and had no further constipation. Another patient (case 3) felt nauseated for 10 to 15 minutes after every dose. He continued to take the cholestyramine, however.

In the control group only one patient (case 7) noted an improvement in pruritic symptoms.

There were no significant differences between the blood values before and after treatment in either group.

Discussion

Our results indicate that cholestyramine reduces the severity of pruritus in patients on chronic haemodialysis. The mechanism by which this occurs is unknown. Cholestyramine is a non-absorbable anion-exchange resin capable of intraluminal binding of organic acids.¹ Many organic acids are present in raised concentrations in the blood of uraemic patients,² and some of these may be concerned in the production of pruritus, though we did not measure any of these in this study. The improvement in our patients, however, was not associated with any significant change in blood urea, creatinine, calcium, phosphate, alkaline phosphatase, electrolytes, albumin, cholesterol, or triglyceride concentrations.

Cholestyramine reduces the pruritus associated with obstructive jaundice.³ Possibly this improvement is due to its binding of bile acids in the gut, with subsequent lowering of the bile acid concentration in the blood.³ Pruritus has, however, been relieved in some patients who have shown no fall in bile acids,⁴ so the cause of the pruritus and the mechanism of benefit from cholestyramine are uncertain in this condition as well. Chanarin and Szur have also reported that cholestyramine reduces the pruritus associated with polycythaemia vera.⁵ They showed that pruritus promptly improved in four patients, and the improvement lasted for up to 15 months. In one case the drug was discontinued, and pruritus returned within three weeks. Re-institution of treatment again relieved the pruritus. The mechanism of action of the drug in this condition is also unknown.

The dose of cholestyramine that we used (5 g twice daily) is similar to that usually recommended.¹ In four of our five patients this dose seemed to be effective. The fifth patient, however, obtained relief only after taking double this dose (5 g four times a day).

Cholestyramine can bind vitamin K in the gut,¹ but we found no significant change in the prothrombin time in any patient. The drug also releases chloride into the gut and may cause hyperchloraemic acidosis,⁶ but we found no evidence of this in any of our patients.

Uraemic pruritus has been treated with antihistamines, heparin infusions,⁷ sauna baths,⁸ low protein diets and amino-acid supplementation,⁹ parathyroidectomy,^{10 11} and control of serum calcium and phosphate concentrations.¹¹ None of these methods have been uniformly effective. Cholestyramine treatment therefore seems to be a useful adjunct to the treatment of uraemic pruritus.

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SIDE EFFECTS OF DRUGS

Paracetamol-induced acute pancreatitis

Although pancreatic inflammation may be seen at necropsy in patients with fulminant hepatitis,¹ clinical evidence of pancreatitis is rare. We present the first report of paracetamol poisoning producing a clinical attack of acute pancreatitis.

Case report

The patient was a 31-year-old White housewife with no significant medical history and taking no regular medication. There was no history of self-poisoning or adverse drug effects. She was a part-time barmaid and admitted that she had had a regular heavy alcohol intake for three years.

Drug exposure—Fifty-four hours before admission she took 60 g paracetamol (120 Panadol tablets) in a suicide attempt. No other drugs were taken.

Adverse effects—She was admitted to hospital complaining of severe upper abdominal pain that radiated into her back and vomiting that had lasted for 36 hours. Initially she gave no history of drug overdose but admitted to this four weeks later. On examination she was in pain, dehydrated, and mildly icteric. Her pulse rate was 140/min, blood pressure 105/65 mm Hg, and temperature 36.9°C. A petechial rash was noted over her upper arms and chest. There was considerable upper abdominal tenderness with guarding, rebound tenderness, and absent bowel sounds. Liver and spleen were not palpable. Acute pancreatitis was diagnosed clinically.

