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Evaluating Acetaminophen and Salicylate Poisoning in an Emergency Setting

Case Presentation

A 48-year-old woman arrived at the emergency department complaining of nausea, vomiting, and abdominal pain. She said she had ingested "two handfuls" of acetaminophen and aspirin (acetylsalicylic acid) from her bathroom medicine cabinet after an argument with her husband about 2 hours earlier. She said that her health was normally good and denied ingesting any other drugs, except that she did "wash the pills down with a little wine."

The patient's skin was moist and her pulse was 100 beats/min, respiratory rate 32 breaths/min, and temperature 38.1°C (100.6°F). Except for some moderate midepigastric tenderness and dark blood seen in the stool, the physical examination was normal. The liver was normal in size.

Suspecting acetaminophen and salicylate poisoning, the physician ordered the tests listed in Table 1. The results, especially the low pH, P_{CO_2}, and potassium and the high blood urea nitrogen and glucose (noted with salicylate poisoning) and the high liver function tests (observed in acetaminophen poisoning) along with the high acetaminophen and salicylate levels, confirmed acetaminophen and salicylate poisoning.

The patient was administered gastric lavage followed by oral activated charcoal in the emergency department and was admitted to the hospital. She also was administered an oral course of the antidote acetylcysteine (140 mg/kg loading dose, with 70 mg/kg every 4 hours for 17 additional doses). Her liver function tests were mildly elevated after 48 hours after her arrival, but later returned to normal. Because her serum salicylate level continued to increase (102 mg/dL 12 hours after ingestion), she underwent hemodialysis under the advice of the hospital's nephrologist. Her recovery was followed closely by the psychiatry service. She was discharged from the hospital 2 weeks after admission.

ABSTRACT *The poisoned patient often presents as a diagnostic and therapeutic dilemma. The emergency department physician (or medical toxicologist) not only depends upon the history of the patient and clinical findings of a specific drug or toxin, but also relies heavily on the clinical laboratory to provide information to guide proper patient management. The medical necessity of these results can often vary in an acute vs a chronic overdose. Two of the most common poisonings encountered in the emergency department are overdoses of acetaminophen and aspirin (acetylsalicylic acid). With both drugs, the laboratory plays a major role in the diagnosis and treatment of these patients.*

This is the first article in a four-part series on clinical toxicology. On completion of this series, the reader will be able to correlate clinical findings from the poisoned patient with data provided by the clinical laboratory that leads to a diagnosis; differentiate the medical necessity between an acute *vs* chronic therapeutic overdose; and describe the therapeutic interventions used by clinicians for patient management.

Acetaminophen

Acetaminophen is the most commonly prescribed analgesic agent. Additionally, many over-the-counter medications contain acetaminophen as an added pain reliever. In 1976, 50 brand-name medications and more than 200 proprietary compounds contained acetaminophen worldwide. Recently, extended-relief preparations also have become available to the public.

Acetaminophen has analgesic and antipyretic properties similar to salicylates, but has very weak antiinflammatory properties. Absorption is rapid and occurs within 1 to 2 hours after ingestion. Therapeutic peak levels can be obtained 40 to 120 minutes after ingestion, but toxic doses or concomitant drugs may delay absorption. The elimination half-life of acetaminophen is 1 to 3 hours in therapeutic doses.[1]

This drug undergoes three pathways of metabolism: glucuronidation (40%), sulfonation (50%), and cytochrome P-450 (5%). The drug also is eliminated unchanged in urine (5%). Toxicity

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TABLE 1. LABORATORY TESTS FOR PATIENT SUSPECTED OF HAVING ACETAMINOPHEN AND SALICYLATE POISONING

