Vasculitis with Alclofenac Therapy

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Summary

Three patients developed a vasculitis while taking alclofenac. Two recovered with corticosteroid therapy, and the third, who had continued to take the drug for a further week despite epistaxis, haemoptysis, haematuria, and cutaneous vasculitis, developed a more persistent vasculitis with histological evidence of progressive renal involvement.

Introduction

Alclofenac has been shown to have both analgesic and anti-inflammatory properties (Aylward and Davies, 1972). Transient rashes have been reported in 6% of patients taking alclofenac (Aylward, 1973), and recent correspondence has suggested that there may be a relatively high incidence of adverse effects to this drug (Mansel-Jones, 1974). We report three cases of the development of a vasculitis while taking alclofenac.

Case 1

The patient, a 66-year-old woman suffering from osteoarthritis, was prescribed alclofenac 1 g three times a day. She soon felt unwell and within five days developed a widespread petechial rash, redness and swelling of the mucous membrane, dysphagia, and profuse diarrhoea.

On examination she was febrile, dehydrated, and confused. Her pulse was regular at 90/min and blood pressure was 90/60 mm Hg. Investigations: haemoglobin was 10.3 g/100 ml, W.B.C. 4,900/mm³ (80% neutrophils), platelets normal, and E.S.R. 19 mm/hr (Westergren). A mid-stream specimen of urine gave no growth, albumin was present, blood urea was 143 mg/100 ml, liver function test results were normal and no L.E. cells were found. A chest x-ray picture and E.C.G. showed no significant abnormality. She responded well to intravenous fluids, hydrocortisone, and chlorpheniramine maleate. Her blood urea fell to 43 mg/100 ml and her rash faded slowly.

Case 2

This 76-year-old woman, who had a mastectomy four years previously for carcinoma, was prescribed alclofenac 1 g three times a day for pain in the hip. After two days the dose was reduced to 1 g twice daily. On the seventh day she developed an extensive purpuric eruption over the whole body (fig. 1) with swelling of the eyelids, ulceration, and bleeding from mouth, nose, and vagina. Fresh blood was noticed in her stools.

Investigations: haemoglobin was 11.0 g/100 ml, W.B.C. 7,900/mm³, platelet count 110,000/mm³, bleeding time normal, Thrombotest 100%, blood urea 168 mg/100 ml, total protein 5.4 g/100 ml,

FIG. 1—Case 2. Patient on admission with widespread petechial rash.

albumin 2.5 g/100 ml, and globulin 2.9 g/100 ml. Electrophoresis showed a slight increase in α 1 and 2 bands and no paraprotein band was seen. A mid-stream specimen of urine contained red blood cells and protein. X-ray pictures of chest and pelvis showed lytic lesions in the right femur and possibly in the 3rd and 5th ribs consistent with secondary deposits. Her clinical condition improved rapidly with prednisolone 20 mg daily. The blood urea fell to 49 mg/100 ml, her skin and mucous membrane lesions settled, and after three weeks steroids were discontinued. Her bone metastases were treated with radiotherapy and anabolic steroids. There was no further recurrence of her vasculitis.

Case 3

The patient, a 52-year-old man who had complained of occasional muscle and joint pain for 20 years in the absence of either degenerative or inflammatory joint disease, was prescribed alclofenac 500 mg three times a day. After 48 hours he felt unwell and developed epistaxis, haematuria, and two small haemoptyses. Despite this he continued to take the drug and within one week developed a purpuric eruption on his hands and feet with a generalized maculopapular eruption on the trunk. His temperature was 38.5°C, pulse regular at 100/min, and blood pressure 150/100 mm Hg.

Investigations: haemoglobin was 13.8 g/100 ml, W.B.C. 12,000/mm³ (polymorphs 62%, eosinophils 13%), platelets 257,000/mm³, and E.S.R. 65 mm/hr (Westergren). Bleeding and clotting times were normal and the result of the direct Coombs's test negative. Urine contained red cells, urinary protein was 0.3 g/l, glomerular filtration rate (⁵¹Cr editic-acid clearance) 92 ml/min. Total protein was 5.4 g/100 ml, albumin 2.2 g/100 ml, globulin 3.2 g/100 ml, IgA 260 mg/100 ml, IgG 1,450 mg/100 ml, IgM 42 mg/100 ml, and serum complement (C3) normal. Serological investigations showed rheumatoid factor and the differential agglutination titre was 1/2048. Tests for autoimmune profile, L.E. cells, hepatitis-associated antigen, and Wassermann reaction were all negative.

