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A Lethargic Infant with Vomiting

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CASE PRESENTATION

History

A 5-month-old female infant whose family recently immigrated to the United States from Gambia was brought to the emergency department (ED) by her mother because of a 4-day history of progressively worsening fever, vomiting, and lethargy. The mother spoke only an African dialect. She reported with difficulty through an interpreter that 4 days previously, her daughter had developed a fever and swelling in her right inguinal area; the infant had been taken to a primary care physician's office and given amoxicillin and acetaminophen. Two days later, she had begun vomiting. She had been alert until the morning of her coming to the ED, when she became lethargic. She had no recent history of upper respiratory symptoms, cough, or rashes. The patient was born in the United States and had never traveled outside of the country. Her birth history was normal, with a normal weight of 3.5 kg (7.7 lb) at delivery. She had no history of hospitalization or surgery. The remainder of the medical history, review of systems, family history, and social history was unremarkable.

Key Point

It is essential to obtain a complete patient history. Physicians should collect information concerning all medications, including any over-the-counter medications, that the patient may be taking. The initial symptoms of most drug toxicities are very nonspecific, and, occasionally, a diagnosis of early drug toxicity may be missed. Physicians should include in their differential diagnosis the possibility of an overdose of toxic substances in children who present with lethargy and a history of fever.

Physical Examination

On physical examination, the infant was lethargic and appeared ill. Her vital signs were as follows: rectal temperature, 36.1°C (97°F); heart rate, 140 bpm; respiratory rate, 42 breaths/min; systolic blood pressure, 85 mm Hg. Her weight was 7.4 kg (16.3 lb; 50th percentile for age). Although not measured, the infant's height and head circumference appeared within normal limits. She was lethargic but cried on sternal rubbing. She had no dysmorphic features, a small anterior fontanelle, normal tympanic membranes, a supple neck, and no nasal discharge. Examination of her lungs and heart revealed no abnormalities. Abdominal examination revealed a palpable liver 2 cm below the costal margin. A tender fluctuant mass was palpated in the right inguinal area. The infant's peripheral pulses were weak and her skin was mottled, cool, and clammy, but there was no jaundice or rash. Neurologic examination revealed no focal findings.

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Key Point

It is imperative to perform a thorough physical examination in critically ill patients, including a complete examination of the abdomen and neurologic system in patients with vomiting and change in mental status. The findings of a decreased level of consciousness without focality, an enlarged liver, and an abscess in the inguinal area may be key in making a diagnosis and could be missed if a comprehensive examination is not performed.

Laboratory Studies

While the infant was being evaluated and stabilized, she had a generalized seizure. Her blood glucose level was 29 mg/dL, which was immediately corrected with intravenous administration of glucose. After the seizure stopped, the patient remained lethargic. Results of laboratory studies obtained in the ED are summarized in **Table 1**. Urinalysis revealed a specific gravity of 1.037 and was negative for the presence of bilirubin; the remainder of the examination was unremarkable. A blood gas analysis while the patient was breathing room air revealed a pH of 7.29, a P_{CO_2} of 24 mm Hg, and a P_{O_2} of 71 mm Hg.

Key Point

All patients with an acute change of mental status must have an immediate blood glucose evaluation performed. In patients who are critically ill, arterial blood gas measurements should be obtained to determine the adequacy of oxygenation and ventilation and to look for the presence of a metabolic acidosis. An acetaminophen level should be immediately obtained in patients with evidence of acute hepatic failure.