Test	Patient's Level	Normal Range
Arterial blood gases		
pH	7.35	7.35–7.45
Po_2	98 mm Hg	80–90 mm Hg
Pco_2	24 mm Hg	35–45 mm Hg
Complete blood count		
Hematocrit	0.39	0.37–0.47
Hemoglobin	130 g/L	120–160 g/L
Platelet count	120×10^9/L	$150–400 \times 10^9$/L
RBC count	3.5×10^{12}/L	$4.2–5.4 \times 10^{12}$/L
WBC count	15.4×10^9/L	$4.8–10.8 \times 10^9$/L
Drugs		
Acetaminophen (4h)	350 μg/mL	10–20 μg/mL
Ethanol	30 mg/dL	Below detectable limit
Salicylate (6 h)	65 mg/dL	5-35 mg/dL
Salicylate (12 h)	102 mg/dL	5–35 mg/dL
Electrolytes		
Bicarbonate	17 mmol/L	22–28 mmol/L
Chloride	103 mmol/L	99–109 mmol/L
Potassium	3.2 mmol/L	3.5–5.0 mmol/L
Sodium	138 mmol/L	136–145 mmol/L
Glucose	10.0 mmol/L (180 mg/dL)	3.9–5.8 mmol/L (70–105 mg/dL)
Liver function tests		
Alanine aminotransferase	210 U/L	10–60 U/L
Aspartate aminotransferase	120 U/L	10–40 U/L
Bilirubin (total)	1.8 mg/dL (30 μmol/L)	0–1.2 mg/dL (0–20 μmol/L)
Partial thromboplastin time	24 s	25–40 s
Prothrombin time	14 s	11–14 s
Renal function tests		
Blood urea nitrogen	10.4 mmol/L (29 mg/dL)	3.6–7.2 mmol/L (10–20 mg/dL)
Creatinine	90 μmol/L (1.0 mg/dL)	50–110 μmol/L (0.6–1.2 mg/dL)

results when glucuronidation and sulfonation pathways are saturated, shunting the drug's metabolism to the P-450 pathway. This depletes glutathione stores and forms the toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine and superoxide anions, which ultimately result in hepatic centrolobular necrosis and liver failure.[1]

An acute overdose of acetaminophen classically results in four clinical phases as summarized in Table 2. The diagnosis of acetaminophen poisoning can be made by a detailed clinical history. In children, 140 mg/kg is considered a toxic dose. An acute ingestion of more than 7.5 g at once is considered potentially poisonous to the liver of an adult. An accurate time of ingestion is a critical fact to interpret subsequent serum levels properly. Ethanol (as with this patient) may be hepatoprotective in acute doses because it competitively inhibits the cytochrome P-450 pathway. Alcoholic patients with hepatitis and cirrhosis, however, are more susceptible to acetaminophen-induced liver damage at lower doses.[2,3]

Laboratory studies should include a serum acetaminophen level optimally drawn 4 hours after ingestion. The results should be plotted on the acetaminophen, or Rumack-Matthew, nomogram to assess potential hepatotoxicity (Fig 1). The nomogram is limited to single acute ingestions identified within 24 hours of the overdose. If the time of ingestion is unknown, two serum levels should be drawn during a period of 8 hours because serum levels drawn before 4 hours after ingestion may not represent peak levels. If the half-life exceeds 4 hours, it is likely that liver toxicity has occurred. For overdoses involving the new extended-relief Tylenol product (McNeil, Spring House, Pa), 4- and 8-hour postingestion acetaminophen levels should be measured;[4] a 12-hour level should be obtained if the patient is receiving multiple drugs. With any acetaminophen poisoning, baseline liver function levels, prothrombin time, CBC, blood urea nitrogen, creatinine, and electrolytes also should be measured.

Management of acetaminophen includes decontamination methods such as gastric lavage ("stomach pumping") with a large-bore orogastric tube if the patient appears for treatment within 2 hours after ingestion.[5–8] Additionally, oral activated charcoal, a black watery suspension with tremendous absorptive properties, effectively adsorbs acetaminophen pills still present in the stomach if given up to 4 hours after ingestion.[9] A cathartic agent, such as sorbitol or magnesium citrate, commonly is added to the first dose of activated charcoal to enhance the elimination of the toxin through the gastrointestinal tract and to avoid the constipation caused by charcoal administration.

