CHAPTER 35

Salicylates

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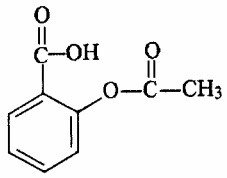
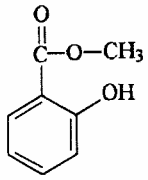


Acetylsalicylic acid



Methylsalicylic acid

Salicylic Acid

MW	=	138 daltons
Therapeutic serum level	=	15–30 mg/dL
	=	1.1–2.2 mmol/L

Case

A 22-year-old woman came to the emergency department complaining of abdominal pain, nausea, and vomiting. She had a history of depression but stated that she currently was not being treated by a psychiatrist or taking any psychiatric medications. Upon further questioning, the patient said that 6 hours earlier she had been severely depressed and had ingested at least half a bottle of aspirin tablets in a suicide attempt, after which she vomited once. She denied tinnitus but said that she was short of breath. She denied significant past medical or surgical problems.

On physical examination, the patient appeared to be well developed, well nourished, and diaphoretic. Vital signs were: blood pressure, 120/60 mm Hg; pulse, 110 beats/min; respiratory rate, 30 breaths/min; rectal temperature, 100.2°F (37.9°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. The neck was supple, and there was no jugular venous distension. The chest was clear to auscultation and percussion. Cardiac examination revealed normal heart sounds and no murmurs, rubs, or gallops. Bowel sounds were normal, but the abdomen was diffusely tender, without guarding; stools were negative for occult blood. There was no clubbing, cyanosis, or edema. The patient was alert and fully oriented. No cranial nerve abnormalities were noted; deep tendon reflexes were intact and symmetric with plantar flexion of the toes; motor and sensory testing was normal.

An intravenous catheter was inserted. Blood was drawn and sent for determination of blood urea nitrogen (BUN), glucose, and electrolyte concentrations, complete blood count, coagulation studies, and salicylate and acetaminophen concentrations. Cardiac monitoring was instituted, and an arterial blood gas (ABG) specimen was obtained from the patient prior to administering supplemental oxygen. A Foley catheter was inserted, and a bedside ferric chloride test of the urine was positive. With the patient in the left lateral decubitus position, orogastric lavage was performed using a 40-French lavage tube. After food and particulate matter were recovered and a total of 2 L of fluid instilled and removed, the lavage fluid was clear. Sixty grams of activated charcoal in a slurry of water and 60 g sorbitol were administered next, after which the lavage tube was removed.

The initial laboratory data revealed urine pH 5.5; specific gravity 1.025; 1+ protein; 2+ ketones; no red blood cells or white blood cells. ABG values on room air were: pH 7.51; PCO_2 11 mm Hg; PO_2 134 mm Hg. Serum electrolytes were Na^+ 144 mEq/L; K^+ 3.8 mEq/L; HCO_3^- 8 mEq/L; Cl^- 98 mEq/L; BUN 23 mg/dL; creatinine 0.9 mg/dL; glucose 88 mg/dL; calcium 9.6 mg/dL. Urine pregnancy test was negative.

A bolus of 88 mEq sodium bicarbonate was administered, and a bicarbonate drip consisting of 132 mEq sodium bicarbonate in 1 L of 5% dextrose in water (D_5W) was started at a rate of 250 mL/h. Potassium replacement was initiated.

After 2.5 hours, the patient's pulse had increased to 140 beats/min, and her blood pressure had dropped to 106/64 mm Hg. Although the salicylate concentration was not yet available, a nephrology consultation was requested. Fluid rates were increased, and a second dose of activated charcoal was administered. A repeat ABG determination revealed pH 7.48; PCO_2 13.9 mm Hg; PO_2 116 mm Hg.

Approximately 1 hour later (4 hours after presentation), a third ABG analysis on room air revealed pH 7.44; PCO_2 14 mm Hg; PO_2

93 mm Hg. At this time, the initial salicylate concentration was reported to be 107 mg/dL, and the acetaminophen concentration was negative. Arrangements for hemodialysis were made. Another ABG determination on room air 30 minutes later revealed pH 7.37; PCO_2 24 mm Hg; PO_2 64 mm Hg. At this time, rales could be auscultated at both bases. The bicarbonate infusion was reduced to 125 mL/h, and a third dose of activated charcoal was administered.

The patient became agitated shortly thereafter. A fifth ABG determination on 4 L nasal O_2 revealed pH 7.20; PCO_2 46 mm Hg; PO_2 92 mm Hg. ABG determination was immediately repeated, and the results were pH 7.10; PCO_2 63 mm Hg; PO_2 80 mm Hg.

Because of her rapidly deteriorating condition, the patient was intubated and hyperventilated, but her systolic blood pressure fell to 80 mm Hg by palpation and did not respond to a fluid bolus of 1 L of 0.9% sodium chloride solution. Postintubation ABG determination revealed pH 6.90; PCO_2 41 mm Hg; PO_2 182 mm Hg. Ventilation was increased, a second bolus of 88 mEq bicarbonate was administered, and an intravenous dopamine infusion was started. Systolic blood pressure was maintained at approximately 100 mm Hg while hemodialysis was started in the medical intensive care unit.

After 4 hours of hemodialysis, the patient's salicylate concentration was 22 mg/dL, and her ABG was pH 7.42; PCO_2 36 mm Hg; PO_2 190 mm Hg. Eight hours following hemodialysis completion, the patient appeared to be significantly improved clinically. A psychiatric consultation was obtained the next day. Three days later the patient was transferred to the psychiatric service from which she was later discharged home. One week after discharge, the patient returned to her job.

EPIDEMIOLOGY

Between 1999 and 2003 the number of analgesic exposures in the United States annually reported by the American Association of Poison Control Centers (AAPCC)/Toxic Exposure Surveillance System (TESS) increased from 214,066 to 269,982. During that same period, the number of analgesic-related deaths increased from 340 to 656 (Chap. 130). Since 2000, "analgesics" has consistently ranked first among both the substances most frequently involved in human exposures and the substances responsible for the largest number of deaths. Of the analgesic-related deaths reported, acetaminophen, alone or in combination, accounts for slightly more than 50%, and aspirin, alone or in combination, accounts for approximately 12.6% (somewhat less than a decade ago). If "aspirin, alone or in combination with other analgesics" were listed as a separate category, it would be the seventh or eighth most common cause of death from toxic exposures recorded by AAPCC/TESS.

Safety packaging, increasing use of nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or other alternatives to aspirin for adults, and use of acetaminophen instead of aspirin for children to avoid Reye syndrome[10,59] have contributed to the decreased incidence of unintentional salicylate poisoning. On the other hand, the historic widespread availability of salicylate preparations without prescription, the increasing confusion regarding specific ingredients suggested by product names and brand names, and the toxicity caused by small increments in salicylate dosage when used chronically make salicylate poisoning a common and sometimes fatal occurrence.[64]

Over the past 2 decades, popular brand and product names previously associated exclusively with salicylates or acetaminophen have been applied to other analgesic-containing products. For example, the names Alka-Seltzer, Anacin, and Excedrin, which once were used exclusively for salicylate-containing products, now are used as brand names for products containing aspirin, acetaminophen, or both. Bayer, a company once associated exclusively with aspirin, now markets, in addition to its aspirin products, a line of products called Bayer Select, which contains ibuprofen or acetaminophen. Clinicians should be aware that parents and healthcare providers seeking to use acetaminophen for children with viral illnesses to avoid Reye syndrome may inadvertently select a product containing aspirin either alone or in combination with acetaminophen, and an overdose in this setting might involve aspirin.[23] Another source of confusion associated with salicylate toxicity concerns correct dosage: Terminology such as grains and milligrams, and "baby," "children's," "junior," and "adult" aspirin are confusing and often misinterpreted. Maximum doses of aspirin should never be based on age range; instead, doses should always be based on body weight.

Unintentional salicylate toxicity may occur in patients who are unaware that fixed-dose cold preparations often contain aspirin and then ingest additional aspirin tablets. Another popular medication, Pepto Bismol, or bismuth subsalicylate, contains 8.7 mg of salicylic acid/mL[38] and travelers using large quantities (200–300 mL) of this antidiarrheal may expose themselves to high doses of salicylates.

