Acute and Chronic Effects of Aspirin Toxicity and Their Treatment

Anthony R. Temple, MD

* Salicylate poisoning remains a major clinical hazard, usually resulting from accidental ingestions in preschool children, suicidal overdoses in adults and teenagers, and therapeutically acquired intoxication in all ages. Alkalemia or acidemia, alkaluria or aciduria, hypoglycemia or hyperglycemia, and water and electrolyte imbalances may occur; nausea, vomiting, tinnitus, hyperpnea, hyperpyrexia, disorientation, coma, and/or convulsions are common. With chronic, therapeutically induced salicylism, these symptoms may be mistaken for symptoms resulting from the illness for which the salicylates were administered. For acute ingestions, the magnitude of the poisoning is clearly dose related. Blood level determinations are good prognostic indicators for acute ingestions but are of limited value in chronic, therapeutically induced salicylism. Fluid and electrolyte management is the mainstay of therapy. Diuresis, hemodialysis, and hemoperfusion are effective, but the latter two rarely are necessary.

**Table 1.**—Pathophysiologic Effects Seen With Salicylate Poisoning

<table>
<thead>
<tr>
<th>Primary Effects</th>
<th>Secondary and Tertiary Effects</th>
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<tbody>
<tr>
<td>Direct CNS respiratory center stimulation</td>
<td>Respiratory alkalosis with excretion of base</td>
</tr>
<tr>
<td>Uncoupling of oxidative phosphorylation</td>
<td>Metabolic acidosis with excretion of acids</td>
</tr>
<tr>
<td>Inhibition of Krebs cycle enzymes</td>
<td>Impaired glucose metabolism</td>
</tr>
<tr>
<td>Inhibition of amino acid metabolism</td>
<td>Water and electrolyte loss</td>
</tr>
<tr>
<td>Interference with hemostatic mechanisms</td>
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**From McNeil Consumer Products Co, Fort Washington, Pa.**

Reprint requests to Director of Medical Affairs, McNeil Consumer Products Co, Camp Hill Road, Fort Washington, PA 19034 (Dr Temple).

* Salicylate poisoning remains a major clinical problem involving accidental ingestion in children and intentional overdose in adults and as a result of therapeutic intoxication in persons of all ages. The purpose of this article is to review the pathophysiologic findings and certain epidemiologic features, as well as the management of salicylate poisoning, that are of concern to the practicing physician.

**PATHOPHYSIOLOGIC FINDINGS**

While the primary pathophysiologic effects of salicylate intoxication are of a complex nature, fortunately, most clinicians deal only with the secondary and tertiary effects of salicylate poisoning (Table 1). The primary effects include direct stimulation of the CNS respiratory center, uncoupling of oxidative phosphorylation, inhibition of Krebs cycle enzymes, stimulation of gluconeogenesis, increased tissue glycolysis, stimulation of lipid metabolism, inhibition of amino acid metabolism, and interference with hemostatic mechanisms. Secondary and tertiary effects of salicylate intoxication include respiratory alkalosis with excretion of base, metabolic acidosis with excretion of acid, impaired glucose metabolism, and water and electrolyte loss.

Because these secondary and tertiary effects are so important in the management of salicylate intoxication, it is essential to review briefly the mechanisms associated with each. Stimulation of the CNS respiratory center seems to be a direct toxic effect of salicylates, independent of increased oxygen consumption or of increased carbon dioxide production.

This respiratory stimulation is characterized by increases in both the depth and the rate of respiration. Both hyperpnea and tachypnea occur, eventually leading to increased exhalation of carbon dioxide and decreased PCO₂. Accompanying the decrease in PCO₂, is an increase in plasma pH and a compensatory increase in renal excretion of bicarbonate.

Concurrently, other mechanisms...
are at work that lead to metabolic acidosis. Inhibition of Krebs cycle enzymes results in increased amounts of pyruvic acid and lactic acid. Increased metabolism and peripheral demand for glucose, in turn, stimulate lipid metabolism. The metabolism of lipids leads to increased formation of ketone bodies. Inhibition of aminotransferases causes an increase in the levels of amino acids and an aminoaciduria. Together, these changes produce a decrease in plasma pH and excretion of organic acids (aciduria).

Depending on the balance between these two mechanisms, either alkalemia or acidemia and either alkaluria or aciduria may be present. Early in the course of most adult salicylate poisonings and in cases of mild to moderate poisoning in older children, respiratory alkalosis alone and possibly alkaluria may be observed. In cases of severe poisoning in older children, acute poisonings in smaller children, and chronic therapeutically induced intoxication, a mixed metabolic acidosis and respiratory alkalosis is present, with acidosis predominating.