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The symptoms and signs settled within a week of beginning prednisolone 60 mg daily. As the dosage was reduced, however, the patient relapsed with a transient right hemiparesis, periumbilical pain, melaena, haematuria, and widespread cutaneous vasculitis. Alkaline phosphatase rose to 59 K.A. units, 5-nucleotidase to 39 IU/l., and his E.S.R. was 84 mm/hr (Westergren). His clinical condition and abnormal liver function test results returned to normal with a further increase in his steroids. Renal biopsy showed focal proliferative lesions with partial sclerosis of several glomeruli.

In the past year the patient was readmitted three times with recurrence of purpuric skin lesions, haematuria, and haemoptysis, the latter being associated with transient patchy consolidation on a chest x-ray picture. While in remission he had no arthralgia, his E.S.R. returned to normal, his serum became negative for rheumatoid factor, and the differential agglutination titre became negative. There has been no radiological evidence of rheumatoid arthritis. Because of his recurrent haematuria and fall in glomerular filtration rate to 64 ml/min a second renal biopsy was performed. This showed considerable progression of changes with complete hyalinization of some 30% of the glomeruli, and mesangial thickening was evident in most of the remainder (figs. 2 and 3). There was extensive hyaline change in the arteriolar walls, and immuno-

fluorescent studies showed glomerular deposition of IgG, IgM, C3, and fibrin.

In view of his recurrent episodes of multifocal vasculitis with deteriorating renal function while on steroid therapy, azathioprine 150 mg/day was introduced as well as prednisolone 15 mg/day. He has remained normotensive with no further relapses and returned to work.

Discussion

In each of these three patients a widespread cutaneous vasculitis with systemic manifestations developed within one week of starting alclofenac therapy. In the first two cases the drug was discontinued as the vasculitis developed and with prompt corticosteroid therapy the side effects quickly resolved. The third patient, however, continued to take alclofenac for a further week after the first symptoms of hypersensitivity had developed. He subsequently developed vasculitic lesions in mucous membranes, skin, liver, lung, gastrointestinal tract, and central nervous system. Since then he has experienced recurrent episodes of haemoptysis, haematuria, and purpura, the lesions appearing together and resolving simultaneously. His serum was strongly positive for rheumatoid factor with a raised E.S.R. during "active" disease, yet it returned to normal as the vasculitis became quiescent. In a previous review of 15 cases of "allergic angiitis" some 50% of patients had positive results of tests for rheumatoid factor, raised E.S.R., and eosinophilia in the absence of clinical evidence of rheumatoid arthritis (Winkelmann and Winston, 1964).

The term necrotizing vasculitis has been used to describe collectively a group of vascular lesions which in their fully developed state are characterized by fibrinoid necrosis and inflammatory reaction in the vessel walls (Zeek, 1953). Hypersensitivity angiitis and polyarteritis nodosa are two of the diseases within this group and it is often difficult to differentiate between them. Hypersensitivity angiitis due to circulating immune complexes may be diagnosed if there are clinical features suggesting a drug hypersensitivity reaction with involvement of smaller vessels and if renal biopsy shows a necrotizing mesangiopathic glomerulonephritis. Pulmonary lesions are often present in this syndrome. Immunofluorescent studies may show concentration of the normal plasma constituents in the glomerular lesion (Germuth and Rodriguez, 1973).

Polyarteritis nodosa on the other hand affects medium-sized arteries, rarely involving the pulmonary circulation or glomeruli, and renal arterial disease is usually accompanied by hypertension (Knowles and Kaplan, 1953).

Vascular reactions to drugs such as iodine (Rich, 1945), thiourea (Gibson and Quinlan, 1945), and sulphonamides (Rose and Spencer, 1957) have long been recognized, but many other drugs have been reported to be associated with vascular side effects (Miller and Nelson, 1945; Hill and Damiani, 1946; Dalgleish, 1952; Winton and Nora, 1955; Hodge and Lawrence, 1957; Symmers, 1962; Dewar and Peaston, 1964; Winkelmann and Winston, 1964; Björnberg and Gisslen, 1965; Gutiérrez *et al.*, 1967; Sloan and Weaver, 1968; Jarzobski, *et al.*, 1970; Zanicini and Porciello, 1970; Swarc and Kaminski, 1971; Goldman and Brame, 1972; Koff *et al.*, 1973; Wharton and Pietroni, 1974).

