SHORT REPORTS

Possible hepatotoxicity of zimelidine

Zimelidine (Zelmid, Astra), which acts on the 5-hydroxytryptamine neuronal system, is a recent preparation for treating depression. Cholinergic and cardiovascular side effects are reportedly fewer than with established antidepressent drugs.[1 2] We report on a patient who developed hepatocellular jaundice and fever during treatment with zimelidine and whose symptoms recurred on inadvertent rechallenge with the drug.

Case report

A 47 year old insulin dependent diabetic consulted her general practitioner eight times over two months with varied physical symptoms including premenstrual tension, nausea, dizziness, anorexia, weight loss, and paraesthesia. She was often weepy and lacked confidence. She was treated unsuccessfully with lorazepam, ketazolam, betahistine, metoclopramide, amitriptyline, and cyclizine and was then given zimelidine 100 mg twice daily and lorazepam 1 mg as required.

Nine days later she was admitted to this hospital with increasing nausea, vomiting, and lassitude. She did not have headache. She was febrile (temperature 38·5°C) and jaundiced but did not have hepatomegaly. Serum bilirubin concentration was 72 μmol/l (4·2 mg/100 ml) with aspartate aminotransferase activity 235 IU/l (reference range 9-25 IU/l), alanine aminotransferase activity 300 IU/l (5-59 IU/l), lactate dehydrogenase activity 895 IU/l (72-395 IU/l), and alkaline phosphatase activity 176 IU/l (30-140 IU/l). Viral hepatitis was suspected. All drugs were stopped, and she was treated symptomatically. Her vomiting and fever persisted for a week but then settled, and she was discharged. Results of serological tests showed no evidence of infection with hepatitis A, hepatitis B, cytomegalovirus, or Epstein-Barr virus. At review six weeks later all results of liver function tests were normal but she remained depressed and tired.

She continued to complain of depressive symptoms and six months later was again prescribed zimelidine but in a lower dose (25 mg twice daily). After one week she was readmitted with nausea, vomiting, right hypochondrial pain, and jaundice. She was feverish (39°C) with tenderness in the right hypochondrium but did not have hepatomegaly. Plasma bilirubin concentration was 77 μmol/l (4·5 mg/100 ml) and activities of aspartate aminotransferase 462 IU/l, alanine aminotransferase 596 IU/l, lactate dehydrogenase 853 IU/l, γ-glutamyltransferase 197 IU/l (6-31 IU/l), and alkaline phosphatase 307 IU/l. Results of blood cultures, repeat viral serological tests, smooth muscle and antimitochondrial antibody tests, Widal's test, and ultrasonography of the biliary tree were all normal. Zimelidine was stopped, and her temperature and symptoms settled over five days. After one month all results of liver function tests had returned to normal.

Comment

Our patient suffered the most severe hepatic reaction so far reported in association with zimelidine. Nevertheless, on both occasions she recovered rapidly, both clinically and biochemically. Permission to undertake liver biopsy was refused. Coppen *et al*[2] described one patient with a history of hepatitis after treatment with chlorpromazine and amitriptyline who developed jaundice and fever two weeks after starting zimelidine. The patient was withdrawn from their trial and the jaundice rapidly subsided, but no details were given. Our patient had previously taken amitriptyline for over a year without ill effect. In a report on two patients[3] the principal symptom in both was headache with transient increases in transaminase activities. Bilirubin concentrations remained normal and the patients were afebrile.

Zimelidine is eliminated almost exclusively by hepatic metabolism, initially to norzimelidine, an active metabolite with a long plasma half life.[4] Plasma concentrations are raised in elderly patients,[5] and a reduced daily dose (100 mg) is recommended. Our patient was prescribed 50 mg a day on the second occasion but the disturbance of liver function was biochemically more severe than with the initial, higher dose. This suggested a hypersensitivity reaction rather than one related to dose.

We suggest that careful monitoring and reporting of side effects of zimelidine should continue, particularly as the drug is being increasingly prescribed. Patients should be reviewed one to two weeks after starting treatment, when adverse effects of this type seem most likely to develop. The drug should be withdrawn and liver function assessed if severe headache, vomiting, fever, jaundice, or abdominal pain has developed.

