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THE PENETRATION OF LINCOMYCIN INTO NORMAL HUMAN BONE

Determinations of Penetration into Compact Bone, Spongy Bone and Bone Marrow

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The penetration of lincomycin into normal bone was studied in 10 patients with fracture of the neck of the femur, a separate determination being made of the lincomycin concentration in serum, bone marrow, spongy bone and compact bone. The concentration of lincomycin in bone marrow was found to be at the same level as that in the serum. The concentration in spongy bone amounted in most cases to 50 to 75 per cent of the concentration in the serum, whereas the concentration in compact bone varied from 0 to 15 per cent of that in the serum.

Key words: lincomycin; bone tissue; bone marrow; compact bone; spongy bone

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Since lincomycin became available at the beginning of the 60's (Mason et al. 1963), this antibiotic has acquired a leading role in the treatment of acute and chronic osteomyelitis. A number of investigations have been done to elucidate the ability of lincomycin to penetrate bone. These studies, animal experiments (Grady & Stern 1965, Evaskus et al. 1969) as well as studies of its penetration into human bone (Mason et al. 1963, Holloway et al. 1964, Geddes et al. 1967, Vacek et al. 1967), have shown somewhat varying relationships between the concentrations of lincomycin in serum and in bone, and cannot validly be compared. This is because various types of bone have been investigated, and also because different and often very inadequately described homogenization procedures have been employed.

The aim of the present study was to examine the penetration of lincomycin into normal human bone, employing a well-defined, reproducible homogenization procedure. A further aim was to examine separately the penetration of lincomycin into bone marrow, spongy bone and compact bone.

MATERIAL AND METHODS

Material. The material consists of 10 patients, two men and eight women, aged 50 to 89 years, mean age 72.4 years. All patients had a unilateral fracture of the neck of the femur. In four patients, alloplasty *ad modum* Moore was performed, and six patients had a MacLaughlin

osteosynthesis. The osteosynthesis was performed, on average, 4 days after the fracture. All patients had normal renal function, evaluated by two determinations of serum creatinine.

Bone biopsies. The biopsies were obtained peroperatively from the proximal end of the femur as soon as the bone was exposed for the commencement of the osteosynthetic or alloplastic procedure. A block of compact bone was removed, about 1 cm^3 in size, and this was immediately cleaned of periosteum, spongy bone and blood. By means of a curette, spongy bone was taken from the inner surface of the femur. Finally, bone marrow was aspirated through a metal cannula, the position of which was monitored by fluorescent screening. In all cases the aspirate was typical for bone marrow, i.e., there was an admixture of fat and bony trabeculae. All bone biopsies were obtained from macroscopically normal bone some distance from the line of fracture.

Serum concentration determination. Blood samples to determine the serum concentration of lincomycin were drawn twice before and twice after the bone biopsies were obtained, at intervals of ½ to 1 hour.

Intake of lincomycin. The lincomycin was administered as lincomycin chloride (Lincocin®) intramuscularly, in doses of from 13 mg to 24 mg per kg per 24 hours, as two doses at intervals of 12 hours (Table 1). Table 1 also shows the duration of treatment.

Homogenization procedure. Samples of bone marrow were homogenized undiluted in a Potter-Elvehjem homogenizer. A vibration mill was employed to homogenize the spongy bone and the compact bone. This method of homogenization has been described in detail in a previous study (Hansen et al. 1975). The method permits reproducible homogenization to a particle size of 0.3–3.2 μ.

Barteriological method. A microbiological method was employed to determine the lincomycin concentration using *Sarcina lutea* ATCC 9341 as test-organism and Antibiotic Medium No. 4 (Difco) as medium. Serum and marrow specimens were examined using "disc-plate" diffusion method whereas the specimens of compact bone and spongy bone were examined using the "agar-cup" diffusion technique. The plates were seeded with broth culture in dilution 1:6 after incubation for 24 hours at 37° C. The detailed principles have been described previously (Nielsen & Hansen 1972). The lower limit for sensitivity in the two methods was 1.5 and 0.30 μg/ml, respectively. Bone marrow and serum were examined undiluted. Compact bone and spongy bone were examined after dilution with phosphate buffer (pH 7.8) in the proportion 1:3 and 1:5, respectively. Standard solutions of lincomycin in pooled human serum were used for examining serum and marrow. Standard solutions of lincomycin in phosphate buffer were used for examining compact bone and spongy bone, studies also being made in which homogenized, antibiotic-free bone was added to the standard solutions.

In three patients who had *not* received any lincomycin, specimens of serum, bone marrow, spongy bone and compact bone had no anti-

Table 1. Concentrations of lincomycin in serum (μg lincomycin per ml serum) and in bone tissue (μg lincomycin per g tissue) 3–9 hours after the final intramuscular administration of lincomycin. Serum concentrations were determined at intervals of ½–1 hour before and after time of biopsy of bone tissue.

