

Effect of clindamycin and lincomycin therapy on faecal flora

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SUMMARY Bacterial counts were carried out on the faeces of 160 patients receiving clindamycin or lincomycin treatment for bacterial infections. In all the patients the total bacteroides count was significantly reduced while strains of Enterobacteriaceae, yeasts, and streptococci were correspondingly increased. Severe diarrhoea developed in 25 (16%) patients, but this could not be related to a change in faecal flora. Diarrhoea was most common when clindamycin was given prophylactically, women were more affected than men, and the incidence was highest in those aged over 60 years. No cases of pseudomembranous colitis were seen. Although clindamycin is a valuable antibiotic for treating established severe anaerobic bacterial infections it should be used cautiously in elderly patients.

The clinical use of many antibiotics is associated with changes in gastrointestinal function in some patients. The incidence varies with the particular antibiotic, and the nature may range from a slight increase in bowel movements or less consistency of the faeces to severe watery diarrhoea with blood and mucus and possibly pseudomembranous colitis. The cause of the gastrointestinal dysfunction is not clear. Many explanations such as a direct toxic effect of the antibiotic or its metabolites; the overgrowth of certain pathogenic organisms such as *Staphylococcus aureus*, *Candida albicans*, and *Pseudomonas aeruginosa*; viruses; and toxins have been put forward. While quantitative studies have been carried out in normal patients there is little information about changes in the faecal flora of patients with diarrhoea or colitis.

In 1974 a prospective study of all patients in the High Wycombe group of hospitals receiving clindamycin or lincomycin was started and quantitative bacterial counts were carried out on the faeces of 160 patients. This paper describes the results and compares the changes with the development of gastrointestinal side effects.

Patients and methods

Specimens of faeces were collected from 160 patients—79 men and 81 women—including seven with

colostomies. Of the 160 patients, 131 were receiving clindamycin (66 parenterally, eight orally, and 57 by both routes) and 29 lincomycin (nine parenterally, six orally, and 14 by both routes). Other antibiotics, most commonly ampicillin or amoxycillin, were being received by 102 patients on clindamycin and 22 on lincomycin. Established bacterial infection related to the gastrointestinal or genital tracts was present in 143 patients, usually confirmed at operation, and 17 patients received prophylactic treatment: 61 of the infections were considered to be severe, 76 moderate, and six minimal.

Specimens for bacteriological culture were collected from the site of infection in 106 of the 160 patients and pathogens were isolated in 82 (77%), the commonest being *Bacterioides fragilis* (21 patients), various species of streptococci (25 patients), and *Staph. aureus* (15 patients). The patients were asked regularly by a research sister about the development of gastrointestinal side effects. Antibiotic-induced diarrhoea was defined as the passage of watery faeces more than five times a day. Many patients had mild changes in bowel function which resolved within a few days of starting treatment. These were considered to be a result of surgery and not antibiotic therapy.

Specimens of faeces collected from the patients during the course of clindamycin or lincomycin therapy were delivered to the laboratory immediately and were examined within one hour. The faeces were selectively cultured to determine the counts of

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four bacterial species—bacteroides, representing the predominant anaerobic organisms, Enterobacteriaceae, streptococci, and yeasts.

A sample of faeces weighing about 1 g was disintegrated in 5 ml nutrient broth, serial hundred-fold dilutions (0.1 ml in 9.9 ml) were made in nutrient broth, and surface viable counts using 0.1 ml inocula were carried out on blood, MacConkey, and a special yeast agar incubated aerobically and blood and neomycin blood agar (0.1 g/l) incubated anaerobically by the Gaspak method. The anaerobic agar was not pre-reduced. The plates were incubated for two days and the bacterial colonies counted. Bacteroides species were identified by their ability to grow on neomycin blood agar and confirmed by either the API technique (API Products Limited, Rayleigh, Essex) or the Mastring (MID8) (Mast Laboratories Ltd., Bootle, Merseyside). Strains of Enterobacteriaceae and streptococci were identified by routine laboratory techniques and yeasts by growth on the special yeast agar confirmed by staining (Gram).

It was impossible to examine pretreatment faecal specimens because most patients had been admitted as surgical emergencies which required immediate antibiotic treatment. The accuracy of the faecal collection and culture techniques was tested by examining specimens from a similar group of pre-operative surgical patients not receiving antibiotic therapy. Comparable bacterial counts to those reported in normal volunteers were found (Leigh *et al.*, 1976). Changes in the faecal bacterial counts were related to these normal findings and were considered significant when there was a decrease of 10^6 or more organisms in the expected bacteroides count, and an increase in the counts of Enterobacteriaceae (10^6 or more), streptococci (10^5 or more), and yeast (10^3 or more). Smaller changes in the bacterial counts were not considered significant in view of the techniques used.

