in combination with the usual, large doses of anticholinesterases would have to be reconsidered.

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References

- BENDER, A.N., RINGEL, S.P., ENGEL, W.K., DANIELS, M.P. & VOGEL, Z. (1975) Myasthenia gravis: a serum factor blocking acetylcholine receptors of the human neuromuscular junction. *Lancet*, **i**, 607.
- BRUNNER, N.G., NAMBA, T. & GROB, D. (1972) Corticosteroids in the management of severe, generalized myasthenia gravis. *Neurology*, **22**, 603.
- CAPE, C.A. & UTTERBACK, R.A. (1972) Maintenance adrenocorticotrophic hormone (ACTH) treatment in myasthenia gravis. *Neurology*, **22**, 1160.
- ELMQVIST, R., HOFFMAN, W.W., KUGELBERG, J., QUASTEL, D.M.J. (1964) Electrophysiological investigation of neuromuscular transmission in myasthenia gravis. *Journal of Physiology*, **174**, 417.
- GENKINS, G., KORNFIELD, P. & OSSERMAN, K.E. (1971) The use of ACTH and corticosteroids in myasthenia gravis. *Annals of the New York Academy of Sciences*, **183**, 369.
- LIVERSEDGE, L.A., YUILL, G.M., WILKINSON, I.M. & HUGHES, R. (1974) Benefit from adrenocorticotrophin in myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 412.
- MILEDI, R. (1960) The acetylcholine sensitivity of frog muscle fibres after complete or partial denervation. *Journal of Physiology*, **151**, 1.
- TURNER, A. (1974) Myasthenia gravis. *Proceedings of the Royal Society of Medicine*, **67**, 763.
- WILSON, R.W., WARD, M.D. & JOHNS, T.R. (1975) Corticosteroids: a direct effect at the neuromuscular junction. *Neurology*, **24**, 1091.

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Pseudomembranous enterocolitis complicating ampicillin therapy

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Summary

A case of fatal pseudomembranous enterocolitis associated with ampicillin therapy is described and possible mechanisms for its production discussed.

Introduction

The association of pseudomembranous enterocolitis with antibiotic therapy is well recognized (Leading Article, 1975; Tedesco, Barton and Alpers, 1974). Most reports have been associated with clindamycin or lincomycin (Tedesco *et al.*, 1974; Crapp *et al.*, 1975), but tetracycline (Klotz, Palmer and Kirsner, 1953), chloramphenicol (Reiner, Schlesinger and Miller, 1952) and ampicillin (Schapiro and Newman, 1973; Keating *et al.*, 1974) have also been incriminated. A case is now reported of fatal pseudomembranous enterocolitis associated with ampicillin and cloxacillin therapy.

Case report

A 73-year-old woman with a long history of arthritis underwent a Manchester condylar arthroplasty of the right knee in September 1975. Rheuma-

toid arthritis had been diagnosed in 1967 when she had a successful left hip replacement, and since then she had been taking prednisolone 2.5 mg b.d. Cover for the operation included hydrocortisone 100 mg 6-hourly, ampicillin 250 mg 6-hourly and cloxacillin 500 mg 6-hourly. Both antibiotics were continued for 23 days. Initial postoperative progress was uneventful, but on the seventh day she developed dysuria and pyrexia; urine culture grew *Klebsiella aerogenes* resistant to ampicillin. Co-trimoxazole produced an immediate hypotensive reaction, with an itchy erythematous rash and generalized oedema; it was withdrawn after one dose. Nitrofurantoin 100 mg q.i.d. for 10 days cleared the infection, and subsequent urine and blood cultures were not infected. From the tenth postoperative day diarrhoea and vomiting became a problem. The vomiting stopped when the ampicillin and cloxacillin were given intramuscularly, but loose watery stools continued up to six times a day with faecal incontinence at night. The wound edges were necrotic but clean. The antibiotics were stopped and intravenous fluids started on the twenty-third postoperative day. Seven days later she developed a pyrexia and slime was noticed in the motions. Sigmoidoscopy showed numerous

