

## Guidance Document: Management Priorities in Salicylate Toxicity

### Disclaimer

While individual practitioners may differ, this is the position of the College at the time written, after a review of the issue and pertinent literature. This document identifies critical management priorities for the salicylate-poisoned patient. It is not intended as a clinical guideline or substitute for clinical consultation with a medical toxicologist and a nephrologist.

### Introduction

Salicylate toxicity is a complex problem that may develop with either acute or chronic exposure to salicylates. Salicylates are found in over-the-counter medications including aspirin, bismuth subsalicylate, effervescent antacids, ointments, liniments and oil of wintergreen (methyl salicylate) and alternative medication products (e.g., willow bark) as well as numerous prescription medications. Patients with salicylate toxicity may have involvement of multiple organ systems including particularly the central nervous system (cerebral edema, coma, agitation, tinnitus, seizures), the pulmonary system (hyperventilation/tachypnea, acute lung injury), and the gastrointestinal system (nausea, vomiting). Salicylate-poisoned patients are almost universally volume depleted at the time of presentation to medical care (as much as 4-6 L in most symptomatic adults) from both sensible (e.g., vomiting and natriuresis) and insensible (e.g., fever, increased respiratory losses) losses. Volume resuscitation should be addressed early in the course. Acid-base disturbances including respiratory alkalosis, elevated anion gap metabolic acidosis, and mixed abnormalities are common. *Serum salicylate concentrations should be interpreted in the context of the acuity of the exposure and the overall clinical condition.* Significant toxicity with chronic salicylate exposure can occur at relatively low serum concentrations. Once the diagnosis of salicylate toxicity is seriously considered, treatment should begin promptly. While an abundance of case reports, case series and textbook chapters serve to identify critical issues and provide recommendations for therapy, there have not been direct comparisons of specific treatment regimens. The following document highlights clinically important issues that both demand attention in the salicylate-poisoned patient and suggest avenues for future clinical research.

### Management Priorities

The management of salicylate toxicity can be difficult due to its complex pathophysiology. There is no specific antidote for salicylate poisoning. Good supportive care and attention to the following specific issues are important.

#### 1. Salicylate Concentration

Initial and subsequent frequent salicylate concentrations should be determined and interpreted in the individual clinical context. Factors that may influence the interpretation of the salicylate concentration include exposure acuity, product formulation, coingestions, comorbidities and clinical condition, particularly acid-base status. The Done nomogram is not reliable for interpretation of concentrations in either acute or chronic toxicity.<sup>1-3</sup> Furthermore, while the earliest time-concentration plot on the Done nomogram is six hours post ingestion, earlier salicylate determinations are typically advisable and clinically useful.

Attention to reported salicylate concentration units is important as they may be reported as mg/dL, mg/L, or mmol/L (e.g., 100 mg/dL is equal to 1000 mg/L or 7.24 mmol/L). Clinical laboratories are encouraged to standardize their reporting of salicylate units.

Serial concentrations should be determined until they are clearly declining, documenting lack of ongoing absorption. However, the patient's overall clinical condition, and not the salicylate concentration alone, should guide management. Clinical deterioration, even in the setting of a falling serum concentration, is ominous, suggestive of increasing central nervous system (CNS) salicylate concentration. As blood pH falls, there is an increased proportion of nonionized salicylate that more readily distributes into the cerebrospinal fluid (CSF) and other tissues.<sup>4,5</sup> Therefore, blood pH must be considered in conjunction with the salicylate concentration.

There are some substances (e.g., diflunisal) that can interfere with the laboratory quantitation of salicylate concentration.<sup>6</sup> Consultation with the laboratory and/or medical toxicologist will help identify the most appropriate specific analytic methodology and may assist in the clinical interpretation of laboratory findings, particularly when they are inconsistent with the clinical condition.

