TREATMENT GUIDELINES FOR SALICYLATE POISONING

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INCIDENCE AND SEVERITY

OTC analgesic medications are the most commonly involved agents in accidental and intential drug overdoses.

OTC Analgesic Exposures	64% acetaminophen 19% ibuprofen 17% aspirin
OTC Analgesic Fatalities	62% aspirin 34% acetaminophen 04% ibuprofen

AVAILABLE FORMS

A. ANALGESICS

- Aspirin (acetylsalicylic acid; ASA) is the most common agent associated with salicylic acid poisoning.
- Be aware that aspirin may still be found in a number of combination drug preparations.

B. TOPICAL PREPARATIONS

- Methylsalicylate (Oil of Wintergreen; common ingredient in topical analgesic balms such as Ben Gay (10-15%)) is the most dangerous salicylate formulation by strength, but it is an infrequent cause of death.
- One teaspoonful of Oil of Wintergreen contains 7000 mg salicylate which is also equivalent to 21 x 325 mg aspirin tablets.
- Methylsalicylate is topically absorbed, therefore extensive percutaneous application may lead to toxic serum salicylate levels.

C. BISMUTH SUBSALICYLATE (Pepto Bismol_)

- 1 ml of Pepto Bismol_ is equivalent to 8.77 mg of salicylic acid
- 60 ml of Pepto Bismol_ is equivalent to a therapeutic dose (650 mg) of aspirin.

ESTIMATE OF ACUTE TOXICITY

INGESTED DOSE (mg/kg)	ESTIMATED TOXICITY
< 150	No toxic reaction expected
150-300	Mild to moderate toxic reaction
300-500	Serious toxic reaction
> 500	Potentially lethal toxic reaction

Adapted from Ellenhorn:

ESTIMATE OF CHRONIC TOXICITY

- Risk for developing chronic salicylate toxicity is highly patient specific, although ingestions exceeding 100 mg/kg/day for two or more days have been a consistant finding in cases involving chronic salicylism.

- Chronic salicylate poisoning is one of the most often misdiagnosed tox related disorders. This is especially true in cases involving elderly patients where an accurate medication history or toxicology laboratory testing is not obtained. These patients often simply present with nausea/vomiting, confusion, and disorientation which later progress to mixed electrolyte, acid/base, and pulmonary disorders. One of the key initial indicators that should prompt the clinician to include salicylate intoxication on the differential diagnosis is the presence of an unexplained anion gap.

PHARMACOKINETICS

A. ABSORPTION
   - Rapid absorption, therefore the rate limitng factor is the rate of dissolution.
   - The acid media of the stomach renders ASA poorly soluble. Precipitates may coalesce to form concretions (bezoars) in cases involving large ingestions. These concretions will delay absorption, and thus toxicity 8 to 24 hours!! Continued absorption from the concretion can occur for hours or days, essentially mimicking a sustained release phenomena. **It is imperative that the peak and subsequent decline in salicylate concentrations be verified by obtaining serial salicylate levels.**

B. DISTRIBUTION
   1.) Concentration dependant protein binding (50 to 80% with therapeutic serum concentrations)

2.) Saturation of binding sites or a decrease in binding sites (e.g. cirrhosis, hypoalbuminemia, competitive drugs) produces greater tissue distribution of free salicylate and increased toxicity.

3.) Peak concentration occurs 2 hours post-ingestion of therapeutic doses; peak concentrations following an overdose is highly variable and patient dependent (see discussion under absorption).

4.) Vd = 0.1 to 0.3 L/kg; dependent on protein binding and physiologic pH. Acidosis increases Vd because of enhanced tissue penetration by unionized salicylic acid in a more acidic environment.

5.) The biologic half-life of Acetyl Salicylic Acid (ASA) is only 20 minutes since both the stomach and blood rapidly hydrolyze ASA to the pharmacologically active form, salicylic acid. The t1/2 of salicylic acid is normally about 2-4.5 hrs but as long as 18-36 hours after overdose.

C. ELIMINATION

Factors Affecting Salicylate elimination

1.) **Dose and urine pH:** Salicylate elimination at therapeutic concentrations consists of predominantly of first-order hepatic elimination with only 10-20% of salicylate eliminated unchanged in the urine. In an overdose situation where metabolic pathways become saturated (zero order kinetic saturation), urinary excretion of free salicylate becomes even more significant, accounting for 60-85% of total elimination if an alkaline urine (pH>7.0) is established.

"Ion Trapping" theory:

- Salicylate is a weak acid (pKa 3.0). therefore an alkaline urine (pH > 7.0) favors the existence of ionized salicylate molecules in the urine. Both ionized and unionized salicylate molecules are filtered by the glomerulus, but only the unionized salicylate can be reabsorbed. By creating an alkaline environment favoring > 99% ionized salicylate molecules in the urine, the ionized salicylate in the renal tubules may be "trapped" preventing salicylate reabsorption.

