- ¹³ *Lancet*, 1976, **2**, 405.
¹⁴ Cohn, J N, *Journal of the American Medical Association*, 1974, **229**, 1911.
¹⁵ Marvin, H M, *Journal of Clinical Investigation*, 19, **3**, 521.
¹⁶ Kahler, R L, *et al*, *Circulation*, 1963, **27**, 397.
¹⁷ Starr, I, and Luchi, R J, *American Heart Journal*, 1969, **78**, 740.
¹⁸ Davidson, C, and Gibson, D, *British Heart Journal*, 1973, **35**, 970.
¹⁹ Weissler, A M, *et al*, *American Journal of Cardiology*, 1966, **17**, 768.
²⁰ Shapiro, W, *et al*, *Circulation*, 1970, **42**, 1065.

- ²¹ Chamberlain, D A, *et al*, *British Medical Journal*, 1970, **3**, 429.
²² Smith, T W, and Haber, E, *Journal of Clinical Investigation*, 1970, **49**, 2377.
²³ Dobbs, S M, *Lancet*, 1976, **2**, 694.
²⁴ Dobbs, S M, *et al*, *British Journal of Clinical Pharmacology*, in press.
²⁵ Prichard, B N C, and Tuckman, J, in *Hypertension, Pathophysiology and Treatment*, ed J Genest. Montreal, McGraw Hill, in press.

(Accepted 10 January 1977)

Cholestyramine in uraemic pruritus

D S SILVERBERG, A IAINA, E REISIN, R ROTZAK, H E ELIAHOU

British Medical Journal, 1977, **1**, 752-753

Summary

In a patient with longstanding severe uraemic pruritus who was undergoing chronic haemodialysis cholestyramine caused the pruritus to disappear completely within a few days. A four-week randomised controlled double-blind study was therefore performed in 10 other patients with uraemic pruritus who were on chronic haemodialysis. The pruritus improved considerably in four of the five treated patients, whereas only one of those treated with placebo experienced relief. The patient who had no relief while on cholestyramine showed a considerable improvement when the dose subsequently doubled. One of the five patients receiving cholestyramine experienced mild and easily reversible constipation, and another suffered nausea. Neither of these complications prevented the patients from continuing treatment. Cholestyramine seems to be useful in treating uraemic pruritus, although it is not known how it acts.

Introduction

Pruritus is common in uraemic patients, and although it may improve after dialysis has been started in some cases, in others it may persist and even worsen. We recently administered cholestyramine (Cuemid), an anion-exchange resin, in a dose of 5 g twice daily by mouth, to a patient on chronic haemodialysis who had longstanding severe uraemic pruritus. Within three days his pruritus had greatly diminished, and by one week it had disappeared entirely. He remained free of pruritus for the next month while on the drug. When it was discontinued pruritus returned within three days but disappeared again three days after restarting it. At the time of writing he had been on the drug continually for two months and the pruritus had not returned. Our favourable experience with this patient prompted us to perform a randomised double-blind controlled study of oral cholestyramine in 10 other patients undergoing chronic haemodialysis who also suffered from pruritus.

Department of Nephrology, Sheba Medical Centre, Tel Hashomer, Israel

D S SILVERBERG, MD, visiting professor of nephrology, University of Tel-Aviv
 A IAINA, MD, senior nephrologist
 E REISIN, MD, senior nephrologist
 R ROTZAK, MD, resident in internal medicine
 H E ELIAHOU, MD, head of department of nephrology

Patients and methods

Ten men with longstanding pruritus were studied. All were undergoing haemodialysis for three to five hours three times a week on either a Dow-Cordis hollow-fibre No 5 dialyser or a Travenol Ultra-Flo No 2 dialyser. All were taking a diet containing 1 g protein/kg body weight/day. Those with raised serum phosphate concentrations were taking aluminium hydroxide by mouth. None had jaundice, liver disease, or hypercalcaemia, and none had had a parathyroidectomy.

The 10 patients were randomly assigned to two treatments: five took cholestyramine 5 g twice daily in juice, and five took a placebo (methylcellulose) in the same dose. The trial lasted for four weeks. For three weeks before the trial and during the four-week trial all patients recorded the severity of their pruritus every day. Points were given for the degree of pruritus: 0 = none; 1 = slight; 2 = moderate; 3 = great. We calculated a daily pruritus score before and after treatment for each patient by taking the mean of all the daily scores. Thus the score for the three weeks before treatment was the mean of 21 days' values and the score during treatment was the mean of 28 days' values.

The following routine laboratory investigations were performed before dialysis just before the start of treatment with drug and placebo and again at the end of the trial: prothrombin time was measured and blood urea and serum creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, cholesterol, and triglyceride concentrations were determined.

Results

During the three-week pretrial period all 10 patients complained of pruritus of varying degrees (see table). During the four-week

Mean daily pruritus score before and after treatment. Highest score possible is 3

Case No:	Patients on cholestyramine					Patients on placebo				
	1	2	3	4	5	6	7	8	9	10
Before	1.9	2.2	2.3	1.9	1.9	1.9	0.9	2.1	1.2	2.2
After	2.0	0.9	1.2	1.0	0.3	1.9	0.5	2.3	1.2	2.3

treatment period four of the five cholestyramine-treated patients noted a reduction in pruritus. In one (case 5) pruritus disappeared entirely and in the other 3 (cases 2-4) it decreased considerably. In all four cases pruritus started to improve within four days and showed its greatest improvement after one to two weeks. After the four-week study the patient who had shown no change on cholestyramine (case 1) was given 5 g four times daily, and his pruritus improved greatly within four days and was minimal thereafter.

One patient (case 4) had developed severe constipation by the fourth day of treatment with cholestyramine. This improved after he was given daily doses of a mild laxative. He continued the treatment

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.

References

- 1 Goodman, L. S., and Gilman, A., *Pharmacological Basis of Therapeutics*, 5th edn, p 748. New York, Macmillan, 1975.
- 2 Bergstrom, J., *Dialysis, Transplantation, Nephrology*, vol 12, p 579. London, Pitman Medical, 1975.
- 3 Carey, J. B., and Williams, G., *Journal of the American Medical Association*, 1961, **176**, 432.
- 4 Schiff, L., *Diseases of the Liver*, 4th edn, p 133. Philadelphia, Lippincott, 1975.
- 5 Chanarin, I., and Szur, L., *British Journal of Haematology*, 1975, **29**, 669.
- 6 Kleinmen, P. K., *New England Journal of Medicine*, 1974, **290**, 861.
- 7 Yatzidis, H., Digenis, P., and Tountas, C., *Journal of the American Medical Association*, 1972, **222**, 1183.
- 8 Snyder, D., and Merrill, J. P., *Transactions of the American Society for Artificial Internal Organs*, 1966, **12**, 188.
- 9 Boulton-Jones, J. M., Sissons, J. G. P., and Harrison, E. R., *Lancet*, 1974, **1**, 355.
- 10 Hampers, C. L., et al, *New England Journal of Medicine*, 1968, **279**, 695.
- 11 Massry, S. G., et al, *New England Journal of Medicine*, 1968, **279**, 697.

(Accepted 28 January 1977)

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