Comment

Reports to the Committee on Safety of Medicines show that skin reactions are the commonest adverse reaction to trimethoprim; the committee has had a few reports of cholestatic jaundice due to trimethoprim and to trimethoprim-sulphamethoxazole. Manufacturers of trimethoprim (Duphar) have received four reports of hepatic reactions: hepatitis (two), jaundice (one), and cholestatic jaundice (one). In previous reports similar hepatic reactions to combination antibiotics have been attributed to the sulphonamide component. I suspect that some of these reactions were due to trimethoprim. The mechanism for such cholestasis is obscure as trimethoprim interferes primarily with the metabolism of folic acid. As the reaction occurred late in life in this patient and was clearly related to exposure to the drug it is unlikely to have been any other form of benign cholestasis.

- 1 Nair SS, Kaplan JM, Levine LH, Geraci K. Trimethoprim-sulfamethoxazole induced intrahepatic cholestasis. *Ann Intern Med* 1980;92:511-2.
- 2 Worsmer GP, Keusch GT. Trimethoprim-sulfamethoxazole in the United States. *Ann Intern Med* 1979;91:420-9.
- 3 Frisch JM. Clinical experience with adverse reactions to trimethoprim-sulfamethoxazole. *J Infect Dis* 1973;128:607-11.

(Accepted 15 July 1986)

North Tees General Hospital, Stockton on Tees, Cleveland TS19 8PE

A R TANNER, DM, FRACP, consultant physician

Possible interaction between heparin and a sulphonylurea a cause of prolonged hypoglycaemia?

Glipizide, a second generation sulphonylurea, has pharmacokinetic properties that lessen the risk of hypoglycaemia. Nevertheless, we describe a patient who suffered recurring hypoglycaemia that lasted for four days after a single 5 mg dose of glipizide.

Case report

A 64 year old diabetic man with peripheral vascular disease was found to be hypoglycaemic (blood glucose 1.9 mmol/l (34.2 mg/100 ml)) immediately before an operation for debridement of a foot ulcer. He had been taking glipizide 5 mg daily since diabetes was diagnosed six months before, with fair control (HbA_{1c} 10.2% (normal 6-9%)) and without hypoglycaemia. He had had his usual dose and food intake the previous day and had been fasting for 10½ hours. He received 25 g glucose intravenously and then a 5% dextrose intravenous infusion during the brief operation. Four hours later hypoglycaemia recurred, and over the ensuing 68 hours five symptomatic episodes occurred (blood glucose 1.4-1.8 mmol/l (25.2-32.4 mg/100 ml)) despite continuous infusions of 5% or 10% dextrose 500 ml every four hours and satisfactory eating. The last episode occurred 99 hours after the last dose of glipizide. Five days later glipizide was prescribed, as he was then hyperglycaemic (glucose 13 mmol/l (234.3 mg/100 ml)), but after only one dose of 5 mg he had four hypoglycaemic attacks (glucose 1.0-1.8 mmol/l (18.0-32.4 mg/100 ml)) over the next 36 hours, convulsing during one, again despite eating and continuous intravenous infusion of dextrose. Subsequent hyperglycaemia during four months of follow up was controlled by metformin without trouble.

The original diagnosis of diabetes had been confirmed by a glucose tolerance test, the fasting and two hour capillary blood glucose concentrations being 10 mmol/l (180.2 mg/100 ml) and 14 mmol/l (252.3 mg/100 ml) respectively. During one of his hypoglycaemic episodes (glucose 1.4 mmol/l (25.2 mg/100 ml)) plasma insulin and cortisol concentrations were measured. The insulin concentration was causally increased at 429.1 pmol/l (59.8 mU/l), and cortisol concentration was 0.61 µmol/l (22.1 µg/100 ml). A repeat measurement of cortisol during another episode was 0.82 µmol/l (29.7 µg/100 ml). Concentrations of thyroxine and thyroid stimulating hormone, plasma urea, and creatinine were normal, as were the results of standard liver function tests.

