Hepatic Failure Despite Early Acetylcysteine Following Large Acetaminophen-Diphenhydramine Overdose

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KEY WORDS

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abstract

We describe the case of a patient with massive acetaminophen-diphenhydramine overdose and a 4-hour serum acetaminophen concentration of 653 $\mu\text{g/mL}$. The patient was treated with acetylcysteine 5 hours after ingestion. Because of a persistently elevated serum acetaminophen level of 413 $\mu\text{g/mL}$ 45 hours after ingestion, a medical toxicologist recommended that the patient be treated with a second bolus of acetylcysteine (150 mg/kg followed by 12.5 mg/kg per hour for 4 hours, then 6.25 mg/kg per hour). On hospital day 3, she developed hepatic failure despite early treatment. Her transaminase levels and hepatic synthetic function began to improve on hospital day 6, and acetylcysteine was discontinued on hospital day 10. In cases of massive acetaminophen overdose, standard acetylcysteine dosing may not be adequate. We suggest that elevated serum acetaminophen concentrations at the end of a standard 20-hour acetylcysteine infusion should be discussed with the local poison center. *Pediatrics* 2011;127:e1077–e1080

Acetaminophen poisoning is common, and early administration of acetylcysteine is strongly associated with good outcomes. Throughout the 1980s and 1990s the vast majority of cases of acetaminophen poisoning in the United States were treated by using a 72-hour oral dosing protocol that provided a total of 1330 mg/kg of acetylcysteine over 72 hours.¹ In 2004, an intravenous formulation of acetylcysteine was introduced that delivered 300 mg/kg over 20 hours.² We describe here the case of a pediatric patient who had markedly elevated acetaminophen concentrations at the end of the 20-hour infusion and who went on to develop hepatic failure despite receiving standard early and complete treatment. We suggest that some patients with acetaminophen overdose may require a modification of the intravenous treatment protocol.

CASE REPORT

A 12-year-old (64-kg) girl had a self-reported ingestion of ~175 tablets of 500-mg acetaminophen and ~48 tablets of 500-mg acetaminophen/25-mg diphenhydramine in a self-harm attempt. The ingestion occurred at 15:30, and total estimates of the ingestion were 1742 mg/kg of acetaminophen and 19 mg/kg of diphenhydramine.

The patient had a history of depression, bipolar disorder, attention-deficit disorder, multiple previous suicide attempts, and inpatient psychiatric admissions. The patient takes dextroamphetamine, risperidone, and citalopram.

Outside Hospital Course

She was initially alert but then became lethargic during private transport to the community hospital. On presentation, she had a serum acetaminophen concentration of 241 $\mu\text{g/mL}$ 1 hour after ingestion. Results of her complete blood count and tests of renal and hepatic function were normal (Fig 1), and

FIGURE 1

Serum alanine aminotransferase (ALT) and acetaminophen concentrations after ingestion of 1742 mg/kg of acetaminophen and 19 mg/kg of diphenhydramine. The patient received a standard course of acetylcysteine starting 5 hours after ingestion. At 21 hours the final infusion rate was continued until 45 hours, when she received a second bolus of acetylcysteine (150 mg/kg bolus followed by 12.5 mg/kg per hour). NAC indicates *N*-acetylcysteine.

a urine toxicology screen was positive for amphetamines. A nasogastric tube and foley catheter were placed; she was given 1 dose of activated charcoal and transferred to a children's hospital for further management. During transportation she was somnolent and required 15 L/minute of oxygen to maintain oxygen saturation above 90%.

Emergency Department Course

She arrived to the tertiary hospital at 19:30. Her blood pressure was 106/28 mm Hg, heart rate was 144 beats per minute, temperature was 96.6°F, respiratory rate was 21 breaths per minute, and oxygen saturation was 97% on 15 L/minute of oxygen. She was minimally responsive to sternal rub, her pupils were 4 mm and reactive, her sclera were anicteric, she had moist mucous membranes, her lung sounds were clear, she was in mild respiratory distress, and snoring was noted. Her cardiac and abdominal examinations were unremarkable, and she had no rashes and no focal movements, eye-opening, or vocalization with sternal rub. Laboratory tests were ordered at the time of arrival. Her transaminase

levels remained normal (Fig 1), and her venous blood gas was 7.22/34/71/14/-13.

She developed hypotension during endotracheal intubation using etomidate and rocuronium for inability to protect her airway. Her blood pressure decreased to 79/25 mm Hg but responded to an infusion of normal saline. Her 4-hour acetaminophen level was 653 $\mu\text{g/mL}$. Five hours after ingestion, acetylcysteine (150 mg/kg intravenously over 60 minutes followed by 12.5 mg/kg per hour for 4 hours followed by 6.25 mg/kg per hour) was initiated.