Results

There was a significant decrease in the bacteroides count in all faecal specimens (Table 1) and in 95%

of cases this was lower than 5×10^3 organisms per gram of faeces. In patients receiving lincomycin streptococci were not increased in numbers as they were in patients receiving clindamycin. Otherwise both antibiotics produced similar changes, which were independent of the route of administration of the antibiotics. There was no difference between men and women in the faecal flora changes and the use of combined antibiotic therapy did not influence the findings.

Antibiotic-induced diarrhoea was seen in 25 (16%) of patients and 87 (57%) patients had mild gastrointestinal dysfunction related to surgery. The relationship of side effects to changes in flora are shown in Table 2. There were no differences between the groups of patients apart from a higher incidence of increased yeast count when antibiotic-induced diarrhoea was present.

Although severe diarrhoea was nearly twice as common in patients who received prophylactic clindamycin or lincomycin (Table 3) this was not

Table 2 *Relation of gastrointestinal side effects to changes in faecal flora in 153 patients (excluding patients with colostomies)*

	Normal bowels	Mild changes	Antibiotic-induced diarrhoea
No. of patients	41	87	25
Decreased anaerobic count	35 (85%)	86 (98%)	24 (96%)
Increased counts			
Enterobacteriaceae	21 (51%)	52 (59%)	16 (64%)
Yeasts	11 (27%)	33 (38%)	14 (56%)
Streptococci	6 (15%)	13 (15%)	7 (28%)

Table 3 *Incidence of gastrointestinal side effects related to the severity of the infection. Colostomy patients excluded*

	Degree of infection			Prophylaxis
	Severe	Moderate	Minimal	
No side effects or mild side effects	48	65	4	11
Antibiotic-induced diarrhoea	10 (17%)	11 (15%)	—	4 (27%)

Table 1 *Changes in faecal flora in patients treated with clindamycin and lincomycin*

	Clindamycin		Lincomycin		Total
	Parenteral	Oral	Parenteral	Oral	
No. of patients	123	8	23	6	160
Decreased anaerobic count*	115 (93%)	8	23	6	152 (95%)
Increased counts					
Enterobacteriaceae	74 (60%)	6 (75%)	11 (48%)	3 (50%)	94 (59%)
Yeasts	46 (37%)	2 (25%)	9 (39%)	3 (50%)	60 (38%)
Streptococci	26 (21%)	2 (25%)	—	—	28 (18%)

*Count $< 5 \times 10^3$ bacteria per gram faeces.

reflected in changes in the faecal flora. Antibiotic-induced diarrhoea was seen more often in women (19%) than men (13%) and this was most marked in those aged over 60 years of whom 30% of women were affected and only 11% of men.

Discussion

Gastrointestinal dysfunction after antibiotic treatment has been related to many causal factors. Certain antibiotics such as tetracycline and fusidic acid are toxic to the gastrointestinal tract either as a direct effect, irrespective of concentration, or owing to poor absorption allowing prolonged contact with the mucosa. The use of broad spectrum antibiotics can result in the overgrowth of pathogenic bacteria and yeasts such as *Staphylococcus aureus*, and *Candida albicans*. In most of these cases quantitative bacteriology has not been investigated and it is not known whether anaerobic bacteria, particularly bacteroides, a major bacterial component of the faeces were significantly altered. Surprisingly, among the large number of reported studies there are few reports that have looked prospectively into the faecal flora associated with diarrhoea and colitis.

We could find no relationship between treatment with clindamycin or lincomycin and the development of diarrhoea. Marr *et al.* (1975) reported that the anaerobic flora was only slightly reduced quantitatively in patients with diarrhoea receiving clindamycin but when pseudomembranous colitis was present the reduction was striking. However, in all our patients there was a considerable effect on the bacteroides count irrespective of the presence of diarrhoea. Metronidazole, another chemotherapeutic agent active against anaerobic bacteria, also causes a significant but lesser reduction in the number of bacteroides.

The role of *Candida* and other yeasts in the causation of diarrhoea is vague since there are increased numbers in the faeces with all antibiotic treatments and the prescription of antifungal treatment does not affect the incidence of diarrhoea. An increase in the numbers of strains of Enterobacteriaceae was common and, as seen with ampicillin (Leigh *et al.*, 1976), there was no relation to diarrhoea.

