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

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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 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.

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