

ASPIRIN AND NONSTEROIDAL AGENTS

Donna L. Seger and Lindsay Murray

ASPIRIN

Perspective

The incidence of aspirin (acetylsalicylic acid [ASA]) overdose and related childhood deaths has decreased significantly in recent years. Reasons include pediatricians' preference for acetaminophen preparations, the Food and Drug Administration's mandate limiting 36 tablets of baby aspirin to each bottle, and the use of child-resistant caps.

Unfortunately, the severity of this poisoning may be underestimated because of the lack of familiarity with the clinical picture. Salicylate toxicity can cause metabolic acidosis, seizure, hyperthermia, pulmonary edema, cerebral edema, renal failure, and death. Morbidity and mortality are increased by delayed diagnosis in elderly patients with chronic medical problems and in young patients diagnosed with an acute illness.¹

Principles of Disease

Pharmacokinetics

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal tract, with appreciable serum concentrations occurring within 30 minutes. Two thirds of a therapeutic dose is absorbed in 1 hour, and peak levels occur in 2 to 4 hours. Large ingestions frequently delay gastric emptying, and ingestions of enteric capsules may cause a prolonged absorption with rising serum levels for 12 hours or more.²

In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin (which contains a genetically determined variable number of salicylate-binding sites). In the liver, salicylate is conjugated with glucuronic acid and glycine (Fig. 149-1). A small fraction is hydroxylated. Free salicylate and its conjugates are eliminated by renal excretion. At therapeutic salicylate concentrations, elimination follows first-order kinetics, and excretion is proportional to salicylate concentration. When serum salicylate concentrations are greater than 30 mg/dL, however, elimination follows zero-order kinetics, and the metabolic rate is constant. The metabolic pathways become saturated, and the pH-sensitive urinary excretion of salicylic acid determines the half-life, which becomes prolonged and may approach 15 to 30 hours with toxic doses.³

Pathophysiology

Acid-Base Disturbances and Metabolic Effects. Salicylate stimulates the medullary respiratory center early and increases the sensitivity of the respiratory center to pH and carbon dioxide partial pressure

(P_{CO_2}). Hyperventilation develops early, then subsequently becomes a compensatory mechanism to the metabolic acidosis. Prolonged high serum concentrations eventually depress the respiratory center. Respiratory alkalosis is compensated by the buffering of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate. Loss of bicarbonate decreases buffering capacity and intensifies the metabolic acidosis.^{4,5}

Toxicity results primarily from salicylate interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation. Inhibition of the Krebs dehydrogenase cycle increases production of pyruvic acid and increases conversion to lactic acid. Increased lipid metabolism increases production of ketone bodies. Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased. Tissue glycolysis predisposes to hypoglycemia. (Hepatic gluconeogenesis and release of epinephrine may cause the less common hyperglycemia.) Inefficiency of anaerobic metabolism results in less energy being used to create adenosine triphosphate, and energy is released as heat, causing the hyperthermia frequently seen in salicylate poisoning.⁴

Only nonionized particles can cross the lipophilic cell membrane and accumulate in the brain and other tissues. Because ASA has a low pK_a ,^{3,5} the majority of salicylate is ionized, and little salicylate enters tissues at the physiologic pH of 7.4. However, as pH decreases, more particles become un-ionized and cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and central nervous system (CNS).^{4,5}

Fluid and Electrolyte Abnormalities. Significant potassium loss in salicylate toxicity is caused by vomiting, secondary to stimulation of the medullary chemoreceptor trigger zone; increased renal excretion of sodium, bicarbonate, and potassium as a compensatory response to the respiratory alkalosis; salicylate-induced increased permeability of the renal tubules with further loss of potassium; intracellular accumulation of sodium and water; and inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation. The net result is rapid depletion of potassium stores.⁴

A salicylate-induced decrease in renal blood flow or direct nephrotoxicity may cause acute nonoliguric renal failure. Salicylate-induced secretion of inappropriate antidiuretic hormone may also affect renal function.⁶

