Penetration into bone and tissues of clindamycin phosphate

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Summary

Clindamycin phosphate is an antibiotic which is effective against both *Staphylococcus aureus* and the anaerobic organisms. In thirteen patients, its concentration following joint replacement was measured by the agar diffusion method. In bone, the concentration was (mean $\pm$ s.e. mean) $5.01 \mu\text{g/ml} \pm 1.16$, $N=10$; in capsule, $3.29 \mu\text{g/ml} \pm 0.71$, $N=12$; measured between 1.75 and 3.75 hr after intramuscular and intravenous injections, and in drainage fluid it amounted to $4.61 \mu\text{g/ml} \pm 0.38$, $N=11$ in 48 hr. Two patients developed diarrhoea which settled within a short period.

Introduction

In orthopaedics, the most frequently encountered pathogenic organism is *Staphylococcus aureus* (Garrod and O'Grady, 1971). However, anaerobic bacteria can cause osteomyelitis (Finegold and Rosenblatt, 1973; Kelly, Wilkowske and Washington, 1973) and joint infections (Ziment, Davis and Finegold, 1969). Anaerobic organisms have also been shown to cause infection following total joint replacement (Kramme *et al.*, 1974).

Among the antibiotics that are available is lincomycin which is effective against both *Staph. aureus* and the anaerobic organisms which include *Bacteroides* sp., *Clostridium* sp. and anaerobic streptococci. Lincomycin has been shown to enter bone in therapeutic levels (Beavis *et al.*, 1975). A derivative of lincomycin is clindamycin. Clindamycin phosphate being a water-soluble ester of clindamycin and phosphoric acid and has been reported as reaching effective levels in bone (Nicholas *et al.*, 1975; Dornbusch *et al.*, 1977).

This paper reports a further study of the penetration of clindamycin phosphate into bone and surrounding tissues following parenteral administration in a group of patients undergoing total joint replacement.

Method

Patients with osteoarthritis, ten female and three male, were given the following course of injections during surgery, which was based upon the regime advocated by Beavis for the study of lincomycin (Beavis *et al.*, 1975). Clindamycin phosphate 300 mg was injected intramuscularly with the premedication one hour before surgery. This was followed by 300 mg of clindamycin phosphate intravenously over a 30-min period which coincided with the exposure of the bone and ended with its removal. After the operation the patient was given 300 mg of clindamycin phosphate intramuscularly every 12 hr for 48 hr. During the operation samples of tissue were taken from muscle, fat, joint capsule, bone and blood. The whole of the drainage fluid was collected for 48 hr.

The age of the patients ranged from 57 to 68 years with an average age of 63 years. Twelve patients had Stanmore total hip replacement and one had a Sheehan total knee replacement. Three had had previous osteotomies of the hip.

Clindamycin phosphate assays were performed using Difco antibiotic medium number 1 and *Sarcina lutea* (ATCC 9341) as the test organism. The serum was assayed undiluted, the tissues excluding bone were macerated, weighed, buffer (pH 7.9) added and the supernatant fluid assayed after centrifuging. The bone was cleaned of extraneous tissue and blood. A representative sample of between 3 and 4 g of bone was removed, broken into fragments and dried under vacuum in a desiccator for 48 hr at 4°C. Specimens were then pulverized, reweighed and buffer added. The supernatant fluid was assayed after extraction and centrifuging.

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Results

A typical collection of individual data is shown in Fig. 1. This patient had levels of clindamycin phosphate in bone 4.8 µg/ml; capsule of 2.5 µg/ml; muscle of 1.1 µg/ml and fat of 2.3 µg/ml, 2.25 hr after the first injection. His serum levels at 1.5 and 3.25 hr were 3.0 and 6.5 µg/ml respectively.

FIG. 1. Concentration of clindamycin phosphate in one patient after intramuscular and intravenous injections.

FIG. 2. Bone and capsule concentrations in all the patients following parenteral infusion.

In bone, clindamycin phosphate achieved therapeutic levels – $5.01 \mu\text{g/ml} \pm 1.16$ (mean $\pm$ s.e. mean, $N = 11$) range 2.4 – 15.6 – µg/ml (Fig. 2). In the capsule, clindamycin phosphate also achieved therapeutic levels – $3.29 \mu\text{g/ml} \pm 0.71$ (mean $\pm$ s.e. mean, $N = 12$) range 0.9 – 10.4 – µg/ml (Fig. 2). The drainage fluid collected over the 48-hr period also had

therapeutic levels – $4.61 \mu\text{g/ml} \pm 0.38$ (mean $\pm$ s.e. mean, $N = 11$) range 2.8 – 7.0 µg/ml.

The results of each tissue are shown in Table 1, all samples except for drainage fluid were taken between 1.75 and 3.75 hr after the first injection.