Initial investigation showed: serum amylase 1440 IU/l, haemoglobin 15.6 g/dl, serum calcium 1.4 mmol/l (5.6 mg/100 ml), white cell count

$15.2 \times 10^9/l$, bilirubin 102 $\mu\text{mol/l}$ (6.0 mg/100 ml), platelets $70 \times 10^9/l$, alkaline phosphatase 10 KA units/l, prothrombin time 62 seconds (control 12 seconds), serum aspartate aminotransferase 300 IU/l, and albumin 29 g/l.

She had acute renal failure and required peritoneal dialysis to control rapidly rising blood urea and plasma potassium concentrations during the first week. After three weeks in hospital her renal function had returned to normal, but she had persistent abdominal tenderness, ileus, and fever. Because of a possible intra-abdominal abscess, she underwent a laparotomy the next week. There was no localised abscess, but there were two litres of cloudy bloodstained peritoneal fluid, loculated in places, and the pancreas was oedematous and haemorrhagic, with areas of fat necrosis. The liver was smooth and non-cirrhotic, and there were no stones palpable in the gall bladder or common bile duct. After operation, she gradually recovered, leaving hospital after a stay of four months.

Comment

Acute hepatitis and hepatic failure are now widely recognised complications of paracetamol poisoning. Although this patient had undoubted hepatitis, the clinical picture was dominated by her acute pancreatitis and subsequent renal failure, and so the underlying cause was not initially suspected.

In all except one case,² the association between fulminant hepatitis and pancreatitis has been observed only at necropsy in patients who have had viral hepatitis. It has therefore been suggested that the pancreatitis and hepatitis have a common viral cause. Our report of paracetamol-induced pancreatitis does not support this, and Gazzard et al reported necropsy evidence of pancreatitis in four patients who died after paracetamol-induced hepatic necrosis.³ Vascular factors in the aetiology of acute pancreatitis are probable,⁴ and disseminated

intravascular coagulation might provide a link between these two conditions.

We are grateful to Mr G Dickson for permission to report on this patient who was under his care.

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Water intoxication due to carbamazepine

The antidiuretic effect of carbamazepine (Tegretol) is well established,^{1,2} and water intoxication induced by carbamazepine has been reported in a patient with psychogenic polydipsia.³ We have not, however, found any previous report of this complication of carbamazepine treatment in patients with trigeminal neuralgia or epilepsy. We describe here two patients, one with trigeminal neuralgia, the other with epilepsy, who developed carbamazepine-induced abnormal water retention.

Case 1

A 74-year-old man developed left-sided trigeminal neuralgia confined to the mandibular branch in 1965. He also had ischaemic heart disease and hypertension, which were treated with debrisoquine, digoxin, and amiloride with hydrochlorothiazide (Moduretic). He had had several attacks of left ventricular failure, and in 1975, when admitted with urinary retention, he had episodic confusion. His plasma sodium concentration was 123 mmol (mEq)/l, although its significance was not appreciated. His trigeminal neuralgia was well controlled by carbamazepine 600 mg/day, which he had been taking for 10 years.

Case 1. Body weight, plasma sodium and osmolality, and dose of carbamazepine.

Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Osmolality: 1 mmol/kg = 1 mOsm/kg.

In February 1976 he was admitted to Nottingham General Hospital with an exacerbation of trigeminal neuralgia and a week's history of anorexia, nausea, vomiting, and ankle oedema. Because of continuing severe pain carbamazepine was increased to 1000 mg/day. After this he became drowsy and confused. Investigations showed: plasma sodium 112 mmol/l, plasma urea 8.3 mmol/l (50 mg/100 ml), plasma osmolality 238 mmol (238 mOsm)/kg, urine osmolality 225 mmol (225 mOsm)/kg, and serum carbamazepine 31.7 μ mol/l (7.5 μ g/ml). A chest radiograph showed no evidence of bronchial carcinoma, and water intoxication due to carbamazepine was suspected. Inferior dental nerve block with alcohol was performed. This resulted in complete relief of pain, and the carbamazepine was discontinued. After this he had a diuresis and lost 5 kg in weight, his ankle oedema cleared, and the electrolyte concentrations returned to normal within two weeks. His general condition improved remarkably and he regained his former alertness and mobility.

