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Emergency Department Management of the Salicylate-Poisoned Patient

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The term salicylate refers to any of a group of chemicals that are derived from salicylic acid. The best known is acetylsalicylic acid (aspirin). Acetylsalicylic acid is metabolized to salicylic acid (salicylate) after ingestion. The salicylates originally were derived from salicin, the active ingredient in willow bark, which Hippocrates used 2500 years ago for treating pain and fever [1,2]. Salicylates also occur naturally in many plants such as strawberries, almonds, and tomatoes [3].

Poisoning by aspirin is common and is under-represented in poison center data, because it is often not recognized [4–6]. The in-hospital mortality for unrecognized chronic aspirin poisoning is reportedly three times higher than if the diagnosis is made in the emergency department [7]. Familiarity with the clinical presentation during the various stages of acute and chronic aspirin poisoning is important for the practice of emergency medicine. The most challenging aspect of the clinical evaluation and management of the aspirin-poisoned patient may be recognition of the subtle signs and symptoms of chronic, nonintentional aspirin overdose (Box 1).

Epidemiology

Salicylate poisoning continues to be an important overdose that frequently presents to emergency departments [8–10]. There were over 21,000

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Box 1. Pitfalls in the emergency department management of salicylate–poisoned patients

Failure to recognize the presence of salicylate toxicity
Failure to appreciate the presence of continued absorption of salicylate
Misinterpreting clinical significance of serum salicylate levels, because units of measure were unclear
Reliance on one or two serum levels of salicylate that may not describe a trend of decreasing total body burden of aspirin clearly
Misinterpretation of low serum salicylate levels as nontoxic and failure to comprehend the changing acid–base status of the patient
Waiting until serum salicylate levels are determined before beginning urinary alkalinization
Accidentally adding bicarbonate to isotonic saline (creating a hypertonic solution) rather than intravenous dextrose/water solutions to alkalinize the urine
Forgetting to add potassium to the urinary alkalinization infusion
Failure to recognize the emergent need for definitive therapy (hemodialysis) on the basis of impending end organ injury (Box 2).
Inappropriately or prematurely initiating intubation and mechanical ventilation without hyperventilation and without simultaneous hemodialysis
Prematurely discharging patients without demonstrating metabolic stability, declining salicylate levels, and the absence of an aspirin bezoar

aspirin and nonaspirin salicylate exposures reported to the United States poison centers in 2004, with 43 deaths and 12,968 patients requiring hospital treatment [11]. Because poison center data are collected passively, that statistic is certainly an underestimate of the true incidence of salicylate poisoning occur in the United States. One half of the reported exposures (10,786) were categorized as intentional overdoses. The incidence of chronic aspirin poisoning is not known, but it is misdiagnosed frequently [12].

In recent years, packaging strategies such as child-resistant packaging and reducing the amount of medication in each package of over-the-counter analgesics have impacted the incidence of poisoning. It is estimated that the use of child-resistant packaging for salicylate-containing medications has resulted in a 34% reduction in the salicylate-related child mortality rate [13]. In England, Australia, and Ireland, analgesics are packaged and sold in

small amounts (ie, 4 g of acetaminophen). This has resulted in a 30% decrease in the number of patients requiring liver transplantation for acetaminophen-induced hepatic failure and a 22% reduction in suicidal deaths from acetaminophen and salicylate [14]. Large aspirin overdoses were reduced by 39% on average in the countries in which the limited package formulation is required [14,15].

Pathophysiologic basis for poisoning

Salicylate is a metabolic poison. Understanding the pathophysiology of its metabolic effects can help to understand the clinical manifestations of toxicity. The metabolic derangements induced by salicylate poisoning are multifactorial, but the principal pathophysiologic mechanism in salicylate poisoning is interference with aerobic metabolism by means of uncoupling of mitochondrial oxidative phosphorylation [15a,16]. This leads to the interruption of a series of enzyme-mediated mitochondrial functions and increased anaerobic metabolism with cellular conversion of pyruvate to lactate and rapid development of lactic acidosis [17,18]. The inefficiency of anaerobic metabolism results in less energy being used to create ATP and release of the energy created during the metabolism of glucose in the electron transport chain as heat, so salicylate poisoned patients may become febrile [19]. The absence of fever, however, does not rule out salicylate poisoning.

The acidosis is caused by anaerobic metabolism and the inability to buffer hydrogen ions, which is reflected by the accumulation of lactate. The presence of acetasalicylic acid or salicylate molecules probably contributes little to the acidotic state [15a,20].