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small, raised, yellowish plaques, suggestive of pseudomembranous enterocolitis. Biopsy was taken which confirmed the diagnosis. The faecal incontinence failed to respond to codeine phosphate and the knee wound became contaminated. Blood cultures remained negative but the patient became confused and toxic. Hypoproteinaemia was treated with intravenous feeding with Aminosol, Intralipid, plasma and purified protein fraction, but she remained catabolic with a rising blood urea, fever and leucocytosis. Her condition deteriorated, gross oedema of the legs developed terminally and she died 43 days after the operation. Post-mortem examination showed a large recent pulmonary embolus, with ante-mortem thrombus in both common iliac veins and the lower part of the inferior vena cava. The colonic mucosa was very oedematous, with areas of superficial haemorrhagic ulceration and an extensive purulent exudate on the surface. The changes were present throughout the colon, but most extensive in the distal part. The small intestine was normal.

Discussion

It has been suggested that ampicillin is associated with diarrhoea in 16% of adults and 20% of children, but only in about 5% is it severe (Leading Article, 1975). Pseudomembranous enterocolitis has been associated with ampicillin in three previous case reports. Schapiro and Newman described a 49-year-old man given ampicillin 500 mg q.i.d. for 5 days as prophylaxis for urinary tract instrumentation, who developed pseudomembranous enterocolitis involving the colon and small intestine and died 29 days later (Schapiro and Newman, 1973). The two other reports are from children (Keating *et al.*, 1974) who received courses of ampicillin and developed pseudomembranous enterocolitis which resolved spontaneously. Cloxacillin has not been associated with acute enterocolitis (Tedesco *et al.*, 1974), and it seems likely that ampicillin was the cause in the present patient.

Pseudomembranous enterocolitis has been described more commonly with clindamycin therapy and Tedesco has suggested an incidence as high as 10% (Tedesco *et al.*, 1974). He concluded that the course of the colitis was relatively benign provided the diagnosis was made early and the antibiotic discontinued. In patients in whom the diagnosis was delayed and antibiotics were continued in the face of diarrhoea, the course of the illness was prolonged and more severe. This group also tended to develop electrolyte imbalance and hypoproteinaemia. In the present patient, ampicillin and cloxacillin therapy was continued for 2 weeks after diarrhoea had started and the illness was severe and complicated by hypoproteinaemia. As in clindamycin-associated

colitis, lesions were confined to the colon, but in the patient described by Schapiro and Newman (1973) there was also segmental involvement of the small intestine. This patient developed enterocolitis and died after a mere 5-day course of ampicillin.

Various mechanisms have been postulated for antibiotic-induced diarrhoea, including a direct effect on the bowel wall, appearance of bacteria in the proximal small intestine, lactase deficiency and various host factors (Leading Article, 1975). Pseudomembranous enterocolitis on the other hand was thought originally to be due to ischaemia of the bowel wall secondary to circulatory failure, but clinical experience and histological examination do not support this. The aetiology is probably multifactorial but in cases associated with broad-spectrum antibiotics an alteration in bowel flora may be responsible. Steer (1975) has recently demonstrated virus particles in colonic mucosal cells and in the pseudomembrane in four patients with clindamycin-associated colitis. He suggests that alteration of the normal colonic bacterial flora makes the colonic mucosa more susceptible to viral infection.

Some writers reserve the term pseudomembranous enterocolitis for the more severe forms of the disease. Christie and Ament (1975) recently described an acute ulcerating colitis in a 3-year-old girl following 5 days' ampicillin therapy. Confluent yellowish plaques on the colonic mucosa when biopsied showed areas of micro-ulceration and fibrinous exudate. The condition resolved spontaneously and they suggest that this 'antibiotic-associated colitis' is self-limiting when the drug is discontinued. It seems possible, however, that there is a spectrum from mild diarrhoea, through acute ulcerating colitis to severe, even fatal, forms of pseudomembranous enterocolitis. Although ampicillin therapy rarely leads to severe enterocolitis, two fatalities have now been described in adults given ampicillin as prophylaxis for surgical procedures. The place of prophylactic broad-spectrum antibiotics to cover many surgical procedures has not been fully established and needs further study. In the meantime, a strong case will need to be made if broad-spectrum antibiotics are to be continued once diarrhoea has developed, since this may lead to a prolonged and more severe course with a possible fatal outcome.