These drug reactions are frequently encountered, and resolution usually occurs when the drug is withdrawn. It has been emphasized that continued medication with a drug after clinical evidence of hypersensitivity has developed may lead to a disease similar to polyarteritis nodosa (Van Wyk and Hoffman, 1948). A review of hypersensitivity reactions to sulphonamides showed that increasing dosage led to a greater frequency of sensitization reactions. It was concluded that the sensitizing dose may constitute the trigger

FIG. 2—Case 3. Renal biopsy specimen showing collapsed glomerular tuft with surrounding fibrosis within Bowman's capsule. Vessel wall shows thickening and elastic reduplication. (Hexamine silver. $\times 315$.)

FIG. 3—Case 3. Renal biopsy specimen showing glomerulus with segmental thickening and hypercellularity of mesangium. (Hexamine silver. $\times 315$.)

which sets the disease process in motion in the susceptible patient (Lehr, 1972).

In each of our three cases a hypersensitivity vasculitis seemed to develop within seven days of starting alclofenac therapy. This suggests therefore that alclofenac should be included in the list of drugs known to be capable in initiating a vasculitis. Prompt withdrawal of the drug at the first sign of reaction may reduce the risk of inducing a chronic vascular disorder.

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Absorption of Effervescent Aspirin during Migraine

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Summary

The absorption of effervescent aspirin was studied in 42 patients during acute attacks of migraine. When compared with normal controls and with themselves between attacks 19 out of the 42 patients showed impairment of absorption. Impairment of absorption seemed to correlate with the severity of the headache and the gastrointestinal symptoms at the time of treatment but not with the duration of the attack or with the type of migraine. This study probably underestimated the prevalence of impairment of absorption in migraine attacks, and it is concluded that the treatment of acute migraine symptoms by oral drugs should use those formulations which are rapidly absorbed under normal conditions.

Introduction

Gastrointestinal symptoms have been recognized as a major characteristic of migraine since the second century A.D. (Critchley, 1967) and they remain one of the current clinical criteria for diagnosis of migraine (World Federation of Neurology, 1970). It has also been suggested that the gastrointestinal disturbances in migraine could impair the absorption of drugs given orally as treatment during the acute attack (Nimmo,

1973), and to overcome this many of the drugs used in migraine may be administered other than as oral preparations (Wilkinson, 1971). Clinical trials on the administration of ergotamine tartrate (Graham et al., 1960; Sutherland and Eadie, 1961) provide evidence that the efficacy of treatment is related to the route of administration. The relatively poor efficacy of the oral route could be due to impaired absorption of the drug by the gastrointestinal tract. There are at present no methods capable of measuring ergotamine tartrate blood levels from therapeutic doses, however, and none of the studies have been directly concerned with assessment of gastrointestinal symptoms and their relationship to absorption of the drug. This paper reports the gastrointestinal symptoms and the absorption of effervescent aspirin in a group of patients treated during acute migraine attacks.

Patients and Methods

Forty-two patients suffering from acute headaches were studied at the Princess Margaret Migraine Clinic. All gave informed consent to the investigation. The diagnoses were made according to the criteria of the World Federation of Neurology (1970) and were confirmed by at least one other member of the clinic medical staff. Patients were not included in the study if there was any evidence of other illness, any history of dyspepsia, or if analgesic drugs had been taken within 24 hours before arrival at the clinic. Twenty control subjects were taken from the hospital medical, nursing, and administrative staffs. None had a history of headaches or gastrointestinal disease. The controls were not deliberately matched with the patients but the groups were of similar age, weight, and sex distribution (table I).

Aspirin was given as a single dose of three tablets containing a total of 900 mg acetylsalicylic acid in an effervescent base equivalent to 1,800 mg sodium bicarbonate and 1,200 mg anhydrous citric acid (Claradin) dissolved in 150 ml of water.

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