"Diffusion Theory"

** Some argue that limiting reabsorption of the ionizable fraction of filtered salicylate cannot be the primary mechanism responsible for enhanced elimination produced by sodium bicarbonate.

- Since the quantitative difference between the percentage of molecules trapped in the ionized between a pH of 5.0 (99% ionized) and a pH of 8.0 (99.999%) is small, decreases in tubular reabsorption cannot fully explain the rapid increase in urinary elimination seen above a pH of 7.0.

** Based on Fick's Law of Diffusion: The rate of flow of a diffusing substance is proportional to its concentration gradient.

- A concentration gradient between the unionized salicylate in the peritubular fluid (and blood) and the tubular luminal fluid is found in an alkaline urine. Since at higher urinary pH a greater proportion of secreted unionized molecules quickly become ionized upon entering the alkaline environment, more salicylate (ie, unionized salicylate) must pass the peritubular fluid into the urine in an attempt to reach equilibrium with the unionized fraction. Hence, predominantly increased tubular secretion, not decreased tubular reabsorption may account for the increase in salicylate elimination observed in the alkaline urine.

2.) **Potassium**

- Increased potassium excretion as well as systemic acidosis in salicylate overdose leads to hypokalemia.

- Hypokalemia can make urinary alkalinization difficult to achieve, thereby reducing renal salicylate excretion. In the hypokalemic patient, the kidneys will preferentially reabsorb potassium in exchange for hydrogen ions. Thus, replacement of potassium is essential.

3.) **Liver and Kidney Function**

Patients with compromised liver and/or renal excretion are at risk of greater toxicity from a given dose. Additionally, these patients may be more susceptible to chronic salicylism.

PATHOPHYSIOLOGY

A. CENTRAL NERVOUS SYSTEM

1.) Increased central respiratory drive;

- Mechanism of action is unclear. The most likely explanation may be the direct stimulation of medullary regulatory activity by salicylic acid.
- Hyperventilation predominates early in the course of salicylate toxicity resulting in respiratory alkalosis, decreased ionized calcium, and compensatory renal excretion of potassium, sodium, and bicarbonate.

2.) Seizures and coma

<u>etiology:</u>

- As glucose utilization increases, a decrease in brain glucose concentrations may occur producing a relative CNS hypoglycemia despite normal blood glucose concentrations.
- Cerebral edema by an, as yet unexplained mechanism
- Metabolic acidosis

B. METABOLIC

- ***Uncoupling of oxidative phosphorylation*** leads to a disruption in cellular metabolism due to the interference of the Kreb's cycle and impaired carbohydrate and lipid metabolism. ***Substrates are metabolized but the energy produced is dissipated as <u>heat</u> instead of being used to produce adenosine triphosphate (ATP).*** The basal metabolic rate increases, placing increased demands on the cardiorespiratory system. Excess lactic acid results from nonmitochondrial ATP production.

<u>Disrupted cellular metabolism produces:</u>

1. Increased oxygen consumption; compensatory increase in heart rate. (**tachycardia**)
2. Increased CO2 production due to abnormal cellular respiration. (**hypercapnea**)
3. Increased heat production (**hyperthermia**)
4. Patient's commonly present with hyperglycemia but increased glucose utilization, impaired glucose production, and eventually reduced tissue glucose concentrations may lead to (**hypoglycemia**)
5. Increased production of organic acids (**metabolic acidosis**)

C. PULMONARY

1. **Noncardiogenic pulmonary edema**
   - Mechanism of action is unclear, but the most favored postulated mechanism proposes a direct toxic effect of salicylates on pulmonary endothelium producing an extravasation of fluids.

D. HEMATOLOGIC

1. Therapeutic Use: inhibits prothrombin synthesis and platelet aggregation.

2. Overdose:
   - Decreased prothrombin formation
   - Decreased factor VII production
   - Increased capillary fragility

- Decreased platelet adhesiveness

CLINICAL MANIFESTATIONS

A. GASTROINTESTINAL

1.) Nausea, vomiting, epigastric pain usually occur early following an acute ingestion. Hematemesis is an infrequent clinical finding. Rare reports of gastric perforation following massive asprin overdose exist.

2.) Many clinicians may opt to prescribe an H2 antagonist when managing an acute salicylate overdose with the hope of preventing gastrointestinal erosions. The use of H2 blockers, however, has not been shown to alter patient morbidity or mortality in cases of acute salicylate intoxication. Critically ill patients who develop severe metabolic acidosis and shock secondary to salicyate intoxication still require stress ulcer prophylaxis.

