# Penetration of Methicillin, Oxacillin, and Cephalothin into Bone and Synovial Tissues

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The penetrations of methicillin, oxacillin, and cephalothin into cortical bone and synovial tissues were studied 1 h after their intravenous administration in 105 patients having arthroplasty of the hip. Although the lowest serum levels were noted with cephalothin ($P < 0.01$), more patients receiving cephalothin achieved osseous drug levels inhibitory to staphylococci ($P < 0.01$). Differences in the penetration of the three agents into synovial tissues were not statistically significant.

The use of prophylactic antimicrobial therapy for the prevention of infection during total joint arthroplasty has resulted in numerous in vivo studies in an attempt to delineate the ability of various antimicrobials to penetrate bone. Schurman et al. (10) reported that the mean cortical bone concentration of clindamycin in 23 patients was 3.87 ± 2.40 µg/g, with a range of 1.15 to 9.59 µg/g in osseous specimens obtained from the femoral head during total hip arthroplasty. Nicholas et al. (6) noted a mean osseous level of clindamycin of 2.63 ± 1.76 µg/g in 27 patients. However, in 11% the drug concentration failed to reach 1.0 µg/g. In contrast, the concentration of clindamycin in osseous specimens taken from the femoral head failed to reach a concentration of 1 µg/g in five of eight patients studied by Dornbusch et al. (2). When bioassay was performed with an experimental electrophoretic method rather than an agar-diffusion technique, they noted that in seven of the eight patients the concentration reached at least 1 µg/g. Smilack et al. (11) found high concentrations of clindamycin (9.3 and 7.3 µg/g) in two of three bone specimens obtained during either total hip or total knee arthroplasty. These authors (11) also noted methicillin concentrations inhibitory to staphylococci in three of four patients. The mean concentration of methicillin in cortical bone in 22 patients was noted by Schurman et al. (10) to be 2.60 ± 0.18 µg/g. Although the range was reported to be 0 to 7.03 µg/g, the authors failed to provide sufficient data to permit determination of the number of specimens with less than 1.0 µg/g. Whereas Parsons et al. (7) and others (B. A. Cunha et al., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 17th, New York, N.Y., Abstr. no. 315,

1977; C. E. Wiggins et al., Trans. 23rd Annu. Meet. Orthop. Res. Soc., p. 32, 1977) noted that cefazolin concentrations in bone were high enough for inhibition of staphylococci, Smilack et al. (11) were unable to obtain measurable bone levels in three of four patients receiving cefazolin. Failure to detect concentrations of cephalothin in osseous specimens from four of four patients was also reported by Smilack et al. (11). In an attempt to clarify this conflicting information, the penetration of osseous and synovial tissue by methicillin, oxacillin, and cephalothin was investigated during total hip arthroplasty.

## MATERIALS AND METHODS

The study group comprised 105 patients undergoing total hip arthroplasty for various pathological conditions. The three groups of patients studied had similar pathological conditions (Table 1). All patients were managed before and after operation according to a previously detailed protocol (1), except that antimicrobial therapy was administered only after the arrival of the patient in the operating room and no antimicrobial irrigation solution was used during the procedure. Serum specimens were drawn on the arrival of the patient in the operating room. A 1-g amount of methicillin, oxacillin, or cephalothin was administered intravenously at the time anesthesia was induced. At 1 h after the administration of the agent under study, cortical bone specimens were removed from the acetabular side of the hip joint, a synovial tissue specimen was excised from the inframedial aspect of the capsule, and a serum specimen was drawn simultaneously.