Pulmonary and Cerebral Edema. The exact mechanism by which salicylates increase alveolar capillary membrane permeability is unknown. Theories include inhibition of prostacyclin, changes in platelet-vessel interaction, and neurogenic influences. In adults, the risk factors for salicylate-induced pulmonary edema include age older than 30 years, cigarette smoking, chronic salicylate

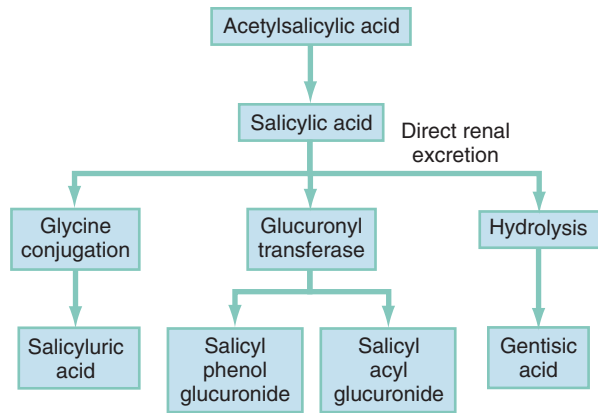


Figure 149-1. Aspirin metabolism.

ingestion, metabolic acidosis, neurologic symptoms, and serum salicylate concentration greater than 40 mg/dL. Risk factors in children include high serum salicylate levels, large anion gap, decreased serum potassium concentration, and low P_{CO_2} .⁷

Any alteration in sensorium is evidence of cerebral edema and is a grave prognostic sign. Factors causing cerebral edema are unknown. Patients with cerebral or pulmonary edema require immediate dialysis.

Chronic Ingestion Physiology. Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion. Decreased liver blood flow rates decrease biotransformation of salicylate, and decreased renal function decreases salicylate clearance. Chronic ingestion allows salicylates more time to pass through the blood-brain barrier. In addition, chronic ingestion of aspirin decreases albumin binding, increasing the free salicylate that can enter the cell. This causes significant clinical illness with a relatively low serum salicylate concentration. A patient with chronic salicylate toxicity and a serum concentration of 40 mg/dL may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dL.⁸

Pediatric salicylism from supratherapeutic dosing may be more serious than acute ingestion. Sweating, fever, and tachycardia caused by salicylism may be attributed to underlying infection. Other sources of salicylate exposure include breast milk, teething gels, and percutaneous absorption of skin ointments, which have high concentrations of methyl salicylate.

Clinical Features

A toxic dose of aspirin is 200 to 300 mg/kg, and ingestion of 500 mg/kg is potentially lethal. The initial manifestations of acute salicylate toxicity include early hyperventilation, vomiting, and dehydration and later tinnitus, impaired hearing, and hyperthermia. Salicylate-induced hyperpnea may be manifested as increased respiratory depth without commensurate increase in rate. Hyperventilation is more common in adults, who usually have an initial respiratory alkalosis. Young children are predisposed to toxicity from the metabolic acidosis, which increases tissue and CNS salicylate concentrations. Vomiting can occur 3 to 8 hours after ingestion. Serious dehydration can occur from hyperpnea, vomiting, and hyperthermia. CNS manifestations are usually associated with acidemia.

Shortness of breath and altered sensorium are caused by pulmonary and cerebral edema, respectively. Noncardiac pulmonary edema may be more common in children than scattered case reports suggest.⁹ Failure to recognize salicylate toxicity as the cause of pulmonary edema increases the likelihood of morbidity and mortality in these patients.