Salicylate poisoning, particularly in children but also in adults, may result from the extensive application of salicylate-containing ointments, keratolytic agents, or other agents containing methyl salicylate (oil of wintergreen).[16] Liniments and products used in hot vaporizers contain high concentrations of methyl salicylate (up to 30% in liniments and 100% oil of wintergreen). The intentional or unintentional *ingestion* of such topicals is usually disastrous: approximately 1–2 teaspoons (5–10 mL) of methyl salicylate can be lethal for a young child.[20] In Hong Kong, medicated oils containing methyl salicylate accounted for 48% of acute salicylate poisoning cases treated in one hospital.[20]

Salicylates continue to be used frequently as antipyretics for children in developing countries. In one study in Kenya, 94% of 250 mothers who purchased drugs for a febrile child purchased nonprescription drugs containing salicylates and 21% administered a dose exceeding the recommended maximum daily dose. More than one salicylate preparation was given to 27% of children, of whom 35% received a dose higher than the recommended maximum.[34]

Serious adolescent and adult salicylate poisonings frequently result from suicide attempts. Even in this setting rapid diagnosis and appropriate therapy initiated quickly may reduce mortality. However, overdose management recommendations written and distributed by pharmaceutical companies may contain inadequate, misleading, or dangerous advice for managing salicylate overdoses, as demonstrated by a published report from Canada.[17] Salicylism must be considered in all patients who have neurologic abnormalities, tachypnea, acid–base disorders, and acute lung injury (ALI), particularly in older patients and children and adults who are candidates for chronic iatrogenic salicylate poisoning.

PHARMACOKINETICS OF SALICYLATES

There are 2 types of salicylic acid esters: phenolic esters (eg, aspirin) and carboxylic acid esters, including methyl salicylate, phenyl salicylate, and glycosalicylate.[27] Most of the studies of salicylate metabolism in the literature involve the phenolic ester aspirin or acetylsalicylic acid.[27]

Therapeutic Doses of Aspirin

Ingested salicylates in the form of aspirin tablets are rapidly absorbed from the stomach. The pK_a of aspirin is 3.5, and approximately 50% of salicylates is nonionized in the acid stomach.[27,54,105] Absorption of salicylates may be less efficient in the small bowel because of its higher pH but occurs rapidly there as well because of the large surface area of the small bowel[82] and because the increase in pH increases the solubility of salicylates and dissolution of tablets.[101] The dosage form of salicylates (effervescent, enteric-coated) often influences the absorption rate.[98,102,120] Delayed absorption of enteric-coated aspirin may result from salicylate-induced pylorospasm, pyloric stenosis,[49,102] gastric outlet obstruction,[106] or bezoar formation.[13,98] Protein-binding abnormalities, urine and plasma pH variations, and delayed absorption all influence the maximum salicylate concentrations and the rates of decline.[82,98]

After ingestion of therapeutic doses of immediate-release salicylates, significant plasma concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour.[27] The volume of distribution is 0.2 L/kg, and 80–90% is protein bound. Salicylates are conjugated with glycine and glucuronides in the liver and eliminated by the kidneys. Approximately 10% of salicylates is excreted in the urine as free salicylic acid, 75% as salicyluric acid, 10% as salicylic phenolic glucuronides, 5% as acylglucuronides, and 1% as gentisic acid.[101] More than 30% of ingested salicylate may be eliminated as free salicylic acid in alkaline urine and as little as 2% in acidic urine.[101,116] Free salicylic acid is filtered through the glomerulus, reabsorbed from the proximal tubules, and secreted from the proximal tubules; salicylic acid elimination is dependent on urine pH and serum concentration. Salicylate conjugates (glycine and glucuronides) are filtered and secreted by the proximal tubules; salicylate conjugates are not reabsorbed across renal tubular cells because of poor lipid solubility and the amount eliminated is dependent on glomerular filtration rate and proximal tube secretion but not urine pH.

Neither age nor gender appeared to affect the absorption rate and plasma clearance of an acute 900-mg dose of aspirin,[82] and systemic availability of salicylate appears to be unaffected by aging alone. An increase in the apparent volume of distribution, a decrease in maximum plasma salicylate acid concentration, and a significant decrease in renal salicyluric acid clearance with age were observed in 22 men 30–85 years of age after a 600-mg oral dose of sodium salicylate. Nevertheless, the authors concluded that age alone does not have a major influence on salicylate deposition in healthy adult men.[1]

To achieve an antiinflammatory effect for chronic conditions such as rheumatoid arthritis, salicylates typically have been prescribed in doses of approximately two regular strength (325 mg × 2 = 650 mg) aspirin tablets every 4 hours. The goal of such dosing is to achieve blood salicylate concentrations of 15–30 mg/dL, which is considered the therapeutic range.[73] Concentrations higher than 30 mg/dL are associated with signs and symptoms of toxicity. The Food and Drug Administration Advisory Panel on Internal Analgesic and Antirheumatic Products recommends that the maximum adult maintenance dose of aspirin for a 70-kg person not exceed 3900 mg in 24 hours for more than 10 days. No more than 650 mg should be given every 4 hours, except for the initial dose, which should not exceed 1000 mg.

TOXICOKINETICS

In overdosage, peak serum concentrations may not be reached for 4–6 hours or longer. There is a decrease in protein (albumin) binding from 90% at therapeutic concentrations to less than 75% at toxic concentrations.[2,14,35] The apparent volume of distribution simultaneously increases from 0.2 L/kg at low concentrations to more than 0.3 L/kg (possibly as high as 0.5 L/kg) at higher concentrations.[75,109] Salicylates also have substantially longer apparent half-lives at toxic concentrations than at therapeutic concentrations, varying from 2–4 hours at therapeutic concentrations to as long as 20 hours at toxic concentrations.[29,74] As the concentration of salicylates increase, 2 of the 5 pathways of elimination—those for salicyluric acid and the salicylic phenolic glucuronide—become saturated and exhibit zero-order kinetics. As a result of this saturation, overall salicylate elimination changes from first-order kinetics to zero-order kinetics.[72] Figure 35–1 illustrates the main features of salicylate metabolism. (Pharmacokinetics and toxicokinetics are discussed in Chap. 9). Finally, the pH of salicylic acid offers a unique opportunity to increase elimination by alkalinizing the urine (see "Increasing Salicylate Elimination by Urine Alkalinization—'Ion Trapping'?").

Topical salicylates used as keratolytics or liniments are rarely responsible for salicylate poisoning when used in the intended manner, as absorption through normal skin is very slow.[16] After 30 minutes of contact time, only 1.5–2.0% of a dose is absorbed, and even after 10 hours of contact with methylsalicylate, only 12–20% of the salicylates is systemically absorbed.[16,100] (Fig. 35–1 shows methylsalicylate metabolism). Although heat, occlusive dressings, young age, inflammation, and psoriasis all increase salicylate absorption, the real danger of salicylate toxicity caused by salicylate-containing topicals results from its intentional or unintentional *ingestion*.[21] Methylsalicylate is rapidly absorbed from the gastrointestinal tract and much, but not all, of the ester is rapidly hydrolyzed to free salicylates. Onset of symptoms usually occurs within 2 hours of ingestion.[21] When ingested, 1 mL of 98% methylsalicylate is as potent as 1.4 g of acetylsalicylic acid. In a 10-kg child, the minimum toxic salicylate dose of approximately 150 mg/kg body weight can almost be achieved with 1 mL of oil of wintergreen, which results in 140 mg/kg of salicylates (Chap. 31).

PHARMACOLOGY

The glycoside salicin was extracted from the willow bark and used as an antipyretic beginning in the early 1800s, but acetylsalicylic acid was first synthesized and commercially introduced as aspirin by Bayer in 1899.[101] Aspirin and other salicylates are analgesics, antiinflammatories, and antipyretics, a combination of traits shared by all medications of varying structures known as "nonsteroidal antiinflammatory drugs" (NSAIDs). Most of the beneficial effects of NSAIDs result from their ability to inhibit cyclooxygenase (COX), the enzyme that enables the synthesis of prostaglandins, which in turn mediate inflammation and fever. Independent of their effects on prostaglandins, salicylates and other NSAIDs may also directly inhibit neutrophils, contributing to their antiinflammatory effects. The type of pain for which salicylates and NSAIDs are purportedly most effective in treating is the pain that accompanies inflammation and tissue injury. Such pain is elicited by prostaglandins, which are liberated by bradykinin and cytokines. Fever is also mediated by cytokines such as interleukin (IL)-β, IL-6, α and β interferons, and tumor necrosis factor-α, all of which increase synthesis of prostaglandin E_2.[101]

