Adverse drug reaction of the month

Low-grade fever after prosthetic valve insertion and captopril therapy: an iatrogenic cause

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A 55-year-old obese woman with previous hypothyroidism had a myocardial infarction followed by sudden papillary muscle rupture and profound cardiac failure. A Medtronic mitral valve prosthesis was inserted as an emergency but she remained in severe left ventricular failure until eventually controlled on frusemide 100 mg/day, isosorbide mononitrate 10 mg bid, digoxin 125 µg once daily, and captopril 12.5 mg bid. She was also receiving warfarin because of the prosthetic valve, thyroxine 150 µg and prednisolone 7.5 mg daily for muscular pains (not associated with other symptoms) diagnosed two years earlier as possible polymyalgia rheumatica.

She was making good progress until four months later when she complained of malaise, myalgia and arthralgia, of feeling flushed and she was noted to have a persistent low grade pyrexia (37.5–38°C), a polymorphonuclear leucocytosis (white blood cell count 13 000, 80% neutrophils), and an erythrocyte sedimentation rate of 50 mm/h (previously steady around 35 mm/h). Endocarditis was considered in the differential diagnosis but extensive investigations over a four-week period including repeated blood cultures, virology screen, auto-antibodies, abdominal computed tomography (CT) scan, transoesophageal echocardiography, and white cell scan failed to detect any abnormality and a prolonged course of antibiotics (including cefuroxime, metronidazole and flucloxacillin) had no effect on her symptoms, temperature or leucocytosis.

At four weeks, she developed an erythema multiforme-like rash which persisted when the antibiotics were discontinued and it was decided that captopril would also be withdrawn. Within 48 hours, her temperature had fallen to 37°C for the first time in four weeks and she remained afebrile, her malaise and myalgia disappeared, as did her rash and she was discharged home. Unfortunately, her cardiac failure slowly returned over the next few months and five months later, she was readmitted and enalapril was instituted at a dose of 10 mg mane and 5 mg nocte. She responded well to addition of this angiotensin-converting enzyme (ACE) inhibitor without recurrence of her malaise, myalgia, arthralgia, rash, leucocytosis or pyrexia.

Discussion

Low-grade pyrexia and myalgia with rash in two patients receiving captopril was first reported nearly 20 years ago.¹ Subsequently,

fever was reported in two of seven individuals with rash associated with captopril therapy which had been started 1–31 weeks earlier.² Fever has also been reported in association with rash and pericarditis.³ The CSM/MCA have received 17 reports of pyrexia in association with captopril up until November 1996 and although fever has sometimes resolved with continuing administration,⁴ it may resolve only after captopril is withdrawn.⁵ In our patient, the persistent pyrexia soon after the insertion of a prosthetic valve led to a long and unsuccessful search for infection, and in particular infection of the prosthetic valve before an iatrogenic (drug-induced) cause was considered. It is likely that only one third of cases of pyrexia of unknown origin have an infective cause and some important drug-induced causes of fever are shown in box 1, although many more agents are occasionally associated with fever.

The rash associated with captopril has been described as pruritic, erythematous, macular or papular affecting the trunk, face and proximal extremities but psoriasiform, lupus erythematosus-like, lichenoid and pemphigus/pemphigoid-like eruptions have also been seen.⁶ The corticosteroids which our patient was receiving could possibly have suppressed the development of a rash until a late stage since steroids have been used in the treatment of captopril-induced rash. Arthralgia has been described in association with captopril treatment,^{2,7,8} with resolution when the drug was discontinued.

Fever, rash and arthralgia are part of a symptom complex which may also include myalgia, serositis, vasculitis, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leukocytosis and photosensitivity seen in association with ACE inhibitors.⁹ It appears to be more commonly (but not

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Accepted 1 May 1997

Some drugs which may cause fever

- anticonvulsants (carbamazepine, lamotrigine, phenytoin)
- anti-infectives (isoniazid, minocycline)
- bisphosphonates (especially intravenous)
- ACE inhibitors (captopril)
- cytokines (aldesleukin)
- cytotoxic drugs
- fibrinolytics (streptokinase, anistreplase)
- interferons (α, β, γ)
- penicillamine
- vaccines

Box 1

exclusively) reported in association with captopril (which, like penicillamine, contains a sulphhydryl group) than with the other ACE inhibitors. The frequency of the reaction with captopril is unknown but it may well be overlooked or not reported to the CSM/MCA. Nevertheless the CSM/MCA had received 31 reports of arthralgia, 26 of myalgia and 19 of erythema multiforme in association with captopril therapy by 30 December 1996.

ACE inhibitor therapy has been a major advance in the treatment of heart failure and this woman who had profound left ventricular failure deteriorated markedly before an ACE inhibitor was re-introduced. Resolution of captopril-induced rash after substitution of enalapril has occurred¹⁰ so we decided to introduce this drug. The failure of recurrence of symptoms and signs is suggestive of a specific and possibly type B (idiosyncratic) adverse reaction to captopril rather than a class

Learning points

- pyrexia of unknown origin may not always have an infective cause and iatrogenic causes may need to be considered
- ACE inhibitors can cause a symptom complex which includes pyrexia, arthralgia, myalgia, rash and raised erythrocyte sedimentation rate
- these features can occur with one ACE inhibitor but not with another and cautious introduction of an alternative agent can be attempted if clinically indicated
- corticosteroids can mask features of adverse drug reactions and delay their diagnosis

Box 2

effect of these agents. Skin testing has been used to investigate possible hypersensitivity to captopril and was reasonably specific but relatively insensitive in patients with cutaneous reactions.¹¹

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