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[2] Coppen A, Rama Rao VA, Swade C, Wood K. Zimelidine; a therapeutic and pharmacokinetic study in depression. *Psychopharmacology* (*Berlin*) 1979;**63**:199-202.

[3] Sommerville JM, McLaren EH, Campbell LM, Watson JM. Severe headache and disturbed liver function tests during treatment with zimelidine. *Br Med J* 1982;**285**:1009.

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Fatal brain oedema due to accidental water intoxication

Death due to water intoxication is uncommon,[1-3] though transient neurological dysfunction (confusion, headache, coma, convulsions) is well recognised. Some of the earlier cases reported were iatrogenic[3 4] but most are psychogenic.[1 2 5] We believe the following to be the first reported case of accidental water intoxication with no psychiatric disorder and ending in death.

Case report

A 40 year old woman was brought to the casualty department confused and with incoherent speech. Initial examination showed no other abnormality. Blood pressure was 150/80 mm Hg and heart rate 88/min and regular. Shortly afterwards she had a short grand mal fit, which terminated spontaneously. During the next one and a quarter hours blood pressure rose to 220/80 mm Hg and pulse rate fell to 48/min. Respiration became irregular in depth and rhythm, and pupils were dilated and fixed; doll's eye movements were still present and the gag reflex preserved. There was no response to sternal pressure or peripheral painful stimuli. There was generalised hyperreflexia but no plantar response. We thought that a catastrophic rise in intracranial pressure was causing tentorial herniation and distortion of the upper brain stem. She was given hypertonic mannitol intravenously then intubated and ventilated. Parenteral dexamethasone was added later.

Laboratory values on admission were: serum sodium 111 mmol(mEq)/l, potassium 3·1 mmol(mEq)/l, bicarbonate 16 mmol(mEq)/l, urea 3·0 mmol/l (18·1 mg/100 ml), and glucose 9·8 mmol/l (177 mg/100 ml).

The patient's brother reported that she had drunk a small amount of diluted household bleach accidentally, mistaking it for water. He telephoned a poisons unit and was advised that she should drink large amounts of fluid. The patient drank about 15 l of water and persisted even after starting to vomit repeatedly. Two hours later she became confused and her brother called an ambulance. She had been perfectly well and had not been taking any medication.

The patient was reassessed on the ventilator. She had deteriorated: the apnoea test was not attempted, but all other brain stem reflexes were absent. A chest radiograph showed "bat's wing" pulmonary oedema. A CT scan showed cerebral and cerebellar oedema with compression of the lateral and third ventricles but without any midline shift. She had a large diuresis (8·6 l) in the first 24 hours, so that the chest *x* ray picture cleared and the serum sodium concentration rose to 129 mmol/l. Lumbar punctures on the second and fourth days gave normal results. Brain stem death was confirmed, and the ventilator was disconnected.

Results of all other investigations had been normal, including cerebrospinal fluid and blood serology and culture, and toxicology screen.

At necropsy the brain was found to be soft. The blood vessels were anatomically normal but there was massive congestion of the ventral blood

vessels and of the midbrain and pons. There was tentorial herniation, greater on the right. There was no evidence of previous cell loss or of inflammatory reaction.

Comment

Water intoxication causes hyponatraemia, which is responsible for the neurological dysfunction by causing intracellular overhydration. Symptoms may occur if the serum sodium concentration is less than 120 mmol/l, but the degree of brain dysfunction corresponds with the rapidity of development of the hyponatraemia. Intracellular potassium concentration is reduced, partly due to increased intracellular water and partly due to loss of intracellular potassium, but it is not clear whether cellular swelling alone or the potassium deficit is responsible for the encephalopathy. The accompanying brain oedema is usually transient but the intracranial hypertension may be catastrophic, causing uncal and tonsillar herniation.[1] The intracranial pressure later reverts to normal.[2]

In our patient signs developed with such rapidity that therapeutic measures succeeded in reducing the intracranial pressure only after irreversible brain stem damage had taken place.

We thank Dr A H James for permission to report this case and for helpful advice.

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Enteritis and colitis associated with mefenamic acid

Diarrhoea is a recognised side effect of treatment with mefenamic acid, although inflammatory bowel disease has not been reported. We describe two cases of acute colitis associated with treatment with mefenamic acid.