Box 149-1 Symptoms of Salicylate Toxicity

Asymptomatic: Occasional subjective but no objective manifestations

Mild: Mild to moderate hyperpnea, tinnitus, sometimes with lethargy

Moderate: Severe hyperpnea, prominent neurologic disturbances such as marked lethargy or agitation, but no coma or convulsions

Severe: Severe hyperpnea, coma, sometimes with convulsions

Diagnostic Strategies

Initial Evaluation

After the primary survey, a general physical examination is conducted to assess vital signs (including oxyhemoglobin saturation and a counted respiratory rate and reliable temperature). Chest auscultation may provide evidence of pulmonary edema, and mental status may suggest CNS toxicity. Early arterial blood gas determinations in symptomatic patients rapidly assess acid-base and compensatory status. A serum salicylate concentration should be measured with a second sample obtained 2 hours later. If the second concentration is greater than the first, serial concentrations should be obtained to monitor continued absorption, which may be prolonged.

Prognosis and treatment of the acutely poisoned patient should be determined by the serum salicylate concentration; the dose of salicylate ingested; and the patient's age, clinical features, and acid-base status. Acid-base status can change quickly, and frequent monitoring of arterial pH is necessary to guide treatment. The outdated Done nomogram should not be used to determine prognosis or treatment.

Low pH and bicarbonate level portend severe disease. The pH begins to drop when the patient is unable to compensate for the acidosis. Lactic acid accumulates, and serum bicarbonate is consumed. When pH is less than 7.4 and both P_{CO_2} and bicarbonate level are low, the patient begins to decompensate hemodynamically. In the intubated patient or the acidotic patient with low P_{CO_2} and bicarbonate level, hemodialysis should be undertaken.¹⁰

Differential Considerations

The symptoms of salicylism (hyperthermia, altered mental status or coma, pulmonary edema, and shock) mimic sepsis and the symptoms of many other diseases (Box 149-1). This is especially true with chronic ingestion; serum salicylate concentration is relatively low, and the severity of the poisoning is not recognized.¹¹ Death is caused by CNS depression and cardiovascular collapse.

Management

Intubation is indicated for patients with refractory shock, pulmonary or cerebral edema, or other manifestations of severe salicylate poisoning. Dialysis is indicated because positive-pressure ventilation cannot maintain the hyperventilation and respiratory rate required, and hemodynamic instability and worsening acid-base status usually follow intubation.

Specific treatment of salicylate toxicity has two main objectives: (1) to correct fluid deficits and acid-base abnormalities and (2) to increase excretion (Box 149-2). Electrolyte values are helpful to guide replacement and to assess renal function necessary to excrete salicylates. Serum salicylate levels should be repeated until they are decreasing to measure the effectiveness of treatment and to guide the decision for dialysis.

Box 149-2 Treatment of Acute Salicylate Poisoning

Treat dehydration; maintain urine output at 2-3 mL/kg/hr with 5% dextrose (D₅) in lactated Ringer's solution or normal saline. Correct potassium depletion.

Alkalinize urine.

Obtain baseline arterial blood gas values.

If pH is <7.4, administer sodium bicarbonate to obtain pH of 7.4 (50 mL bicarbonate increases serum pH by 0.1 in an adult).

Infuse intravenous fluids: D₅ with bicarbonate 100-150 mEq/L.

Monitor serum pH; do not cause systemic alkalosis.

Do not attempt forced diuresis.

Monitor for dialysis indications.

Coma, seizure

Renal, hepatic, or pulmonary failure

Pulmonary edema

Severe acid-base imbalance

Deterioration in condition

Serum salicylate concentration \geq 100 mg/dL after acute ingestion

Serum salicylate concentration \geq 40 mg/dL after chronic ingestion

Activated Charcoal

Although activated charcoal (AC), in a single dose or multiple doses, somewhat reduces salicylate absorption and has been recommended in the past, there is no evidence of outcome benefit. Whereas there is no evidence that AC in general decreases toxicity or alters therapy or course of the illness, this has not been specifically examined for salicylates.¹² In chronic salicylate poisoning, because the presentation is long after absorption, AC would not be expected to be of any benefit.