B. METABOLIC ABNORMALITIES

1. Hyperthermia
   - Significant hyperthermia requiring cooling blankets and ice-water lavage is a possibility
   - Increased production, accumulation, and excretion of organic acids.

2. Acid-base disturbances (respiratory alkalosis, metabolic acidosis)
   - **Anion-gap acidosis is a significant finding**
   - Increased production, accumulation, and excretion of organic acids.

3. Dehydration (tachycardia, orthostatic pressure changes)

4. Electrolyte imbalance (hypokalemia)

5. Altered glucose levels (blood glucose concentrations may be elevated, normal, or low; CNS glucose concetrations may be low despite normal or even high blood glucose concentrations, thus contributing to cerebral dysfunction)

C. CENTRAL NERVOUS SYSTEM

Mild: Nausea, vomiting, tinnitus, Kussmaul respirations, lethargy.

Moderate: Irritability, disorientation

Serious: Asterixis, hallucinations, seizures, and coma.

- Presence of seizures indicates a serious prognosis that may be attributed to an electrolyte and/or metabolic disorder in addition to direct salicylate induced toxicity.

- Key clinical manifestations of **chronic salicyalte intoxication** are confusion, bizarre behavior, stupor, movement disorders, papilledema, and cerebral edema.

D. RESPIRATORY

1. Noncardiogenic pulmonary edema

   Risk Factors:
   - Age > 40 years
   - Smoking
   - chronic salicylate ingestion
   - metabolic acidosis
   - Neurologic symptoms
   - Salicylate levels > 55 - 60 mg/dl

2. Tachypnea, hyperpnea secondary to the stimulation of CNS dependent processes controlling respiration.

E. CARDIOVASCULAR

- **SHOCK!!**

DIFFERENTIAL DIAGNOSIS

A. Encephalopathy secondary to Reye's Syndrome

B. Encephalopathy secondary to unknown etiology

C. Cardiopulmonary disease

D. Ethanol withdrawal

E. Metabolic acidosis of unknown etiology

F. Miscellaneous psychosis

MANAGEMENT

A. EMERGENCY AND SUPPORTIVE MEASURES: Maintain airway and assist ventilation if necessary. Administer supplemental oxygen and establish intravenous access.

B. PREVENTION OF ABSORPTION

1.) **Prehopsital:** Syrup of Ipecac (SOI) induced emesis may be useful for initial treatment of children at home if it can be given within minutes of ingestion. SOI use is declining secondary to lack of demonstrable benefit in the majority of cases. Its' use for patients with Salicylate intoxication should be made on a case by case basis.

2.) Hospital:

a.) Gastric lavage is the preferred route of stomach evacuation. Patients may require gastric lavage **up to four or more hours post-ingestion!**. The Minnesota Regional Poison Center was recently consulted on a case where gastric lavage attempted 10 hours post-ingestion resulted in significant returns of aspirin tablets.

- Lavage with a large bore orogastric tube (30-40 French for Adults; 16-26 French for children) utilizing warm water and an epigastric massage to break up aspirin concretions if present. A minimum of 2 liters should be administered. It is not uncommon for stomach evacuations to require 10 liters in order to achieve clear lavage returns.

b.) Following gastric lavage, **administer activated charcoal (AC) and cathartic**

- **adult = 50-100 gm AC in a 70% sorbitol slurry (Actidose_)**
- **pediatric = 1-2 gm/kg AC in a 70% sorbitol slurry (Actidose_)**
- Ideally, a 10:1 ratio of activated charcoal to ingested aspirin is needed to theoretically bind all the salicylate and prevent absorption. This may require that AC be given in 25-50 gm doses every 3 to 5 hours until the serum salicylate levels begin to significantely decline. If multiple-dose activated charcoal is used, it is important to insure that patient is maintaining active gut motility. Multiple dose charcoal places the patient at risk for developing a charcoal-induced bowel obstruction.

C. LABORATORY

1.) Electrolytes (calculation of an anion gap)

2.) Arterial blood gases (may require frequent determinations)

3.) Glucose

4.) CBC

5.) PT/PTT

6.) BUN/Creatinine

7.) Chest x-ray if evidence of pulmonary complications.