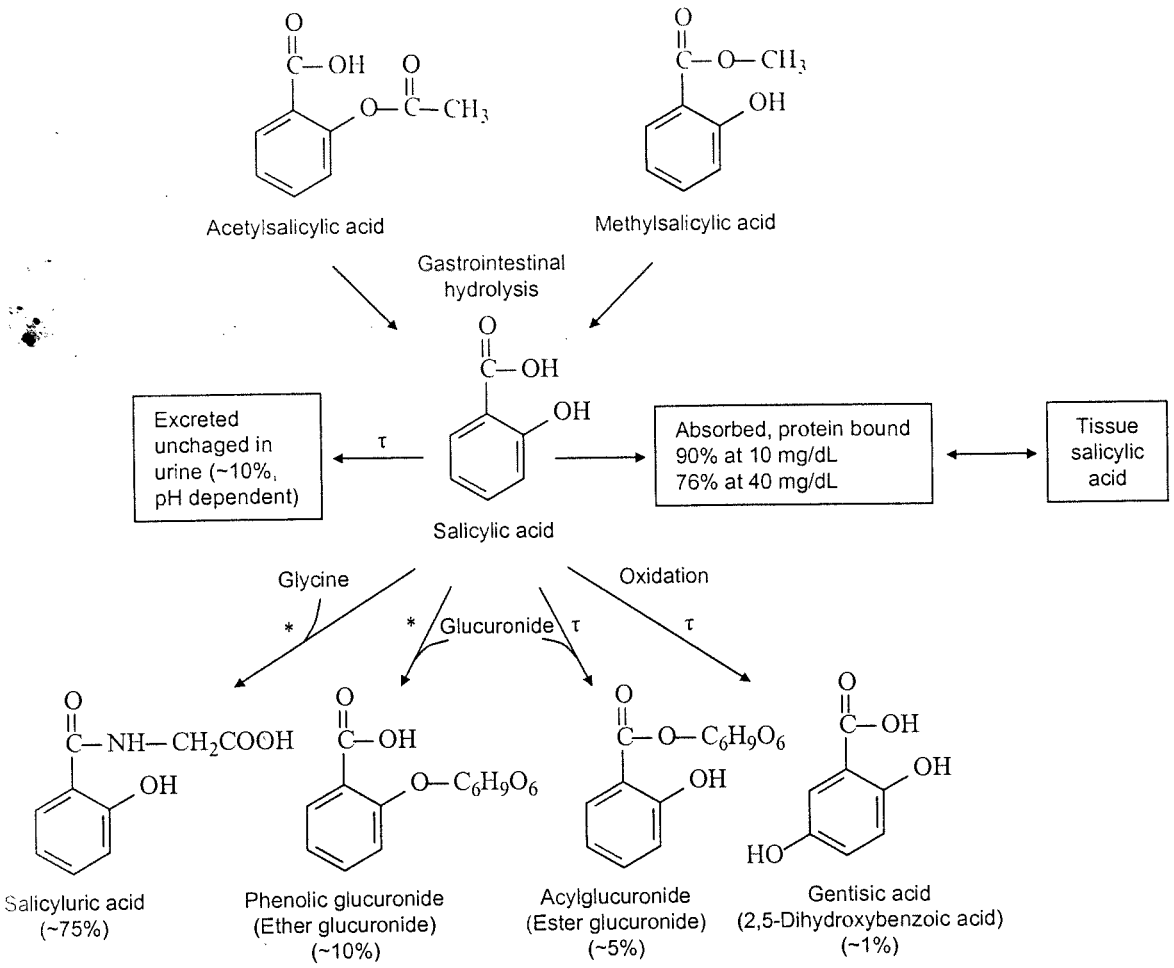


Figure 35–1. Salicylate metabolism. At excessive doses, the d mechanisms of salicylic acid metabolism are overloaded, leading to increased tissue binding, decreased protein binding, and increased excretion of unconjugated salicylic acid. * = Michaelis-Menten kinetics; τ = first-order kinetics.

Because platelets cannot regenerate COX, a daily dose of as little as 40 mg of aspirin inhibits COX for the 8- to 11-day life of the platelet.[101] Frequent aspirin use appears to reduce the incidence of colon cancer, but the reason is not clear.

Adverse effects of aspirin and some NSAIDs include gastrointestinal ulcerations and bleeding, interference with platelet adherence,[99] and a variety of metabolic and organ-specific effects described below in "Gastrointestinal Effects."[101]

PATHOPHYSIOLOGY

Acid–Base Disturbances Caused by Salicylate Poisoning: Differences Between Adult and Pediatric Patterns

Salicylates stimulate the respiratory center in the brainstem, leading to hyperventilation and respiratory alkalosis.[113] In addition, salicylates are weak acids and in toxic concentrations replace 2–3 mEq per liter of plasma bicarbonate. Impaired renal function resulting from salicylate toxicity leads to accumulation of sulfuric and phosphoric acids, both strong acids.[101] Salicylates interfere with the Krebs cycle, which limits production of adenosine triphosphate (ATP),[62] and salicylates uncouple oxidative phosphorylation, which causes accumulation of pyruvic and lactic acids and generates large amounts of heat.[68] Salicylate-induced increased fatty acid metabolism generates ketone bodies: β-hydroxybutyric acid, acetoacetic acid, and acetone. The net result of all of these metabolic processes is a wide anion gap metabolic acidosis (Chaps. 17 and 103). A significant part of this metabolic acidosis is a ketoacidosis.

Although metabolic acidosis begins with the earliest stages of toxicity, a primary respiratory alkalosis predominates initially. At the time an adult patient typically presents to the hospital after a substantial acute salicylate overdose, this mixed respiratory alkalosis and metabolic acidosis is discernible by arterial blood gas (ABG) and serum electrolyte analysis.[45] It is important to understand that the respiratory alkalosis of salicylate poisoning is not merely compensatory for the metabolic acidosis (or vice versa), but that adults acutely poisoned by salicylates characteristically present with 2 primary acid–base disturbances.[45]

By the time children typically present to the hospital after salicylate poisoning, the predominant respiratory alkalosis that initially characterizes *adult* salicylate poisoning may be missed because the metabolic acidosis may already be significant.[46,110] Ultimately, a respiratory acidosis may replace the initial respiratory alkalosis

that is seen so typically early after adult salicylate poisonings. Possible reasons for not seeing a predominant respiratory alkalosis in children are that they may present later, the exposure to salicylates per body weight in children may be much larger, or children do not respond to salicylate poisoning with the same degree of sustained hyperventilation or hyperpnea as do adults. The typical acidotic presentation of a seriously poisoned child led some investigators in the past to incorrectly suggest that pediatric salicylate poisoning produces only a metabolic acidosis. Although some children present with a mixed acid–base disturbance and a normal pH after a significant salicylate ingestion, most such children present with acidemia.[46]

Mixed respiratory alkalosis and metabolic acidosis is found in the majority of adults with serum salicylate concentrations <40 mg/dL[45] and respiratory alkalosis initially predominates. This pattern is so characteristic of adult salicylate poisoning that any salicylate-poisoned adult who presents early with a respiratory *acidosis* almost certainly has either salicylate-induced ALI (formerly called salicylate-induced pulmonary edema [SIPE]), central nervous system (CNS) depression from a mixed overdose, or severe fatigue from the strenuous exercise of hyperventilating for a prolonged period. Mixed xenobiotic overdoses in the adult population are fairly common, as demonstrated by the findings of one study that one third of patients with a presumed primary salicylate overdose had taken other xenobiotics;[45] benzodiazepines, barbiturates, alcohol, and cyclic antidepressants all appear to blunt the centrally induced hyperventilatory response to salicylates, resulting in either an actual respiratory acidosis (PCO_2 >40 mm Hg) or a metabolic acidosis without the appropriate respiratory compensation (PCO_2 <40 mm Hg, but inappropriately high for the concomitant pH). The combination of metabolic *and* respiratory acidosis from salicylate poisoning in an adult resulting in severe and worsening acidemia indicates an exceedingly grave prognosis and almost invariably is a preterminal event.[92]

Glucose Metabolism

Salicylate poisoning appears to produce a discordance between plasma and cerebrospinal fluid (CSF) glucose concentrations. Despite normal plasma glucose, CSF glucose concentration fell 33% in salicylate-poisoned mice compared to controls.[114] In other words, the rate of CSF glucose use exceeded the rate of supply, even in the presence of normal serum glucose concentration. There was also a marked increase in oxygen consumption in mice, even with low salicylate concentrations.[52] A case report of refractory hypoglycemia secondary to poisoning from topical salicylate absorption underscores the problems of glucose metabolism caused by salicylates.[96]