One of the less often mentioned but still important mechanisms of salicylate intoxication is interference with normal glucose metabolism. An understanding of these alterations is crucial if salicylate intoxication is to be managed successfully. Initially, patients may have either transient or prolonged hyperglycemia in response to failure of the tissues to utilize glucose adequately. Eventually, however, as supplies of glucose are depleted, hypoglycemia may occur. While hypoglycemia is a less common manifestation than hyperglycemia, it is found mainly in chronic salicylate intoxication or late in the course of acute intoxication. In animals, it has been demonstrated that CNS hypoglycemia occurs even in the presence of normal blood glucose levels. If CNS hypoglycemia occurs in man, it would clearly result in a life-threatening situation.

One well-recognized problem associated with salicylate intoxication is water and electrolyte imbalance. The reasons for these imbalances include increased metabolism and heat production; interference with oxidative mechanisms; increased cutaneous insensible losses, principally of water, but also of sodium as a result of sweating; organic aciduria accompanied by increased excretion of solute and increased renal output of sodium, potassium, and water; emesis caused by the toxic effect of the salicylates; increased respiratory rate, producing increased pulmonary insensible losses; and increased renal excretion of bicarbonate, leading to increased renal excretion of potassium and depletion of both potassium and sodium. Overall, a patient may lose fluid at the rate of 4 to 6 L/sq m with severe salicylate intoxication.

While salicylates have been reported to affect renal function, the effects are relatively minor. Celluria, the shedding of renal tubular epithelium, and albuminuria have been described, but they do not seem related to any serious toxic effects. Oliguria resulting from dehydration and decreased renal blood flow also may occur. Anuria or renal failure is usually associated only with severe shock, with hemorrhage, or with cardiovascular collapse. A few years ago, we reported the occurrence, in children with therapeutic salicylate intoxication, of a syndrome resembling inappropriate secretion of antidiuretic hormone. Despite adequate hydration, these children continued to have oliguria with concentrated urine and fluid retention that eventually resulted in cerebral edema. Interestingly, further cases of this syndrome have not been reported.

Occasionally, in cases of severe salicylate poisoning, evidence of a hepatic toxic reaction is manifest by elevations of liver enzyme levels. Such effects are reversible, and no permanent residual effects have been reported.

All of these pathophysiologic changes result in a constellation of characteristic clinical symptoms (Table 2)—nausea, vomiting, tinnitus, hyperpyrexia, disorientation, coma, and/or convulsions. Obviously, sound clinical judgment and a good differential diagnosis are essential in evaluating these clinical manifestations.

### ASSESSMENT OF THE DEGREE OF TOXIC REACTION

An assessment of the degree of potential toxic reaction should be made early, so that the subsequent course of the salicylate intoxication can be estimated. In the case of an acute ingestion, this can be done by assessing the amount of drug reported to be ingested, by evaluating the clinical status of the patient, and by measuring salicylate blood levels. In cases of chronic intoxication, the manifesting clinical abnormalities are the only useful factors of assessment.

The magnitude of the toxic effects in acute intoxication can be predicted if one can determine the amount of drug ingested (Table 3). If a patient ingests less than 150 mg/kg of salicylate, the likelihood of any serious symptoms developing is negligible. In the range of 150 to 300 mg/kg, patients experience mild to moderate toxic reactions; these patients can be cared for easily on an outpatient emergency basis. At doses in excess of 300 mg/kg of salicylate, patients will show prolonged and more severe effects, even when appropriate emergency measures have been given. A dose of more than 500 mg/kg of salicylate is considered potentially lethal. Obviously, these guidelines are not applicable to chronic salicylism, but personal experience suggests that a toxic reaction occurs in cases of chronic administration when more than 100 mg/kg/24 hr has been given for two or more days.

Patients with mild toxic reactions are considered to be those patients in whom mild to moderate hyperpyrexia develops, sometimes with lethargy (Table 4). Those with moderate toxic reactions have severe hyperpyrexia and prominent neurologic disturbances (marked lethargy and/or excitability), but neither coma nor convul-
sions occur. In cases of severe intoxication, severe hyperpnea and coma or semicona, sometimes with convulsions, are the usual findings.