8.) **ASPIRIN SERUM CONCENTRATIONS**

a.) Obtain stat serum salicylate concentrations **upon presentation** and then obtain serial concentrations until you can verify that salicylate concentrations are clearly falling. Peak salicylate concentrations may not be achieved for 12 or more hours post-ingestion.

b.) Levels drawn > 6 hours post-ingestion may be plotted on the Done nomogram to estimate expected toxicity in patients with single acute ingestions. It is imperative that more than one salicylate level be obtained because of the possibility of prolonged or delayed absorption from sustained-release preparations or a aspirin bezoar. **It is important to note that many toxicologists have abandoned dependence on the Done nomogram to determine toxicity due to the unpredictable pharmocokinetic and pharmacodynamic properties of ASA in the settings of a drug overdose. The nomogram has limited, if no utility in chronic intoxications.**

c.) Be aware that despite relativley low serum salicylate concentrations, sytemic acidosis increases brain concentrations of unionized salicylic acid, worsening toxicity. During long-term aspirin intoxication, progressive neurologic deterioration may occur at the same time that alkalinization has produced a rapidly declining serum concentration of salicylate. This deterioration may result from the "trapping" of salicylate in the CNS and subsequent CNS hypoglycemia.

d.) Chronic salicylate intoxication correlates poorly with serum salicylate concentrations and the Done nomogram should not be used in such cases. A salicylate level > 55-60 mg/dl accompanied by an anion gap acidosis and significant neurologic findings is considered extremely serious in chronic .

D. FLUID AND ELECTROLYTES

1.) Initial hydration

a.) Replacement with intravenous crystalloid solutions. Fluid and electrolyte deficits may be significant due to vomiting and hyperventilation. Optimal

hydration is of paramount importance in the treatment of salicylate intoxication. Although aggressive fluid therapy is advocated, clinicians must use caution because excessive fluid administration may contribute to pulmonary edema.

- **If clinical s/sx of dehydration, rehydrate woth 10-15 ml/kg/hour x 2 hours or until a brisk urine output of 2-3 ml/kg/hour is obtained. Patients with clinical evidence of potentially severe salicylate intoxication will require a Foley catheter to monitor urine output as well as urine pH.**

- **Maintenance fluids of 2-4 ml/kg/hour. Potassium replacement as necessary (see below).**

- **Administer glucose-containing intravenous fluids, and give concentrated glucose bolus if patient is hypoglycemic.** Some clinicians favor administering concentrated glucose boluses to those patients exhibiting significant neurologic sequelae despite normal blood glucose concentrations.

b.) Sodium bicarbonate is frequently required to prevent acidemia and promote salicylate elimination by the kidneys. **To correct metabolic acidosis caused by salicylate intoxication, administer 0.5-1.0 mEq/kg IV bolus; repeat as need to maintain a blood pH of 7.4 to 7.5.**

c.) Patients who develop hemodynamic compromise and shock will obviously require more aggressive supportive measures.

E. TEMPERATURE CONTROL

1.) Begin external cooling with tepid sponging and fanning. Note that shivering may occur with rapid external cooling, thus generating more heat.

2.) Iced gastric or colonic lavage or even ice-water immersion may lower core temperature.

3.) Rapidly gain control of seizures and agitation.

4.) Extreme cases of hyperthermia may require neuromuscular paralysis provided adequate mechanical ventilation is established as well as EEG monitoring for seizure activity. There may also be a theoretical consideration for the use of Dantrolene although there is no data one way or the other.

F. ENHANCED ELIMINATION

1.) Urinary alkalinization is effective in enhancing urinary excretion of salicylate, although often difficult to achieve in dehydrated or critically ill patients.

a.) Add 100 mEq of sodium bicarbonate to 1 L of D5-1/2 NS, and infuse intravenously at 200 ml/hour (3-4 ml/kg/hour). If the patient is dehydrated, start with a bolus of 10-20 ml/kg. Fluid and bicarbonate administration is potentially dangerous in patients at high risk for pulmonary edema (eg. chronic intoxication).

b.) Unless renal failure is present, add potassium, 30-40 mEq, to each liter of intravenous fluids (potassium depletion inhibits alkalinization).

c.) Alkalemia is not a contraindication to bicarbonate therapy, considering that patients often have a significant base deficit in spite of the elevated blood pH.

2.) Hemodialysis is the most effective means of removing salicylate from the body. Hemodialysis is also effective in correcting acid-base and fluid abnormalities caused by salicylate intoxication.

Indications:

a.) Patients with acute ingestion and serum levels higher than 120 mg/dl, and/or with severe acidosis and other manifestations of intoxication.

b.) Patients with chronic intoxication with serum levels higher than 60 mg/dl accompanied by acidosis, confusion, or lethargy, especially if the patient is elderly or debilitated.

c.) Any patient with severe manifestations of salicylate intoxication.

3.) Hemoperfusion is also very effective but does not correct acid-base or fluid disturbances.

4.) Multiple-dose activated charcoal (25 to 50 gm AC every 3 to 5 hours) therapy effectively reduces the serum salicylate half-life (principle of gastrointestinal dialysis), but it is not as effective as hemodialysis. Frequent stooling may contribute to dehydration and electrolyte disturbances. Multiple-dose activated charcoal therapy also places the patient at risk for developing bowel obstruction or charcoal ileus. Cathartics should be used judiciously and may be given with every second or third dose of activated charcoal.