PICU Course

She remained intubated during her PICU course for 2 days. She required an insulin drip for 2 days for hyperglycemia. Her acetylcysteine infusion was continued at 6.25 mg/kg per hour until 45 hours into her hospital course, when the medical toxicology service was consulted regarding her persistently elevated serum acetaminophen concentration of 470 $\mu\text{g/mL}$ and rising serum transaminase levels (Fig 1). At that time she was treated with a second bolus of intravenous acetylcysteine (150 mg/kg over 60 minutes followed by 12.5 mg/kg per hour for 4 hours) followed by resumption of the 6.25 mg/kg per hour infusion. Over the next several days her transaminase levels continued to rise, she developed mild hepatic encephalopathy, and her international normalized ratio became elevated and peaked at 4.8 on hospital day 4; her serum creatinine remained normal throughout her hospitalization. On hospital days 3 and 4 she had some coffee-ground emesis and was treated with fresh-frozen plasma, vitamin K, and 2 doses of factor VII. She was temporarily placed on the liver-transplant list but was removed when her transaminase levels began to decrease, her international normalized

ratio began to normalize, and her encephalopathy resolved on hospital day 6. She also received a course of cefotaxime for blood cultures that grew *Haemophilus influenzae*. Acetylcysteine was discontinued on hospital day 10. After a 12-day hospitalization, she was transferred for inpatient psychiatric care.

DISCUSSION

Our adolescent patient ingested a large amount of acetaminophen and diphenhydramine and developed acute hepatic failure despite early and complete treatment with acetylcysteine. In general, patients who receive acetylcysteine within 8 hours of acetaminophen ingestion do not develop significant liver injury.¹ We believe that 2 factors contributed to our patient's course. First, she ingested a very large dose of acetaminophen. Second, she also ingested diphenhydramine, an anticholinergic medication that has previously been associated with delayed absorption of acetaminophen.^{3,4} These 2 factors resulted in a very high acetaminophen concentration >20 hours after the ingestion. With the standard intravenous protocol, the vast majority of the acetylcysteine (200 mg/kg) is administered during the first 5 hours of the infusion. We believe the dose she received during the final infusion (6.25 mg/kg per hour) was not adequate to protect her from her such a high serum acetaminophen concentration.

Rationally, hepatic injury despite standard therapy is feasible when one considers the mechanism of action of acetylcysteine. Acetylcysteine prevents acetaminophen toxicity primarily by restoring hepatic glutathione, which detoxifies the metabolite of acetaminophen (commonly known as *N*-acetyl-*p*-benzoquinone imine [NAPQI]).⁵ The dose of acetylcysteine must be sufficient to restore and maintain hepatic glutathione while

the acetaminophen is metabolized. In the vast majority of cases, 300 mg/kg over 20 hours is more than sufficient. However, if the rate of NAPQI production exceeds the rate of glutathione replenishment, hepatic injury can occur.

Acetylcysteine has been used successfully to treat acetaminophen overdose for >40 years. Between 1976 and 2004, the vast majority of patients with acetaminophen overdose in the United States were treated with the 72-hour protocol.¹ During that time there were no published cases of patients who developed hepatic failure when they were treated within 8 hours using either route. However, after the adoption of the 20-hour intravenous protocol, there have been several adults who have received early therapy following a large overdose, had very high serum acetaminophen concentrations at the end of the 20-hour treatment protocol, and developed hepatic injury, liver failure, and even death.^{6,7} The majority of these cases also involved ingestion of diphenhydramine, but a similar course was described after a 48-g single-substance acetaminophen ingestion.⁸ These cases suggest that large acetaminophen overdoses may place patients at risk of acetaminophen toxicity despite early treatment with the standard 20-hour intravenous protocol.

There are several alternatives that may be more effective than the standard 20-hour intravenous protocol for massive acetaminophen overdose. The first alternative is using the standard 72-hour oral protocol. There are theoretical benefits of the oral dosing of acetylcysteine protocol; a higher total and maintenance dose is administered, and the first-pass effect may lead to a higher antidote concentration reaching the liver when compared with the standard intravenous proto-

col. Anecdotal evidence suggests that the oral protocol is effective after massive overdose; a patient with concentrations similar to ours did not develop liver injury after treatment using the oral acetylcysteine protocol.⁹ However, oral therapy may not be practical because of central nervous system depression caused by co-ingestion (such as diphenhydramine, the likely cause in our case) or vomiting. A second alternative is using a higher-dose intravenous protocol. One potential solution is intravenous administration using the oral dosing protocol (140 mg/kg loading dose followed by 70 mg/kg every 4 hours). This protocol was shown to be safe in 1 clinical trial.¹⁰ In our center, current practice is to treat with a second bolus of 150 mg/kg if the serum acetaminophen concentration exceeds 75 $\mu\text{g/mL}$ at the end of the 20-hour treatment protocol, and we would continue acetylcysteine at 6.25 mg/kg per hour until the serum concentration is <10 $\mu\text{g/mL}$. However, there is substantial variation in practice, and we would recommend contacting the local poison center or toxicologist for treatment recommendations. Finally, other treatment modalities, such as hemodialysis to increase acetaminophen clearance, may also have a role.¹¹

Our case also illustrates the importance of documenting the serum acetaminophen concentration before ending acetylcysteine therapy. Because the half-life of acetaminophen is generally <4 hours, the vast majority of patients will have undetectable or very low serum concentrations at the end of 20 hours of treatment. However, several published case reports have described prolonged absorption of acetaminophen after large overdoses of acetaminophen and diphenhydramine. Although some guidelines have suggested that obtaining additional serum acetaminophen con-

centrations is not needed,¹² our poison center recommends measuring the concentration before stopping therapy. If

the acetaminophen concentration remains high, additional acetylcysteine should be considered.¹³

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