To confirm the diagnosis of salicylate intoxication, a blood level determination should be obtained six hours or more after an acute ingestion, or at any time chronic intoxication is suspected. For patients who have acute intoxication, these levels can be compared with the findings of the Done nomogram (Fig 1), which uses the serum salicylate level at varying intervals after ingestion as a means of estimating the severity of the intoxication and the expected symptoms. Unfortunately, it is not helpful in predicting the severity of a chronic salicylate intoxication. Blood levels determined before six hours are still in the absorption-distribution phase of salicylate pharmacokinetics, and although they may be useful in confirming a salicylate overdose, such early levels cannot be used as predictors of severity of poisoning. Serial determinations are often useful in clarifying the nature of the patient's clinical manifestations and in monitoring the effectiveness of the emergency therapy given. In massive overdoses, plasma salicylate levels may continue to rise for as long as 24 hours after ingestion.

**MANAGEMENT**

Management of acute salicylate intoxication requires a knowledge of basic poisoning management techniques—gastric emptying by either emesis or lavage, administration of activated charcoal, dilution, and use of a cathartic. Dilution is not indicated in the management of salicylate intoxication, since it may enhance the absorption of the drug. In children, emesis is easier than lavage and possibly more effective. In adults, gastric lavage seems more effective than emesis. After either emesis or lavage, an appropriate dose of activated charcoal with repeated administration of a saline cathartic until the charcoal has been passed is an adequate indication that the gut has been cleansed successfully.

With poisoning in general, after the basic emergency measures have been carried out and supportive therapy has been provided, procedures and antidotes specific for the ingested substance are started. Since there are no specific antidotes for salicylate poisoning, the therapeutic objectives are to correct any fluid, electrolyte, or metabolic imbalance and to enhance salicylate elimination.

Appropriate fluid therapy in patients with salicylate intoxication is crucial. Some basic guidelines for fluid therapy are presented in Table 5. Because of dehydration, the volume of fluid given initially must be rather large, in the range of 10 to 15 mL/kg/hr for one to two hours. An appropriate fluid for this initial rehydration should contain 75 mEq/L of sodium, with an appropriate balance of chloride and bicarbonate. This fluid is intended for volume expansion only, not to correct acidosis. If the patient has severe acidosis, additional bicarbonate must be given. Subsequent hydration with fluid volumes in the range of 4 to 8 mL/kg/hr should be continued until the blood salicylate level decreases to within the therapeutic range, which may require several hours to several days. Fluid maintenance using volumes of fluids of 2 to 3 mL/kg/hr with the same basic composition as those listed in Table 5 may then be given as needed.

Table 6 lists the composition of several commercially available solutions. Of these, electrolyte No. 75 preparations contain the appropriate balances of fluid and electrolytes needed for all but initial hydration, and they are the preferred intravenous solutions for the management of salicylate intoxication. Appropriate amounts of sodium bicarbonate will need to be added to this solution.

To enhance the elimination of salicylate, several procedures, including forced diuresis coupled with alkalization of the urine, may be beneficial. Figure 2 illustrates the rationale for alkalization of the urine. Salicylate

| Table 3—Assessment of the Severity of Salicylate Intoxication Based on the Estimated Dose Ingested |
|-----------------|----------------------------------|-----------------|
| Ingested Dose, mg/kg | Estimated Severity |
| < 150 | No toxic reaction expected |
| 150-300 | Mild to moderate toxic reaction |
| 300-500 | Serious toxic reaction |
| > 500 | Potentially lethal toxic reaction |

*Number of tablets ingested times the milligrams of aspirin per tablet divided by patient weight in kilograms equals the acute ingested dose. If a patient has been receiving aspirin therapeutically during the previous 24 hours, the potential toxicity of the acutely ingested dose will be increased.

<table>
<thead>
<tr>
<th>Table 4—Usual Clinical Manifestation With Various Levels of Severity of Salicylate Intoxication</th>
</tr>
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<tbody>
<tr>
<td>Symptom Category</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
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*Adapted to coincide with Done nomogram.

Fig 1—Done nomogram for estimating severity of poisoning using serum salicylate levels (adapted from Done).
Table 5.—Recommendations for Fluid Management

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rate of Administration, mL/kg/hr</th>
<th>Duration</th>
<th>Sodium mEq/L</th>
<th>Potassium mEq/L</th>
<th>Chloride mEq/L</th>
<th>Bicarbonate mEq/L</th>
<th>Dextrose, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hydration</td>
<td>10-15</td>
<td>1-2 hr</td>
<td>75</td>
<td>0</td>
<td>50</td>
<td>20</td>
<td>5-10</td>
</tr>
<tr>
<td>Subsequent hydration</td>
<td>4-8</td>
<td>Until salicylate level is therapeutic</td>
<td>40</td>
<td>35</td>
<td>50</td>
<td>20</td>
<td>5-10</td>
</tr>
<tr>
<td>Maintenance</td>
<td>2-3</td>
<td>As necessary</td>
<td>25</td>
<td>20</td>
<td>25</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

*For severe acidosis (pH 7.15), give an additional 1 to 2 mEq/kg of sodium bicarbonate every one to two hours. Usual fluid loss is approximately 200 to 300 mL/kg; suggested minimum urine flow, 15 to 20 mL/hr.