Comment

Glipizide has a short half life (mean four hours) and is metabolised by the liver; its metabolites, which are excreted by the kidneys, are inactive.¹ It is therefore judged less likely to cause hypoglycaemia in patients with renal impairment and safer to use in the elderly. Prolonged hypoglycaemia of up to 36 hours, however, has been reported in the presence of impaired liver function, treatment with aspirin, or gastroenteritis.² In our patient there was no recognised precipitating factor. The results of standard tests of liver and kidney function were normal. His food intake in addition to substantial

intravenous glucose was adequate. There was also an adequate cortisol response to hypoglycaemia, which was confirmed to be due to hyperinsulinaemia. That this was secondary to glipizide seems evident.

It was difficult to understand why he should suddenly have become sensitive to glipizide after six months of uncomplicated treatment. He had not received any counteracting diabetogenic drug before admission. The only other drugs given to him in hospital were diamorphine and subcutaneous heparin calcium, neither of which have been reported as interacting with sulphonylureas. Sulphonylureas, however, are highly bound to protein,³ and even small doses of heparin decrease indirectly the binding of drugs by increasing free fatty acid concentrations, an effect more pronounced in patients with diabetes.⁴ Moreover, glipizide may be more susceptible to drug displacement interactions because of its low volume of distribution.⁵ The heparin, 5000 units every 12 hours, was begun 36 hours before his last (preoperative) glipizide dose and continued during three weeks of post-operative immobility. Despite glipizide's short half life and the expected compensatory rapid elimination of an increased concentration of unbound drug a sufficiently large amount of free glipizide displaced by heparin could possibly have caused the protracted hyperinsulinaemia and hypoglycaemia. Heparin could possibly also have inhibited the metabolism or excretion of glipizide. Oral anticoagulants may potentiate sulphonylureas,^{1,3} but we are unaware of any reports implicating heparin.

We thank Dr C E McKean, hospital pharmacist, for help in preparing this report

- 1 Jackson JE, Bressler R. Clinical pharmacology of sulphonylurea hypoglycaemic agents. *Drugs* 1981;22:211-45,295-320.
- 2 Goran B, Bo B, Martin F, Per M. Glipizide-induced severe hypoglycaemia. *Acta Endocrinol* 1981;98(suppl 245):13.
- 3 Asmal AC, Marble A. Oral hypoglycaemic agents: an update. *Drugs* 1984;28:62-78.
- 4 Estes JW. Clinical pharmacokinetics of heparin. *Clin Pharmacokinet* 1980;5:204-20.
- 5 Marble A, Selenkow HA, Rose LI, Dluhy RG, Williams GH. Endocrine diseases: diabetes mellitus. In: Avery GS, ed. *Drug treatment*. Sydney: ADIS Press, 1980:498-515.

(Accepted 31 July 1986)

Medical Division, Victoria Infirmary, Glasgow G42 9TY

G MCKILLOP, MB, MRCP, medical registrar

M FALLON, MB, CHB, house surgeon

S D SLATER, MD, FRCP, consultant physician

Correspondence to: Dr McKillop.

Carotid artery stenosis exposed by an adverse effect of captopril

Captopril is being administered to an increasing number of patients with arterial hypertension. Cerebral complications are rarely reported. We use the short term captopril test to evaluate patients with hypertension. During this test we observed reversible cerebral symptoms in two patients.

Case reports

Arterial blood pressure and heart rate in the supine position are measured before and every 15 minutes for 90 minutes after the administration of captopril 6.25 mg orally. Plasma renin activity is measured before and 90 minutes after the administration of captopril.

Case 1—The patient was a 67 year old woman who had had hypertension for over 35 years. Sympathectomy in 1954 had not had any appreciable effect. The blood pressure was 220/130 mm Hg, decreasing spontaneously to 160/110 mm Hg. She was treated with prazosin 10 mg, atenolol 25 mg, and a combination of hydrochlorothiazide 50 mg and amiloride 5 mg, all twice daily. Plasma renin activity was 95 mU/l (normal 6-60 mU/l), and serum creatinine concentration 128 µmol/l (1.45 mg/100 ml). Renography and computed tomography of the kidneys showed complete lack of renal function on the left side and a contracted kidney. Seventy five minutes after the administration of captopril she became absent, complaining of paraesthesia of both hands and spots before the eyes. The blood pressure had dropped to 100/85 mm Hg, and the heart rate was 100 beats/min and stable. She regained consciousness within a couple of minutes without any sequelae. Digital subtraction angiography showed stenosis of the internal carotid artery, external carotid artery, and vertebral artery on the right side. This had not been apparent on auscultation of the vessels.