The ultimate antidote for acetaminophen poisoning is acetylcysteine (*N*-acetyl-L-cysteine [NAC]), which replenishes depleted liver glutathione stores. After treatment is started, the full course should be finished unless it is later

determined that the initial levels were nontoxic. Acetylcysteine is most effective if given within 8 hours of ingestion.[10] This antidote is administered orally (intravenously in Europe and Canada) but possesses a foul sulfur taste that often causes patients to vomit their initial loading dose. Although this antidote classically is recommended only for those patients who appear for treatment within 24 hours of ingestion, new evidence suggests that patients may benefit from it even 24 hours after the overdose.[11,12] For those patients with continued liver failure and encephalopathy despite adequate antidotal therapy,[13] liver transplantation may be necessary to prevent death.

Acetylsalicylic Acid

Acetylsalicylic acid is a common analgesic, antiinflammatory agent widely available to the public in over-the-counter preparations. Salicylate poisoning in children prompted the creation of nationwide poison control centers in the 1950s. Acetaminophen and nonsteroidal antiinflammatory agents poisonings are more frequent, but salicylate poisoning is still a common overdose not taken seriously. Despite improved clinical care and more rapid laboratory methods for detection, the overall case fatality rate of salicylate poisoning still remains high at 0.5%.[14]

Therapeutic doses of acetylsalicylic acid are rapidly absorbed from the gut. For an overdose, absorption may be delayed because of concretion (clumping of the numerous aspirin tablets) in the stomach. Peak levels are reached 6 hours after ingestion but may continue to rise up to 24 hours after ingestion. The amount of free acetylsalicylic acid is determined by the urinary pH. As the pH falls, acetylsalicylic acid is reabsorbed, and minimally excreted through the kidneys.

Metabolically, acetylsalicylic acid causes hyperthermia and uncouples oxidative phosphorylation of the Kreb's cycle. This causes increased production of lactic acid, acetoacetic acid, and β-hydroxybutyrate resulting in metabolic acidosis. Early in the clinical course, patients have an increased respiratory drive and respiratory alkalosis to compensate for this acid accumulation. As a result, the majority of patients, as in this case, will have a mixed acid-base disturbance, ie, metabolic acidosis superimposed on a respiratory alkalosis.[15] An increased demand for glucose also exists. Patients initially will be hyperglycemic because of increased glycolysis. With severe poisoning, however, patients often will suffer hypoglycemia as glucose stores are depleted. This is seen particularly in children. Severe water loss with dehydration may be profound owing to increased heat production, fever, diaphoresis, vomiting, and rapid breathing. Additionally, profound hypokalemia is common in salicylate poisoning because potassium shifts intracellularly.[15]

TABLE 2. CLINICAL PHASES OF ACETAMINOPHEN POISONING

	Onset After Ingestion	Symptoms
I	0–24 h	Gastrointestinal symptoms, nausea/vomiting
II	24–48 h	Resolution of symptoms, first abnormalities in liver enzymes
III	72–96 h	Hepatic necrosis, encephalopathy, bleeding, jaundice, death
IV	4–21 d	Recovery

