

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 antidepressant 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 patients³ 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.
- 4 Brown D, Scott DHT, Scott DB, Meyer M, Westerlund D, Lundström J. Pharmacokinetics of zimelidine. Systemic availability of zimelidine and norzimelidine in human volunteers. *Eur J Clin Pharmacol* 1980;**17**:111-6.
- 5 Dehlin O, Bjornsson G, Lundström J. Zimelidine to geriatric patients: a pharmacokinetic and clinical study. *Acta Psychiatr Scand [Suppl]* 1981;**63**, suppl 290:410-24.

(Accepted 15 June 1983)

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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 iatrogenic⁴ 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