- **What is the differential diagnosis of a lethargic infant with vomiting?**

Table 1. Initial Laboratory Values of Case Patient

Variable	Result	Normal Range
Hematologic values		
Leukocyte count	$29.7 \times 10^3/mm^3$	$6–17.5 \times 10^3/mm^3$
Differential		
Segmented neutrophils	67%	40–60%
Lymphocytes	15%	20–40%
Platelet count	$676 \times 10^3/mm^3$	$150–350 \times 10^3/mm^3$
Hemoglobin	11.5 g/dL	11.1–14.1 g/dL
Serum values		
Blood urea nitrogen	8 mg/dL	7–22 mg/dL
Electrolytes		
Sodium	134 mEq/L	135–148 mEq/L
Potassium	5 mEq/L	3.5–5 mEq/L
Chloride	112 mEq/L	96–109 mEq/L
Bicarbonate	18 mEq/L	20–25 mEq/L
Serum glucose	30 mg/dL	70–115 mg/dL
Serum creatinine	0.5 mg/dL	0.3–0.7 mg/dL
Total protein	4.6 g/dL	4.2–7.4 g/dL
Albumin	3.1 g/dL	2.8–5 g/dL
Alanine aminotransferase	455 U/L	0–35 U/L
Aspartate aminotransferase	1907 U/L	0–35 U/L
Alkaline phosphatase	603 U/L	150–420 U/L
Bilirubin		
Total	2.7 mg/dL	0.1–1.2 mg/dL
Direct (conjugated)	1.9 mg/dL	0.1–0.3 mg/dL
Ammonia	189 µg/dL	41–98 µg/dL
Prothrombin time	53.5 s	10.6–11.4 s
Partial thromboplastin time	75 s	24–36 s

DIFFERENTIAL DIAGNOSIS

A young infant with acute onset of vomiting and lethargy presents a great challenge to the emergency physician. The differential diagnosis is broad and includes a wide range of conditions, each requiring a very different approach.

Vomiting is a common presenting symptom in pediatrics, because it has both systemic and gastrointestinal causes. Vomiting may be the initial symptom of a benign condition (eg, gastroenteritis) or part of a symptom complex of a serious illness (eg, sepsis, meningitis). Systemic illnesses that may present with vomiting are shown in **Table 2**. The presentation may be dramatic (eg, vomiting, lethargy, hypoglycemia), or the signs and symptoms of sepsis may be as subtle as poor feeding. The history may vary, and some infants may have been ill for several days, whereas others deteriorate more rapidly. A single symptom or a combination of symptoms such as lethargy, irritability, vomiting, or fever may be a manifestation of sepsis. Fever generally is an unreliable finding in the septic infant. Many septic infants younger than 2 months will be hypothermic instead. On physical examination, an infant with sepsis may be

Table 2. Systemic Causes of Vomiting in Infants

Infectious
Sepsis
Genitourinary
Pyelonephritis
Ureteropelvic junction obstruction
Urinary tract infection
Central nervous system
Encephalitis
Increased intracranial pressure
Meningitis
Reye's syndrome
Metabolic
Inborn error of metabolism
Renal or hepatic failure
Toxic ingestion
Acetaminophen
Digoxin
Iron
Salicylates
Theophylline

pale, ashen, or even cyanotic. The skin is often cool and may be mottled because of poor perfusion.

Inborn errors of metabolism should be suspected in the differential diagnosis of any acute illness of infancy, including those that present with persistent vomiting. Historic elements that may aid in the diagnosis of a metabolic disorder include early or unexplained death of a sibling, multiple spontaneous maternal abortions, or a history of consanguinity. Associated features of metabolic disease may include neurologic signs and symptoms, such as lethargy, hypotonia, and convulsions.

The differential diagnosis of acute hepatitis with fulminant hepatic failure includes septic shock with ischemic hepatic necrosis, viral hepatitis, Reye's syndrome, metabolic disorders (eg, galactosemia, tyrosinemia, Wilson's disease, medium-chain acyl-CoA dehydrogenase deficiency, urea cycle defects), and hepatitis caused by drugs and toxins. Common drugs that can cause a fulminant hepatitis include acetaminophen, iron, and salicylates.