Interference with oxidative phosphorylation by salicylate also will impact glucose homeostasis negatively by causing glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids, the end result being low serum glucose levels and central nervous system (CNS) hypoglycemia relative to serum glucose levels [15a].

Absorption and metabolism of salicylate

The pharmacokinetic profile of aspirin is unique and explains the unique characteristics of clinical poisoning. The ionization constant (pKa) of aspirin is 3, which means that at a pH of 3, approximately half of the available chemical is in the ionized state. In an acidic environment like the stomach, more of the drug will be absorbed compared with tissues at a higher pH [21]. The absorption of aspirin from the stomach can be delayed by the presence of food in the stomach and the formulation of the aspirin, (eg, enteric coating of pills may create concretions and bezoars that limit available surface area for absorption) [22]. Aspirin is thought to cause spasm of the pyloric sphincter, increasing gastric transit time and prolonging the time that aspirin is in the acidic environment of the stomach, favoring increased

absorption [21]. Salicylates also are absorbed readily in the unionized form from the small intestine [23,24].

Dermal salicylate formulations typically do not result in tissue penetration much deeper than 3 to 4 mm in animal studies [25,26] and human volunteer experiments [27]. Methyl salicylate has less dermal absorption than either camphor or menthol, with lower mean plasma levels and shorter elimination half-life than either compound in people [28]. Significant amounts of salicylate typically are not absorbed through the skin except in select patients, such as children and patients with compromised skin such as burn patients or patients who have severe psoriasis [29–31].

In therapeutic doses, the major route of salicylate biotransformation is conjugation with glycine in the liver. A small amount of aspirin is excreted unchanged in the urine [15a]. In overdose, the liver's ability to metabolize the drug is overwhelmed, and unchanged salicylate excretion through the kidney becomes a much more important elimination route.

Salicylate–induced acid-base changes

Respiratory alkalosis

Salicylate toxicity initially will create a pure respiratory alkalosis because of direct stimulatory effects on the respiratory centers of the cerebral medulla. This is characterized in the blood gas by a decrease in the partial pressure of dissolved CO_2 accompanied by an elevated pH and normal to slightly lower levels of serum HCO_3 [32]. There is some controversy as to whether pediatric aspirin poisoned patients demonstrate this phase of acid–base derangement. Pediatric patients may present later in the course of the poisoning, or the centrally mediated hyperventilatory phase of aspirin poisoning may be so subtle in children that it often is missed [33–36].

Mixed acid–base disturbances

As the poisoning progresses and more of the aspirin is absorbed into the serum and is incorporated into the mitochondria, uncoupling oxidative phosphorylation, lactic acid accumulates in the serum, and metabolic compensatory mechanisms are initiated [16]. Hyperventilation becomes a true compensatory mechanism in addition to the byproduct of central medullary stimulation [20]. This phase is characterized metabolically by a continued decrease in the pCO_2, marked decline in measured HCO_3 and possibly a decrease in serum pH, depending on the ability of the patient to maintain the respiratory demands of the developing acidosis and to retain bicarbonate in the kidney [37]. A common error at this stage of the poisoning is to acknowledge that the serum pH is close to 7.4 or slightly higher than 7.4, and assume that the patient is compensating adequately for the acidosis.

Metabolic acidosis

As the ability to compensate for the acidosis is overwhelmed, pH drops; lactic acid accumulates, and serum bicarbonate is consumed. Patients who

reach the stage of aspirin poisoning where pH is less than 7.4 with decreased pCO2 and low serum bicarbonate are dangerously unstable, likely to decompensate hemodynamically and will begin to demonstrate other symptoms of end-organ injury [37].

Clinical presentation

Classic salicylism

The triad of salicylate poisoning consists of hyperventilation, tinnitus, and gastrointestinal (GI) irritation [38,39]. Physicians should remain aware that patients may hyperventilate with a normal respiratory rate by increasing tidal volume (hyperpnea) and should make it a habit to observe respiratory patterns carefully. Ototoxicity is a well-described phenomenon with salicylism, and it is thought to be secondary to interference with chloride channels in the cochlear hair cells that transmit sound waves [40,41]. The ototoxicity is most noticeable in the range of serum salicylate from 20 to 40 mg/dL [40,42]. Aspirin, especially enteric-coated formulations, are known to develop concretions and bezoars in the stomach and act as a direct GI irritant leading to nausea, vomiting, and abdominal pain [22,43,44].

