Captopril-associated agranulocytosis

A report of 3 cases

P. I. PILLANS, A. KOOPOWITZ

Summary

Three cases of captopril-associated neutropenia are described, which illustrate the clinical presentation, variable predisposing factors and outcome of this rare but potentially serious adverse event. Particular risk factors of renal failure and collagen vascular disease were present in only 1 patient, while a second patient had reversible mild renal impairment. The doses of captopril used ranged from 25 mg to 50 mg 3 times a day. Two patients recovered after withdrawal of the drug but the third died of septicaemia. Captopril-associated agranulocytosis is reviewed.

S Afr Med J 1991; **79:** 399-400.

Case reports

Case 1

A 56-year-old woman with longstanding hypertension suffered a myocardial infarction in May 1989. In November 1989 she was admitted to hospital with pulmonary oedema and was subsequently started on captopril, the dosage being increased to 50 mg 3 times a day. Previous medication, namely amiloride 5 mg plus hydrochlorothiazide 50 mg once daily and aspirin 150 mg daily was continued. Three weeks later she was again admitted to hospital with a temperature of 38,3°C and a septic lesion on the right little finger with lymphangitis extending up the forearm. Although there was clinical evidence of cardiomegaly she was not in cardiac failure. A full blood count revealed a haemoglobin level of 13,4 g/dl and platelet count of 291 × 10^9/l. The white cell count was reduced at 3,4 × 10^9/l with 0% neutrophils, 51% lymphocytes, 44% monocytes, 2% eosinophils and 3% basophils. Biochemical investigations gave normal results except for a mildly elevated serum urea value of 10,5 mmol/l (normal 1,7 - 6,7 mmol/l) and creatinine of 145 μmol/l (normal 75 - 115 μmol/l), both of which had returned to normal by the 4th day in hospital. Urine examination, three blood cultures, VDRL test and lupus profile were all negative. Chest radiography was non-contributory except for left ventricular cardiomegaly. Captopril was discontinued and the infection treated with cloxacillin and clindamycin. On the 2nd day in hospital the white cell count was 2,67 × 10^9/l with 4% neutrophils but the following day it had risen to 4,0 × 10^9/l with 35% neutrophils and on the 6th day to 6,71 × 10^9/l with 53% neutrophils. The temperature settled and the patient made an uneventful recovery. The white cell count 34 days after admission to hospital was 6,47 × 10^9/l with 58% neutrophils. Rechallenge was not attempted.

Departments of Pharmacology and Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town
P. I. PILLANS, M.B. B.CH., F.C.P. (S.A.), M.D.
A. KOOPOWITZ, M.B. B.CH.

Accepted 21 Aug 1990.

Case 2

A 31-year-old woman with systemic lupus erythematosus, membranous nephropathy, chronic renal failure and hypertension was on medication that included prednisone 40 mg daily, nifedipine 10 mg 3 times a day, furosemide 1 g daily, metolazone 5 mg daily, and atenolol 100 mg daily. On 4 October 1989 enalapril was started at 2,5 mg daily and the dose was subsequently increased to 5 mg daily with no untoward effect. On 21 November 1989 the angiotensin-converting enzyme (ACE) inhibitor was changed to captopril, reaching a maximum dose of 50 mg 3 times a day. Other medication was continued. On 4 December 1989 at a routine follow-up examination the haemoglobin value was 7,4 g/dl, the white cell count 11,3 × 10^9/l with 95% neutrophils, in keeping with high-dose corticosteroids, and platelets 406 × 10^9/l.

On 11 January 1990 the patient was admitted to hospital with a 2-week history of generalised erythematous maculopapular rash, intermittent fever, myalgia and arthralgia. On examination she was pale, the temperature was 37,8°C, an infected right thumb was noted and there was ascites considered to be secondary to the nephrotic syndrome.

Chest radiography showed bilateral pleural effusions with consolidation of the apical segment of the right lower lobe. Blood cultures were negative, sputum and urine revealed mixed organisms and there was no growth from the ascitic fluid. A swab from the infected right thumb grew *Staphylococcus aureus*. A full blood count revealed a normochromic normocytic anaemia with a haemoglobin value of 8 g/dl and a platelet count of 379 × 10^9/l. The white cell count was markedly decreased at 0,32 × 10^9/l with 5% neutrophils, 66% lymphocytes, 10% monocytes, 4% basophils and 15 large unstained cells. Biochemical investigations were remarkable for elevated serum urea of 49,6 mmol/l and creatinine of 394 mmol/l, decreased serum albumin of 25 mmol/l (normal 35 - 50 mmol/l), elevated inorganic phosphate of 3,2 mmol/l (normal 0,8 - 1,4 mmol/l) and increased cholesterol of 7,3 mmol/l (normal 3,1 - 7,1 mmol/l) in keeping with chronic renal failure and the nephrotic syndrome. Captopril was stopped, but other medicines continued, and intravenous penicillin was started, which was changed the following day to intravenous ceftriaxone. The pyrexia settled and the patient's symptoms improved. Fourteen days later, on 25 January 1990, the white cell count was 1,35 × 10^9/l with 37% neutrophils, on 30 January it was 3,84 × 10^9/l and on 17 April 1990 it was 6,12 × 10^9/l with 79% neutrophils. Rechallenge with captopril was not attempted.

