SEVERE HEPATOTOXICITY FROM ESCHERICHIA COLI L-ASPARAGINASE

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A 51-year-old black woman with diabetes mellitus developed severe hepatotoxicity after receiving high-dose L-asparaginase (Elspar) for acute lymphatic leukemia. Patients with diabetes should be given this drug cautiously. Glutaminase-free L-asparaginase from Vibrio succinogenes has been reported to be less hepatotoxic in mice; it might be a safer product for this group of patients.

While L-asparaginase has been an efficacious agent for the treatment of acute lymphatic leukemia, toxic effects on the liver, kidneys, pancreas, immune system, central nervous system, and coagulation factors have limited its use. The authors' recent experience with a patient who developed severe hepatotoxicity from Escherichia coli L-asparaginase (Elspar, Merck Sharp & Dohme) prompted a review of the literature with regard to its hepatotoxicity. To the authors' knowledge, liver toxicity to the degree the case study patient experienced has not been reported previously.

CASE REPORT

A 51-year-old, insulin-dependent diabetic black woman with acute lymphatic leukemia was begun on chemotherapy with vincristine and prednisone. On physical examination her tongue and pharynx revealed oral candidiasis. The liver was enlarged, having a span of 14 or 15 cm. There was no lymphadenopathy. The neurological examination was within normal limits. After a negative skin test, a planned 10-day course of high-dose L-asparaginase, 1,000 IU/kg (80,000 units) per day, was begun on day 21 of the chemotherapy regimen. However, by day 27 her bilirubin level had increased from 1.0 to 1.8 mg/dL (normal, 0.2 to 1.2 mg/dL) and the drug was discontinued on day 29. By day 30 her bilirubin level was 9; it peaked at 25.5 by day 12. The patient's alkaline phosphatase level was elevated at the onset, 400 mU/mL, (normal, 30 to 115 mU/mL); it was over 1,650 by day 38. The aspartate aminotransferase (SGOT) rose from 29 mU/mL (normal, 8 to 40 mU/mL) to a peak of 480 by day 29. The patient's cholesterol level did not fall as expected, rather it rose from 344 mg/dL (normal, 160 to 330 mg/dL) to 1,920 on day 39. The blood ammonia level was 360 μmol/L (normal, 11 to 35 μmol/L) on day 31. The fibrinogen fell from 165 to 60 mg/dL (normal, 200 to 400 mg/dL); no other coagulation abnormalities were noted. The amylase remained normal. Serological tests for hepatitis were negative. One month after receiving the drug, a liver scan was taken and the liver was found to have a span of 22 cm. Four months after receiving the L-asparaginase, the patient's liver function abnormalities had returned to normal except for a persistently high cholesterol level. The liver had become reduced in size but was still about 14 to 15 cm in width at the right midclavicular line. Triglycerides were elevated at that time, and a lipoprotein electrophoresis revealed a type IIB abnormality.

The patient died suddenly of acute respiratory fail-

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ure while in complete remission 1½ years from the date of diagnosis. Permission for autopsy was not granted.

DISCUSSION

The toxicity of E coli of L-asparaginase is well known.[1-3] Currently this product is the only commercial source of the enzyme. Erwinia cartovora L-asparaginase is an equipotent enzyme available from the National Cancer Institute and has been used in patients who have had allergic reaction to Elspar. Except for a decrease in hypersensitivity reactions, its toxicity has been considered to be similar to the E coli product.

Oettgen et al[2] reviewed the toxicity of the E coli preparation in 131 children and 143 adults with various neoplastic diseases. Their data suggest that the drug may be more toxic to the adult liver. When treated for at least one week, the serum alkaline phosphatase was elevated in 31 percent of children vs 47 percent of adults. Increased levels of SGOT were observed in 46 and 63 percent, respectively, and for bilirubin, 29 and 51 percent, respectively. Levels of bilirubin greater than 4 mg/dL were rare; one adult patient who had received 200 U/kg/d had a serum bilirubin of 10 mg/dL. Haskell et al[1] reported that liver dysfunction occurred in 33 of 35 of their patients, most of whom were adults. However, increments in liver function tests (bilirubin, SGOT, and alkaline phosphatase) were mild, perhaps because of the relative low doses given (200 IU/kg/d) in most of their patients. Pratt and Johnson,[3] doing an autopsy study, cautioned that hepatic lipoidosis may persist for up to 261 days after the last dose of L-asparaginase in children who died from various hematologic malignancies. There was a suggested relationship between the severity of the hepatic changes and dose.

It has been postulated that the hypoalbuminemia, pancreatitis, toxic hepatitis, and coagulation abnormalities of L-asparaginase may be secondary to contamination with glutaminase or endotoxin. Wade and Phillips[4] demonstrated that both E coli and Erwinia cartovora L-asparaginase were contaminated with varying amounts of glutaminase; it accounted for 2 percent of the activity in the E coli preparation and 10 percent of the Erwinia cartovora product. Distasio et al[5] and Durden et al[6] recently demonstrated in mice that the glutaminase-free L-asparaginase obtained from Vibrio succinogenes did not induce the fatty infiltration of the liver associated with L-asparaginase from E coli.

A liver biopsy was not done in the study patient because it was not considered to be clinically justified, but it is possible that she had fatty metamorphosis of the liver associated with her diabetes and type IIB lipoprotein abnormality. She was found to have the abnormality in lipid metabolism after receiving the L-asparaginase; whether the drug induced it is speculative. In any event, it would appear that L-asparaginase, especially in a high-dosage regimen, should be used with caution in diabetics, patients with lipoprotein abnormalities, and patients with underlying liver disease. Investigation of the value of the Vibrio succinogenes product for these groups of patients would seem worthwhile.

Literature Cited

1. Haskell CM, Canellos GP, Leventhal BG, et al. L-Asparaginase—Effects in patients with neoplastic disease. N Engl J Med 1969; 281:1018–1033.

2. Oettgen HF, Stephenson PA, Schwartz MK, et al. Toxicity of E coli L-asparaginase in man. Cancer 1970; 28:253–278.

3. Pratt CM, Johnson WW. Duration and severity of fatty metamorphosis of liver following L-asparaginase therapy. Cancer 1971; 28:361–364.

4. Wade HE, Phillips AP. Automated determination of bacterial asparaginase and glutaminase. Anal Biochem 1971; 44: 189–199.

5. Distasio JA, Salazar AM, Nadji M, Durden DL. Glutaminase-free asparaginase from Vibrio succinogenes: An anti-lymphoma enzyme lacking hepatotoxicity. Int J Cancer 1982; 30:343–347.

6. Durden D, Salazar AM, Distasio JA. Kinetic analysis of hepatotoxicity associated with anti-neoplastic asparaginases. Cancer Res 1983; 43:1602–1605.