Early presentation

Patients who present early in the course of salicylate poisoning may have modest symptoms, and the hyperventilation may be mistaken for emotional excitation or anxiety. GI irritation may or may not be present, and tinnitus or other symptoms of ototoxicity may be overlooked unless the physician specifically tests for them with direct questioning or confrontational hearing testing. Vital signs may reflect emotional agitation and CNS stimulation with tachycardia, increased work of breathing (increased minute ventilation), and overall autonomic up-regulation. Early in the course of acute poisoning, fever generally will be absent [39]. Clinical symptoms will be variable if the patient ingested more than one drug, or the ingested aspirin formulation contained a CNS depressant, which might blunt the expected hyperventilation and respiratory alkalosis [45].

Laboratory values early in the course of aspirin poisoning will be largely normal or will reflect the direct stimulatory effect of salicylate on the cerebral respiratory center. Serum aspirin levels may be elevated modestly (20 to 40 mg/dL), and blood gas analysis may demonstrate pure respiratory alkalosis with elevated pH and low pCO_2 with normal or near-normal HCO_3 [39]. The decision to determine serum salicylate concentrations is not difficult. Although serum salicylate levels may not be required to screen every asymptomatic overdose, liberal use of the laboratory to make the diagnosis and follow resuscitative efforts is advisable [46–48].

Late presentation

As salicylate enters the mitochondria, dramatic changes in vital signs and clinical stability occur. Serum salicylate levels alone are not adequate to accurately assess and follow seriously poisoned patients [49]. Serum salicylate levels do not reflect the total body burden of salicylate, and so to evaluate the rapidly changing acid base status of an aspirin poisoned patient, serial salicylate levels should be accompanied by serial blood gas analysis [5]. Patients who present in the late phases of salicylate toxicity often are misdiagnosed as sepsis [50], myocardial infarction [51], or as agitated or otherwise psychiatrically disturbed [43,52,53].

Death from salicylism

The progression to death from salicylate poisoning is particularly tumultuous. The toxic effects of the salicylate molecule on mitochondrial function and subsequent basement membrane leakage overwhelm the compensatory capacity of the organism. This leads to marked metabolic acidosis with development of pulmonary and cerebral edema. Myocardial depression and hypotension secondary to the acidosis and volume deficit occur, and CNS depression with seizures secondary to hypoxia, hypoglycemia, and direct CNS toxicity often precedes cardiopulmonary arrest [54].

In one study, nearly half (45%) of the patients who died from salicylate poisoning arrived at the emergency department alert and deteriorated while there [55]. In another study, 39% of the patients who had severe salicylate poisoning requiring ICU management arrived alert with minimal symptoms [56]. Mean postmortem salicylate serum levels on 16 patients who presented dead on arrival after aspirin overdose were 51 mg/dL (range 17 to 101 mg/dL) [55]. Postmortem examination of salicylate-poisoned patients demonstrated several unique findings including myocardial necrosis suggestive of toxic myocarditis [57], pulmonary congestion, hemorrhagic gastritis with unabsorbed salicylate and GI ulceration, cerebral edema, and paratonia (extreme muscle rigidity) [55,56].

Emergency department evaluation of the salicylate-poisoned patient

Done nomogram

The aspirin nomogram, commonly referred to as the Done nomogram, after its creator Done [58,59], was first published in 1960. Data from pediatric patients who ingested a one-time dose of aspirin were plotted over time to create an instrument to predict toxicity. Several important limitations exist with regards to the development of the Done nomogram that limit its generalizability, including the fact that patients who had polydrug ingestion were included in the analysis, making the clinical correlation difficult to interpret. In addition, the nomogram assumed an elimination

half-life of 20 hours in all patients and did not allow for the change from first-order to zero-order elimination kinetics that occurs when serum levels exceed the elimination enzyme systems [60]. Although innovative and often accurate for the intended (pediatric) population, the Done nomogram has been demonstrated to have very limited applicability and usefulness for most aspirin-poisoned patients, and its routine use is discouraged [49].