These figures compare favourably with those reported by Beavis *et al.* (1975) and Nicholas *et al.* (1975) (Table 2). Dornbusch *et al.* (1977) measured concentrations of clindamycin in bone in eight patients ranging from 0.4 to 4.9 µg/g of bone using an agar diffusion method, both by applying pieces of bone to agar plates and measuring the zone inhibition and by assaying the suspension. For the present cases the latter technique was preferred (Hughes *et al.*, 1975).

TABLE 1. Individual tissue levels (µg/ml)

Patient	Femur	Capsule	Muscle	Fat	48-hr drainage
1	5.8	4.0	3.6	2.2	5.8
2	4.6	2.9	2.7	2.2	5.0
3	—	10.4	2.5	3.4	—
4	3.0	—	1.6	0	—
5	7.0	3.2	0	2.4	2.8
6	3.0	3.3	0	0	5.2
7	3.0	2.1	1.5	1.6	5.5
8	2.4	2.0	0	0	3.0
9	1.7	4.5	1.6	2.2	4.0
10	15.6	1.6	2.2	2.2	4.0
11	—	0.9	0.6	0	7.0
12	4.2	2.1	1.2	1.5	3.0
13	4.8	2.5	1.1	2.3	4.2
Mean	5.01	3.29	1.43	1.54	4.61
$N = 11$	$N = 12$	$N = 13$	$N = 13$	$N = 11$	
$\pm$ s.e. mean	1.16	0.71	0.31	0.32	0.38

TABLE 2. Comparison of lincomycin/clindamycin levels

	(µg/ml)	
Lincomycin (Beavis <i>et al.</i> , 1975)	8.00 ± 0.11 (mean $\pm$ s.e. mean)	$N = 5$
Clindamycin phosphate (Nicholas <i>et al.</i> , 1975)	2.63 ± 1.76 (mean $\pm$ s.d.)	$N = 10$
Clindamycin (Dornbusch <i>et al.</i> , 1977)	Range 0.4–4.9 µg/g of bone	$N = 8$
Clindamycin phosphate	5.01 ± 1.16 (mean $\pm$ s.e. mean)	$N = 11$

Two patients out of the thirteen developed diarrhoea. One developed profuse watery diarrhoea after leaving hospital, 18 days after surgery; the other settled after one week. The other patient developed diarrhoea two days after surgery. There was no blood in the stools and it settled after 48 hr. Both patients had no other antibiotics, were not allergic to antibiotics and did not have sigmoidoscopy or biopsy.

Discussion

The authors have shown that the antibiotic clindamycin phosphate enters bone in high concentrations, following intravenous and intramuscular injection. The minimal inhibitory concentration (MIC) for clindamycin against *Staph. aureus* is 0.5 µg/ml with 97% of strains inhibited at this level (Geddes *et al.*, 1970). For anaerobes, the MIC is 1.6 µg/ml (Martin, Gardner and Washington, 1972).

Therefore, there is an effective therapeutic level of clindamycin in the bone and surrounding tissues following parenteral administration.

The place of anaerobic infection in orthopaedics is of great interest. Osteomyelitis is probably caused by anaerobic bacteria much more frequently than is recognized. Accurate bacteriology is needed to isolate the organisms. The anaerobes most commonly isolated are the Gram-negative bacilli and the anaerobic cocci which are effectively treated by clindamycin (Finegold *et al.*, 1972). Clindamycin has been used in the treatment of osteomyelitis and septic arthritis in children with good results (Feigin *et al.*, 1975) and lincomycin has been successfully applied in the treatment of osteomyelitis in children and adults (McMillan, McRae and McDougall, 1967).

There were two patients in the present study who developed diarrhoea. Diarrhoea following antibiotics has been well documented (Leading Article, 1975). The development of the syndrome of pseudomembranous colitis is closely associated, however, with the antibiotics lincomycin, clindamycin and ampicillin, but the pathogenesis is by no means clearly established (Price and Davies, 1977). Pseudomembranous colitis usually presents as an acute illness, the patient is ill with fever, lower abdominal pain and profuse watery diarrhoea (Cammerer *et al.*, 1976). Oral clindamycin has been found to produce diarrhoea and pseudomembranous colitis when given to orthopaedic patients as prophylaxis in joint replacement (Smart *et al.*, 1976). Beavis, Parsons and Jalfield (1976) reviewed the notes of 1158 patients at Guy's Hospital, however, and found three patients with 'colitis', two of whom had had lincomycin and one, clindamycin. On the basis of their review they felt that the continued use of these antibiotics was fully justified for prophylaxis.

There is no doubt, though, that once diarrhoea develops these antibiotics should be stopped (Wells, Cohen and McNeil, 1974).

The authors conclude that this study has demonstrated that clindamycin phosphate enters bone and surrounding tissues in therapeutic levels following intramuscular and intravenous injections, and can be used for the treatment of infections in bone and joints where *Staph. aureus* and anaerobic bacteria are likely to occur.

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