CASE STUDY

PARACETAMOL TOXICITY — A CASE STUDY

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SUMMARY

This paper presents a case of a healthy man who ingested a massive dose of paracetamol in a suicide attempt, to serve as a basis for a discussion of paracetamol toxicity. The temporal sequence of signs and symptoms manifested is typical of paracetamol toxicity. Liver function tests showed striking increases in plasma aspartate aminotransferase and lactic dehydrogenase activity. Prothrombin time was prolonged. The serum level of peracetamol 48 h after ingestion was 40 µg/ml. After symptomatic treatment, the patient recovered rapidly; within 2 weeks liver function had returned to normal. N-Acetylcysteine is a highly effective antidote for paracetamol toxicity, particularly if given within 10 h of paracetamol ingestion. If 24 h or more have elapsed, only supportive measures are indicated. During the early phase of intoxication, gastric lavage or induction of emesis should be performed to decrease continuing absorption of the drug.

Paracetamol (acetaminophen), because of its remarkable safety at recommended doses, is one of the most widely used analgesic and antipyretic medications. In potency and duration of effect it is equivalent to aspirin but has little anti-inflammatory action (1). At usual doses, paracetamol does not cause the gastrointestinal irritation or decreased platelet aggregation sometimes associated with aspirin (2). Despite this lack of significant adverse effects, however, massive overdose can cause hepatic

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necrosis and even death (2). There has been an increase in the incidence of acute overdose with paracetamol, particularly in Western countries (3-5). In adults this increase is due mainly to suicide attempts, whereas accidental poisoning accounts for the incidence in children, especially in the age group 1-4 years (5,6). In Thailand, because of the increased availability of paracetamol and its growing popularity with both physicians and consumers, overdose may become a significant factor in the Thai drug toxicity picture.

This paper presents a case study of a healthy man who ingested a massive dose of paracetamol in a suicide attempt. The findings serve as the basis for a discussion of various aspects of paracetamol toxicity, including its treatment.

CASE REPORT

D. H., a 39-year-old white man, was referred to the Strong Memorial Hospital, University of Rochester (Rochester, N.Y.), for the treatment of paracetamol overdose. He stated that he had always been in good health, but occasionally drank excessive amounts of alcohol and smoked one pack of cigarettes a day. Three days before admission, depressed and angry over discordant marital relations, he had taken about 60 tablets of paracetamol (Extra-Strength Tylenol, 400 mg/tablet) over a 1.5-h period, with one bottle of beer. Four hours later he had vague abdominal pain, felt nauseated, and vomited. The vomitus was blood-stained and contained food and some tablet particles. At that time he felt lethargic and light-headed; he described himself as "stumbling around and seeing stars". During the night he again became nauseated and vomited several times. He also had pain in the lower back and the right rib cage, and experienced hot sweats alternating with chills. The following morning the chills had subsided, but he felt feverish and nauseated. In the course of the day he had 3 to 5 episodes of diarrhea, consisting of loose brown stools. His urine appeared darker. He had some eructations, with much flatus.

Initially the patient had been taken to another hospital, where some laboratory tests were done. The significant findings were: serum aspartate aminotransferase, 4250 U/ml; lacticdehydrogenase, 3580 U/ml; and decreased platelets on blood smear analysis.

The patient was first seen at this hospital approximately 48 h after drug ingestion. He was a well-built man who appeared acutely ill and tired. No petechial hemorrhages were seen. The only unusual finding on physical examination was a slight tenderness in the upper right quadrant of the abdomen.

The urine was normal except that the test for bile was 2+ positive. The hematocrit was 47%; the hemoglobin was 16.5 g/100 ml; the white cell count was 9,300, with 78% neutrophils. The platelet count was 50,000. The prothrombin time was 21.3 seconds, with a control of 10.6 seconds, and partial thromboplastin time was 32.8 seconds. The urea nitrogen was 72 mg/100 ml; the creatinine, 1.1 mg/100 ml; the glucose, 118 mg/100 ml; the conjugated bilirubin, 1.2 mg/100 ml; the total bilirubin, 1.9 mg/100 ml; the cholesterol, 126 mg/100 ml; and the protein, 6.2 g (the albumin, 3.8 g, and the globulin, 2.4 g) per 100 ml. The sodium was 139 mmol; the potassium, 4.2 mmol; the chloride, 107 mmol; the carbon dioxide, 28 mmol, the calcium, 9.0 mmol, and the phosphorus, 3.2 mmol per liter. The serum aspartate aminotransferase (SGOT) was 6268 U/ml; the lactic dehydrogenase (LDH), 2911 U/ml, and the alkaline phosphatase, 135 mU/ml.

Toxicological studies revealed small amounts of paracetamol and of nicotine in the urine. A serum level of paracetamol taken 48 h after the ingestion was reported at 40 µg/ml.

The patient was closely observed for signs of hepatic failure and was treated symptomatically. Antidotes for paracetamol, such as acetylcysteine, were not administered because his physician felt that it was

too late for any of the recommended treatments to be of benefit. However, the patient recovered rapidly and was discharged after 7 days. At that time he was well and had regained his appetite. Blood chemistry values had returned to normal.

DISCUSSION

The temporal sequence of signs and symptoms manifested in this case is typical of paracetamol toxicity. Usually there are no abnormal physical signs within the first 24 hours. Patients complain of nausea, vomiting, anorexia, and abdominal pain, however. Clinical indications of liver damage appear within 2 to 6 days of ingestion of toxic doses (2,7). Liver function tests often show striking increases in plasma aspartate aminotransferase and lactic dehydrogenase activity, with little or no increase in alkaline phosphatase. The prothrombin time is often prolonged. In non-fatal cases, liver function tests show a return to normal values within 1-2 weeks, with full recovery.

