Comment

In the present case the evolution of the clinical findings clearly indicated a relation of this lupus-like syndrome to administration of methylodopa. Methylodopa induces a positive Coombs' test in about 20% of patients. Furthermore, a clear association exists between methylodopa and the development of antinuclear antibodies.¹⁻³ Only a few cases of lupus erythematosus cells being induced by methylodopa, however, have been reported. Sherman *et al* in 1967⁴ were the first to report positive results to tests for lupus erythematosus cells in two elderly patients with methylodopa-induced haemolytic anaemia in whom a Coombs' test was positive. In 1968 Harth reported on another patient in whom a Coombs' test was positive who had lupus erythematosus cells but no symptoms suggestive of systemic lupus erythematosus. Three patients have been reported in whom lupus erythematosus cells were found in association with methylodopa-induced hepatic necrosis. One of them also had transient arthritis.⁵ Chan in 1977 reported on a patient with methylodopa-induced fever associated with the development of antinuclear antibodies, lupus erythematosus cells, and ocular disturbance. Antithyroid antibodies have been sought in several cases but have not been found.^{1,4}

To our knowledge the association of Raynaud's phenomenon with arthralgia and lupus erythematosus cells induced by methylodopa has not been reported. Thus in addition to the rare appearance of lupus erythematosus cells the development of a lupus-like syndrome during administration of methylodopa must be added to the list of possible side effects of the drug.

¹ Breckenridge A, Dollery CT, Worledge SM, Holborow EJ, Johnson GD. Positive direct Coombs' tests and antinuclear factor in patients treated with methylodopa. *Lancet* 1967;ii:1265-8.

² Perry HM, Chaplin H, Carmody S, Haynes C, Frei C. Immunologic findings in patients receiving methylodopa: a prospective study. *J Lab Clin Med* 1971;78:905-17.

³ Wilson, JD, Bullock JY, Sutherland DC, Main C, O'Brien K. Antinuclear antibodies in patients receiving non-practolol beta-blockers. *Br Med J* 1978;ii:14-6.

⁴ Sherman JD, Love DE, Harrington JF. Anaemia, positive lupus and rheumatoid factors with methylodopa. *Arch Intern Med* 1967;120:321-6.

⁵ Eliastam M, Holmes AW. Hepatitis, arthritis and lupus cell phenomena caused by methylodopa. *Am J Dig Dis* 1971;16:1014-8.

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Benoxaprofen and papillary necrosis

The cause of renal papillary necrosis remains controversial. Clinical evidence suggests that phenacetin usually taken with aspirin is almost always responsible, but in animal studies nearly all analgesic drugs have been implicated to some degree. We report on a patient who developed papillary necrosis during treatment with the non-steroidal anti-inflammatory agent benoxaprofen.

Case report

A 53-year-old man was referred with an eight-month history of rheumatoid arthritis. His renal function was normal, with urea concentration 4.1 mmol/l (24.6 mg/100 ml) and creatinine concentration 75 µmol/l (848 µg/100 ml). Indomethacin was given initially but changed after a few months to flurbiprofen for better control of symptoms. He took no other analgesics. One year later he developed acute pancreatitis, which settled after 13 days. Renal function was normal during admission, with maximum urea concentration 6.5 mmol/l (39 mg/100 ml) and creatinine concentration 75 µmol/l (848 µg/100 ml). He took no drugs for the next four months but then, because of worsening symptoms, benoxaprofen 600 mg daily was given for 10 weeks. He then presented with a two-week history of haematuria and dysuria associated with a 'flu-like illness and a one-week history of epigastric pain and vomiting.

On examination he was feverish, jaundiced, dehydrated, confused, and oliguric. Investigations showed urea concentration 57 mmol/l (342 µg/100 ml), creatinine concentration 960 µmol/l (10.9 mg/100 ml), alkaline phosphatase

activity 514 U/l, aspartate transaminase activity 68 U/l, alanine transaminase activity 70 U/l, bilirubin concentration 149 µmol/l (8.7 mg/100 ml), and amylase activity 198 U/l. Haemoglobin concentration was 9.9 g/dl and white cell count $11.7 \times 10^9/l$. The initial diagnosis was acute renal failure secondary to septicaemia related to urinary or biliary tract infection. He required haemodialysis and received gentamicin and metronidazole. Urine cultures grew *Escherichia coli*, and intravenous pyelography showed normal-sized, poorly functioning kidneys. The jaundice cleared after a week but his oliguria persisted.

A month later retrograde pyelography showed a normal right kidney but the left ureter could not be catheterised. Renal biopsy showed 17 normal glomeruli with florid interstitial nephritis, interstitial oedema, and mononuclear cell infiltrate. One interlobular artery was seen showing pronounced crescentic subintimal thickening. As prednisolone did not improve his renal function regular dialysis was begun. Two months later he collapsed and died during dialysis. Necropsy showed a fresh papillary muscle infarct. The kidney showed extensive in-situ papillary necrosis with virtually all papillae necrotic and partially sloughed (figure). A walled off perforation of the sigmoid colon was found, which in retrospect may have been responsible for his septicaemia.

Extensive in-situ papillary necrosis.

Comment

Our patient had taken modest amounts of indomethacin and flurbiprofen before taking about 45 g benoxaprofen. We consider benoxaprofen to be the most likely cause of the papillary necrosis since there was no history of consumption of any other analgesic despite repeated questioning, and the finding that all papillae were at the same stage of necrosis suggested a recent insult.

The Committee on Safety of Medicines has received one other notification of papillary necrosis associated with benoxaprofen (personal communication), and we have found three documented cases of papillary necrosis associated with other non-steroidal anti-inflammatory drugs—namely, phenylbutazone,¹ fenoprofen,² and fenoprofen with aspirin.³ In our patient we suspect that administration of benoxaprofen led to interstitial nephritis with subsequent development of papillary necrosis. While there is no reason to suggest that benoxaprofen is particularly nephrotoxic, clearly phenacetin is not the only drug that can cause papillary necrosis. Awareness of this effect of non-steroidal anti-inflammatory drugs should lead to tests of renal function and urine analysis for blood and protein being done more often; in this way the incidence of interstitial nephritis and papillary necrosis could be more accurately defined.

¹ Wiseman EH, Reinert H. Anti-inflammatory drugs and renal papillary necrosis. *Agents Actions* 1975;5:322-5.

² Husserl FE, Lange RK, Kantrow CM. Renal papillary necrosis and pyelonephritis accompanying fenoprofen therapy. *JAMA* 1979;242:1896-8.

³ Huskisson EC, Wojtulewski JA, Berry H, *et al*. Treatment of rheumatoid arthritis with fenoprofen: comparison with aspirin. *Br Med J* 1974;ii:176-80.

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