Intravenous Fluids

Dehydration occurs early in salicylate intoxication because of the hypermetabolic state and should be treated with intravenous fluid. Potassium depletion must be corrected. Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr and should not exceed the estimated replacement because overly excessive fluid administration can worsen cerebral and pulmonary edema. Intravenous fluid should contain dextrose, and the serum glucose level should be frequently monitored to prevent hypoglycemia. In animal studies, hypoglycemia consistently occurs with death.

Urine Alkalinization

Because salicylates have a low pK_a and are renally excreted, alkaline urine traps the salicylate ion and increases excretion. Urine alkalinization is advisable in patients with salicylate levels greater than 35 mg/dL, significant acid-base disturbance, or increasing salicylate levels. A urine pH of 7.5 to 8.0 is necessary to increase excretion. Sodium bicarbonate (1-2 mEq/kg) can be administered during 1 to 2 hours, with subsequent dosage adjustment determined by urine and serum pH.

Urine alkalinization is difficult to achieve because the excretion of salicylic acid in the urine decreases urine pH. In addition, potassium depletion must be corrected to attain an alkaline urine. Alkaline urine should not be produced at the cost of systemic alkalemia. Forced diuresis does not significantly increase salicylate excretion and may potentiate cerebral and pulmonary edema. Salicylate clearance varies in direct proportion to flow rate but increases exponentially with pH.¹³

Hemodialysis

Hemodialysis is indicated for patients with the following: serum salicylate levels greater than 100 mg/dL in acute and 50 mg/dL in chronic salicylate poisoning; altered mental status, including coma; seizure; endotracheal intubation other than for coagulants; renal or hepatic failure; pulmonary edema; severe acid-base imbalance; rapidly rising serum salicylate level; and failure to respond to more conservative treatment. Exchange transfusion can be considered in young infants or unusual cases of congenital salicylism.¹⁴

Pregnancy

Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning. Salicylate poisoning during pregnancy is associated with fetal demise, and delivery of the distressed fetus should be considered if the fetus is viable.¹⁵

Disposition

In patients with acute intoxication, hospital admission is required for pulmonary edema, CNS symptoms (other than tinnitus), seizures, acidosis, electrolyte disorders, dehydration, renal insufficiency, or increasing serum levels during serial testing. In patients with chronic intoxication, remarkably low serum salicylate concentrations may accompany severe salicylism. Any indication of infant salicylism requires hospital admission. The mortality rate for chronic salicylate intoxication is 25%, compared with a mortality rate of 1% after acute salicylate intoxication.

In patients with acute ingestion, repeated serum salicylate measurement is essential to determine that the serum concentration is decreasing before the patient is discharged. With any case of intentional overdose, psychiatric evaluation is essential.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**Perspective**

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of agents with variable analgesic, anti-inflammatory, and antipyretic activities. They are usually classified according to chemical structure, although classification based on cyclooxygenase (COX) selectivity may be more clinically relevant. NSAIDs are widely prescribed for a variety of conditions. Ibuprofen and naproxen are available in over-the-counter and prescription strengths.

Principles of Disease**Physiology**

The therapeutic anti-inflammatory effect of the NSAIDs is achieved by inhibition of COX and consequent blockade of prostaglandin production. Of the two discrete COX isoenzymes, COX-1, the constitutive enzyme, is concentrated in platelets, vascular endothelial cells, gastric mucosal cells, and renal collecting tubules. It is a physiologic maintenance enzyme, producing the prostaglandins critical for the autocrine-paracrine responses to circulating hormones and the maintenance of normal renal function, gastric mucosal integrity, and hemostasis. COX-2, the inducible enzyme, is expressed only in response to certain inflammatory stimuli. The benefits of NSAIDs are believed to result from COX-2 inhibition, whereas the principal gastrointestinal and renal adverse effects are attributed to inhibition of COX-1.

