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Vasculitis due to metolazone

Sir,

A 65 year old man had severe cardiac failure following a myocardial infarction 2 years previously. He had subsequently suffered 2 episodes of haemolytic anaemia, apparently due to captopril and then to lisinopril. In September 1990 he developed an acute, widespread, small vessel cutaneous vasculitis which increased over the next 2 weeks. Four weeks before the onset of vasculitis, his oral medication had been changed from bumetanide and spironolactone to frusemide with amiloride (Frumil®) and isosorbide mononitrate; after 2 weeks the Frumil had been discontinued, frusemide 120 mg daily substituted, and metolazone (Metenix®) 5 mg twice daily had been commenced. The patient had previously taken frusemide without any adverse effect.

On admission to hospital he had extensive vasculitis, without frank necrosis or ulceration, and asymptomatic haematuria. Metolazone was stopped, and the vasculitis resolved within 5 days. No steroid therapy was required, and none of the other medication was stopped; his frusemide dose was actually increased during the following weeks without recurrence of vasculitis. Skin biopsy confirmed a leukocytoclastic vasculitis, mainly affecting small venules; direct immunofluorescence of the biopsy showed deposition of IgG, IgA, IgM and complement C3 in vessel walls. Despite intensive treatment, the patient died a few weeks later; his intolerance of several potentially useful agents limited the therapeutic options.

Although a bullous eruption is more frequent, vasculitis due to frusemide has been documented¹ and is probably better recognized by dermatologists than the small number of cases reported to the CSM would suggest (23 cases recorded; Committee on Safety of Medicines – personal communication). Both frusemide and thiazides are listed as drugs which may cause vasculitis in a monograph on cutaneous effects of drugs.² The only previous report of vasculitis received by the manufacturers of Metenix was thought to be due to concomitant frusemide therapy, but in our patient the timing of changes of medication and the rapid resolution after stopping the drug strongly suggested that metolazone rather than frusemide was the cause of the vasculitis. The occurrence of skin and renal vasculitis due to thiazides has been previously reported in a patient who developed vasculitis related to both hydrochlorothiazide and chlor-thalidone, confirmed by rechallenge.³ The CSM has received two reports of vasculitis in patients taking metolazone, and other rashes reported to the manufacturers or to the CSM include purpura, 'erythema multiforme' and epidermal necrolysis, photosensitivity, and pruritus.

The potential difficulties in management of drug eruptions in patients with severe conditions, and taking multiple essential drugs of which two or more can cause the same pattern of eruption, is well demonstrated by this case. The presence of severe cardiac failure precluded discontinuing both diuretics, yet the rapidly increasing extent of vasculitis in an already severely ill patient required prompt intervention; institution of oral steroid therapy was considered but with reluctance because of the potential for further fluid retention. The timing of the eruption, and the previous uneventful exposure to frusemide, suggested that metolazone was the more likely cause of vasculitis and this was confirmed by the rapid improvement after it was withdrawn; rechallenge was not considered. Cutaneous reactions to diuretics are not rare in dermatological practice but this patient was unusual in having adverse reactions to a number of potentially useful drugs used in treatment of severe cardiac failure.

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