Hepatic Effects

Salicylate-poisoned mice had a marked decrease in glycogen and a dramatic increase in lactate compared to controls[52] as increased glycolysis apparently compensates in part for the uncoupling of oxidative phosphorylation.[80] In humans, the increased metabolic demands resulting from salicylate poisoning stimulate peripheral use of glucose and fat with resultant hypoglycemia and ketosis. Salicylates reduce lipogenesis by blocking the incorporation of acetate into free fatty acids, inhibiting epinephrine-stimulated lipolysis in fat cells and displacing long-chain fatty acids from human plasma proteins. All of these effects lead to increased entry of fatty acids into muscle and liver and to their oxidation inside. As a result, the concentrations of *plasma* free fatty acids, phospholipids, and cholesterol decrease. Ketone body oxidation is increased.[101]

Salicylate-induced hepatitis occurred in children who were being treated with high (average concentration, 30.9 mg/dL) or chronic doses of salicylates for rheumatic fever and juvenile rheumatoid arthritis.[48,76,104]

Another form of liver disease associated with salicylates, also primarily seen in children, is Reye syndrome, which is characterized by nausea, vomiting, hypoglycemia, elevated concentrations of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], fatty infiltration of the liver, and coma following a viral illness, usually influenza or varicella.[7,10] Although the nature of the link between Reye syndrome and salicylates has never been fully elucidated, the existence of such a link is fairly certain. The mean serum salicylate concentration in biopsy-proven Reye syndrome was 12.3 mg/dL, and the mean serum salicylate concentration in patients who died of or survived Reye syndrome with neurologic deficits was 15 mg/dL.[23,87]

Further evidence of a causal relationship between salicylate use for a viral illness and Reye syndrome is suggested by the finding that the incidence of Reye syndrome has fallen steadily concomitantly with the decreased use of salicylates in children.[10,97,117] From December 1980 through November 1991, 1207 cases of Reye syndrome were reported in the United States in patients younger than 18 years, with a peak incidence of 555 cases in 1980. Between 1994 and 1997, no more than 2 cases each year were reported.[10] However, the problem has not completely disappeared, as evidenced by 2 fatal cases reported in 2003.[12,23] In one case, a 3-year-old boy who presented in 1999 with signs of Reye syndrome had an initial salicylate concentration of 3.9 mg/dL.[12] In the case of a 10-year-old girl who presented in 2002, the *reported* amount of aspirin that she had knowingly ingested was two 325-mg tablets, which did not correlate with the serum salicylate concentration of 16 mg/dL obtained on admission to the hospital 3 days later. The discrepancy may have resulted from confusion between brand or product labeling or an inability to accurately determine the contents of the nonprescription medications used.[23]

Neurologic Effects

Toxic doses of salicylates first stimulate and then depress the CNS. Confusion, dizziness, delirium, psychosis, and then ultimately stupor and coma may occur.[101]

Otolaryngologic Effects

The pattern of salicylate-induced auditory sensorineural alterations is different than the pattern characterizing other ototoxic drugs.[18] Tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sounds are the 3 effects resulting from exposure to large doses of salicylates.[18] Tinnitus followed by mild to moderate reversible hearing loss typically occurs with serum salicylate concentrations of 20–45 mg/dL or higher.[15,18,84] Occasionally investigators have questioned whether salicylate ototoxicity can be used as an indicator of serum salicylate concentration, only to note that some patients with therapeutic concentrations of salicylates complained of tinnitus and many with higher or toxic concentrations had no tinnitus. In a study of 94 patients with salicylate concentrations >30 mg/dL on one or more occasions, the majority (55%) had no tinnitus, which only correlated with blood salicylate concentrations in 30%, although audiologic testing results usually were abnormal regardless of the presence or absence of tinnitus. The authors concluded that symptomatic ototoxicity is

too nonspecific and too insensitive to serve as an indicator of serum salicylate concentrations.[47]

The mechanism of ototoxicity is not completely understood but appears to be multifactorial. Inhibition of COX by salicylates prevents prostaglandin synthesis, which interferes with the Na^+-K^+-adenosine triphosphatase (ATPase) pump in the stria vascularis and the vasoconstriction decreases cochlear blood flow.[15,19,36,61] Membrane permeability changes cause a loss of outer hair cell turgor in the organ of Corti, which may impair otoacoustic emissions.[94,95] For a more complete description of the pathophysiology of salicylate-induced ototoxicity and sensorineural alterations and comparisons to the patterns of other ototoxic xenobiotics, see Chap. 21.

Pulmonary Effects

When a patient with salicylate poisoning presents with the clinical and radiographic manifestations of pulmonary edema or ALI, major etiologies that must be considered include aspiration pneumonitis, viral and bacterial infections, postictal and neurogenic ALI, and salicylate-induced ALI (formerly known as salicylate-induced pulmonary edema [SIPE] or noncardiogenic pulmonary edema)[57,63] (Chap. 22).

Many different causes of ALI result in increased pulmonary capillary permeability and subsequent exudation of high-protein edema fluid into the interstitial or alveolar spaces. Severe traumatic CNS injuries and elevation of intracranial pressure may be responsible for a form of "central" ALI (formerly called postictal pulmonary edema).[58] Hypothalamic lesions from trauma, increased intracranial pressure, or salicylate poisoning may be the critical factor, with resultant adrenergic overactivity producing a shift of blood from the systemic to the pulmonary circulation, loss of left ventricular compliance with left atrial and pulmonary capillary hypertension, and subsequent pulmonary edema (Chap. 22).

In 111 consecutive patients with peak salicylate concentrations >30 mg/dL, ALI occurred in 35% of patients older than 30 years of age and none of the 55 patients younger than 16 years of age. Risk factors for developing ALI included cigarette smoking, chronic salicylate ingestion, and presence of neurologic symptoms on admission. The average arterial blood pH was 7.37 ± 0.022 in the 6 adult patients with ALI and 7.46 ± 0.010 in the 30 adults without ALI. There was no significant difference in salicylate concentrations, which were approximately 57 mg/dL in both groups.[118] In a 2-year review of all salicylate deaths in Ontario, Canada, 51 patients were studied, with autopsies performed in 39. The autopsies revealed that 59% had pulmonary pathology. The presence of pulmonary pathology, mostly "pulmonary edema," was significantly associated with therapy for >4 hours.[79]

Although the exact mechanism for ALI is obscure, hypoxia may be an important factor.[56,57] Hypoxia can result in pulmonary arterial hypertension and a local release of vasoactive substances. Severe salicylate poisoning has been identified as a distinct cause of ALI in children and in adults.[41]

Gastrointestinal Effects

Gastrointestinal manifestations of salicylate use include nausea and vomiting, which probably result from local gastric irritation at lower doses and from stimulation of the medullary chemoreceptor trigger zone at higher doses (27 mg/dL).[101] Hemorrhagic gastritis, decreased gastric motility, and pylorospasm also result from the direct gastric irritant effects of salicylates.[102] The effects appear more pronounced or consequential in the elderly.[64]

Renal Effects

The kidneys clearly play a major role in the handling and excretion of salicylates, and many believe in turn that salicylates are significantly nephrotoxic, but the majority of studies and experimental evidence do not strongly support this notion.[26,37,88] Most of the adverse renal effects historically associated with salicylates occurred with use of combination products such as aspirin–phenacetin–caffeine (APC) tablets and appear to have been due mostly to the nonsalicylate ingredient(s), that is, phenacetin,[37] or to a synergistic effect contributed to by salicylates. The synergistic nephrotoxicity of aspirin and acetaminophen results from the effects of each on depleting glutathione.[33,89,121] Renal papillary necrosis (RPN) and chronic interstitial nephritis initially characterized by reduced tubular function and reduced concentrating ability are rarely seen in adults using aspirin or salicylates unless they have chronic illnesses that already compromise renal function.

Although extremely high doses of aspirin have produced RPN experimentally in 1 rat species, RPN has not been demonstrated following excessive doses of aspirin alone in humans or other species, or after lesser doses of aspirin in other rats.[26] Similarly, neither chronic nephrotoxicity nor an increased risk of end-stage renal disease (ESRD) from long-term use of aspirin alone has been demonstrated in humans, with the exception of 1 case control series demonstrating a low but statistically significant risk of ESRD. In adults with preexisting glomerulonephritis, cirrhosis, or chronic renal insufficiency and in children with congestive heart failure, short-term therapeutic doses of aspirin may precipitate reversible acute renal failure, possibly because of inhibition of the vasodilatory prostaglandins necessary to maintain renal blood flow in these conditions.[26] In healthy adults, however, short-term therapeutic doses of aspirin do not adversely affect creatinine clearance, urine volume, or sodium and potassium clearance. Aspirin doses >300 mg/kg can cause acute renal failure, and chronic aspirin poisoning can cause reversible or irreversible acute renal failure associated with a pseudosepsis syndrome.[26]

Hematologic Effects

Hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction.[44] Anemia in patients who chronically abuse salicylates may be a result of the effects of both platelet dysfunction and gastric mucosal barrier breakdown (gastrointestinal bleeding),[44] particularly in the elderly.[6,25] Hemolysis is unusual, and alterations in leukocyte function are of no apparent clinical significance.[103]

Musculoskeletal Effects

Rhabdomyolysis after pure salicylate overdoses probably is another result of the dissipation of heat and energy from uncoupling oxidative phosphorylation.[71,80,81] Paratonia, characterized by extreme muscle rigidity, was present in 3 of the 51 cases of salicylate deaths reviewed in Ontario between 1983 and 1984.[79] Rapid rigor mortis and paratonia (which are not unique to salicylate poisoning) probably are related to the extreme depletion of ATP and the inability of the muscle fibers to relax.