Traditional NSAIDs are nonselective and inhibit both COX-1 and COX-2. Newer, specific COX-2 inhibitors (e.g., celecoxib, rofecoxib, parecoxib, meloxicam) have fewer side effects than traditional NSAIDs while maintaining analgesic and anti-inflammatory efficacy. However, COX-2 inhibitors permit unopposed thromboxane A₂ production by platelets, thereby potentiating platelet aggregation, thrombosis, and vasoconstriction.¹⁶ Therapeutic use of rofecoxib, particularly at higher doses, was associated with increased risk of myocardial infarction and stroke, and it has subsequently been withdrawn from the market.^{17,18}

Pharmacokinetics

The NSAIDs are almost completely absorbed from the upper small intestine after oral administration. The presence of food may alter the site and timing of drug uptake. As weak organic acids (pK_a, 4-5), NSAIDs are largely nonionized in the stomach and readily diffuse across the bipolar layer lipid membrane of gastric lining cells. Once it is intracellular, the drug can become ionized again at the relatively high pH of normal cytoplasm and become trapped within the mucosal cell. This relatively high local concentration of drug contributes to the frequent gastrointestinal symptoms associated with NSAIDs.

The NSAIDs are highly bound to plasma proteins, mainly albumin, and therefore have small volumes of distribution (0.10-0.17 L/kg). They are eliminated by hepatic biotransformation, principally oxidation and glucuronidation, with the metabolites being excreted in the urine. Metabolites are inactive, except for those of sulindac, nabumetone (inactive parent drugs metabolized to active agent *in vivo*), and phenylbutazone. Plasma half-lives are short (1-4 hours), except for naproxen (12-15 hours), oxaprozin (25-50 hours), piroxicam (45 hours), and phenylbutazone (50-100 hours). Elimination half-lives are not substantially prolonged in overdose.¹⁹

Clinical Features

Most NSAID overdoses, even with large amounts, are asymptomatic or cause only minor CNS or gastrointestinal disturbances. Significant toxicity has not been reported after overdose of the newer COX-2 inhibitors. Of all isolated celecoxib exposures reported to the Texas poison control centers during a 5-year period, no more than minor effects were reported and then in only 12% of cases.²⁰

Ibuprofen is the most common NSAID ingested in overdose and is representative of the propionic acid derivatives. Despite rare case reports of coma, seizure, hypotension, hypothermia, upper gastrointestinal tract bleeding, acute renal failure, and metabolic acidosis, most ibuprofen overdoses follow a benign, rapidly self-limited course. About 50% of adults and 7% of children have symptoms. Symptomatic overdose occurs only after ingestion of at least 100 mg/kg, and all those who develop symptoms do so within 4 hours of ingestion. Life-threatening symptoms or signs are rare, and most toxicity is a mild gastrointestinal or CNS disturbance that resolves in 24 hours.²¹⁻²⁵ Less common clinical effects include mild metabolic acidosis, muscle fasciculations, mydriasis, chills, diaphoresis, hyperventilation, mildly elevated systolic blood pressure, asymptomatic bradycardia, hypotension, dyspnea, tinnitus, and rash.

Renal dysfunction is seen only after massive acute overdose and in association with a period of relative hypovolemia with hypotension.²¹⁻²⁶ It is reversible and usually responds to supportive measures, but rare deaths have been reported.²⁷ Serum ibuprofen concentrations do not predict toxicity.²¹

Overdose with mefenamic acid, a fenamate, is associated with a relatively high incidence of seizures, which occur 2 to 7 hours

after ingestion.²⁸ Rapid recovery is the rule with supportive care and intravenous benzodiazepines. Serum mefenamic acid concentrations correlate with seizures but do not aid in acute management.

