Pseudomembranous colitis following cephradine prophylaxis

M. SANKARANKUTTY
M.Ch. Orth., F.R.C.S.

D. MCGEORGE
M.B., Ch.B.

C. S. B. GALASKO
Ch.M., F.R.C.S.

Department of Orthopaedic Surgery, University of Manchester, Clinical Sciences Building, Hope Hospital, Salford
M6 8HD

Summary

Two patients on antibiotic prophylaxis with cephradine after orthopaedic implant surgery developed pseudomembranous colitis. Routine administration of antibiotics after such surgery is the policy at many centres. Development of diarrhoea in these patients should be viewed seriously lest this condition is overlooked. Despite recent advances, pseudomembranous colitis can still have a fatal outcome.

Introduction

Most cases of pseudomembranous colitis during the last thirty years have been ascribed to different antibiotics (Scott, Nicholson and Kerr, 1973; Tedesco, Barton and Alpers, 1974; Keating *et al.*, 1974; Newman and McCollum, 1979; Boriello, Jones and Phillips, 1981). Reiner, Schlessinger and Miller in 1952 first drew attention to this condition in a patient treated with chlorotetracycline and chloramphenicol. Many orthopaedic surgeons routinely administer antibiotics to their patients undergoing implant surgery (Ericson, Lidgeon and Lindberg 1973; Fitzgerald *et al.*, 1977). In a study of a large number of orthopaedic in-patients on different antibiotic therapy regimes Beavis, Parsons and Salfeld (1976) did not find that cephalosporins caused diarrhoea. There have been, however, a few reports (Tures, Townsend and Rose, 1976; Tedesco *et al.*, 1978; Hutcheon *et al.*, 1978; Newman and McCollum 1979; Tan, Bayne and McLeod, 1979), of cephalosporin-associated pseudomembranous colitis in the English literature and these have been in non-orthopaedic patients. We report here two patients who developed pseudomembranous colitis while receiving a prophylactic cephalosporin after surgical insertion of orthopaedic implants. We stress that this condition should be borne in mind when patients on antibiotic therapy develop diarrhoea.

Case reports

Case 1

A 73-year-old woman with rheumatoid arthritis underwent right total knee arthroplasty on 4 August 1980. She was given prophylactic cephradine (Velo-sef) 500 mg four times daily immediately after the operation. On the fourth postoperative day she developed fever, lower abdominal pain and diarrhoea. This was treated symptomatically and the cephradine stopped. Cultures of her stool grew *Clostridium difficile* and its toxin was isolated. Sigmoidoscopy showed the appearance of severe colitis. Microscopic examination of a rectal mucosal biopsy specimen showed dense acute inflammatory cell infiltration in the lamina propria with polymorphs around focal surface ulcerations. There was surface mucopus and fibrinous exudate elsewhere. She was treated by intravenous fluids, cortisone and vancomycin 125 mg four times daily. She relapsed on three occasions with recurrence of diarrhoea when the vancomycin was stopped after each 7-day course. On each occasion she had a further 7-day course of vancomycin. *Clostridium difficile* continued to be grown and its toxin isolated until 22 October 1980. The diarrhoea eventually cleared with metronidazole treatment.

Case 2

An obese 76-year-old woman was admitted on 16 August 1980 with a subcapital fracture (Garden Grade I) of the left femur. This was treated by internal fixation with a Jewett nail plate. Postoperatively she was put on cephradine (Velo-sef) 500 mg four times daily. She developed diarrhoea on the seventh postoperative day. Cultures of her stool did not grow *Clostridium difficile*. The antibiotic was discontinued and she was treated symptomatically.

Subsequent cultures grew *Clostridium difficile* and the toxin was isolated. Sigmoidoscopic findings were those of a non-specific colitis. Histological examination of a rectal mucosal biopsy showed focal surface ulceration with fibrinous exudate and inflammatory cell infiltration in the lamina propria, and submucosal micro-abscesses.

Despite energetic treatment with intravenous fluids, cortisone 100 mg four times daily and vancomycin 125 mg four times daily, her condition deteriorated and she died on 2 September 1980.

Discussion

Pseudomembranous colitis is characterized by oedematous, hyperaemic and friable colonic and rectal mucosa which may bleed when touched. A pseudomembrane may or may not be present. When present, it is composed of leucocytes, red cells, mucin and the lamina propria of the mucosa enmeshed in a fibrinous exudate. The condition may present as mild diarrhoea or fulminant colitis. There may be a concomitant fever and leucocytosis. Fluid and protein loss may be severe enough to cause prostration and even death.

The pathogenesis of pseudomembranous colitis is not fully understood. *Clostridium difficile* has been incriminated as the causative organism (Bartlett *et al.*, 1978; George *et al.*, 1978; Larson, 1979). The finding of this organism and the isolation of its toxin from the stool is diagnostic. Vancomycin (Scott *et al.*, 1973; George *et al.*, 1978) has been found to be useful in treating these patients. Other agents such as cholestyramine and metronidazole (Larson, 1979) have been tried but with less effect. The associated antibiotic should be discontinued and the patient treated with adequate intravenous fluids. Intravenous cortisone and oral vancomycin should be started immediately. Early diagnosis and adequate treatment is essential to minimize the morbidity.

Recurrence after vancomycin treatment (Ritchie and Pannington, 1980) and even a fatal outcome despite eradication of *Clostridium difficile* (Hawker *et al.*, 1981) has been recently reported. In one of our patients (Case 1) the condition relapsed on three occasions but eventually settled with treatment. The other patient deteriorated and died, despite energetic treatment.

The insertion of orthopaedic implants is now commonplace. Replacement arthroplasty is carried out for advanced osteoarthritis or rheumatoid arthritis and many centres routinely advocate prophylactic antibiotic therapy. These patients often are elderly and may be frail.

Miller and Hershel (1977) studied 26,000 patients over a 10-year period and in their opinion drug-induced colitis was rare. However, Beavis *et al.* (1976)

reported a 4.9% incidence of diarrhoea and 0.2% of pseudomembranous colitis in their survey of over 1,000 orthopaedic in-patients on various antibiotic regimes. They found none in a group of 55 patients on cephalosporins (15 on cephaloride, 3 on cephalothin, 36 on cephalexin and one on cephradine). Both our patients were on cephradine. We now use flucloxacillin as prophylaxis with no case of pseudomembranous colitis to date.

If we are to minimize the morbidity and mortality of this condition, the mildest form of diarrhoea in patients on antibiotics should be investigated thoroughly and treated early and effectively. Pseudomembranous colitis continues to pose problems in diagnosis and treatment and can still be fatal a century after Finney (1883) first described the condition.

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