Laboratory evaluation

Physicians should make liberal use of blood tests in the evaluation of potentially aspirin-poisoned patients. Different clinical laboratories may report salicylate levels in different units of measure (mg/dL versus mmol/L). Clinicians should maintain consistent use of the respective units of measure to avoid confusion. Seriously aspirin-poisoned patients may display symptoms that allow an astute practitioner to perform comparative serial examinations and assess developing toxicity. Accurate recognition of worsening signs of toxicity, however, is an inexact science with uncertain sensitivity and specificity, especially in the event of polypharmaceutical ingestion or pediatric patients [45,61–63]. Serum salicylate levels frequently do not reflect the severity of the poisoning. Depending on the time since ingestion, presence of food in the stomach, coingestants, and presence of concretions, among other variables, symptoms may or may not correlate with serum salicylate levels. Symptomatic patients suspected of aspirin ingestion or salicylate poisoning should have serial aspirin levels and blood gas analysis performed until a clear trend toward decreasing (not plateau or modestly increasing) levels and metabolic stability as described by the blood gas is present.

Radiographic evaluation of the aspirin poisoned patient is rarely helpful, except for seriously ill patients who may have pulmonary edema or patients who have altered mental status that might require CT scanning of the head to eliminate the possibility of an alternative cause for a changed level of consciousness. Large bezoars of ingested enteric-coated aspirin tablets may or may not be visible on a radiograph, and the absence of opacity on an abdominal radiograph is not adequate to rule out the presence of a large amount of salicylate in the gut [64].

Treatment of the salicylate-poisoned patient

Resuscitation

Depending on the acuity of the poisoning and the presence of end-organ injury and hemodynamic instability, patients may require early, aggressive resuscitation and treatment. Most patients who have consequential aspirin overdose will be somewhat volume deficient because of fluid losses caused by increased respiration, fever, and metabolic activity [15a]. Volume resuscitation with alkalinized intravenous fluids is reasonable and advisable and

should be initiated early in the course of the patient's treatment so that valuable time is not lost waiting for laboratory confirmation of elevated salicylate levels [65]. Begin by placing a sufficient volume of sodium bicarbonate (three ampules $NaHCO_3$ with 44 mEq Na+/ampule) into a liter of a glucose-containing hypotonic solution, such as 5% dextrose and water and infusing at 2 to 3 mL/kg per hour to promote brisk urine output. A total of 40 mEq of KCl per liter should be added to prevent hypokalemia.

Salicylate-poisoned patients who require advanced airway management are particularly challenging. Salicylate-intoxicated patients who have depressed mental status from the salicylate-induced cerebral hypoglycemia or acidosis or coingestants who require endotracheal intubation and mechanical ventilation pose a clinical no-win situation for emergency physicians, because positive pressure ventilation simply cannot maintain the respiratory rate and metabolic demands of seriously salicylate-poisoned patients. Hemodynamic instability and worsening of acid–base status will almost definitely be the consequence [66]. Patients who require endotracheal intubation for airway protection and maintenance almost always should be hemodialyzed simultaneously to remove salicylate and the accumulated organic acids. Careful attention to maintaining a favorable acid–base status through the judicious manipulation of ventilator settings should occur so as not to allow hypoventilation and the accumulation of CO_2.

Gastric decontamination

The unique characteristics of aspirin in the stomach make gastric decontamination particularly problematic. Gastric irritation, induction of nausea, and decreased mental alertness all combine to put the salicylate-poisoned patient at substantial risk for vomiting and aspiration from any attempt at GI decontamination. Clinicians must weigh the very real risk of aspiration versus the possible benefits from any method of gastric decontamination.

Activated charcoal has been demonstrated to be effective in decreasing the area under the curve for absorbed aspirin, and it is the most widely used method of gastric decontamination for salicylate-poisoned patients [67,68]. Multidose activated charcoal similarly has been shown to reduce absorption of aspirin and results in decreased serum levels, but this has not translated into an improved morbidity or mortality rate [69]. Given that multiple doses of activated charcoal are quite safe and generally well tolerated and seem to result in lower total body burden of aspirin, it is reasonable to recommend 25 g of activated charcoal without sorbitol given orally every 3 hours while the patient is being monitored with serial aspirin and blood gas measurements. Before each 25 g dose of activated charcoal, bowel sounds should be checked, and if absent, the activated charcoal should not be withheld.

Whole-bowel irrigation is not recommended in aspirin-poisoned patients, because there are very little data to support its use in salicylate poisoning.

What data do exist do not demonstrate an improved outcome [70,71]. Whole-bowel irrigation with balanced electrolyte solutions decreases gut transit time but may increase total surface area available for absorption and possibly lead to increased serum levels of aspirin. It is universally poorly tolerated and difficult to perform [70,71].