Phenylbutazone, a pyrazolone, is now rarely used because of its association with aplastic anemia and agranulocytosis. Although phenylbutazone overdose is rare, it is much more severe than overdose with other NSAIDs.²⁹ Mild poisoning consists of nausea, abdominal pain, and drowsiness. Severely poisoned patients have early onset of abdominal pain, nausea, vomiting, hematemesis, diarrhea, restlessness, dizziness, coma, convulsions, hyperpyrexia, electrolyte disturbances, hyperventilation, alkalosis or acidosis, respiratory arrest, hypotension, cyanosis, edema, electrocardiographic abnormalities, or cardiac arrest. Late sequelae of severe poisoning (2-7 days) include renal, hepatic, and hematologic dysfunction.^{29,30} The clinical course is prolonged compared with that of other NSAID poisoning, reflecting the prolonged elimination half-lives of phenylbutazone and its principal metabolite, oxyphenbutazone.³⁰

Diagnostic Strategies

The diagnosis and assessment of severity and risk are based on history and clinical features. Plasma NSAID concentrations are not useful, but screening for unsuspected acetaminophen should be done. Serum electrolyte levels, renal and hepatic function tests, serum salicylate level, urinalysis, and chest radiograph are usually not necessary but should be undertaken as indicated by specific clinical concerns.

Management

The management of NSAID overdose is supportive, and there is no specific antidote. Pyrazolone (e.g., phenylbutazone) and fenamate (e.g., mefenamic acid) overdoses are associated with significantly higher morbidity and may require more aggressive supportive care measures, including control of seizures, fluid resuscitation, correction of electrolyte disturbances, and ventilatory support.

Children with ingestions of less than 100 mg/kg of ibuprofen do not require medical evaluation. Those who ingest more than 300 mg/kg should be evaluated. With ingestion of 100 to 300 mg/kg, children need treatment only if symptoms develop. All patients with pyrazolone and fenamate ingestions should be evaluated in the emergency department. For other agents, home observation is adequate unless the amount ingested is more than five times the maximum daily therapeutic dose, the patient is symptomatic, or a suicide attempt is suggested.

There is no evidence supporting the use of gastric emptying or AC for NSAID overdose. All patients with nontrivial overdoses should be observed until 4 hours after ingestion and until symptoms are noted to be mild or improving. Hypotension, if it occurs, is managed with intravenous crystalloid solution. Although it is rarely indicated and not studied, extracorporeal membrane oxygenation has successfully managed refractory hypotension after massive ibuprofen overdose.³⁰

Because of high protein binding and rapid metabolism, urine alkalization, hemodialysis, or hemoperfusion is not clinically useful. Enhanced elimination with plasmapheresis has been attempted in severe phenylbutazone poisoning.³¹

Disposition

Patients who are only mildly symptomatic or asymptomatic for more than 4 hours after an NSAID overdose do not require further medical care. Patients who have ingested a pyrazolone or fenamate require longer observation for possible seizures and admission to

the emergency department observation unit until 8 hours after ingestion. Patients who have CNS symptoms, acidosis, or renal insufficiency and who require supportive care should be admitted to the hospital or an emergency department observation unit for ongoing medical treatment. Patients with only gastrointestinal or neurologic symptoms may be observed in the emergency department until they are asymptomatic or improving. Patients for whom the ingestion represents a suicidal gesture should undergo psychiatric assessment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

KEY CONCEPTS

- ASA intoxication, especially chronic salicylism, should be considered in the differential diagnosis of altered mental status in the elderly.
- Potassium stores are rapidly depleted in patients with salicylate intoxication.
- The acute toxic dose of ASA is 300 mg/kg, and 500 mg/kg is potentially lethal.
- Acidosis signifies severe salicylism as unbound salicylate is moving into the cell.
- Signs of pulmonary or cerebral edema, coma, seizures, hepatic failure, renal failure, circulatory collapse, and refractory acidosis or acute levels greater than 100 mg/dL and chronic levels of 40 mg/dL require immediate hemodialysis.
- Hyperthermia, altered mental status, coma, pulmonary edema, and shock may be presenting signs of salicylism.
- Serial salicylate concentrations should be obtained after acute ingestion until the salicylate concentration is decreasing.
- NSAID overdose, other than ASA, is usually self-limited, with predominantly gastrointestinal toxicity, except for pyrazolones and fenamates, which can cause seizures.

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