

# Plasma and bone concentrations of cefuroxime and flucloxacillin

## Oral versus parenteral administration in 20 arthroplasties

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Our objective was to determine and to compare the range of bone levels of cefuroxime and flucloxacillin achieved after oral and intravenous administration in 20 arthroplasty patients, allocated to 4 groups: 1 × 500 mg or 7 × 500 mg oral cefuroxime was followed by 2000 mg Flucloxacillin i.v.; 1 × 500 mg and 7 × 500 mg oral flucloxacillin was followed by 1500 mg cefuroxime i.v. Bone samples of hip and knee were obtained. Oral administration did not result in a measurable bone concentration of any of the antibiotics.

Intravenous administration resulted in measurable bone concentrations of both cefuroxime and flucloxacillin, with large inter-individual variations. The bone concentrations of intravenous cefuroxime were higher than those of flucloxacillin, despite the lower dose.

Oral pretreatment had no effect on the bone concentrations after intravenous administration. No accumulation of the drugs in bone was observed.

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Good bone penetration of flucloxacillin and cefuroxime after parenteral administration has been reported (Lopiteaux et al. 1978, Leigh et al. 1982). The bone concentration of cefuroxime after regional administration has also been determined (Hoddinott et al. 1990). There is little published information on the bone penetration of orally administered antibiotics in general, and no information concerning the recently introduced cefuroxime axetil specifically (Cunha 1984).

The value of a high bone concentration of antibiotics is difficult to ascertain, although it is reasonable to assume that it is advantageous because the MIC value of the bacteria thus is exceeded (Levine and McCain 1978, Bryson et al. 1979, Glover and Geddes 1981, Nelson et al. 1982, Prober 1982, Gold and Rodriguez 1983, Vree and Hekster 1990, Wymenga et al. 1991).

We determined the range of bone levels of cefuroxime and flucloxacillin achieved after oral and intravenous administration of cefuroxime axetil and flucloxacillin.

### Patients and methods

20 patients, 14 women and 6 men, undergoing elective total hip or total knee surgery were selected for this

study. With the approval of the hospital's Ethics Committee, an informed written consent was obtained from all patients before their participation.

Patients with a known hypersensitivity to cephalosporin or penicillin were excluded. Also excluded were those who had received such drugs within a week prior to surgery, or patients who had had a previous episode of sepsis in the region to be operated on. 3 times during the study an operation time was changed by external factors; new probands were selected. The median age was 67 (55-89) years. The preoperative diagnosis was osteoarthritis in 14 cases and rheumatoid arthritis in 6. A total hip arthroplasty was carried out in 17 cases and a total knee arthroplasty in 3 cases.

**Surgery.** Hip arthroplasty was carried out in a routine fashion with Palacos cement without gentamicin (Essex, Amsterdam, The Netherlands). After the dislocation of the hip, the osteotomy of the femoral neck was made. A slice containing cortical and cancellous bone was taken. All the blood on the outside of the bone sample was wiped off carefully, and the bone was stored separately at -20 °C pending analysis. The knee arthroplasty was carried out using an anterolateral straight incision of the skin, with a tourniquet in place. After dislocation of the patella, the bone cuts were made, and a cortico-cancellous slice of the distal femoral condyle was taken.

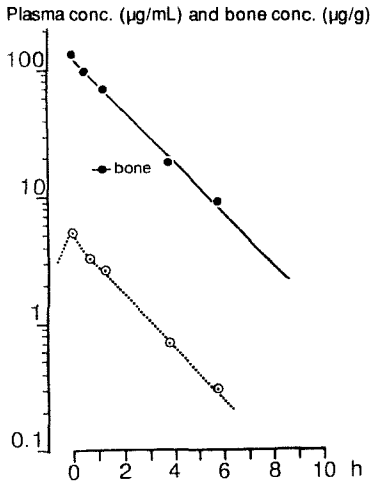


Figure 1. Plasma concentration-time curves and bone concentrations of cefuroxime (●) and flucloxacillin (○) in a patient after administration of 1500 mg i.v. cefuroxime at the start of the operation (t 0) and 1 oral dose of 500 mg flucloxacillin 3 h prior to surgery. Cefuroxime t<sub>1/2</sub> 1.5 h and flucloxacillin t<sub>1/2</sub> 1.4 h.