Gastric lavage largely has been abandoned in the management of poisoned patients with the possible exception of overdose with a life-threatening drug and early presentation of the patient in the course of the poisoning [72–74]. Serious aspirin poisoning is certainly a life threat and given the unique potential of enteric-coated aspirin to form concretions and remain in the stomach due to pylorospasm [22], it is reasonable to consider gastric lavage with a large-bore endogastric tube (36 French or larger) if substantial salicylate poisoning is suspected, and there is no likelihood of airway compromise [74–76].

Enhanced elimination

Restoring intravascular volume and alkalinization of the serum and urine is an important first-line treatment for acetasalicylic acid toxicity. Bicarbonate diuresis is the mainstay and first-line treatment for aspirin toxicity, and it should be initiated early in every case of moderate salicylate poisoning [65]. The (pKa) is a logarithmic function, so a small change in urine pH will have a disproportionately larger effect on salicylate clearance, so theoretically elimination of salicylic acid is increased substantially in alkaline urine [77]. The most practical method of creating an isotonic alkaline solution in the emergency department is to add sodium bicarbonate to 5% dextrose in water. In general, one 50 mL ampule of 40% sodium bicarbonate should contain 43 mEq of sodium. By putting three ampules (150 mL total volume) of sodium bicarbonate into one liter of D5W, the resulting solution should have 132 mEq of sodium, which is essentially 0.9% (normal) saline [15a]. A total of 40 mEq of KCl per liter should be added to prevent hypokalemia. This solution should be infused rapidly at a rate of at least 2 to 3 mL/kg/hour to maintain a brisk urine output of 1 to 2 mL/kg/hr. The enhanced excretion of salicylate requires not just raising the pH of the urine, but also increasing the glomerular filtration rate [65].

The development of cerebral or pulmonary edema following salicylate poisoning is an important consideration, but a concern for possibly causing these complications should not lead to inadequate or inefficient urinary alkalinization or intravascular volume restoration. Patients who develop worsening respiratory function with increased work of breathing and hypoxia consistent with pulmonary edema or who develop altered or decreased mental status consistent with cerebral edema should have their hydration and urinary alkalinization interrupted and be evaluated immediately for definitive treatment (hemodialysis).

Box 2. Indications for hemodialysis in salicylate—poisoned patients

Severe acidosis or hypotension refractory to optimal supportive care (regardless of absolute serum aspirin concentration)
Evidence of end-organ injury (ie, seizures, rhabdomyolysis, pulmonary edema)
Renal failure
High serum aspirin concentration (>100 mg/dL) despite relatively stable metabolic picture
Consider for patients who require endotracheal intubation unless that indication for mechanical ventilation is respiratory depression secondary to a coingestant.

Potassium replacement long has been an important aspect of urinary alkalinization despite a paucity of clinical evidence to support the routine practice [15a]. Chronic potassium depletion causes increased reabsorption of bicarbonate in the proximal renal tubules and difficulty achieving an alkaline urine. The effects of acute potassium depletion on urinary excretion of bicarbonate are uncertain [78]. It seems reasonable to infuse potassium and NaHCO3 simultaneously, especially in patients who are already hypokalemic. Urinary alkalinization should be delayed while attempts are made to replace the serum potassium [15a].

Hemodialysis is the definitive treatment to prevent and treat salicylate-induced end-organ injury [79]. Indications for dialysis are listed in Box 2. Hemodialysis will remove aspirin in the serum and lactate efficiently [80]. Patients may have metabolized their aspirin and have a low measured serum concentration of salicylate, but they still may benefit from hemodialysis to remove the byproducts of mitochondrial poisoning. Charcoal hemoperfusion is not practical in most circumstances [81], and hemodialysis has become the preferred method of enhanced elimination of excess serum salicylate.

Summary

Aspirin carries both significant adverse effects in therapeutic doses and a substantial risk in overdose, for which there is no antidote. Its risk-benefit profile is probably the poorest of all analgesics currently available over the counter; this is reflected in current trends in analgesic use and overdose figures [8] Emergency physicians must have a healthy respect for the erratic and unpredictable absorption and elimination kinetics of aspirin, the devastating physiologic effects of aspirin overdose and the subtle manifestations,

presentation, and increased mortality of chronic aspirin toxicity. Consultation with the regional poison control center is advised to assist with the management and follow-up of all poisoned patients.

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