis, and coagulopathy may occur.

Ingestions of less than 150 mg/kg are typically asymptomatic, those of 150 to 300 mg/kg produce mild-to-moderate symptoms, those of more than 300 mg/kg lead to severe symptoms, and ingestions of more than 500 mg/kg may be lethal. Management of salicylism commences with evaluation of the ABCs, keeping in mind that if intubation is indicated, it must be accompanied with relative hyperventilation to prevent worsening acidosis. GI decontamination is performed with at least one dose (and potentially multiple doses) of activated charcoal. Whole bowel irrigation should be considered in large overdoses or if sustained-release products were ingested. Laboratory examination includes arterial blood gas, serum electrolytes (including a blood capillary glucose), salicylate level, and urinalysis. An acetaminophen value should also be obtained because this is a common co-ingestant.

Fluid resuscitation with isotonic fluids and correction of hypoglycemia with intravenous dextrose is crucial. Urinary alkalization with sodium bicarbonate added to intravenous fluids results in inhibited salicylate reabsorption from the kidneys and increased excretion. Maintaining a serum pH between 7.45 and 7.55 and a urine pH of 7.5 to 8.0 traps salicylates in these respective compartments, enhancing renal elimination and preventing central nervous system distribution. Potassium replenishment is vital to alkalinizing the urine. Hemodialysis is indicated for manifestations of end-organ damage (renal failure, persistent neurologic dysfunction), profound acidemia or electrolyte disturbance, or a serum salicylate concentration greater than 100 mg/dL.

COMMENT: In a note the day after he submitted this manuscript, Dr Fein reported that ironically he had just

treated a child for aspirin ingestion. The child was fortunate to have an expert to manage his care, but the problem is how easily accessible the medication was, thus allowing the ingestion. As pediatricians, we know that prevention trumps treatment, but with more than 30 **billion** tablets sold over-the-counter in the United States every year, the ubiquity of NSAIDs in our homes enables both accidental and purposeful overdoses. It may give us a headache, but we must keep reminding parents how important it is to keep potential poisons securely away from the prying hands of children and adolescents.

– Henry M. Adam, MD
Associate Editor, *In Brief*