†In case of persistent acidosis, these constituents should be increased by the addition of 15 mEq/L of sodium bicarbonate.

Table 6.—Comparison of Some Commercially Available Intravenous Solutions

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Normal Saline Solution</th>
<th>0.5N Saline Solution</th>
<th>5% Dextrose in Water</th>
<th>Lactated Ringer’s Injection</th>
<th>Electrolyte No. 75 Solution</th>
<th>Electrolyte No. 48 Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium*</td>
<td>154</td>
<td>77</td>
<td>0</td>
<td>130</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Potassium*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>Chloride*</td>
<td>154</td>
<td>77</td>
<td>0</td>
<td>109</td>
<td>48</td>
<td>22</td>
</tr>
<tr>
<td>Bicarbonate* (or lactate)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Calcium*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Phosphate*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Dextrose</td>
<td>0</td>
<td>0</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Measures are made in milliequivalents per liter.

Fig 2.—Rationale for alkalinization is three-compartment concept.

in its undissociated form moves from one tissue compartment to another. At equilibrium states, because more salicylate is in its dissociation form in more alkaline medium, correction of acidosis and alkalinization of the urine favor movement of salicylate from intracellular sites to plasma to urine.

Alkalinization can be an effective procedure. The administration of high doses of sodium bicarbonate (1 to 2 mEq/kg) during one to two hours, with subsequent adjustment of the dose and careful monitoring of the urine pH to maintain it at a level of 8.0 or more, will substantially enhance the elimination of salicylates. However, in children, even high doses of bicarbonate may not produce a sufficiently alkaline urine because (1) the high level of inorganic acid production with its accompanying aciduria cannot be compensated for by the administration of bicarbonate, and (2) the alkalinization cannot be accomplished adequately until potassium depletion has been corrected. Consequently, alkalinization with bicarbonate alone is not an effective modality in most children. The use of acetazolamide as an adjunct after acidemia has been corrected by bicarbonate administration has been advocated, but its use is dangerous and can lead to more severe complications (except when administered by experts). A final area of concern is whether—und, if so, when—patients with salicylism should undergo hemodialysis or hemoperfusion. Both methods are effective in removing salicylates. However, we have used strict criteria for recommending hemodialysis or hemoperfusion, ie, high blood salicylate levels (S, > 160 mg/dL or > 130 mg/dL at six hours), unresponsive acidosis (pH < 7.1), clinical features indicating renal failure, persistent CNS manifestations, or progressive deterioration when all other measures have been appropriately used. As a result, we have rarely seen a need for hemoperfusion or hemodialysis.

EPIDEMIOLOGIC ASPECTS

Table 7 presents some features of cases of salicylate ingestion reported in 1975 to the Intermountain Regional Poison Control Center, which, at the time of the survey, served approximately 1.2 million people. During that year, about 25,000 cases of poisoning were reported to the center, 807 of which were caused by salicylates. Of these, 73.7% of the patients in all age categories were cared for at home with careful monitoring by the center, including repeatedly calling patients back and the induction of emesis at home for those patients who had ingested substantial but not potentially serious amounts. Seventeen percent of patients were at home initially but were referred to a physician or an emergency room because they had ingested potentially serious amounts, and another 9% were already in the physician’s office or emergency room. Only 4% of these persons were eventually admitted to the hospital.

Among preschool children, 90% of the salicylate ingestion cases were managed at home, whereas only 31% of older children, adolescents, or adults were cared for at home. This difference is apparently based on the
fact that small children ingesting aspirin accidentally ingest smaller amounts than do adolescents and adults who ingest the drug intentionally. Similarly, hospitalization rates for children younger than 5 years were low, whereas those for adults were considerably higher (7% vs 26%, respectively). The only death seen during 1975 was in an adult who had taken salicylates to commit suicide.

However, in contrast to the outcome in acute ingestions, salicylates pose a major problem in children and adults when therapeutic or chronic overdoses occur. Such episodes occur as a result of the nonlinear, saturable kinetics of salicylate elimination, i.e., repeated doses of the drug can lead to accumulation in the body, resulting in "chronic salicylism." The term "therapeutic salicylate poisoning" is used because, in most cases, the salicylate was given for therapeutic reasons, and the poisoning was not the result of an accidental or intentional overdose.