Although there was no doubt that he had been suffering from water intoxication, we were unsure whether carbamazepine had been responsible. Since it was possible that he might need the drug again, rechallenge was thought to be justified. Six weeks later, with his informed consent and under carefully controlled conditions in hospital, he was restarted on carbamazepine 1000 mg/day. Within three days he developed nausea, vomiting, and dizziness. By the fourth day the plasma sodium concentration had dropped to 120 mmol/l and he had gained 2 kg in weight. Serum carbamazepine was 25.4 μ mol/l (6 μ g/ml). The drug was stopped but eight hours later he developed acute pulmonary oedema, which was successfully treated. Within two weeks his electrolyte concentrations had returned to normal and he had regained his former wellbeing. The dose of carbamazepine, the changes in body weight, and the plasma sodium and osmolality levels are shown in the figure.

Case 2

A 38-year-old woman with a 16-year history of post-traumatic epilepsy was admitted to the Maudsley Hospital in February 1976 because of recurrent fits on multiple drug therapy. She had been taking carbamazepine 600 mg/day for 18 months and her serum level was 19.0 μ mol/l (4.5 μ g/ml). She was also taking phenytoin 400 mg/day, phenobarbitone 120 mg/day, diazepam 45 mg/day, and clonazepam 9 mg/day. Serum phenytoin and phenobarbitone levels on admission were within the optimum range, but she was drowsy and had gross gum hypertrophy. Serum and red cell folate levels were low, as was the plasma calcium level (2.2 mmol/l (8.56 mg/100 ml)), but the alkaline phosphatase was normal. Plasma sodium was 140 mmol/l and chloride 105 mmol (mEq)/l.

Treatment with phenytoin and phenobarbitone was withdrawn gradually and diazepam reduced to 10 mg/day. Concurrently carbamazepine was increased gradually to 1200 mg/day. Later sodium valproate 1200 mg/day, calcium gluconate 1200 mg/day, and vitamin D (calciferol) 1.25 mg twice weekly were added. During March and April 1976 her serum carbamazepine was 63.5 μ mol/l (15 μ g/ml) but she had no symptoms of toxicity and the dose was not reduced until 1 May, when laboratory tests showed plasma dilution with a plasma sodium concentration of 123 mmol/l and osmolality of 258 mmol/kg. Electrolyte concentrations became normal when the serum carbamazepine level had fallen to 42.3 μ mol/l (10 μ g/ml) and were maintained when the drug was finally withdrawn. During the period of low plasma osmolality the urine osmolality was consistently higher with values between 324 and 440 mmol/kg. Seizures remained difficult to control throughout the period of observation.

Comment

In our first case the rapid development of the symptoms and biochemical changes of water intoxication shortly after restarting carbamazepine confirmed that the drug was responsible, even though the serum carbamazepine remained within the optimum range (16.9–42.3 μ mol/l (4–10 μ g/ml)). This patient may have been particularly vulnerable because of his previous cardiac failure and the interaction between the carbamazepine and other drugs (debrisoquine, digoxin, and Moduretic). Our second patient was much younger and the abnormal water retention was associated with toxic levels of carbamazepine. Her electrolyte concentrations returned to normal when the dose was reduced and serum carbamazepine fell within the optimum range.

Although carbamazepine¹ has antidiuretic effects and is effective in treating diabetes insipidus,² its mode of action remains unclear. There is conflicting evidence from studies in which plasma antidiuretic hormone levels have been assayed, and there are few data on the effect of carbamazepine in normal people.^{4,5} In our first case, although the urine osmolality was lower than that of the plasma, the difference was too small to prevent severe overhydration. In our second case the inappropriately high urine osmolality supports the hypothesis that there was an antidiuretic effect when the serum carbamazepine levels were in the toxic range.

Water intoxication as a side effect of carbamazepine may occur more often than has been recognised. Some of the common side effects of