In adults, liver damage may occur after ingestion of a single oral dose of 10-15 g of paracetamol (5). However, correlation of dose with degree of liver damage may be complicated by several factors; namely, inaccurate information regarding total amount of drug ingested, vomiting, and concurrent drug administration. Some individuals, such as chronic alcoholics and those who concurrently ingest alcohol or medications that have enzyme-inducing ability, may be more susceptible to the hepatotoxicity of paracetamol.

Liver damage caused by overdoses of paracetamol is generally believed to result from a chemically reactive metabolite (7,8). Most of the paracetamol is metabolized to conjugates of glucuronide and sulfate. A small fraction of ingested paracetamol is converted, via the mixed function oxidase enzyme system, to an active metabolite

which binds with glutathione and is then excreted as mercapturic acid. Large doses of paracetamol lead to increased formation of this toxic metabolite and depletion of glutathione. The excess metabolite is then free to combine covalently with proteins of the cytosol and of the endoplasmic reticulum of liver cells, leading to cell damage and death. Therefore, the level of activity of the liver microsomal mixed function oxidase system and the tissue level of glutathione are obviously critical to the toxic effects of the drug. Both microsomal enzyme inducers and fasting have been shown to enhance hepatotoxicity of paracetamol (8), perhaps through increased production of the toxic metabolite or decreased inactivation of it.

Postulating from the mechanism of liver injury induced by paracetamol, any form of treatment that prevents formation of the toxic metabolite, either by inhibiting the mixed function oxidase system, preventing glutathione depletion, or acting as an alternative nucleophilic source, should be useful in the treatment of paracetamol overdose. In fact, several compounds have been shown to be effective in preventing paracetamol-induced liver damage in experimental animals through various mechanisms: metyrapone (10) and cimetidine (11) by enzyme inhibition; sodium sulfate (12) by increasing the capacity of the sulfate conjugation process, and propylthiouracil (13) by direct chemical interaction with the reactive metabolite of paracetamol.

Other, more thoroughly studied methods of treatment include the administration of sulfhydryl compounds, which probably act mainly by increased availability of glutathione. Methionine, cysteamine, and acetylcysteine have been given to man with some success in the prevention of paracetamol-induced hepatotoxicity (14-17). N-Acetylcysteine is the most widely used antidote for paracetamol intoxication. Cysteamine may cause unpleasant gastrointestinal and central nervous system toxic

reactions and must be administered intravenously (18). Methionine is contraindicated in severe liver disease and may precipitate hepatic encephalopathy (19).

N-Acetylcysteine is available as a sterile 10 or 20 per cent solution and can be administered either orally or intravenously. The drug should be given with a loading dose of 140 mg/kg followed by a maintenance dose of 70 mg/kg every 4 h for 17 doses (16). The manufacturer recommends the use of the 20 per cent solution diluted to 5 per cent with cola, fruit juice, or water. After mixing, the solution should be consumed withine 1 h. Intravenous acetylcysteine is also effective, with minimal side effects (20) and may be used in patients who cannot tolerate oral doses.

The decision for starting the specific antidote should be based, whenever possible, on the plasma levels of paracetamol rather than on the amount of drug reportedly ingested. The plasma levels should be plotted on a nomogram (21) to estimate the degree of potential hepatotoxicity. Acetylcysteine therapy should be initiated if the paracetamol level is more than 200 µg/ml after 4 h, or more than 50 µg/ml after 12 h, or if the half-life is more than 4 h. However, if the history of drug-taking suggests a massive overdose, treatment should be started immediately, without waiting for the result of paracetamol level measurement. If the result later indicates the paracetamol level to be in the toxic range, the patient should receive the full course of treatment; if not, the acetylcysteine may be discontinued.

The other major determinant of the decision to initiate treatment with an antidote is the amount of time that has elapsed since ingestion of the paracetamol. If treatment is started within 10 h of intoxication, the chance of success is better than it would be later (16, 20). The

critical ingestion-treatment interval for protection against liver damage seems to be the same for acetylcysteine, cysteamine, and methionine. Some experts recommend the use of acetylcysteine even up to 24 h after drug ingestion. In the case presented here, the patient was seen 72 h after ingestion; the specific antidote was therefore not given.

As in other drug overdoses, procedures to decrease continuing absorption of the drug (i.e., gastric lavage and induction of vomiting) must be begun immediately. Gastric lavage is indicated if the drug has been taken within 8 h. If another drug which delays gastric emptying, such as anticholinergics or narcotic analgesics, has been taken concurrently, it is still worthwhile to perform a gastric lavage up to 24 h after ingestion. Activated charcoal should not be given if acetylcysteine is to be used because the acetylcysteine would be adsorbed to the charcoal. If charcoal has been given, another gastric lavage should be performed before acetylcysteine is administered. Forced diuresis has not been shown to increase drug elimination significantly. Hemodialysis may be useful if performed within the first 12 h in patients with a plasma level of paracetamol exceeding 120 µg/ml 4 h after drug ingestion (2).

CONCLUSION

N-Acetylcysteine is widely accepted as a safe and highly effective antidote for paracetamol poisoning in man. However, successful treatment is usually achieved when acetylcysteine therapy is initiated within 10 h of drug ingestion. If 24 h or more have elapsed since the estimated time of ingestion, only supportive measures are indicated. Nonspecific treatment of poisoning, such as gastric lavage or induction of emesis, should be performed immediately in all cases during the early phase of intoxication.

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