Cases of salicylate overdose in preschool children reported in the medical literature before 1969 were reviewed by Tainter and Ferris.27 Of the cases reported, serious salicylate intoxication occurred as a result of accidental overdose in 58%, while in the remaining 42%, it was the result of therapeutic overdose. However, 84% of all the reported fatalities were the result of therapeutic overdose. These data are surprising, because it is commonly assumed that most deaths caused by salicylate poisoning are the result of accidental overdose.

My personal experience confirms these data. During the period in which I served as medical director at the Intermountain Regional Poison Control Center, half of all hospitalizations for salicylate poisoning in preschool children at the Primary Children’s Medical Center in Salt Lake City, a general pediatric and referral children’s hospital, were due to therapeutic overdose. Furthermore, the only deaths in preschool children were caused by chronic or therapeutic administration.

Causative factors associated with cases of salicylate poisoning also were examined. There was no single issue that was associated with the improper administration of salicylates. Frequently, the cause of intoxication was simply the administration of too large a dose of aspirin, as in the case of the mother who mistakenly gave her child aspirin for adults instead of children’s aspirin. Often, the cause of administration was the concomitant administration of several medications containing aspirin, e.g., cold preparations, stomach remedies, and other agents that the mother had not known contained aspirin. Other cases were the result of prolonged use of normal therapeutic doses of aspirin given in the presence of dehydration or other alterations in body homeostasis.

One striking feature of the mild to moderate cases of chronic salicylate intoxication we observed was that the diagnosis often was delayed because there was always an accompanying illness, the symptoms of which were similar to those of salicylate intoxication. Most illnesses for which the salicylates were given were either respiratory tract disease or gastroenteritis, the symptoms of which (fever, nausea and vomiting, tachypnea, irritability, and disorientation) are similar to those of salicylate poisoning. As a result, treating physicians often were slow to make the correct diagnosis. While chronic salicylism is preponderantly seen in small children, it may also occur in older children or adults.28

**CONCLUSION**

In summary, salicylate intoxication offers a number of interesting epidemiologic, pathophysiologic, and management features. Acute overdose in preschool children is generally a relatively benign condition, although occasionally it will result in toxic reactions. Intentional ingestions of an overdose of salicylate, as attempted suicide, are more serious. The most serious salicylate poisonings are a result of therapeutic or chronic administration of aspirin, producing much more severe metabolic derangements; frequently, the chronic salicylism is not readily recognized.

**References**

QUESTION: Dr Temple, what kind of blood levels do you find in comatose patients?

Dr Temple: One has to define what is meant by the term "coma" in patients with salicylate intoxication. Great disorientation generally occurs at blood levels in excess of 80 to 90 mg/dL at six hours.

James F. Winchester, MB, MRCP: That is my experience as well. Any other questions?

Laurie F. Prescott, MD, FRCPE: I was interested in the fact that your method of treatment includes catharsis. Don't you think it is a rather barbaric imposition that only adds to the patient's misery? Do you have any evidence to show that it actually does any good?

Dr Temple: There is no good evidence demonstrating whether catharsis is beneficial or not. Appropriate studies to examine the relative benefit of catharsis have not been done.

Dr Prescott: It is unlikely that catharsis helps. The aspirin would have to pass unab sorbed through the entire length of the gut. It seems unlikely that aspirin would survive unab sorbed all the way down.

Dr Temple: Generally speaking, we use catharsis with the idea that large amounts of aspirin may not dissolve so rapidly and thus may not be absorbed as readily as it might be otherwise.

Dr Winchester: Dr Prescott, an important point is that Dr Temple was talking about catharsis in patients who have been treated with activated charcoal; the binding of salicylates to activated charcoal is excellent.

Dr Prescott: So perhaps the aspirin might pass unab sorbed through the gut.

Dr Winchester: Yes.

Dr Temple: Once activated charcoal is given, administration of a cathartic to hasten its elimination seems to make sense.

QUESTION: In the group from 2 to 5 years old, can you think of any benefit from the combined use of aspirin and acetaminophen in the presence of greatly elevated temperatures, such as 40.5 to 41.1 °C?

Dr Temple: There is a strong trend among practicing physicians to use concomitant or alternating therapy with aspirin and acetaminophen for high temperatures. In the one study that Dr Yaffe discussed yesterday (see p 286), full therapeutic doses of both drugs produced a more prolonged decrease but not a greater reduction in fever. However, even temperatures of 40.5 to 41.1 °C are not usually dangerous in children. First of all, I would give single appropriate doses of antipyretics, preferably acetaminophen in the small child. Then, for additional comfort, I would undress the child, sponge him down, and reduce the environmental temperature. From a clinical standpoint, I see no reason for using two drugs in combination.

Discussion