SIDE EFFECTS OF DRUGS

Jaundice during cyproheptadine treatment

Cyproheptadine is a potent antagonist of histamine and serotonin and is widely used as an appetite stimulant, for symptomatic relief of pruritus, and in Cushing's syndrome.1 Although it has a similar structure to the phenothiazine antihistamines (see fig), we know of no previous reports of jaundice attributable to the drug.

Case report

A 25-year-old Iraqi woman had had intermittent pruritus for several years. In October 1975, while temporarily resident in the United Kingdom, symptoms recurred and she consulted one of us (TD). She had received no drug treatment except for oral contraceptives, which had been discontinued one year previously for non-medical reasons. No clinical abnormality was detected and cyproheptadine hydrochloride (Periactin) 12 mg day was prescribed. In November 1975, one month after starting the drug, she developed right upper abdominal discomfort and jaundice with pale stools and darkened urine. The liver was non-tender and enlarged 2 cm, and the spleen was palpable. Liver function tests confirmed cholestatic jaundice: serum bilirubin 112 μmol l (6-5 mg 100 ml); serum aspartate transaminase (SGOT) 107 U l; serum alanine transaminase (SGPT) 210 U l; serum alkaline phosphatase 2400 U l (normal range for our laboratory 80-280 U l). Cyproheptadine was discontinued and chlorpheniramine (Piriton) 16 mg day substituted. One month later she was still jaundiced, though the liver was impalpable. Serum bilirubin was 130 μmol l (7-6 mg 100 ml); SGOT 120 U l; SGPT 201 U l; and alkaline phosphatase 418 U l. Coagulation screen was normal, and tests for hepatitis-B-associated antigen, smooth-muscle and mitochondrial antibodies, and antinuclear factor gave negative results. A pregnancy test was negative. Exploratory laparotomy showed no abnormality of gall bladder or cystic and common bile ducts. No calculi were detected at operative cholangiography; flow of dye into the duodenum was not obstructed, and normal hepatic ducts were outlined. Histological examination of a wedge biopsy specimen of the liver showed extensive intrahepatic cholestasis with slight non-specific portal hepatitis and no evidence of extrahepatic biliary obstruction. The appearances were typical of drug-induced cholestasis of the type associated with phenothiazines.

Cyproheptadine is structurally similar to the phenothiazines (fig). Our patient's clinical features, biochemical abnormalities, histological appearances of the liver biopsy specimen, and slow resolution of jaundice suggested drug-induced cholestasis of the phenothiazine type. We believe that the jaundice was probably caused by cyproheptadine.

2 Karkali, Y, and Lal, H, Clinical Toxicology, 1971, 4, 47.

Fever, abdominal pain, and leucopenia during treatment with cimetidine

Fever reactions to cimetidine have not been reported, and leucopenia has been recorded in only two patients.1 2 We report a case in which abdominal pain, fever, transient leucopenia, and a rise in serum transaminase concentrations occurred during treatment with cimetidine.

Case report

A 44-year-old woman with a history of duodenal ulceration was treated with cimetidine 1 g daily by mouth. She noted rapid relief of symptoms but over the next 10 days had occasional episodes of deep-seated epigastric aching pain. On the 13th day after starting cimetidine she felt unwell, with epigastric pain, shivering, and fever. Her general practitioner stopped the cimetidine and prescribed co-trimoxazole, two tablets twice daily, for possible urinary tract infection. Next day she still felt unwell. On admission to hospital she was found to be rapidly improving, and temperature and physical findings were normal. Co-trimoxazole was continued, and on the evening of the 16th day after first starting cimetidine she had a recurrence of dyspepsia. Since no abnormality had been found cimetidine was reinstated. Within 12 hours the epigastric pain recurred together with shivering and a temperature of 39.5°C. Cimetidine was stopped after only 600 mg and the fever settled over the next 72 hours.

At that time estimation of the following yielded normal results: serum urea, sodium, potassium and bicarbonate, ammonia, calcium, albumin, alkaline phosphatase, and glucose concentrations; erythrocyte sedimentation rate; urine microscopy and culture; and a Monospot test for glandular fever. On day 17 haemoglobin was 11.1 g/dl and total white cell count 5 x 10^9/l (5000 mm^3) (95%, neutrophils, 3%, lymphocytes, 2%, monocytes). On day 19 the total white cell count had fallen to 2.7 x 10^9/l (67% neutrophils, 25% lymphocytes, 8%, monocytes); on day 21 it had risen to 4.3 x 10^9/l (65% neutrophils, 29% lymphocytes, 4%, monocytes, 2% eosinophils), and by day 23 it was 5 x 10^9/l. Serum transaminase concentrations were slightly raised on day 17, and by day 23 aspartate transaminase was 67 U/l and alanine transaminase 100 U/l. These values had returned to normal two weeks later.

Comment

This patient experienced epigastric pain and fever while taking cimetidine, which disappeared when the drug was withdrawn. Reinstitution of cimetidine was associated with the return of these symptoms within 12 hours, and there was a transient leucopenia with initially an absolute lymphopenia. Serum transaminase concentrations

Phenothiazine nucleus

Structure of phenothiazines and cyproheptadine.

Cyproheptadine is structurally similar to the phenothiazines (fig). Our patient's clinical features, biochemical abnormalities, histological appearances of the liver biopsy specimen, and slow resolution of jaundice suggested drug-induced cholestasis of the phenothiazine type. We believe that the jaundice was probably caused by cyproheptadine.