Case 2—This 67 year old man had had ischaemic heart disease since the age of 58. Hypertension had been diagnosed six months previously, and three years previously an aortic prosthesis had been inserted because of intermittent claudication. Blood pressure was 190/120 mm Hg, and he was treated with clonidine 75 µg twice daily, methyldopa 125 mg thrice daily, and bendrofluazide 5 mg twice daily. Serum creatinine and plasma electrolyte concentrations and clearance of edetic acid labelled with chromium-51 were normal. Catheterisation of the renal veins showed a plasma renin activity of 1000-2000 mU/l on the right

side. Digital subtraction angiography showed a thin right renal artery without stenosis. The aortic prosthesis was patent. Eighty minutes after administration of captopril the blood pressure dropped to 120/80 mm Hg; the heart rate was unchanged at 100 beats/min. He experienced dizziness and blurred vision and then developed aphasia. Intravenous dopamine was started, and the symptoms resolved within a few minutes. No abnormalities were shown on subsequent neurological examination, and an electrocardiogram was unremarkable. On physical examination no abnormality of the arteries of the neck was found, but digital subtraction angiography showed stenosis of the right external and internal carotid arteries.

Comment

Most probably the cerebral symptoms observed in these patients were caused by a combination of extracerebral obstruction to the cerebral blood flow and the reduction of blood pressure induced by captopril. Similar cases have been described, but the importance of narrowed neck arteries has not been mentioned.^{1,2} It is noteworthy that in our patients the mean arterial blood pressure was 95 and 107 mm Hg, respectively, when the cerebral symptoms occurred, pressures that would usually be regarded as safe and reasonable results of treatment. The pulse rate was unaltered, which excludes increased parasympathetic activity. The observed phenomenon implies that captopril even in small doses may be dangerous in patients with arterial hypertension and arteriosclerotic stenosis of the great arteries of the neck.³

- 1 Hodsman GP, Isled CG, Murray GD, *et al*. Factors related to first dose hypotensive effect of captopril: prediction and treatment. *Br Med J* 1983;286:832-4.
- 2 Christensen HR, Kampmann JP, Svendsen TL. Severe hypotension after captopril. *Ugeskr Laeger* 1983;145:22.
- 3 Ebert TJ. Captopril potentiates chronotropic baroreflex responses to carotid stimuli in humans. *Hypertension* 1985;7:602-6.

(Accepted 28 July 1986)

Department of Medicine 4, Kommunehospital, DK 1399 Copenhagen K, Denmark

HERLUF JENSEN, MD, consultant physician
HELMER RING-LARSEN, MD, consultant physician
PER GARSDAL, MB, research assistant
PER FRUERGAAARD, MB

Correspondence to: Dr Jensen.

Blood disorders associated with pirenzepine

Pirenzepine is a new drug for peptic ulcer disease recently introduced in the United Kingdom. We report the following blood disorders attributed to this agent.

Case 1

An 86 year old woman with a history of heart failure, chronic obstructive lung disease, and peptic ulcer was admitted with dyspnoea and chest pain. On examination she was found to have congestive heart failure. Blood investigations showed increased leucocyte count ($13.2 \times 10^9/l$) with a normal differential count, haemoglobin concentration 10.8 mmol/l (174 g/l), platelet count $174 \times 10^9/l$ (figure), and normal red cell morphology. She had been treated with propranolol 30 mg daily, theophylline 600 mg daily, and frusemide 40 mg daily, and these

Temporal relation between treatment with pirenzepine and platelet count in case 1.

were continued on admission. Because she was thought to have a superimposed respiratory infection, and pulmonary embolism could not be excluded, treatment was started with digoxin 0.25 mg daily, doxycycline 100 mg daily, prednisone 10 mg daily, and heparin 20000 units daily (for two days), followed by nicoumalone. She improved and stopped taking doxycycline and theophylline but then developed a gastric ulcer, which was confirmed at gastroscopy and treated with pirenzepine 100 mg daily (figure). Eight days later her platelet count decreased to $43 \times 10^9/l$ (figure); her white cell count and haemoglobin concentration were normal, and she stopped taking pirenzepine six days later. One week later her platelet count had returned to normal and she was discharged.