CLINICAL MANIFESTATIONS OF ACUTE AND CHRONIC SALICYLATE POISONING

Acute Toxicity

The earliest signs and symptoms of salicylate toxicity include nausea, vomiting, diaphoresis, and tinnitus, which is a subjective sensation of ringing or hissing, with or without hearing loss.[15,44,110] As CNS salicylate concentrations increase, tinnitus is rapidly followed by diminished auditory acuity that sometimes leads to deafness.[15] Other early CNS effects may include vertigo and hyperventilation manifested as hyperpnea or tachypnea (Chap. 3), hyperactivity, agitation, delirium, hallucinations, convulsions, lethargy, and stupor. Coma is rare and generally occurs only after massive ingestions (serum salicylate concentrations >100 mg/dL) or mixed overdoses (Table 35–1).[44] A marked elevation in temperature resulting from the uncoupling of oxidative phosphorylation caused by salicylate poisoning[80] is an indication of severe toxicity and typically a preterminal condition.

Unfortunately, many of the signs and symptoms of salicylate toxicity may be mistakenly attributed to the illness for which the salicylates were administered, with disastrous consequences.[24,110]

TABLE 35–1. Clinical Manifestations and Diagnostic Testing Results of Salicylate Toxicity

Acid–base and electrolyte disturbances
- Anion gap increased
- Metabolic acidosis
- Metabolic alkalosis (vomiting)
- Respiratory alkalosis (predominates early)
- Respiratory acidosis (late, grave prognosis)
- Hyponatremia or hypernatremia
- Hypokalemia

CNS
- Tinnitus
- Diminished auditory acuity
- Vertigo
- Hallucinations
- Agitation
- Hyperactivity
- Delirium
- Stupor
- Coma
- Lethargy
- Convulsions
- Cerebral edema
- Syndrome of inappropriate antidiuretic hormone

Coagulation abnormalities
- Hypoprothrombinemia
- Inhibition of factors V, VII, X
- Platelet dysfunction

Gastrointestinal
- Nausea
- Vomiting
- Hemorrhagic gastritis
- Decreased motility
- Pylorospasm

Hepatic
- Abnormal liver enzymes
- Altered glucose metabolism

Metabolic
- Diaphoresis
- Hyperthermia
- Hypoglycemia
- Hyperglycemia
- Hypoglycorrhachia
- Ketonemia
- Ketonuria

Pulmonary
- Hyperpnea
- Tachypnea
- Respiratory alkalosis
- Acute lung injury

Renal
- Tubular damage
- Proteinuria
- NaCl and water retention
- Hypouricemia

In the review of all salicylate deaths in Ontario, Canada, in 1983 and 1984, the author noted that in 6 of the 23 (26%) patients who arrived alert, no salicylate determination appears to have been made and that probably neither the diagnosis nor severity of the lethal salicylate poisoning was recognized.[79]

Chronic Toxicity

Chronic salicylate poisoning most typically occurs in the elderly as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis and osteoarthritis.[5,32,64] Although neither age nor gender appears to affect the absorption rate or plasma clearance of acute therapeutic doses of aspirin (900 mg) administered to healthy adults,[82] when used chronically, a small increase in dosage (eg, in response to increasing pain) or a small decrease in metabolism or renal function can result in substantial increases in serum salicylate concentrations and toxicity.[64]

Presenting signs and symptoms of *chronic* salicylate poisoning include hearing loss and tinnitus, nausea, vomiting, dyspnea and hyperventilation, tachycardia, hyperthermia, and neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, and coma.[4,44,70] In one review, the authors went so far as to suggest that the diagnosis of salicylate poisoning should be borne in mind when an older patient presents with recent deterioration in activities of daily living of no known cause.[31] Although there is considerable overlap with some of the presenting signs and symptoms of *acute* salicylate poisoning, the slow onset and less severe appearance of some of these signs of chronic poisoning in the elderly frequently cause delayed recognition of the true etiology of the patient's presentation.[45]

Typically, ill patients who suffer from chronic salicylate poisoning may be misdiagnosed as having delirium, dementia, encephalopathy of undetermined origin, diseases such as sepsis (fever of unknown origin), alcoholic ketoacidosis, respiratory failure, or cardiopulmonary disease, especially congestive heart failure, acute pulmonary edema, or even unstable angina.[4,8,24,34,44]

In a study of 73 consecutive adults hospitalized with salicylate poisoning, 27% were not correctly diagnosed for as long as 72 hours after admission.[4] These patients manifested toxicity with standard or excessive therapeutic regimens and had significant associated diseases without a history of previous overdoses. In this group, 60% previously had a neurologic consultation before the diagnosis of salicylism was established. When diagnosis is delayed in the elderly, the morbidity and mortality associated with salicylate poisoning are high. Mortality was reported to be as high as 25% in the 1970s,[4] and no data suggest that survival after delayed diagnosis is substantially better today (Table 35–2).

Underrecognition or misdiagnosis of chronic salicylate poisoning is not confined to the elderly and may be a problem at the other end of the age spectrum. In one study of all children admitted to a district hospital in Kenya over a 3-month period with the primary diagnosis of severe malaria, 90% had detectable blood salicylate concentrations, and 6 of 143 had plasma concentrations ≥20 mg/dL. All 6 of the children with plasma salicylate concentrations of ≥20 mg/dL had neurologic impairment and metabolic acidosis, and 4 had hypoglycemia, suggesting that salicylates cause or contribute to those complications of malaria that are associated with high mortality.[34]

TABLE 35–2. Differential Characteristics of Acute and Chronic Salicylate Poisoning

	Acute	Chronic
Age	Younger	Older
Etiology	Overdose usually intentional	Therapeutic misadventures; iatrogenic
Diagnosis	Easily recognized	Frequently unrecognized
Other disease states	None	Underlying disorders (especially chronic pain conditions)
Suicidal ideation	Typical	No
Clinical differences	Rapid progression of signs	Acute lung injury (ALI)
		CNS abnormalities
Serum concentrations	Marked elevation	Intermediate elevation
Mortality	Uncommon when recognized, unless ingestion massive	Approximately 25%

DIAGNOSTIC TESTING

Rapid Confirmation of Salicylate Use

Serum salicylate concentrations are relatively easy to obtain in most hospital laboratories and with proper attention to the units reported (mg/dL vs. mg/L) and concomitant arterial blood pH values, clinicians can quickly confirm or exclude toxic salicylate concentrations. Salicylate *use* may be rapidly confirmed qualitatively with a simple point-of-care ferric chloride ($FeCl_3$) test that uses several drops of 10% $FeCl_3$ added to 1 mL of urine. A purple color indicates the *presence* of salicylic acid, acetoacetic acid, or phenylpyruvic acid.[119] However, because this test is extremely sensitive to very small quantities of salicylates, a positive result indicates only salicylate usage and not necessarily poisoning or overdosage. A positive $FeCl_3$ test result must be confirmed by determination of actual serum salicylate concentration, whereas false-negative $FeCl_3$ results either do not occur or are exceedingly rare.[42] A false-positive $FeCl_3$ test may also result from use of a small quantity of urine that has already been subjected to dipstick analysis with N-Multistix or Bili Labstix reagent strips. Presumably in this instance impregnated chemical from the dipstick that has dissolved in the urine subsequently causes a false-positive $FeCl_3$ reaction.

When urine is not available for $FeCl_3$ testing (because of anuria or oliguria, too short a time after ingestion, or chronic use of salicylates), a possible salicylate-containing product itself can be tested with $FeCl_3$. All 15 of the salicylate-containing products tested in one study demonstrated a positive $FeCl_3$ reaction, whereas none of the 15 nonsalicylate containing controls did.[55] $FeCl_3$ reagent is rarely available in hospital emergency departments, and the unsupervised performance of $FeCl_3$ testing outside of a certified laboratory is not consistent with the federal Clinical Laboratory Improvement Amendments (CLIA) in the United States.