The problems of relating faecal flora to symptoms and side effects are complex. Besides the difficulties of collection and laboratory culture, the flora is in a dynamic state and is probably constantly changing. The relationship of the specimen to the last dose or the route of administration may significantly alter the bacteriology and the condition of the patient may considerably affect the pharmacology of the antibiotic. However, in a study using amoxycillin, ampicillin, and talampicillin consecutive faecal

samples showed similar results and the normal quantitative flora was restored after treatment was stopped (Leigh, unpublished).

The incidence of diarrhoea (16%) with clindamycin and lincomycin in our patients was similar to that found by Tedesco *et al.* (1974), but no cases of pseudomembranous colitis were seen in our 160 patients or in those in a longer follow-up study (Leigh *et al.*, 1977). Possibly many of the reported cases of pseudomembranous colitis follow the irrational use of clindamycin and lincomycin for respiratory infections. The susceptibility of the patient is different when a severe anaerobic infection is present. Strikingly, Bartlett *et al.* (1972), Fass *et al.* (1973), Gorbach and Thadephalli (1974), and Chow *et al.* (1974) using clindamycin and lincomycin in severe anaerobic infections have reported few cases of diarrhoea and no instances of pseudomembranous colitis.

Although changes in faecal flora could not be related to side effects there was a definite correlation between clindamycin and lincomycin and gastrointestinal side effects in respect of sex and age in our patients, women aged over 60 years being more likely to be affected. This confirms the findings of Swartzberg *et al.* (1976) and Smart *et al.* (1976). It is still uncertain why most patients receiving clindamycin develop diarrhoea and why some of them progress to pseudomembranous colitis.

Larson *et al.* (1977) have reported an undescribed cytotoxin in a patient who developed pseudomembranous colitis after penicillin therapy. This condition has also occurred with many other antibiotics—ampicillin (Keating *et al.*, 1974), amoxycillin (Simila *et al.*, 1976), chloramphenicol (Reiner *et al.*, 1952), tetracycline (Klotz *et al.*, 1953), cephalosporins (Tures *et al.*, 1976), and co-trimoxazole (Cameron and Thomas, 1977). There have been reports of pseudomembranous colitis following lincomycin (Scott *et al.*, 1973; Viteri *et al.*, 1974) and clindamycin (Cohen *et al.*, 1973; Tedesco *et al.*, 1974), but although the term clindamycin-associated colitis is in constant use this condition probably cannot be directly related to any particular compound.

The aetiology of pseudomembranous colitis is not clear and its development seems to be unrelated to the clinical condition of the patient or any one factor. The histology of tissue from patients with pseudomembranous colitis suggests various causes—a local Swartzman phenomenon (Hjort and Rapaport, 1965), ischaemia (McGovern and Goulston, 1965), or capillary thrombosis (Whitehead, 1971; Bogomoletz, 1976). But as these changes are not seen in all stages of the condition it seems more likely that they follow an initiating factor, since

idiopathic pseudomembranous colitis is rarely reported (Jackson and Anders, 1972) and geographical differences have been suggested by Geddes (1974). A viral or bacterial aetiology has been reported (Steer, 1975; Marr *et al.*, 1976), but there is little indication that an altered faecal flora in terms of the normal bacteria or usual pathogens plays a major role.

The possibility of genetic influence is interesting and cannot be excluded (Harrod *et al.*, 1975). The increased incidence of diarrhoea among patients receiving lincomycin and atropine-diphenoxylate (Lomotil) or codein phosphate (Novak *et al.*, 1976) suggests that decreased intestinal motility may increase the contact time between the antibiotic and its metabolites and the intestinal mucosa, allowing a toxic reaction to occur. However, decreased intestinal motility is common after gastrointestinal surgery, and few reports of pseudomembranous colitis are seen in these patients. Probably the initiating factor is a toxic agent acting directly on the intestinal mucosa (Pittman *et al.*, 1974) leading to a two-stage process of a local Schwartzman phenomenon and capillary microthrombi (Price and Davies, 1977), but its nature is unknown. Although the true incidence of pseudomembranous colitis is not well documented, and its frequency is overemphasised by the large number of single cases reported, a common association in its development is antibiotic therapy. Since which patients will develop the complication cannot be predicted chemotherapy must be used carefully, especially for prophylaxis.

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