The serum specimens were analyzed for antimicrobial concentrations by the disk-plate method with *Sarcina lutea* (ATCC 9431) as the assay organism (4). Although the sensitivity of this assay is usually 0.1 µg of oxacillin or methicillin per ml and 0.4 µg of cephalothin in buffer per ml (12), small bone sample size and

TABLE 1. *Distribution of agents studied by pathological condition of the hip*

| Underlying pathology | No. of patients studied with the following antimicrobial agent: | | |
|---|---|---|---|
| | Methi-cillin | Oxa-cillin | Cepha-lothin |
| Coxarthrosis | 15 | 18 | 13 |
| Post-trauma | 4 | 3 | 2 |
| Congenital hip dysplasia | 1 | 2 | 1 |
| Ancient septic arthritis | | 2 | 1 |
| Osteonecrosis | 1 | 1 | 2 |
| Failed prosthesis | 2 | 2 | 1 |
| Rheumatoid arthritis | | | 1 |

the dilution required for its processing precluded detection of antibiotic in several patients. The cortical bone specimens were washed in saline solution to remove any residual serum and then weighed and crushed into a fine powder. The powder was suspended in 0.1 M phosphate buffer, pH 6.0. Samples of the suspension were assayed in triplicate by the cylinder-plate method with *S. lutea.* The zones of inhibition were compared with a standard reference of the antibiotic suspended in a phosphate buffer. The synovial tissue was washed, weighed, cut into small pieces, and suspended in trypsin solution; it was then ground and assayed in triplicate by the cylinder-plate method with *S. lutea.*

## RESULTS

Inadequate sample size of the cortical bone specimen in 32 patients and the synovium specimen in 5 patients prevented determination of the antimicrobial concentration in tissue. In 10 of the 32 patients with inadequate osseous specimens (7 receiving methicillin, 3 receiving oxacillin), the antimicrobial agent under study was not present in a concentration inhibitory to staphylococci, that is, the concentration was less than 1 $\mu$g/g of tissue.

**Serum level.** Among the 72 patients in whom tissue antimicrobial concentrations were determined, 4 patients with coxarthrosis were noted to have antimicrobial activity in the serum before the administration of the agent (methicillin, 1; oxacillin, 3). Only the data for the remaining 68 patients were evaluated. At 1 h after 1 g of cephalothin was administered intravenously, the serum levels in 21 patients ranged from 6.6 to 20.8 $\mu$g/ml, with a mean level of 11.9 $\mu$g/ml. In 25 patients the serum level of oxacillin at 1 h after 1 g was given intravenously ranged from 5.0 to 32.8 $\mu$g/ml, with a mean of 18.9 $\mu$g/ml. The serum level of methicillin at 1 h after 1 g was administered intravenously in 22 patients ranged from 4.3 to 36.4 $\mu$g/ml, with a mean of 17.1 $\mu$g/ml. The mean serum level of cephalothin

was significantly lower than that of either oxacillin or methicillin ($P < 0.02$).

**Osseous tissue levels.** The cortical bone levels of cephalothin in 21 patients at 1 h after intravenous administration of 1 g ranged from 0.9 to 17.5 $\mu$g/g, with a mean of 3.9 $\mu$g/g. In 22 patients receiving 1 g of oxacillin and in whom the exact level could be determined, the cortical bone level after 1 h ranged from 0.3 to 14.5 $\mu$g/g, with a mean of 2.1 $\mu$g/g. The cortical bone level of methicillin in 15 patients in whom the exact level could be determined ranged from 0.5 to 10.3 $\mu$g/g, with a mean of 3.1 $\mu$g/g. There was no statistical difference in the mean cortical levels of the three agents studied.