Another rapid colorimetric urine test for determination of salicylate usage is the Trinder spot test,[66] which uses a premixed reagent consisting of mercuric chloride, ferric nitrate, deionized water, and concentrated hydrochloric acid. When 1 mL of urine containing salicylates is mixed with 1 mL of Trinder reagent, it instantly turns violet or purple. The sensitivity of the test was 100% when applied to urine collected 2–4 hours after oral ingestion of 975 mg of salicylate by volunteers.[66] (Because of the composition of the testing reagents, this test presumably would be available only in a laboratory.)

"Point-of-care" determinations that may help rapidly indicate salicylate *poisoning* are (A) a positive urine ketone determination reflecting ketogenesis from increased fatty acid metabolism[53] and perhaps the ketone forms of salicylates present; (B) a whole-blood glucose and electrolyte determination performed on a handheld analyzer (I-stat and others); this test can quickly demonstrate decreased HCO_3^{-2} (indicating a possible wide anion gap metabolic acidosis) and other glucose and electrolyte abnormalities characteristic of salicylate toxicity; and (C) a whole-blood ABG determination performed on a handheld analyzer indicating acid–base disturbance(s) characteristic of salicylate poisoning.

Serum Salicylate Concentrations and Correlation with Toxicity

Serum salicylate concentrations should be requested when clinically significant salicylate exposures are suspected and not as part of a general toxicologic screen. For some, the confusion in correctly identifying aspirin and acetaminophen products and the consequent possibility that either or both may be used in a suicide attempt, coupled with the initial absence (acetaminophen) or unreliability (salicylates) of clinical findings associated with these poisonings, make toxicologic analysis for both salicylates and acetaminophen reasonable when either one is implicated in an intentional poisoning.

The authors of two studies concluded that universal salicylate screening is not indicated for patients with acute self-poisonings (Hong Kong)[22] or patients with suicidal ingestions or altered mental status (United States).[107] The latter study found that 0.16% of patients with suicidal ingestions had a toxic salicylate exposure *not* suggested by history, compared to 0.3% of patients with potentially toxic acetaminophen exposures not suggested by history. Although these authors recommended universal acetaminophen screening to evaluate patients with suspected ingestions, they concluded that salicylate screening was unnecessary because severe salicylate exposures are less frequent and usually are accompanied by an elevated anion gap and altered mental status.[107]

Except in certain narrowly defined situations, the toxicity of salicylates correlates poorly with serum concentrations. The Done nomogram,[29] first published in 1960, continues to be republished in texts despite severely limited applicability. It was based on data from a predominantly pediatric population and intended to be applied only 6 hours or more after a single acute ingestion of nonenteric-coated, orally ingested aspirin. Moreover, the patient's blood pH must be approximately 7.4 or higher. Such conditions rarely apply to patients with serious acute and chronic salicylate overdoses and poisonings. An example of the shortcomings of the nomogram is a patient who presents with lethargy and/or a coagulation abnormality associated with salicylism. Such a patient can be classified on the Done nomogram as "mild" or "moderate," although it is obvious clinically that the patient must be considered severely poisoned. The poor predictive value of the Done nomogram when applied retrospectively to a group of 55 predominantly adults with salicylate poisoning is evident from a 1989 study.[32]

Patients with acute exposures whose initial serum salicylate concentrations are considered acceptable, low, or moderate sometimes

deteriorate rapidly thereafter. For this reason, careful observation of the patient, correlation of the serum salicylate concentrations with blood pH values, and repeat determinations of serum salicylate concentrations every 2–4 hours are essential until the patient is clinically improving and has a low salicylate concentration in the presence of a normal or high blood pH. Methyl salicylate exposures have resulted in deaths in <6 hours, emphasizing the need for early determinations of salicylate concentrations in addition to frequent testing after such exposures. In all cases, once a peak serum salicylate concentration has been reached, at least one additional concentration should be obtained after several hours and more frequent concentrations obtained in managing the seriously ill patient to assess efficacy of treatment and possible need for hemodialysis (HD).

A concurrent arterial blood pH should be determined when a blood salicylate concentration is obtained because in the presence of acidemia, more salicylic acid leaves the blood and enters the CSF and other tissues (Fig. 35–2), increasing the toxicity. Therefore, meaningful interpretation of *serum* salicylate concentrations must take into account the effect of blood pH on salicylate distribution, unless the serum salicylate concentration is so high that HD is indicated regardless of the pH. A decreasing serum salicylate concentration may be difficult to interpret because it can reflect either an increased tissue distribution with increased toxicity or an increased clearance with decreased toxicity. A decreasing serum salicylate concentration accompanied by a decreasing or low blood pH should be presumed to reflect a serious or worsening situation, not a benign or improving one.

When the patient's clinical signs and symptoms are given the highest priority and the serum salicylate concentration is interpreted in conjunction with a simultaneously obtained arterial blood pH, the severity of toxicity usually can be predicted and the need for HD accurately determined.

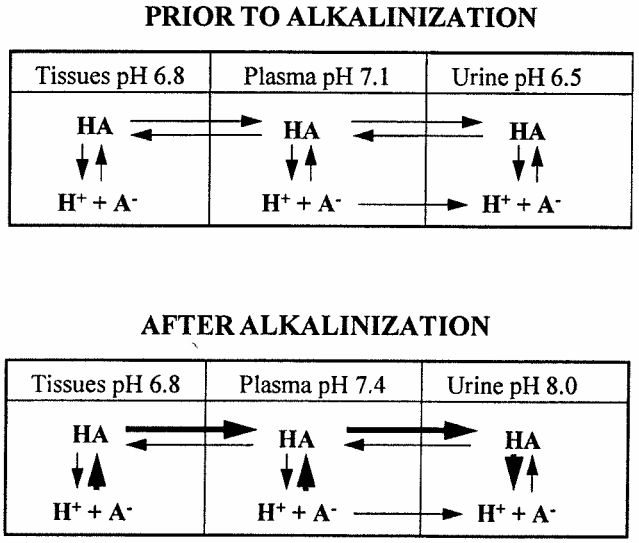


Figure 35–2. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues (including the brain). This equilibrium shift results in "ion trapping." *(Adapted, with permission, from Temple AR: Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981;141:367.)*

Errors in Reporting Serum Salicylate Concentrations

Laboratory errors probably are more common and problematic when reporting serum salicylate concentrations compared to other drug concentrations. Analyzing and reporting salicylate concentrations as mg/L when the clinician is accustomed to receiving results as mg/dL or inadvertently reporting actual mg/L results erroneously as "mg/dL" multiplies the true salicylate concentration by 10 and suggests a toxic salicylate concentration in a patient whose serum salicylate concentration is actually within the therapeutic range (eg, "165" instead of "16.5"). Most errors can be eliminated prior to initiation of aggressive therapy, such as HD, by determining whether the reported salicylate concentration is consistent with the clinical presentation and ABG results and, when time permits, repeating the salicylate determination with appropriate consideration for methodology and conversion calculations.

Correlation Between CSF and Serum Salicylate Concentrations

Although peak serum salicylate concentrations may provide useful clinical correlations at a normal or high blood pH, serum salicylate determinations not reflecting the peak concentration may be of limited value. Experimentally, there appeared to be a critical CSF salicylate concentration that correlated closely with mortality.[52] In addition, the CSF salicylate concentration correlated best with the peak serum salicylate concentration and reequilibrated more slowly than the serum salicylate concentration. As noted above in "Serum Salicylate Concentrations and Correlation with Toxicity," a serum salicylate concentration in the presence of acidemia may have little or no correlation with the CSF salicylate concentration. However, even if CSF salicylate concentrations in humans are more accurate predictors of toxicity, their use in clinical management is currently impractical.