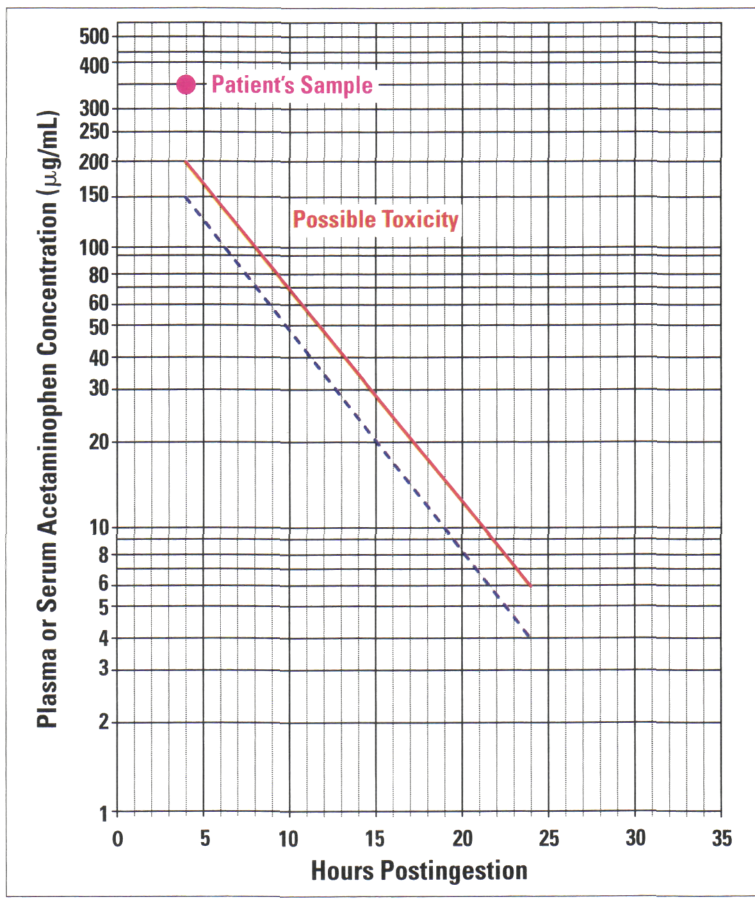

Fig 1. Acetaminophen (Rumack-Matthew) nomogram. If serum is drawn 4 or more hours after ingestion and the acetaminophen level falls above the broken line, the entire course of acetylcysteine treatment is administered. If serum is drawn 4 or more hours after ingestion and the acetaminophen level falls below the broken line, acetylcysteine treatment is not necessary or can be discontinued. The broken line represents 25% allowance from solid line for possible errors in acetaminophen assays and estimated time from ingestion of the overdose. Adapted from: Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose: 662 cases with evaluation of acetylcysteine treatment. *Arch Intern Med.* 1981;141:382. Copyright 1981, American Medical Association.

The diagnosis of salicylism can be established by a detailed history regarding the medicinal preparation and the amount and time of ingestion. Laboratory data should include a serum salicylate level best drawn at 6 hours after ingestion. The salicylate, or Done, nomogram (Fig 2), is useful only for acute (not chronic) ingestions.[16] It cannot be applied to enteric-coated or sustained-release salicylate preparations.[17] It is recommended that a series of salicylate levels be measured every 2 to 4 hours until a downward trend is established because salicylate poisoning is notorious for presenting delayed peak serum levels as a result of the concretion in the stomach.