However, in plotting the relationship between the drug concentration in cortical bone and the concentration simultaneously in serum for each of the three agents studied (Fig. 1, 2, and 3), several facts became apparent. No consistent relationship existed between the serum level and the cortical bone level. If we included the 10 patients (7 receiving methicillin and 3 receiving oxacillin) in whom inadequate osseous tissue sample size prevented determination of the exact concentration of tissue but the cortical bone level failed to reach a concentration inhibitory to staphylococci (<1.0 $\mu$g/g), the drug concentration in 50% of the patients receiving methicillin, 44% of the patients receiving oxacillin, and 4.8% of the patients receiving cephalothin was less than 1 $\mu$g/g of cortical bone. In fewer patients receiving cephalothin than either methicillin or oxacillin were the osseous drug concentrations inhibitory to staphylococci (>1.0 $\mu$g/g) ($P < 0.01$).
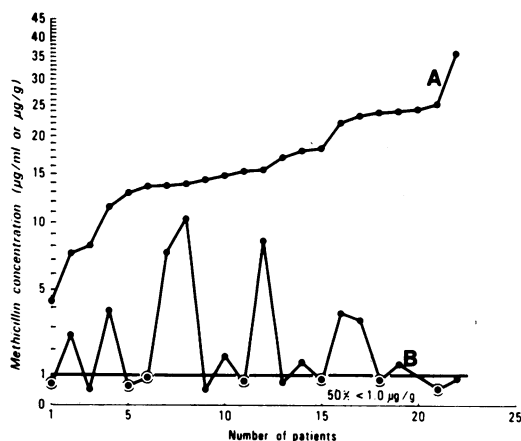


FIG. 1. *Simultaneous concentrations of methicillin in serum and cortical bone at 1 h after 1 g of methicillin was given intravenously. Line A, serum ($\mu$g/ml); line B, cortical ($\mu$g/g).* ⊙, <1 $\mu$g/g.
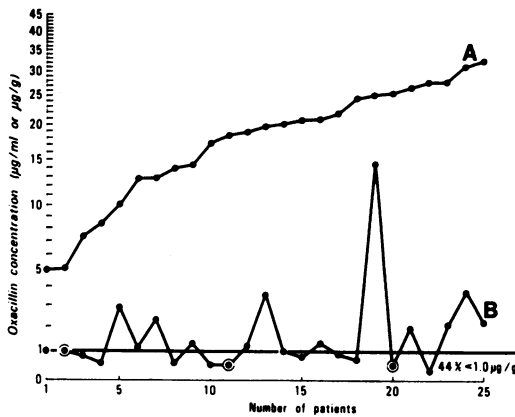
FIG. 2. *Simultaneous concentrations of oxacillin in serum and cortical bone at 1 h after 1 g of oxacillin was given intravenously. Line A, serum (μg/ml); line B, cortical bone (μg/g).* ⊙, <1 μg/g.
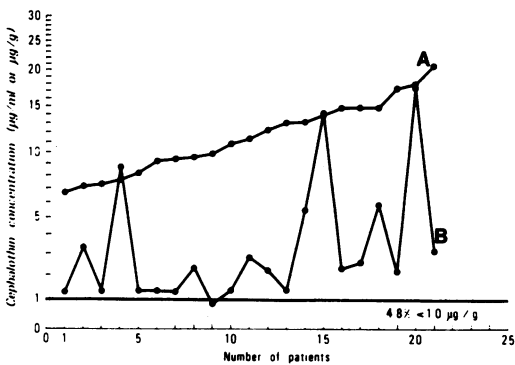


FIG. 3. *Simultaneous concentrations of cephalothin in serum and cortical bone at 1 h after 1 g of cephalothin was given intravenously. All but one patient achieved a concentration of more than 1 μg/g of cortical bone. Line A, serum (μg/ml); line B, cortical bone (μg/g).*

**Synovial tissue levels.** Antimicrobial levels in the synovial tissue specimens of adequate size were determined in 53 patients. In 19 patients receiving cephalothin, the synovial tissue levels ranged from 0.9 to 5.6 μg/g, with a mean of 2.4 μg/g. In 14 patients receiving oxacillin, the range was from 0.3 to 5.6 μg/g, with a mean of 1.8 μg/g. The range among 20 patients receiving methicillin was from 0.8 to 3.4 μg/g, with a mean of 1.9 μg/g. No significant differences existed among the mean synovial tissue levels of the three agents. In five patients (three receiving methicillin and one each receiving oxacillin and cephalothin) the drug concentrations did not reach 1 μg/g of synovial tissue.