CLINICAL COURSE

The infant was intubated for airway protection. Because of the patient's history of acetaminophen administration, a serum acetaminophen level was obtained and measured 78.5 μg/mL. On further questioning, the patient's mother reported giving her daughter 2 mL of infant acetaminophen (80 mg/0.8 mL) every 4 hours, equivalent to giving 27 mg/kg body weight every 4 hours (almost double the usual therapeutic dose). Most likely because of the language barrier, the patient's mother confused the doses of acetaminophen and amoxicillin. Instead of administering 1 mL of acetaminophen every 4 hours as instructed, she administered 2 mL and only 1 mL of amoxicillin (instead of 2 mL) every 8 hours. She did this for 4 consecutive days and inadvertently administered a toxic dose of acetaminophen (162 mg/kg every 24 hours) to her daughter.

The diagnosis of hepatic failure due to acetaminophen toxicity was made. The infant was given a loading dose of N-acetylcysteine (NAC) and was transferred to a regional transplant center. She received a total of 18 doses of NAC. Clinical recovery was rapid and progressive. The liver enzyme levels returned to near normal by the fifth hospital day, and the patient made a complete recovery over 3 weeks without the need for a transplant. The swelling in her right inguinal area was a small abscess, and it resolved with intravenous administration of antibiotics.

ACETAMINOPHEN POISONING

Acetaminophen is generally considered to be a safe drug, but administration of an incorrect dose can result in significant morbidity and mortality. Acetaminophen toxicity causes liver injury and can result in liver failure. Typically, coma and metabolic acidosis are associated with the onset of hepatic encephalopathy during the course of severe acetaminophen poisoning. Acetaminophen (N-acetyl-p-aminophenol [APAP]) is the most popular pediatric analgesic/antipyretic agent and has now become one of the most common pharmaceutical preparations accidentally ingested by young children. Acetaminophen is the most commonly reported pharmaceutical exposure in children younger than age 6 years.[1] Fortunately, accidental ingestion in young children has been associated with low morbidity, although occasional cases of hepatotoxicity occur, particularly in the context of inadvertent repetitive overdosing.[2–5] Because the symptoms of acetaminophen toxicity are nonspecific, however, the diagnosis and treatment are often likely to be delayed in unintentional cases of toxicity.

Pathophysiology

The toxicity of acetaminophen is closely linked to its metabolism. The metabolism of acetaminophen is

Table 3. Stages of Acetaminophen Toxicity

Stage	Time Following Ingestion	Characteristics
I	0.5–24 hours	Anorexia, nausea, vomiting, malaise, pallor, diaphoresis
II	24–48 hours	Resolution of above symptoms; right upper quadrant abdominal pain and tenderness; elevated bilirubin level, prothrombin time, and hepatic enzyme levels; oliguria
III	72–96 hours	Peak liver function abnormalities; anorexia, nausea, vomiting, and malaise may reappear
IV	4 days – 2 weeks	Resolution of hepatic dysfunction

Adapted with permission from Linden CH, Rumack BH. Acetaminophen overdose. Emerg Med Clin North Am 1984;2:110.

primarily hepatic, with a half-life of 2 to 4 hours. Over 90% of acetaminophen is metabolized in the liver to nontoxic glucuronide and sulfate conjugates that are eliminated in the urine. APAP, the parent compound, is nontoxic, but hepatic metabolism of a small fraction of the drug (approximately 5%) leads to formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Hepatotoxicity results from the formation of NAPQI by the cytochrome P-450 mixed function oxidase pathway. Glutathione, a tripeptide consisting of glutamate, cysteine, and glycine, can detoxify harmful compounds such as NAPQI. Glutathione binds to NAPQI and leads to formation and excretion of nontoxic mercapturate conjugates. As glutathione stores are diminished, as occurs in a significant acetaminophen overdose, NAPQI is not detoxified and can bind to hepatocytes, causing centrilobular necrosis. Usually, because of the relatively small amount of NAPQI formed and the adequate supply of glutathione, acetaminophen has an excellent safety profile.