MANAGEMENT

Gastric Decontamination and Use of Activated Charcoal

The use of gastric decontamination (orogastric lavage) and activated charcoal (AC) are discussed throughout this text, but their effects on the absorption and elimination of salicylates probably have been studied more extensively than with any other xenobiotic. In vitro studies suggest that each gram of AC can adsorb approximately 550 mg of salicylic acid.[75,85] In vitro, aspirin is adsorbed to AC with moderate efficacy. In humans, AC reduces the absorption of therapeutic aspirin doses by 50–80%, effectively binding aspirin from enteric-coated and sustained-release preparations in addition to immediate-release tablets.[75] Presumably, the sooner AC is given after salicylate ingestion, the more effective it will be in reducing absorption. A 10:1 ratio of AC to salicylate ingested appears to result in maximal efficiency. Although peak serum concentrations are markedly decreased from predicted concentrations, aspirin desorption from the aspirin–AC complex may diminish the impact on total absorption.[40,77,85] The addition of a cathartic to the initial dose of AC has been questioned and largely abandoned for most xenobiotics, but the benefits of adding sorbitol to AC in preventing salicylate absorption have been demonstrated in one study.[65]

Repetitive or multiple-dose activated charcoal (MDAC) appears to increase the elimination of unabsorbed salicylates over that achieved by single-dose AC,[9,53] although the charcoal used in one of these studies contained "substantial amounts of sodium bicarbonate."[3,53] MDAC probably prevents desorption, which may reduce the concentration of initially absorbed salicylate to only 15–20%.[40] It is not clear, however, that MDAC enhances the excretion of salicylates that have already been systemically absorbed.[3,60]

In one volunteer study of 2800 mg of aspirin followed by 25 g of AC at 4, 6, 8, and 10 hours after ingestion, the total amount of salicylate excreted from the body increased by 9–18% but was not considered statistically significant.[67] The authors hypothesized that MDAC was more effective in enhancing salicylate excretion in the *overdose* situation, when more salicylate is available because of decreased protein binding. However, in another study of the effects of MDAC on the clearance of high-dose intravenous aspirin in a porcine model, MDAC did not enhance the clearance of salicylates under alkaline conditions, that is, when the venous bicarbonate was kept at ≥15 mEq/L and urine pH kept at ≥7.5.[60] In contrast to the findings of both of these studies, two pediatric patients with salicylate overdoses were successfully treated with MDAC given every 4 hours for 36 hours, and the authors concluded that MDAC is effective in an overdose situation, even after alkalinization.[115]

Theoretical support may be found for use of whole-bowel irrigation (WBI) consisting of polyethylene glycol electrolyte lavage solution (PEG-ELS) in addition to AC to diminish potential desorption, particularly for enteric-coated aspirin preparations.[112] Moreover, WBI alone may be effective in preventing absorption of other xenobiotics. However, the addition of WBI to MDAC did not increase the clearance of *absorbed* salicylate.[77]

The value of MDAC in enhancing salicylate elimination may be considered controversial, and the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists (AACT/EAPCCT) position statement concludes that data are presently insufficient to recommend MDAC for salicylate poisoning.[3] Nevertheless, the use of MDAC probably is warranted in attempting to decrease gastrointestinal absorption of salicylate overdoses (see Antidotes in Depth: Activated Charcoal).

Fluid Replacement

There is a need to differentiate between restoration of fluid and electrolyte balance in salicylate-poisoned patients as opposed to increasing the fluid load presented to the kidneys in an attempt to achieve "forced diuresis." Fluid losses from salicylate poisoning are prominent, especially in children, and can be attributed to tachypnea, vomiting, fever, a hypermetabolic state, hyperpnea, and insensible perspiration.[111] The kidneys also respond to salicylate poisoning by excreting an increased solute load, including large quantities of bicarbonate, sodium, potassium, and organic acids, but renal tubular damage leading to renal failure is rare. Ketoacidosis, hypoglycemia, or hyperglycemia may occur.[5] For all of these reasons, the patient's volume status must be adequately assessed and corrected if necessary, along with any glucose and electrolyte abnormalities. As in other cases, accurate management of volume status in the poisoned patient may require invasive monitoring with a central venous pressure monitor or, preferably, a pulmonary artery catheter, especially in patients with cardiac disease, ALI, or renal compromise.

Increasing fluids *beyond* restoration of fluid balance in order to achieve a forced diuresis is a practice that was inappropriately promoted in the past. Although forced diuresis theoretically increases renal tubular flow and reduces the urine tubular cell diffusion gradient for reabsorption, renal excretion of salicylate depends much more on urine pH than on flow rate, and use of forced diuresis alone is not effective regardless of whether diuretics, osmotic agents, or fluid volumes are used to achieve the diuresis.[90] Although renal salicylate clearance varies in direct proportion to flow rate, its relation to pH is logarithmic.[69] In summary, although fluid imbalance must be corrected, forced saline diuresis does little more than oral fluids to enhance elimination over a 24-hour period[90] and subjects the patient to the hazards of fluid overload.

Salicylate Elimination by Urine Alkalinization

Because salicylic acid is a weak acid (pK_a 3.5), it will be ionized in an alkaline milieu and theoretically can be "trapped" there. Alkalinization of the blood by a substance that does not easily cross the blood–brain barrier (ie, intravenously administered sodium bicarbonate) can keep salicylates from entering the brain and CSF; alkalinization of the urine (defined as pH ≥7.5) will enhance urinary salicylate excretion. Alkalinization with sodium bicarbonate for salicylate poisoning results in enhanced excretion of the ionized acid form of salicylate in an alkaline urine.

In 2004, an AACT/EAPCCT position paper on urine alkalinization concluded that to increase the urinary elimination of salicylates, "urine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis."[93] The paper only briefly discusses how this is achieved and the specific role of ion trapping. However, in a separate paper, the coauthor of the AACT/EAPCCT position paper points out that salicylic acid is almost completely ionized within *physiologic* pH limits; therefore, alkalinizing the urine could not significantly increase the extent of ionization further, making impossible the conventional explanation for the increased excretion of salicylic acid in alkalinized urine.[91] At least one other investigator maintained many years ago that ion trapping alone does not account for the increased excretion caused by sodium bicarbonate.[78] In any case, renal excretion of salicylic acid *is* very dependent on urinary pH[90,116] (Fig. 35–2; see Antidotes in Depth: Sodium Bicarbonate).

Alkalinization increases free salicylate secretion from the proximal tubule but does not affect renal elimination of salicylate conjugates. The percentage of a single dose of 1.5 g of sodium salicylate administered to volunteers that was excreted unchanged increased from 2.3 ± 1.5% under acidic conditions to 30.5 ± 9.1% under alkaline conditions. When urine acidity was maintained using ammonium chloride, salicylic acid had a terminal plasma $t_{1/2}$ value of 3.29 ± 0.52 hours, which was significantly reduced to 2.50 ± 0.41 hours when an alkaline urine was maintained with sodium bicarbonate treatment. The total body clearance of salicylic acid was significantly less under acidic urine conditions (1.38 ± 0.43 L/h) than under alkaline urine conditions (2.27 ± 0.83 L/h).[116]

Alkalinizing the urine from a pH of 5 to 8 logarithmically increased *renal* salicylate clearance from 1.3 to 100 mL/min.[83] Assuming an overdose Vd of 0.5 L/kg, this increased clearance would decrease salicylate half-life from 310 to 4 hours. However, alkalinizing the urine from a pH of 5 to 8 has a more modest

effect on *serum* salicylate clearance.[90] The apparent serum half-life decreased from 48 to 6 hours at a fixed rate of 2 hours per unit pH change. This difference between serum and renal half-lives reflects the fact that renal clearance only applies to free salicylate, whereas serum clearance applies to both free and protein-bound salicylate.

Because acidemia enhances salicylate transfer into tissue, and particularly into the brain, it must be treated aggressively by raising the blood pH compared to the brain pH, thereby shifting the equilibrium from the tissues to the plasma[50,110] (Fig. 35–2). To accomplish this, hyperventilation alone should not be relied upon, and $NaHCO_3$ (but not acetazolamide) should be used for alkalinization. Although the administration of acetazolamide, a noncompetitive carbonic anhydrase inhibitor, results in the formation of a bicarbonate-rich alkaline urine, it also causes a systemic metabolic acidosis and acidemia.[39,50] The effect of acetazolamide usually is self-limited and mild but nevertheless increases the concentration of freely diffusible nonionized molecules of salicylic acid, thereby increasing the volume of distribution and most probably enhancing the penetrance of salicylate into the CNS.[74] Because salicylate also appears to inhibit acetazolamide plasma protein binding and acetazolamide renal tubular secretion, older patients with diminished protein binding and renal function may be at even greater risk for significant metabolic acidosis from acetazolamide use.[50,108]

Alkalemia by Hyperventilation versus Sodium Bicarbonate and the Risks Associated with Assisted Ventilation

Endotracheal intubation followed by assisted ventilation of a salicylate-poisoned patient poses particular risks and may contribute to mortality in several ways. Death has occurred following sedation during initial airway management.[11] Additionally, although early endotracheal intubation to *maintain* hyperventilation may aid in the management of patients whose respiratory efforts are faltering after many hours, few healthcare providers are trained or skilled at maintaining the appropriate concentration of hypocarbia and hyperventilation necessary for managing a salicylate-poisoned patient who is receiving assisted ventilation on a respirator. Even when achieved, a respiratory alkalosis sustained by hyperventilation (assisted or unassisted) alone should *never* be considered a substitute for use of either sodium bicarbonate (to achieve both alkalemia and alkalinuria) or HD (when indicated). Because sodium bicarbonate does not easily cross the blood–brain barrier whereas CO_2 does, sodium bicarbonate will create a compartmentalized environment conducive to keeping salicylates in the blood and away from the brain and liver (Fig. 35–2).