Pt. no.	Age	Sex	Intake of lincomycin (mg per kg body weight per 24 h)	Days of treatment with lincomycin	Lincomycin in serum at time of biopsy of bone tissue (μg/ml)	Lincomycin in bone marrow (μg/g)	Lincomycin in spongy bone (μg/g)	Lincomycin in compact bone (μg/g)
1	59	M	23	1	5.9	9.5	5.9	1.4
2	74	F	20	1	7.3	5.8	4.4	< 1.2
3	56	F	23	1	10.3	11.5	6.5	< 1.0
4	77	F	20	5	12.0	10.0	7.7	< 1.0
5	89	F	20	5	12.1	14.3	11.0	< 1.0
6	70	F	13	3	14.8	13.8	10.7	< 1.2
7	76	M	17	1	15.2	14.0	6.8	< 1.2
8	87	F	24	1	15.8	14.7	5.2	1.8
9	50	F	16	2	20.2	14.5	11.0	< 1.0
10	86	F	20	1	20.2	14.4	4.8	2.2

bacterial effect on the test bacterium used to determine the concentrations of lincomycin.

RESULTS

Table 1 shows the concentrations of lincomycin in serum, in bone marrow, in spongy bone and in compact bone. There is no significant difference between the concentrations of lincomycin in serum and in bone marrow (Wilcoxon test for pair differences, $P > 0.10$). In seven patients the concentration of lincomycin in the bone marrow was at the same level as the serum concentration, while in one patient it was more than 50 per cent higher and in two patients 30 per cent lower. The median content of lincomycin in bone marrow was 93 per cent of that in serum (range 71–161 per cent).

Concentrations of lincomycin in spongy bone were significantly lower than concentrations in serum and bone marrow (Wilcoxon test for pair difference, $P < 0.01$ for both comparisons). The median content of lincomycin in spongy bone amounted to 62 per cent of that in serum (range 24–100 per cent), and to 59 per cent of that in bone marrow (range 33–77 per cent). In compact bone, concentrations of lincomycin were significantly lower than concentrations in serum, in bone marrow and in spongy bone (Wilcoxon test for pair differences, $P < 0.01$ for all comparisons). In seven cases lincomycin was not detectable in specimens of compact bone; in two cases it amounted to 11 per cent and in one case to 24 per cent of the corresponding serum concentrations.

DISCUSSION

The present study deals only with normal human bone tissue. Evaluated on the basis of the minimum inhibitory concentration (MIC) of lincomycin for *Staph. aureus* (0.5 to 2 μg/ml) (Garrod & O'Grady 1972), the concentrations of lincomycin found in bone marrow were at a therapeutic level (MIC × 5). The concentrations found in spongy bone were at the therapeutic level for Staph. aureus strains with an MIC $\leqq 1$ μg/ml. It nevertheless appears reasonable to assume that the concentration of lincomycin in spongy bone at the peak period is considerably higher, so that a therapeutic level is achieved in the case of strains with an MIC of 2 μg/ml. The concentrations in compact bone, on the other hand, are considerably below the therapeutic level.

Investigations attempting to measure separately the concentrations of lincomycin in bone marrow, spongy bone and compact bone, have not previously been carried out. In an examination of the lincomycin content of *total bone* (spongy bone + compact bone) Varek et al. (1967) found that following the intake of varying amounts of lincomycin in 33 patients, in three cases the lincomycin concentrations in bone were greater than the corresponding serum concentrations, in one case the concentration in bone and serum was the same, and in 29 cases the concentration of lincomycin in bone was lower than in serum. In these latter cases, the concentration of lincomycin in the bone was in most cases one fifth to one third of the corresponding serum concentration. The type of bone investigated in the individual cases is not stated. Geddes et al. (1967) investigated 12 non-infected patients who underwent elective orthopaedic surgery. The type of bone investigated is not stated, but presumably total bone was involved. In three cases, the concentrations found in the bone were higher than the corresponding serum concentrations; in the remaining cases the concentrations in bone were generally one quarter to one third of the corresponding serum concentrations. Linzenmeier et al. (1968) examined the content of lincomycin in infected bone from 30 patients with

chronic osteomyelitis or gangrene, following the intake of varying doses of lincomycin. It was not reported whether spongy bone or compact bone was employed. In two cases, the results showed concentrations in bone which were higher than the corresponding serum concentrations, while in 28 patients the concentration of lincomycin in bone was lower than the serum concentration, and in most cases amounted to one third to two thirds of this value.

Evaskus et al. (1969) carried out *animal experiments*, and found that in rats there was a considerable difference in the penetrating power of lincomycin into bone with a large proportion of spongy bone (femur) and bone with a small spongy bone content (mandible). At intervals of ½ and 2 hours after intramuscular administration, the concentrations of lincomycin found in the femur were at the same level as the corresponding serum concentrations, while after the same intervals, the concentrations found in the mandible were 25 and 0 per cent, respectively, of those in the serum.

The results obtained by Evaskus et al. and the present results show that in evaluating the penetration of antibiotics into bone, allowance must be made for the composition of the bony tissue, including under this heading the relative incidence of bone marrow, spongy bone and compact bone. For similar reasons, an evaluation of the penetration of lincomycin into pathological bone is not possible on the basis of the findings in normal bone. Only scanty information is available regarding the penetration into pathological bone (Mason et al. 1963). A systematic investigation of the penetration of lincomycin into well-defined pathological bony structures would be an advantage.

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