Case reports

CASE 1

A 43 year old man presented with a one year history of loose, bloodstained bowel actions up to 10 times daily, abdominal colic, and weight loss of 16 kg. He had been taking mefenamic acid (Ponstan) 250 mg by mouth three times daily for three years because of psoriatic arthropathy.

Physical examination showed only pallor and dehydration. Results of blood tests included: haemoglobin concentration (10·5 g/dl); white cells $11\,600 \times 10^9$/l (33% eosinophils); serum iron concentration 4·0 μmol/l (22·3 μg/100 ml); total iron binding capacity 62 μmol/l (346 μg/100 ml); erythrocyte sedimentation rate 15 mm in the first hour; and albumin concentration 31 g/l. On sigmoidoscopy the rectal mucosa appeared normal, but a biopsy specimen showed signs of mild chronic proctitis. A barium enema showed no obvious abnormality in the colon. Colonoscopy, however, showed that the mucosa of the descending colon was abnormal, with areas of aphthous ulceration and a cobblestone appearance; biopsy samples from these areas showed excessive plasma cell and eosinophil infiltration; the crypts were normal and there were no granulomas. Stool cultures were negative for salmonella, shigella, campylobacter, virus particles, parasites, and *Clostridium difficile* toxin. Yersinia agglutination and amoebic fluorescence antibody tests gave negative results. Results of a barium follow through examination were normal. Faecal fat excretion was slightly raised (23 mmol/(6·5 g)/24 h (normal < 17 mmol (4·8 g)/24 h)). An endoscopic duodenal biopsy specimen showed a chronic inflammatory cell infiltrate in the lamina propria but was otherwise normal.

He was treated for six weeks with sulphasalazine without improvement. Mefenamic acid was therefore stopped, and within 48 hours his abdominal pain and diarrhoea had stopped. His appetite improved. Ten days later he was again given mefenamic acid; the pain and diarrhoea recurred the same day. He did not take mefenamic acid for the following year during which time he was free of symptoms, he regained his former weight, and all blood variables were normal.

CASE 2

A 69 year old man presented with a two month history of diarrhoea, with up to six bowel actions daily, and weight loss of 4 kg. He had been taking mefenamic acid 500 mg (Ponstan forte) intermittently for eight months while awaiting left ureterolithotomy.

Examination was normal except for atrial fibrillation. On sigmoidoscopy pus was present in the lumen and the mucosa showed loss of vascular pattern. A rectal biopsy specimen showed active proctitis. Stool cultures gave negative results for salmonella, shigella, campylobacter and *Clostridium difficile*, and microscopy showed that no parasites were present. Full blood count, results of thyroid function tests, and serum albumin concentration were normal, but the erythrocyte sedimentation rate was 51 mm in the first hour and seromucoid concentration was raised (2·0 g/l (normal < 1·2 g/l)). Barium enema showed only mild diverticular disease. Barium follow through examination showed slight dilatation of jejunal loops. A duodenal biopsy specimen showed normal villi with a non-specific inflammatory infiltrate.

Mefenamic acid was stopped, and the diarrhoea resolved after four days. He began taking mefenamic acid again after an interval of three weeks, and the diarrhoea returned within three hours. When the drug was stopped again his diarrhoea settled immediately. The erythrocyte sedimentation rate, seromucoid concentrations, and sigmoidoscopic and rectal biopsy appearances were then normal. He did not take mefenamic acid for the four months of follow up and remained well.

Comment

Gastrointestinal side effects of mefenamic acid, although not common, are well recognised. One of our patients had mild steatorrhoea, and both had inflammatory infiltration of the proximal small bowel, both complications that have been reported before.[1 2] Colitis, however, does not appear to be a recognised complication, the manufacturers being aware of only four other possible cases (Warner-Lambert (UK), personal communication). The unmasking of idiopathic inflammatory bowel disease has been reported with other non-steroidal anti-inflammatory drugs.[3] The prompt and permanent resolution of symptoms in both our patients when treatment with mefenamic acid was stopped and their recurrence on re-exposure, however, strongly suggest that this drug caused the colitis. These observations emphasise the need for an adequate drug history in patients presenting with acute proctitis or colitis.

We thank Dr O F W James for permission to report on the patient in case 2.

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