Case 3

A 51-year-old woman with no illness of note except hypertension was treated with captopril 25 mg 3 times a day for 4 months. She presented to hospital with a sore throat and a white cell count of 0,68 × 10^9/l. The neutrophil count was 0,1 × 10^9/l. A previous white cell count was normal at 11,2 × 10^9/l as were the serum urea of 5,7 mmol/l and serum creatinine of 95 mmol/l. The patient developed septicaemia

and died despite treatment with penicillin, cefotaxime, amikacin, imipenim and metronidazole.

Discussion

The ACE inhibitors are gaining wider acceptance in the treatment of cardiac failure and hypertension. Although adverse effects, such as hypotension, rash, proteinurea, taste disturbance and cough are well known, it is important that prescribers are aware of the potentially serious, albeit rare, haematological events.

The neutropenia and agranulocytosis associated with captopril typically occur within 3 - 12 weeks of the start of treatment. Particular risk factors are renal impairment and collagen vascular disease, such as lupus erythematosus or scleroderma.[1-3] In patients with normal renal function and no collagen vascular disease, the overall incidence of neutropenia has been quoted as 0,02%, whereas in patients with both collagen vascular disease and renal failure the incidence is much higher (3,7 - 7,2%).[3,4] Patient 2, who had lupus erythematosus and chronic renal failure, is a typical example of a patient at increased risk. Other reports of neutropenia and agranulocytosis have been in patients on very large doses of captopril — up to 600 mg daily[5-8] — although agranulocytosis has been described in patients on 12,5 - 100 mg captopril daily.[9] Our third patient, who was on maximal, although not an excessive, dose of captopril illustrates the development of agranulocytosis in the absence of predisposing diseases.

Following discontinuation of captopril the neutrophil count usually returns to normal within 3 weeks and this has been reported to occur as early as 2 - 3 days after stopping medication,[9] which is in keeping with our first case. Some patients have been rechallenged with captopril after recovery, often with reduced dosages, and whereas some have experienced recurrence, most have not, possibly suggesting a dose-response phenomenon in those without recurrence.[2] Although septicaemia may be associated with neutropenia the negative blood cultures in the first case and rapid recovery are in keeping with captopril-related agranulocytosis. In the third case septicaemia cannot be positively excluded as the cause for the profound leukopenia and neutropenia.

The renin-angiotensin system appears to contribute substantially to maintenance of glomerular filtration in patients with congestive heart failure in whom renal perfusion is compromised, and renal function may deteriorate during therapy with an ACE inhibitor.[1] This probably occurred in our first case, predisposing to accumulation of captopril, which is primarily eliminated by the kidney. Serum creatinine levels returned to normal after captopril was discontinued.

Captopril-associated neutropenia is reversible, but death has occurred in up to 13% of patients who have developed neutropenia, although most fatalities have been reported in patients with associated serious collagen vascular disease, renal failure or heart failure.[1,10,11] Our third case, however, illustrates that septicaemia complicating neutropenia may be fatal in an otherwise well patient.

There has been considerable discussion about whether the side-effect of neutropenia is drug-specific for captopril or class-specific for the ACE inhibitors. It is hypothesised that the sulphydryl group in captopril as in penicillamine contributes to the development of this adverse effect. Reports from users of captopril and enalapril in the UK, which show a higher incidence of captopril-associated granulocytopenia, pancytopenia or aplastic anaemia (27 of 81 000 patients) compared with only 1 out of 31 000 patients on enalapril, favour a captopril-specific effect.[4] However, experience with other ACE inhibitors is limited in patients with concomitant collagen vascular disease and renal failure.

Except in patients with collagen vascular disease and renal failure, this rare complication is not an indication for routine full blood counts in patients on ACE inhibitors. However, if a patient develops a sore throat or other signs of infection a white cell count, including a differential count, should be performed.

We thank Professor R. van Zyl-Smit for permission to present the second case.

REFERENCES

1. American Hospital Formulary Service. *American Hospital Formulary*. Bethesda, Md: AHFS, 1989: 780.
2. Cooper RA. Captopril-associated neutropenia. *Arch Intern Med* 1983; **143**: 659-660.
3. Di Bianco R. Adverse reactions with ACE inhibitors. *New Ethicals* 1986; **23**: 181-208.
4. Irvin JD, Viau JM. Safety profiles of the angiotensin-converting enzyme inhibitors captopril and enalapril. *Am J Med* 1986; **81**: suppl. 4C, 46-50.
5. Van Brummelen P, Willemze R, Tan WD, Thompson, J. Captopril-associated agranulocytosis (Correspondence). *Lancet* 1980; **1**: 150.
6. Aman FW, Buhler FR, Conen D, Brunner F, Ritz R, Speck B. Captopril-associated agranulocytosis (Correspondence). *Lancet* 1980; **1**: 150.
7. Staessen J, Fagard R, Lijnen P, Amery A. Captopril and agranulocytosis. *Lancet* 1980; **1**: 926-927.
8. Elijovisch F, Krakoff LR. Captopril-associated granulocytopenia in hypertension after renal transplantation. *Lancet* 1980; **1**: 927-928.
9. Edwards IR, Coulter DM, Beasley DMG, Macintosh D. Captopril: 4 years of post-marketing surveillance of all patients in New Zealand. *Br J Clin Pharmacol* 1987; **23**: 529-536.
10. Gavras I, Graff LG, Burton D *et al*. Fatal pancytopenia associated with the use of captopril. *Ann Intern Med* 1981; **94**: 58-59.
11. El Matri A, Larabi MS, Kechrid C *et al*. Fatal bone marrow suppression associated with captopril. *Br Med J* 1981; **283**: 277-278.