Alkalinization with intravenous sodium bicarbonate should be considered for patients whose serum salicylate concentration exceeds 35 mg/dL and for clinically suspected cases of salicylism until a salicylate concentration and simultaneously obtained blood pH are available to guide treatment. Patients on therapeutic regimens of salicylates who feel well with salicylate concentrations of 30–40 mg/dL and who do not manifest toxicity do not require intervention. Oral bicarbonate administration should never be substituted for intravenous bicarbonate to achieve alkalinization because the oral route may increase salicylate absorption from the gastrointestinal tract by enhancing dissolution.[101]

Alkalinization in hemodynamically stable adults and children with significant salicylate concentrations may be achieved with a bolus of 1–2 mEq/kg, followed by an intravenous infusion of 3 ampules of sodium bicarbonate (132 mEq) in 1 L of 5% dextrose in water (D_5W), to run at 1.5–2 times maintenance fluid range. Urine pH must be maintained at 7.5–8.0 and hypokalemia must be corrected (see below) to achieve maximum salicylate excretion. Volume load should remain modest while repleting previous losses. Early HD must be considered when a patient cannot tolerate the increased solute load that results from alkalinization because of congestive heart failure, renal failure, or cerebral edema. However, even when the decision for HD has been made, alkalinization (when possible) helps to achieve a more rapid initial reduction in blood concentrations.[51]

Hypokalemia

Hypokalemia is a common complication of salicylate poisoning and prevents urinary alkalinization unless corrected. Hypokalemia results from the movement of potassium into cells in exchange for hydrogen ions in the presence of alkalemia, potassium loss in the urine, diarrhea as a result of sorbitol use, and vomiting with subsequent metabolic alkalosis and bicarbonaturia.[44] If urinary alkalinization cannot be achieved easily, hypokalemia, excretion of organic acids, and volume depletion should be considered possible reasons. Calcium should be monitored, because decreases in both ionized[30] and total serum calcium[43] are also complications of bicarbonate therapy.

Frequent blood gas monitoring is required for all patients exposed to significant amounts of salicylates. Although maintaining alkalemia clearly is essential for treatment, arterial pH probably should not be allowed to rise above 7.55, as alkalemia shifts the oxyhemoglobin dissociation curve to the left and may be otherwise detrimental. Note, however, that even with blood pH 7.45–7.50 in patients with moderately severe salicylism, boluses of bicarbonate have been given without necessarily further increasing the pH. Perhaps this is a result of sodium bicarbonate–induced metabolic alkalosis causing a decrease in the amount of salicylates acting on the brainstem to cause hyperventilation and a resultant respiratory alkalosis. Frequent reassessment of blood pH (and fluid status) almost always allows administration of more sodium bicarbonate than was initially thought possible.

Indications for Extracorporeal Measures

Extracorporeal measures are indicated if the patient is very ill, has a very high serum salicylate concentration, has severe fluid or electrolyte disturbances, or is unable to eliminate the salicylates (Table 35–3). In most instances of severe salicylate poisoning, HD is the extracorporeal technique of choice, not only to clear the xenobiotic but also to rapidly correct fluid, electrolyte, and acid–base disorders that will not be corrected by hemoperfusion

TABLE 35–3. Indications for Hemodialysis in the Salicylate-Poisoned Patient

Renal failure
Congestive heart failure (relative)
Acute lung injury
Persistent CNS disturbances
Progressive deterioration in vital signs
Severe acid–base or electrolyte imbalance, despite appropriate treatment
Hepatic compromise with coagulopathy
Salicylate concentration (acute) >100 mg/dL (in the absence of the above)

(HP) alone. HP provides better clearance than HD and may be an advantage if a mixed overdose might be better treated with HP. The combination of HD and HP in series is feasible and theoretically may be useful for treating severe or mixed overdoses[28] but is rarely used. Favorable results in rapidly reducing serum salicylate concentrations in severely poisoned patients have been described with use of continuous venovenous hemodiafiltration. This technique may be especially valuable for patients who are too unstable to undergo HD or in situations where HD is unavailable.[122]

A combination of therapies that are both useful and practical is to ensure effective alkalinization with sodium bicarbonate while a patient is waiting and then undergoing HD. In one unique case report, a patient who overdosed twice on salicylates within a 2-month period was treated in the first instance with 4 hours of HD but no effective alkalinization and in the second instance with sodium bicarbonate alkalinization but no HD. In both instances, blood concentrations of salicylates were >65 mg/dL. Although similar decreases in salicylate concentrations were achieved with the two techniques, the rate of decline during the first 4 hours was faster with alkalinization.[51] Combining the two therapies makes sense even if part of the reason for the increased early effectiveness of sodium bicarbonate treatment is related to the rapidity with which it can be achieved compared to the 2–4 hours required to institute HD after a patient presents under even the most favorable circumstances.[51]

Peritoneal dialysis (PD) was sometimes suggested in the past as a simpler extracorporeal procedure for eliminating salicylates in the setting of hemodynamic compromise, coagulopathy, or inability to perform HP or HD. However, PD is only 10–25% as efficient as HP or HD and not even as efficient as renal excretion itself. The 24-hour clearance of salicylates with PD is less than the 4-hour clearance of salicylates by HP or HD; therefore PD is not recommended (Chap. 10).

Pregnancy

Considered a rare event, salicylate poisoning during pregnancy poses a particular hazard to the fetus because of the acid–base and hematologic characteristics of the fetus and placental circulation: salicylates cross the placenta and are present in higher concentrations in the fetus than in the mother. The respiratory stimulation that occurs in the mother after toxic exposures does not occur in the fetus, which has a decreased capacity to buffer acid. The ability of the fetus to metabolize and excrete salicylates is also less than in the mother. In addition to its toxic effects on the mother, including coagulation abnormalities, acid–base disturbances, tachypnea, and hypoglycemia, repeated exposure to salicylates late in gestation displaces bilirubin from protein-binding sites in the fetus.

A case report describing fetal demise in a woman who claimed to ingest 50 aspirin tablets per day for several weeks during the third trimester of pregnancy supports the conclusion that the fetus is at greater risk from salicylate exposures than is the mother and that emergent delivery of near-term fetuses of salicylate-poisoned mothers should be considered very seriously[86] (Chap. 30).

SUMMARY

Initial assessment of a patient who has ingested excessive amounts of salicylates includes a determination of the vital signs, particularly the depth and frequency of respiration, and temperature. The clinical presentation of a patient with a salicylate overdose is characterized by early onset of nausea, vomiting, abdominal pain, blood-tinged vomitus or gross hematemesis, tinnitus, and lethargy. The presence of hyperventilation, hyperthermia, confusion, coma, seizures, and any other nonspecific neurologic presentation should heighten suspicion of salicylate poisoning (Tables 35–1 and 35–2). If either salicylism or salicylate poisoning is suspected, a bedside $FeCl_3$ test can confirm salicylate *exposure* (but may be unnecessary). Using a combination of symptoms, signs, bedside laboratory studies, and characteristic ABG findings, the clinician can rapidly confirm a significant salicylate ingestion, institute immediate alkalinization with sodium bicarbonate, achieve gastric decontamination by orogastric lavage (if indicated), AC, or MDAC (if indicated), and consider the need for HD (or perhaps hemodiafiltration) early in the course of management.

For the salicylate-poisoned patient who presents as severely ill, maintenance of the airway requires an extremely careful approach because during initial airway management, death has occurred following sedation.[11] In patients with pulmonary and CNS manifestations of salicylate toxicity, the protective nature of the hyperpnea or hyperventilation in maintaining alkalemia may be compromised by assisted ventilation, unless the clinician is extremely skilled at adjusting the ventilator to ensure hyperventilation, decreased PCO_2, and high pH (7.5) at all times. Moreover, any unnecessary study, such as obtaining a computed tomographic scan that delays definitive treatment aimed at immediately reducing the patient's burden of salicylates quickly by HD can only place the patient at greater risk of death. Urinary alkalinization with sodium bicarbonate to eliminate salicylates is important, even though use of sodium bicarbonate may further complicate electrolyte abnormalities. Maintenance of eukalemia is important to ensure success, and fluid and electrolyte replacement is essential.

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