Acetaminophen Overdose in the Second Trimester of Pregnancy

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Acetaminophen continues to be the most recommended analgesic used in pregnancy. The adverse publicity aspirin has received as a result of its association with Reye's syndrome has increased acetaminophen use as well. Thus, acetaminophen overdoses are becoming more common.

This report details an experience with an acetaminophen overdose in the second trimester of pregnancy. The earliest prior reported overdose was at 36 weeks' gestation.[1] Appropriate therapy was initiated with apparent good results in both mother and infant. The quantity of acetaminophen reaching the fetus as well as fetal metabolism is still unclear, but it appears that with appropriate treatment, both maternal and fetal well-being are possible.

CASE REPORT

A 21-year-old gravida 2 para 1 woman at 16 weeks' gestation both by dates and prior ultrasound done at six weeks' gestation was admitted to the hospital four hours after the ingestion of 36 g of acetaminophen. Blood studies revealed an initial acetaminophen level of 340 μg/mL (toxic greater than 200 μg/mL). Local poison-control authorities were contacted, and the acetaminophen overdose protocol with oral acetylcysteine (Mucomyst) was initiated (Table 1).

The patient was alert and in no acute distress. Blood pressure was 128/68 mmHg, temperature 37°C, respirations 16/min, and pulse rate 104 beats per minute. Examination of the heart revealed no abnormality. Abdominal findings were consistent with her gestational age with the fundus palpable at approximately 6 cm below the umbilicus. There was no right upper quadrant tenderness or hepatomegaly. Fetal heart rate was 160 beats per minute. The neurologic examination was without focal deficits.

Additional laboratory data revealed the following; hemoglobin 12.8 g/dL, white cell count $10.6 \times 10^3/\mu$L, sodium 137 mEq/L, potassium 3.6 mEq/L, chloride 106 mEq/L, and carbon dioxide 22 mEq/L. Serum glutamic oxalocetic transaminase (SGOT) was 25 IU/L, serum glutamic pyruvic transaminase (SGPT) 2 IU/L, total bilirubin 0.4 mg/dL, glucose 139 mg/dL, and prothrombin time was 14 sec.

The onset of nausea with vomiting preceded the patient's arrival to the hospital and complicated attempts to administer the acetylcysteine orally despite mixing it with a variety of palatable beverages, the use of concomitant intramuscular prochlorperazine, and placing a nasogastric tube. With the passage of time and the lack of success with the oral administration of acetylcysteine, concerns over the potential for hepatotoxicity increased. The Rocky Mountain Poison Control Center was notified, and the decision was made to administer the acetylcysteine intravenously for the first 24 hours or until the nausea subsided.

The patient was transferred to the intensive care unit in the event that anaphylaxis should occur (two cases worldwide), and informed consent was received, as intravenous acetylcysteine is not yet approved by the Food and Drug Administration. The loading dose of acetylcysteine (140 mg/kg) was mixed with 200 mL of 5 percent dextrose in water and run through a .22-μ micropore (Burron Medical) filter over 20 minutes with the remaining doses (70 mg/kg) mixed in 500 mL of 5 percent dextrose in water to run at four-hour intervals for the remaining 48 hours.[2] Fetal heart tones were monitored at four-hour intervals and remained consistently in the 150 to 160 beat per minute range.

The patient's gastrointestinal distress resolved enough so that the remaining doses over the next 48 hours were well tolerated orally. Monitoring of laboratory values revealed no significant changes in SGOT, SGPT, prothrombin time, or electrolytes, with the blood glucose level reaching 190 mg/dL before return-

Submitted, revised, August 26, 1985.

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TABLE 1. ROCKY MOUNTAIN POISON CONTROL CENTER PROTOCOL FOR ADMINISTRATION OF *N*-ACETYL CYSTEINE IN ACETAMINOPHEN OVERDOSE

Indications
Serum acetaminophen level in toxic range (greater than 200 μg/mL)
Less than 24 hours since ingestion
N-acetyl cysteine dosage
Loading dose: 140 mg/kg
Maintenance dosage: 70 mg/kg every 4 hours for 17 total doses

ing to normal. The elevation in blood glucose was coincident with the large volume of 5 percent dextrose in water solution administered with the acetylcysteine and returned to normal values when the intravenous solution was stopped.

Both mother and fetus were in satisfactory condition after the completion of the protocol and were allowed to return home with continuing care through her family physician. Appropriate behavioral science follow-up for the patient and her family was arranged prior to discharge.

The remainder of the pregnancy was uneventful with progressive fundal height growth and weight gain. Maternal liver enzymes and blood glucose levels were followed and remained normal. At 40 weeks' gestation the patient was admitted to the hospital in spontaneous labor and delivered of a 3.4-kg female infant with Apgars of 9 and 9 at 1 and 5 minutes. The postpartum course of both mother and child was uneventful, and they returned home three days later. At one year of age the child is growing and developing normally.

COMMENT

Acetaminophen is eliminated from the body primarily by conjugation with glucuronide and sulfate with subsequent excretion in the urine. A minor pathway uses the cytochrome p-450 mixed oxygenase system to convert acetaminophen to a reactive metabolite, acetamido-quinone, which is metabolized to a glutathione conjugate, with subsequent conversion to cysteine and mercaptopuric acid conjugate. With either short-term or long-term ingestion of large doses of acetaminophen, the glutathione system is depleted to less than 30 percent capacity, and the metabolite formed from the cytochrome p-450 system combines covalently with the nucleophilic protein of hepatocytes causing centrilobular necrosis with periportal sparing.[3]

N-acetyl cysteine is the *N*-acetyl derivative of the amino acid L-cysteine, and constitutes the central portion of the glutathione molecule. The mechanism of *N*-acetyl cysteine as an antidote for acetaminophen overdose is not clear. The presumed explanation is that since *N*-acetyl cysteine is metabolized to cysteine, a glutathione precursor, it thereby provides protective levels of glutathione to detoxify the acetaminophen metabolite.[3]

It is known that both young children and the fetus are able to metabolize acetaminophen through the mixed oxidase system to form the hepatotoxic metabolite.[4] According to case reports, infant acetaminophen overdose with toxic levels rarely causes hepatic damage. The damage that is done is also relatively minor and transient, as case studies of a 6- and 7-week-old infant with acetaminophen overdose suggest.[4] This observation can be extrapolated to the age of 9 to 12 years old, as a dose of almost ten times that used therapeutically is required before a toxic reaction becomes a potential threat.

Studies suggest that younger children have fewer toxic effects from an acetaminophen overdose than older children and adults.[6] Metabolic differences include a more developed and predominant sulphation pathway as opposed to glucuronidation and the ability to stimulate glutathione production in response to acute depletion.[7,8] Furthermore, oxidation in the fetal liver has been shown to be ten times slower than in the adult liver with oxidation rates increasing with fetal age.[4] It would appear that in addition to the appropriate treatment of maternal acetaminophen overdose, there are fetal protective factors.

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