## **2. Acid-Base Status, Volume Status and Electrolytes**

The evaluation of the salicylate-poisoned patient requires measurement of serum/plasma electrolytes and arterial blood gas analysis. The use of electrolytes to identify an abnormally high anion gap is not a reliable screen for salicylate toxicity as many chemistry analyzers report a false elevation of the chloride measurement in the presence of salicylates.<sup>7</sup> Acidemia should be avoided. Continuous intravenous infusion of sodium bicarbonate is also indicated in the presence of mild alkalemia. Alkalemia is a function of salicylate-induced respiratory alkalosis and is almost universally associated with a bicarbonate deficit and paradoxical aciduria, limiting salicylate excretion. The reduction in serum bicarbonate is caused both by concomitant metabolic acidosis and by an initial respiratory alkalosis-induced bicarbonaturia. A slightly alkalemic blood pH limits an increase in CNS salicylate concentration by shifting the ionization equilibrium of salicylate in the blood to the charged form and decreasing passage of salicylate into the CNS. Clinical severity is predicted by the acid-base status, with those adult patients exhibiting only respiratory alkalosis expected to have mild toxicity, while those with a normal or near normal serum pH ( $7.40 \pm 0.05$ ) with underlying respiratory alkalosis and metabolic acidosis are expected to have moderate poisoning. Acidemia ( $\text{pH} < 7.35$ ) is seen in severe poisoning, and the pH itself also worsens the expected course.

Euvolemia should be achieved. Hypovolemia is often underappreciated, and worsens salicylate toxicity as well as impairing treatment measures, especially alkalinization of the urine. Hypovolemia contributes to electrolyte and acid-base abnormalities through enhanced renal sodium and bicarbonate resorption and potassium excretion.

Electrolyte balance should be restored. Particular attention should be paid to glucose supplementation as CNS glucose utilization is increased, and CNS glucose concentration may be lower than the serum glucose. Hypokalemia is multifactorial in etiology and potassium supplementation should be made early. A normal to high-normal serum potassium is believed to facilitate urinary alkalinization. Electrolytes and acid-base status should be closely monitored in order to avoid excessive electrolyte replacement and/or alkalinization, particularly as salicylate toxicity resolves during treatment.

## **3. Gastrointestinal Decontamination**

Gastrointestinal decontamination techniques including administration of activated charcoal administration or even whole bowel irrigation may be considered in specific cases, particularly in those patients with early presentation after ingestion or in cases with rising levels or other signs of incomplete absorption. The use of multiple-dose activated charcoal is controversial. The data from animal and some volunteer studies demonstrated enhanced salicylate clearance with multiple-dose activated charcoal; the data from human overdose cases are mixed in their results. The relative roles of decreased absorption (gastrointestinal decontamination), enhanced adsorption of salicylate within the small bowel, and so-called gastrointestinal dialysis (enhanced elimination) are not clear. Clinical risk/benefit considerations are important given the potential for aspiration in the sick salicylate-poisoned patient with a deteriorating mental status.<sup>8,9</sup>

## **4. Airway Protection and Respiratory Status**

Endotracheal intubation may be indicated in the salicylate-intoxicated patient with deteriorating mental status or acute lung injury and should be considered in those with significant, uncontrollable agitation. Hyperventilation is not itself an indication for intubation. *However, endotracheal intubation and mechanical ventilation can be associated with rapid worsening of clinical salicylate toxicity and increased mortality unless a normal or slightly alkalemic blood pH is maintained via hyperventilation and achievement of a low  $\text{PCO}_2$  and/or intravenous sodium bicarbonate.* Once airway control has been

established, it is imperative that the increased minute ventilation and low PCO<sub>2</sub> usually seen with salicylate intoxication are maintained.<sup>5</sup> The acts of sedation and/or induction of paralysis lead to retention of carbon dioxide and respiratory acidosis. Rapid distribution of salicylate into the CNS can occur consequent to the blood pH decrease associated with the loss of normal or slightly alkalemic (7.45-7.50) blood pH. Administration of sodium bicarbonate by intravenous bolus at the time of intubation in a sufficient quantity to maintain a blood pH of 7.45-7.50 over the next 30 minutes is a reasonable management option during this critical juncture; intravenous sodium bicarbonate bolus and/or bag valve mask hyperventilation should be employed in any patient who is acidemic with a spontaneously ventilating PCO<sub>2</sub> of <20 mm Hg as further deterioration in acid-base status can be expected during intubation. Clinical studies demonstrating benefit from various empiric dosing regimens have not been reported.

Coingestion or therapeutic administration of CNS/respiratory depressant drugs may also suppress hyperventilation and thereby precipitate clinical deterioration in salicylate toxicity.