Clinical Presentation

Acute acetaminophen overdose in an infant has a fairly typical presentation. The infant may exhibit nausea, vomiting, and diaphoresis during the first 24 hours, but clinical improvement invariably occurs. Biochemical abnormalities are evident 48 to 72 hours after ingestion. There is often profound elevation of the serum aminotransferase levels caused by hepatocellular necrosis. Hypoprothrombinemia and hypoglycemia are common, and there is only a modest hyperbilirubinemia and increase of the serum alkaline phosphatase level. The hepatic stage develops 3 to 4 days after ingestion. In this stage, manifestations of hepatic necrosis develop and include nausea, anorexia, vomiting, hypoglycemia, and pain in the right upper quadrant. Fulminant liver failure is rare, but when it does occur, it can manifest as jaundice, bleeding, confusion, lethargy, asterixis, and coma. In the most severely affected individuals, death caused by fulminant hepatic necrosis occurs 4 to 18 days after ingestion.[6] The stages of acetaminophen toxicity are shown in **Table 3**.

Hepatotoxicity caused by acetaminophen overdose was first reported in 1966.[7] It is well known that acetaminophen produces a dose-dependent hepatic necrosis that becomes evident within 2 to 4 days after a toxic dose. A type B lactic acidosis occurs when there is normal perfusion of organs but an imbalance between lactic acid production and its metabolism by the liver, which occurs in hepatic failure.[8] Survivors will recover hepatic functions over a period of 2 weeks following overdose.

Diagnosis

Unlike other types of poisoning, the diagnosis of acetaminophen toxicity depends on the results of laboratory testing, because the initial clinical presentation is nonspecific and thus not helpful. Additionally, the initial manifestations of acetaminophen toxicity are usually delayed. Rumack and Matthew,[9] in their landmark study in 1975, did not indicate a minimum dose for toxicity but emphasized prolongation of the half-life of acetaminophen from liver toxicity. Reports of liver toxicity in pediatric patients have suggested that a minimal, single acetaminophen dose of 120 to 150 mg/kg may be associated with hepatoxicity.[2,10] Generally, an acute toxic dose of more than 150 mg/kg is considered to be associated with liver injury. Fatality has occurred in children with chronically high (4–5 g/day) ingestion of acetaminophen over a period of 2 to 6 days.

Diagnostic testing is directed toward 2 goals: predicting the risk of subsequent acetaminophen toxicity and determining the degree of organ injury. Development of treatment profiles that could predict the development of hepatic injury from a single determination of serum acetaminophen concentration,[11,12] obtained at least 4 hours after ingestion, led to the development of the Rumack-Matthew nomogram.[13] This nomogram is simply a line drawn on a time-log concentration plot

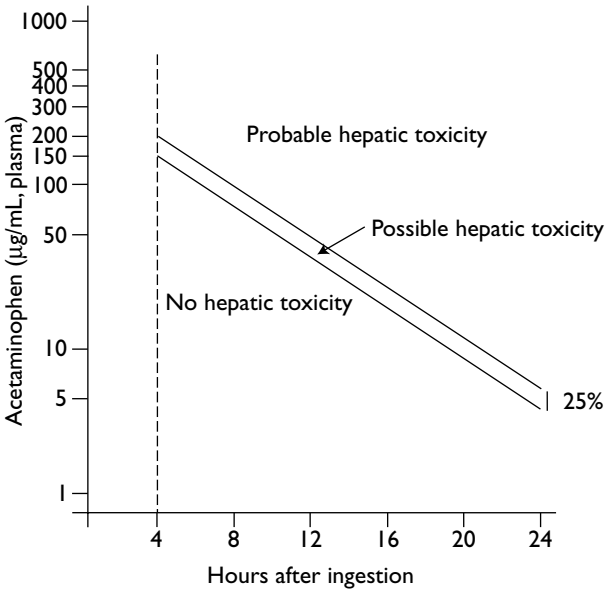

Figure 1. Semilogarithmic plot of plasma acetaminophen levels versus time. (Adapted with permission from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975;55:873.)

from 200 mg/L at 4 hours with a half-life of 4 hours. Any serum concentration obtained 4 or more hours after a single ingestion may be plotted on the nomogram to estimate risk of hepatotoxicity. The Rumack-Matthew nomogram was developed for single acute ingestions of acetaminophen and is based on observational data that have been successfully validated in a large series of patients.[14] The nomogram uses a single level in time to predict the risk of hepatotoxicity; however, it does not predict fulminant hepatic failure or death.