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References

- CHRISTIE, D.L. & AMENT, M.E. (1975) Ampicillin-associated colitis. *Journal of Pediatrics*, **87**, 657.

- CRAPP, A.R., POWIS, J., CLARK, C., KEIGHLEY, M.R.B. & ALEXANDER-WILLIAMS, J. (1975) Postoperative pseudomembranous colitis. (Correspondence) *British Medical Journal*, **3**, 227.
- KEATING, J.P., FRANK, A.L., BARTON, L.I. & TEDESCO, F.J. (1974) Pseudomembranous colitis associated with ampicillin therapy. *American Journal of Diseases of Children* **128**, 369.
- KLOTZ, A.P., PALMER, W.L. & KIRSNER, J.B. (1953) Aureomycin proctitis and colitis: a report of 5 cases. *Gastroenterology*, **25**, 54.
- LEADING ARTICLE (1975) Antibiotic diarrhoea. *British Medical Journal*, **4**, 243.
- REINER, L., SCHLESINGER, M.J. & MILLER, G.M. (1952) Pseudomembranous colitis following aureomycin and chloramphenicol. *Archives of Pathology*, **54**, 39.
- SCHAPIRO, R.L. & NEWMAN, A. (1973) Acute enterocolitis. *Radiology*, **108**, 263.
- STEER, H.W. (1975) The pseudomembranous colitis associated with clindamycin therapy—a viral colitis. *Gut*, **16**, 695.
- TEDESCO, F.J., BARTON, R.W. & ALPERS, D.H. (1974) Clindamycin-associated colitis: a prospective study. *Annals of Internal Medicine*, **81**, 429.

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Valvar aortic stenosis with unusual features

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Summary

This case report documents the co-existence of valvar aortic stenosis and hypertrophic obstructive cardiomyopathy with systemic hypertension and calcific mitral annulus, a combination which has not hitherto been reported. It is the purpose of this paper to help assess the true incidence of the co-existence of aortic stenosis and hypertrophic cardiomyopathy.

Introduction

The co-existence of aortic stenosis and hypertrophic cardiomyopathy (asymmetric septal hypertrophy) has been reported at operation by Ellis, Ongley and Kirklin (1962); after operation by Gordon (1962) and Braunwald *et al.* (1964); at post-mortem examination by Hurst and Logue (1966) who also estimated the prevalence to be 10% of patients with severe aortic valve stenosis. Parker, Kaplan and Connolly (1969), in an attempt to detect subaortic hypertrophy in patients with severe aortic valvar stenosis, discovered ten cases of co-existent aortic valvar stenosis and functional sub-aortic hypertrophy. Nanda *et al.* (1974) found six cases of aortic

valve disease with co-existing idiopathic hypertrophic subaortic stenosis. They regarded the combination to be rare and pointed to the value of echocardiography in the non-invasive diagnosis of this complex situation.

In the absence of aortic valve disease, functional sub-aortic stenosis occurring in the course of systemic hypertension was first documented by Brock (1957).

Case report

Systemic hypertension and aortic stenosis were first detected in a widow aged 67 years when she presented in 1964 with effort dyspnoea and mild angina of recent onset without any previous history of rheumatic fever. Her pregnancies and labour at the ages of 25, 28 and 35 years had been uneventful. Hypertension was controlled with methyldopa and a diuretic. Her symptoms improved and she herself discontinued the drug treatment after a few years. During the last 2 years she had had three syncopal and two near syncopal episodes with increasing effort dyspnoea, angina and relapse of hypertension.

Six months before her present admission, left ventricular failure supervened, since when she had been receiving digoxin and a diuretic. Her blood pressure fluctuated between 150/90 and 180/110 mmHg.

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