## 5. Enhanced Elimination

Techniques for enhanced elimination should be utilized in managing patients with salicylate toxicity. Extracellular volume depletion should be corrected and diuresis should be induced with large volumes of relatively isotonic sodium bicarbonate-containing intravenous fluids, as renal excretion of salicylates is more dependent on urine pH than on urine flow. Urine alkalinization to a pH of 7.5 - 8.0 increases urinary excretion of salicylates more than 10-fold and should be considered for significant salicylate toxicity in patients with intact renal function, alone or in combination with hemodialysis (see below).<sup>10</sup> Intravenous (not oral) administration of sodium bicarbonate as a crystalloid preparation should be used. One commonly utilized intravenous solution consists of one liter of D5W to which three 50 mL-ampules of 7.5% or 8.4% sodium bicarbonate (for a total of 132-150 mEq) and 30-40 mEq of potassium chloride per liter are added. The rate of infusion should be sufficient to induce a urine output of 2-3 mL/kg/hr. Urine pH should be checked frequently. Achievement of the goal urine pH may be difficult in the setting of metabolic acidosis and hypobicarbonatemia, hypokalemia, renal insufficiency, predominant respiratory alkalosis (which also causes hypobicarbonatemia), volume depletion, or volume limitations to intravenous fluid administration (e.g., patients with congestive heart failure, cerebral edema, and/or pulmonary edema).

Hemodialysis is very effective in the treatment of patients with salicylate toxicity since an increased fraction of free salicylate occurs in the serum following saturation of protein binding.<sup>3</sup> Hemodialysis may be life-saving in certain circumstances and it typically resolves toxicity in hours rather than days that may be required with alkaline diuresis. Charcoal hemoperfusion is also very effective at removing salicylate, but is now rarely used. Advantages of hemodialysis over hemoperfusion include correction of acid-base and fluid and electrolyte disturbances in addition to enhancing elimination of the salicylate, and being a much more widely available technique. Peritoneal dialysis is not an efficient means of salicylate removal. Urine alkalinization should be initiated while preparing for hemodialysis and continued during this procedure. Indications for hemodialysis vary depending on the age of patient, acuity of the toxicity, serum salicylate concentration, associated ingestions or other co-morbidities, and ability to tolerate sodium bicarbonate and fluid administration but may include:

- significant CNS abnormalities such as altered mental status, cerebral edema, or seizure;
- acute lung injury or failing respiratory capacity;
- impaired glomerular filtration rate not responsive to volume repletion;
- deteriorating clinical condition, especially in the setting of delay in achievement of or inadequate urine alkalinization;
- significant hyperthermia (an indicator of mitochondrial toxicity from salicylates);
- coingestion of substance that may exacerbate salicylate toxicity;
- refractory/profound acidemia;
- refractory/profound electrolyte disturbance;

- inability to administer sodium bicarbonate for reasons such as renal insufficiency/failure or pulmonary edema;
- rising serum salicylate concentrations despite administration of sodium bicarbonate.

In the presence of any of these conditions or co-morbidities, early notification of the dialysis staff of the possible need for hemodialysis is warranted. The time required to prepare for dialysis may lead to significant delays in initiating therapy, such that prompt warning to a nephrologist is strongly recommended.<sup>11</sup>

The decision to initiate hemodialysis for a patient with presumed *chronic* salicylate toxicity or delayed presentation after acute overdose should be based on the overall clinical condition and not the serum salicylate concentration alone. A patient with chronic salicylate toxicity or delayed presentation after acute overdose, who has significant CNS abnormalities, acute lung injury, or other manifestations of toxicity, but a serum salicylate concentration of 40 mg/dL, warrants consideration for hemodialysis.

The decision to initiate hemodialysis for a patient with *acute* salicylate toxicity should also be based on the overall clinical condition. However, a patient with acute toxicity and a salicylate concentration approaching 100 mg/dL warrants consideration for hemodialysis, even if clinical signs and symptoms are fairly minor or absent.

## Conclusions

Salicylate toxicity is a complex problem with the potential for significant morbidity and mortality. Awareness of the differences in acute and chronic toxicity, anticipation of clinical manifestations and potential complications, appropriate interpretation of salicylate concentrations and timely initiation of enhanced elimination techniques are imperative. Transfer to a facility with appropriate clinical capabilities may be prudent. Early involvement of a medical toxicologist and a nephrologist is encouraged for optimal clinical outcome.

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**Related Positions Statements**

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