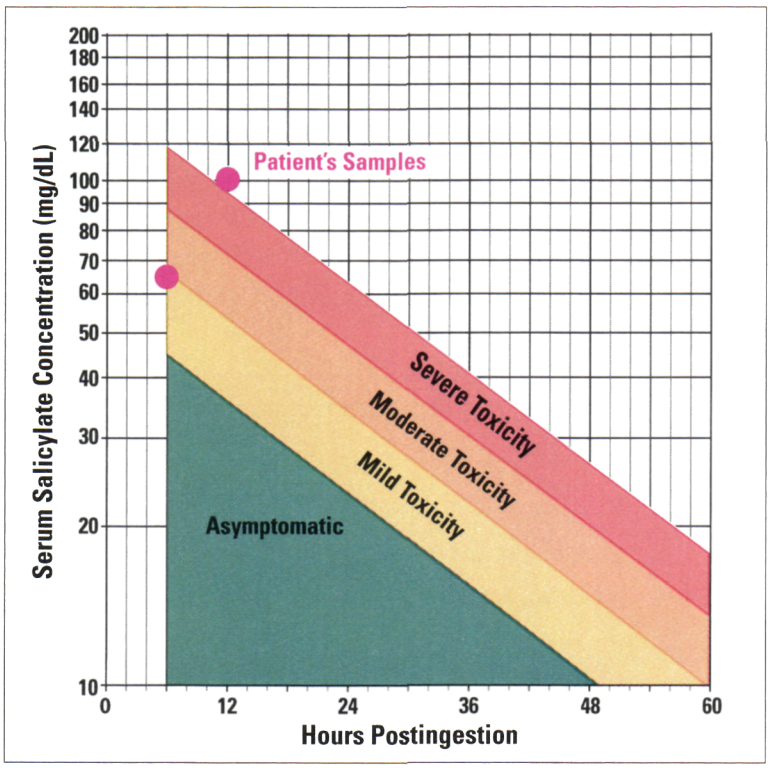

Fig 2. Salicylate (Done) nomogram. If the serum salicylate level is obtained at least 6 hours after ingestion in an acute poisoning, the nomogram can be somewhat useful in predicting the degree of toxicity over the course of several days. Multiple levels should be drawn. Note that the salicylate level increased from 65 mg/dL at 6 hours to 102 mg/dL at 12 hours. Adapted with permission from: Done AK. Salicylate intoxication: measurement of salicylate in blood in cases of acute ingestion. *Pediatrics.* 1960;26:800.

TABLE 3. LABORATORY FINDINGS WITH SALICYLISM

Laboratory Test	Results
Arterial blood gases	Mixed metabolic acidosis or respiratory alkalosis
Blood urea nitrogen and creatinine	Elevated if renal failure
CBC	Leukocytosis, anemia (if the patient is bleeding gastrointestinally)
Electrolytes	Hypokalemia, hypernatremia
Glucose	Hyperglycemia (adults) Hypoglycemia (children)
Serum salicylate	Elevated (>100 mg/dL may be fatal in acute overdose)

A rapid laboratory test (qualitative) sometimes performed in the emergency department is the addition of ferric chloride to a patient's urine sample. This compound will turn purple in the presence of salicylic acid. Other diagnostic studies should include a CBC, blood urea nitrogen, creatinine, electrolytes, and arterial blood gases. Laboratory findings consistent with acute salicylate poisoning are summarized in Table 3.

Patients with salicylate poisoning may have symptoms of nausea, vomiting, tinnitus (ringing in the ears), hyperthermia, mental status change, pulmonary edema, gastrointestinal bleeding, and seizures. Chronic ingestion of salicylates can result in clinically subtle findings that carry a higher mortality rate than acute ingestions.[18] Often these patients are elderly with underlying disease, such as arthritis or cardiac injury. The diagnosis of a salicylate overdose usually is not suspected or recognized, resulting in delayed treatment.[19]

Management of acute salicylate poisoning includes decontamination with gastric lavage and oral activated charcoal. Because salicylic acid may form concretions in the stomach, repetitive dosing of activated charcoal may be necessary.[20] Aggressive fluid, glucose, and potassium replacement is required in most cases. If the patient has hyperthermia or fever, cooling measures should be instituted. Alkalinization with bicarbonate will enhance the renal excretion of acetylsalicylic acid by fourfold. The goal is to establish a urinary pH of 7.5, but adequate potassium levels are necessary for proper alkalinization.[21]

For patients who have ingested an acute dose, more aggressive extracorporeal measures, such as hemodialysis, may be necessary if they have serum levels of greater than 100 mg/dL (>70 mg/dL for chronic overdoses) or rising levels that do not respond to conventional therapies. Coma, seizures, renal failure, and pulmonary edema also may require hemodialysis.[21]

Conclusion

Acetaminophen and acetylsalicylic acid are commonly overdosed drugs because they are widely available to patients without a prescription. With both types of poisonings, gastrointestinal symptoms predominate in the early stages. Acetaminophen overdoses can progress to liver toxicity

requiring aggressive treatment with the antidote acetylcysteine. Serum acetaminophen levels and liver function tests are essential in treating these patients. Salicylate acid overdoses can progress to acidosis, seizures, and pulmonary edema. Serum salicylate levels and arterial blood gases are keys to assisting the clinician manage acute and chronic salicylism.

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