## DISCUSSION

In the literature, comparison of the results of various in vivo studies of the concentrations of antimicrobials in bone is difficult. Osseous specimens to be assayed have been obtained during various surgical procedures. Some authors (D. J. Schurman et al., Trans. 23rd Annu. Meet. Orthop. Res. Soc., p. 30, 1977) maintain that specimens obtained during total knee arthroplasty, which is performed under a tourniquet, permit an accurate reflection of the osseous drug concentration, but others (Cunha et al., 17th ICAAC, Abstr. no. 351) have demonstrated at least a 40% reduction of the osseous drug concentration when a tourniquet is used. Many authors fail to identify the underlying pathological process for which reconstruction was performed. Specimens obtained from the necrotic region of an osteonecrotic femoral head or the sclerotic region of the osteoarthritic femoral head would reflect the altered vascular supply and, therefore, an osseous drug concentration that is not representative.

The time when the osseous specimen is obtained after the last injection of the antimicrobial agent varies within, as well as between, reports. This variable must be standardized if comparisons are to be made.

Most authors use various types of agar-diffusion techniques to quantitate the osseous drug concentrations. However, the standards may be diluted in pooled human serum, a phosphate buffer, or both. Considerable precedent exists for dilution of tissue and fluids other than serum for bioassay in buffer (4, 5). Standard curves in buffer for methicillin, oxacillin, and cephalothin display considerably greater sensitivity than do those in serum (12). Finally, if accurate cortical bone levels reflecting the in vivo environment are to be reported, those agents known to exhibit protein binding should be studied with standards diluted in phosphate buffer (9).

In an attempt to avoid many of these problems, this study was designed to obtain all specimens from the acetabulum 1 h after intravenous administration of the antibiotic. The zones of inhibition produced by the osseous specimen were compared with those produced by standards diluted in a phosphate buffer without human serum. The sensitivity of the bioassay for methicillin and cephalothin required large tissue specimens. Unfortunately, the amount of cortical bone removed from the acetabulum during total hip arthroplasty is small, so that not all assays were definitive. This study was also designed to compare the osseous penetration of the isoxazolyl penicillins with that of cephalothin, as well as to study the influence of differ-

ences in protein binding between the isoxazolyl penicillins on osseous penetration.

A major deficiency of this study, as well as of previously published studies of antimicrobial agents in bone, is the failure to demonstrate either a relationship between serum and osseous drug concentrations or the concentration of the agent under study in the interstitial fluid of bone. Osseous concentrations of an agent obtained by bioassay of crushed or intact specimens cannot differentiate the concentration in the vascular, cellular, crystalline, or interstitial fluid compartments of bone (8). The large standard deviation with tissue drug concentrations noted in this study may reflect contamination by serum or elution of the agent under study during the saline wash. Preliminary experience with triple tracer techniques in dogs indicates that penicillin G enters the interstitial fluid space of bone in concentrations exceeding those measured by bioassay techniques (J. D. Bloom et al., Fed. Proc., p. 428, 1977). In fact, the data suggest that the interstitial fluid drug concentration corresponds closely to the serum level.

Deep wound infection has been reported to occur in up to 9% of patients undergoing total hip arthroplasty. In our experience, staphylococci have been the causal organisms in approximately 60% of deep wounds in infected hips (3). All isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* were resistant to penicillin (minimal inhibitory concentration, ≥1 μg/ml). Any agent chosen as a prophylactic antimicrobial during total joint arthroplasty should achieve concentrations in the synovial and osseous tissues inhibitory to staphylococci.

The osseous and synovial tissue drug levels obtained in this study indicate that cephalothin more consistently reaches concentrations in cortical bone which are inhibitory to staphylococci. The relatively high protein binding of oxacillin did not alter its penetration into osseous or synovial tissues, and there were no significant differences between the osseous or synovial concentrations of methicillin and oxacillin. Thus, when an antimicrobial agent is selected for prophylaxis during total joint arthroplasty, cephalothin would appear to be superior to either of the isoxazolyl penicillins studied.

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