Nomogram tracking begins 4 hours after ingestion and ends 24 hours after ingestion. An adaptation of the Rumack-Matthew nomogram (**Figure 1**) has an upper and lower line. The upper line is the probable line, and 60% of patients with plots above this line develop hepatotoxicity. The lower line, which is the possible line, was added to the nomogram to give a 25% margin of error to allow for variations in measurement of acetaminophen level or uncertainty of time of ingestion. Because it is always better to err on the side of safety, we recommend using the lower "possible" line; patients with a value above this line should be treated. The Rumack-Matthew nomogram, although commonly used to predict risk of hepatotoxicity from serum APAP levels in cases of acute ingestion, is not useful in cases of chronic toxicity.

Key Point

Acetaminophen is the most commonly overdosed medication and is the leading cause of hepatic failure. NAC appears to be beneficial in the treatment of acetaminophen-induced fulminant hepatic failure, in addition to treating less severe acetaminophen toxicity.

Management

Treatment of patients with acetaminophen toxicity consists of gastrointestinal decontamination, the timely use of NAC, and supportive care. Management is dictated by the time at which the patient begins to receive medical care and by the patient's acetaminophen level at the time of presentation.

In most cases of acetaminophen poisoning, adequate gastrointestinal decontamination consists of the early administration of activated charcoal, orally or through a nasogastric tube. Gastric lavage is no longer routine in gastric decontamination. Because acetaminophen is rapidly absorbed, the use of gastric emptying procedures to treat the acetaminophen component of ingestion is not logical more than 2 hours after an overdose. However, gastric emptying performed beyond 2 hours after ingestion may be a reasonable measure to reduce the toxicity of possible coingestants. In patients treated more than 4 hours after an overdose, gastric decontamination usually is not warranted.

It is essential to delineate the time of ingestion, obtain an acetaminophen level no earlier than 4 hours after ingestion, and avoid delay in the administration of NAC, if indicated. The antidote for acetaminophen toxicity is NAC, which has several mechanisms to prevent hepatotoxicity. NAC is converted to cysteine, which can replenish glutathione stores. NAC also directly detoxifies NAPQI to nontoxic metabolites. NAC can provide a substrate for sulfation, thereby increasing the capacity for nontoxic metabolism. NAC can directly conjugate NAPQI to reduce toxicity and is indicated in the following situations: (1) ingestions with potential toxicity; (2) late presentations with potential or ongoing toxicity; and (3) chronic overdose and evidence of ongoing hepatic damage (eg, elevated aminotransferases, elevated prothrombin time, vomiting). The standard 72-hour oral NAC regimen used in the United States in a loading dose of 140 mg/kg followed by a maintenance dose of 70 mg/kg administered intravenously every 4 hours for 17 doses.

The management of patients with chronic acetaminophen toxicity has been primarily supportive. However, NAC is indicated for all toxic ingestions above the "possible toxicity" line on the nomogram. Recent

studies point to the beneficial effects of NAC, even when used more than 24 hours after ingestion[15–17] and even after clinical or laboratory evidence of hepatic toxicity is available, as occurred in the case patient.

CONCLUSION

Acetaminophen toxicity should be considered in any pediatric patient with a febrile illness, lethargy, and vomiting to whom an antipyretic is being administered. Persistent vomiting may be caused by hepatic inflammation from acetaminophen overdose. Dosing errors can only be diagnosed by obtaining a complete history, which must include the exact drug formulation, the dose, the route of administration, the dosage frequency, and the number of doses. Physicians must be careful to educate parents when prescribing medications, especially when a language barrier exists. **HP**

ACKNOWLEDGMENT

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