Comment

Reports to the Committee on Safety of Medicines show that skin reactions are the commonest adverse reactions 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.


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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 (HbA1 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 10 hours. He received 25 g glucose intravenously and then 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 59 hours after the last dose of glipizide. Five days later glipizide was reconstituted, as he was then hyperglycaemic (glucose 13.0 mmol/l [234.5 mg/100 ml]) but after only one dose of 5 mg he had four hypoglycaemic attacks (blood glucose 1.6-1.8 mmol/l [28.8-32.4 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 pmol/l (22.1 μg/100 ml). A repeat measurement of cortisol during another episode was 0.82 pmol/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 months of uneventful treatment. He had not received any counteracting diabetogenic drug before admission. The only other drugs given to him in hospital were diormephine and subcutaneous heparin calcium, neither of which have been reported to interact with sulphonylureas. Sulphonylureas, however, are highly bound to protein,1 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.3 Moreover, glipizide may be more susceptible to drug displacement interactions because of its low volume of distribution.1 The heparin, 5000 units every 12 hours, was begun 36 hours before his last (presumably) glipizide dose was continued during three weeks of postoperative 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 4 but we are unaware of any reports implicating heparin.

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4 Entre WF. Clinical pharmacokinetics of Trimethoprim 1980;5:204-20.

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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 after 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. Symphactomy 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 prozazin 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, methyl dopa 125 mg thrice daily, and bendrofluazide 5 mg twice daily. Serum creatine and plasma electrolyte concentrations and clearance of edetic acid labelled with chromium-51 were normal. Catherisation of the renal veins showed a plasma renin activity of 1000-2000 mU/l on the right side.

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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 dyspepsia 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 frusamide 40 mg daily, and these 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 20 000 units daily (for two days), followed by subcutaneous heparin and haemoglobin concentration returned to 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 dyspepsia 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 (5.2 \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.

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 relaunches 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. 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.


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