She was readmitted two and a half weeks later with increasing dyspnoea and swelling of the right lower leg. Propranolol was stopped, and she started taking verapamil 240 mg daily, triamterene 50 mg daily, and ranitidine 300 mg daily because of dyspepsia; two weeks later pirenzepine 100 mg daily was restarted (figure). Her platelet count was then normal ($271 \times 10^9/l$) but started to diminish six days later, reaching a nadir of $136 \times 10^9/l$ eight days later. After two days she stopped taking pirenzepine and made an uneventful recovery.

Case 2

A 69 year old man with a history of asthmatic bronchitis and cardiac failure after myocardial infarction was treated for gastritis with pirenzepine 100 mg daily. His leucocyte count was normal ($6.1 \times 10^9/l$) with a normal differential count, haemoglobin concentration was 7.1 mmol/l (115 g/l), and platelet count was $353 \times 10^9/l$. Ten days later he developed leucopenia ($0.4 \times 10^9/l$) with complete agranulocytosis (95% lymphocytes, 5% monocytes). Red cell and platelet counts remained normal. He stopped taking amiodarone, potassium chloride, pirenzepine, and spironolactone but continued with glyceryl trinitrate, frusemide, nicoumalone, theophylline, ipratropium bromide, and beclomethasone dipropionate. He became feverish, but his temperature returned to normal after treatment with antibiotics. Daily blood counts showed that his leucocyte count returned to normal ($5.2 \times 10^9/l$) with a normal differential count 13 days after stopping the pirenzepine.

Potassium chloride and amiodarone were later used again without a relapse of leucopenia. Pirenzepine and spironolactone were suspected of causing the agranulocytosis.¹ The results of immunological tests for drug dependent antibodies² against granulocytes were negative for spironolactone but weakly positive for pirenzepine. Because a potassium sparing diuretic was deemed necessary spironolactone was restarted; there was no decrease in the white cell count. Regular blood and differential counts remained normal.

Comment

The temporal relation between the intake of pirenzepine and the onset of agranulocytosis and thrombocytopenia in both of these patients suggests that this drug was causative. Other drugs were either continued or restarted without aggravation or relapse. In case 1 readministration of pirenzepine was followed by a decrease in platelet count to $136 \times 10^9/l$, but this increased before the last dose of pirenzepine was taken, leaving the rechallenge inconclusive.

This transient decrease could be due to compensatory production secondary to increased peripheral destruction of platelets, desensitisation, or destruction by antibodies still circulating from the first episode of thrombocytopenia before rechallenge causes further platelet destruction. A large clinical trial has shown mild leucopenia in 2.8% of patients with normal counts before treatment, but the causal relation with pirenzepine was uncertain.³ Although we cannot exclude a fortuitous relation between the use of pirenzepine and blood disorders in our patients, we think that these cases suggest that pirenzepine is a potential cause of agranulocytosis and thrombocytopenia.

- 1 Stricker BHCh, Oei TT. Agranulocytosis caused by spironolactone. *Br Med J* 1984;289:731.
- 2 Stricker BHCh, Barendregt JNM, Claas FHJ. Thrombocytopenia and leucopenia with mianserin-dependent antibodies. *Br J Clin Pharmacol* 1985;19:102-4.
- 3 Giorgi-Conciato M, Daniotti S, Ferrari PA, *et al*. Efficacy and safety of pirenzepine in peptic ulcer and in non ulcerous gastroduodenal disease. A multicentre controlled clinical trial. *Scand J Gastroenterol* 1982;17(suppl 81):1-41.

(Accepted 22 July 1986)

Netherlands Centre for Monitoring of Adverse Reactions to Drugs, PO Box 439, 2260 AK Leidschendam, The Netherlands

B H CH STRICKER, MB, medical officer
R H B MEYBOOM, MD, head of centre

Department of Internal Medicine, Ziekenhuis Rivierenland, Tiel, The Netherlands

P A BLEEKER, MD, physician

Department of Internal Medicine, Reinier de Graaf Gasthuis, Delft, The Netherlands

K VAN WIERINGEN, MD, resident physician

Correspondence to: Dr Stricker.