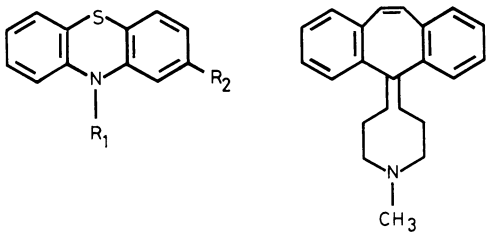
SIDE EFFECTS OF DRUGS

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 impalpable. 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.



Structure of phenothiazines and cyproheptadine.

Her subsequent progress was uncomplicated. Chlorpheniramine 16 mg/day was continued for relief of pruritus, and at follow-up two months later she was well and anicteric. Clinical examination showed nothing abnormal and liver function tests confirmed resolution of cholestasis. Bilirubin and alkaline phosphatase concentrations had returned to normal, but some enzyme disturbance persisted: SGOT was 70 U/l and SGPT 90 U/l. Further follow-up was precluded by her return to Iraq. Eighteen months later she gave birth to a normal child.

Comment

One case of jaundice during treatment with cyproheptadine was reported in 1971 in a patient receiving combined treatment with imipramine and cyproheptadine.[2] Among other features, biochemical evidence of prominent hepatocellular damage suggested changes more commonly associated with imipramine, which is occasionally hepatotoxic.[3] Our patient received only cyproheptadine and chlorpheniramine. Chlorpheniramine cannot be incriminated, however, as it was begun after jaundice had appeared and continued during resolution of the illness.

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.

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Fever, abdominal pain, and leucopenia during treatment with cimetidine

Febrile 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 reinstituted. 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, amylase, 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 5×10^9/l (5000/mm^3) (95% neutrophils, 3% lymphocytes, 2% monocytes). On day 19 the total white cell count had fallen to $2{\cdot}7 \times 10^9$/l (67% neutrophils, 25% lymphocytes, 8% monocytes); on day 21 it had risen to $4{\cdot}3 \times 10^9$/l (65% neutrophils, 29% lymphocytes, 4% monocytes, 2% eosinophils), and by day 23 it was 5×10^9/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

were also raised. The only other drug given in this period was co-trimoxazole, which was administered before, during, and after the reinstitution of cimetidine and thus seems unlikely to have been responsible for the abnormalities observed.

Initial animal studies and clinical trials of cimetidine failed to show any appreciable haematological abnormalities, although rises in serum transaminase concentrations were occasionally seen.[3] In particular, the agranulocytosis noted with the earlier H_2-receptor antagonist metiamide[1] was not seen. Since then, agranulocytosis has been reported in one patient four months after stopping cimetidine.[1] More recently transient neutropenia has been noted in a patient with chronic renal failure associated with a bone marrow picture consistent with peripheral granulocyte destruction.[2] In our patient the leucopenia seems to have been part of a more generalised drug reaction that has not been described with cimetidine.

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Bleeding gastric erosion after oral zinc sulphate

The use of oral zinc sulphate for chronic skin ulcers[1 2] and acne[3] has aroused interest recently. A case of gastrointestinal bleeding is described, which emphasises a potentially serious side effect of this treatment and seems to support the warnings of Glover and White.[4]

Case report

One week before admission a 15-year-old English schoolgirl (weight 68 kg) with no history of dyspepsia had started taking zinc sulphate capsules (Zincomed), 220 mg twice daily, for acne, the treatment having been prescribed by her general practitioner. She was receiving no other medication. After each capsule she experienced epigastric discomfort, and on the day before admission she had fainted after getting up from a chair. She subsequently twice passed melaenic stools.

On admission she was anaemic with a pulse rate of 110/min and a blood pressure of 120/60 mm Hg. Epigastric tenderness was present, and rectal examination confirmed the presence of melaena. Haemoglobin was 5·4 g/dl, platelet count was normal, and no abnormalities were found on clotting screen. Blood urea concentration was initially raised, but results of subsequent renal function tests were normal. Upper intestinal panendoscopy 15 hours after admission showed a normal oesophagus and duodenal cap, but patchy areas of gastritis were seen on the greater curve with a resolving haemorrhagic erosion.

Zinc treatment was discontinued and she was transfused 8 units of whole blood. After endoscopy she was started on a four-week course of cimetidine (1 g/day in divided doses) and made an uneventful recovery. At follow-up one month later she was asymptomatic and had maintained a haemoglobin concentration of 13·3 g/dl.

Comment

Side effects from oral zinc sulphate in patients with normal renal function are rare,[1 5] though the capsule preparation gives rise to nausea, vomiting, and diarrhoea more commonly than the effervescent form.[2] Nevertheless, this is the first report of gastrointestinal bleeding. The patient had no history of dyspepsia, so the epigastric discomfort after taking each capsule and subsequent endoscopic finding of a bleeding gastric erosion are highly suggestive of a direct irritant effect on the stomach. Though the effervescent zinc sulphate preparations are probably preferable to the more readily available capsules for oral treatment, they are at present marketed only in Sweden.

I thank Professor Ivor H Mills for permission to report this case and Dr Richard Machell for performing the endoscopy.

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SHORT REPORTS

Clostridium welchii septicaemia after intrauterine caesium insertion

Two patients with adenocarcinoma of the body of the uterus were treated in the same operating session with intrauterine radiocaesium (^{137}Cs). Both developed *Clostridium welchii* septicaemia.

Case 1

A 57-year-old woman had had a foul-smelling vaginal discharge before operation. She was anaesthetised and the cervix dilated. A rubber-covered tube, 67 mm long and 12·6 mm in diameter containing ^{137}Cs equivalent to 45 mg of radium, was inserted into the uterine cavity. Her obesity (she weighed 112 kg) and a fixed-flexion deformity of the right hip made insertion difficult. At one stage the tube was replaced in the lead-shielded well with other radioactive sources for the treatment session.

Twenty-four hours after the insertion the patient was febrile and slightly jaundiced. Twelve hours later she was bronze coloured and had passed only a little urine, which was black and contained free haemoglobin. Microspherocytes and staining by free haemoglobin were seen in the peripheral blood film. The haemoglobin had fallen from 13·9 g/dl to 6·4 g/dl. The free plasma haemoglobin was 2·15 g/dl, the intracellular haemoglobin 4·5 g/dl, the white cell count 26·3 × 10^9/l (26 300/mm^3), and platelets 60 × 10^9/l (60 000/mm^3). *Cl welchii* septicaemia was suspected. Bacteriological specimens were taken and the patient was started on benzylpenicillin, 4 megaunits intravenously every six hours, and gentamicin. An arteriovenous shunt was constructed in preparation for renal dialysis but before the shunt could be used the patient began to bleed from venepuncture sites, nose, and gut. She died 52 hours after the caesium insertion. Blood cultures and vaginal swabs grew *Cl welchii*.

Case 2

The second patient (aged 49) was treated immediately after the first. A caesium tube was inserted into the uterine cavity without difficulty. Thirty-six hours after operation her temperature was 37·5 C. Blood cultures and high vaginal swabs were sent for bacteriological examination. When the tube was removed 55 hours after insertion her temperature had dropped to 36·5 C but she was slightly jaundiced (bilirubin 45 mmol/l (3 mg/100 ml)). Treatment with benzylpenicillin, 4 megaunits every six hours, was started immediately. Blood cultures gave negative results but *Cl welchii* was isolated from the vagina. Over the next five days the jaundice disappeared but the blood urea concentration rose from 6 to 30 mmol/l (36-180 mg/100 ml).