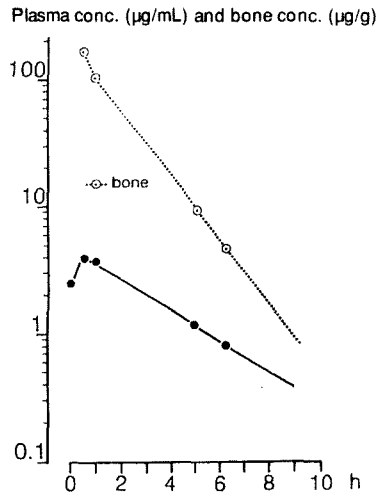


Figure 2. Plasma concentration-time curves and bone concentrations of cefuroxime (●) and flucloxacillin (○) in a patient after administration of 2000 mg i.v. flucloxacillin at the start of the operation (t 0) and 1 oral dose of 500 mg cefuroxime 3 h prior to surgery. Cefuroxime t<sub>1/2</sub> 2.2 h and flucloxacillin t<sub>1/2</sub> 1.2 h.

**Antibiotics.** 4 groups of 5 patients each were formed. Group A received 1 dose of 500 mg cefuroxime Axetil (Glaxo, Nieuwegein, The Netherlands) 3 h preoperatively per os. Flucloxacillin i.v. (Beecham, Rijswijk, The Netherlands) was given at a dose of 2000 mg at the start of the operation, followed at 8 h and 16 h by 2000 mg doses.

Group B received 1 oral dose of 500 mg flucloxacillin 3 h preoperatively. The parenteral dosage of cefuroxime was 1500 mg at the start of the operation and after 8 h and 16 h 750 mg doses.

Group C started 3 days preoperatively with 2 oral doses of cefuroxime Axetil 500 mg, with the last dose 3 h preoperatively (total 7 doses). Flucloxacillin i.v. was administered as in Group A.

Group D started 2 days preoperatively with 3 oral doses of flucloxacillin 500 mg, the last 3 h preoperatively. Cefuroxime i.v. was administered as in Group B.

**Sampling.** 10 mL of venous blood was drawn at the time of induction of anesthesia (Sample 1), at the start of the operation (Sample 2), during the operation at the time of the bone removal (Sample 3), and 2 and 4 hours after the operation (Samples 4 and 5). After centrifugation of the blood samples at 2600 g, the plasma was separated and stored at -20 °C pending analysis.

**Plasma sample treatment.** Cefuroxime: 100 mL of plasma was deproteinized with 400 mL perchloric acid 0.33 M, centrifuged at 11,000 g and 100 mL was injected onto the column.

Flucloxacillin: 200 mL of plasma was deproteinized with 200 mL of acetonitrile, centrifuged at 11,000 g, and 50 mL was injected onto the column.

**Bone sample treatment.** The total bone removed was extracted overnight, at room temperature (21 °C), with a known volume of 0.9% NaCl just immersing the piece of bone. This process was repeated 3-5 times until no measurable concentrations of the antibiotic were present in the extraction fluid. The total diffusible amount of the antibiotic was recorded.

**Analysis.** Cefuroxime and flucloxacillin were analyzed by means of High Performance Liquid Chromatography (HPLC), as described before by van Dalen et al. (1979), Hekster et al. (1979, 1980), Roumen et al. (1990), Vree and Hekster (1990).

**Statistics.** The Student's *t*-test was performed according to standard procedures (SAS) (Ray 1982).

## Results

High bone concentrations of cefuroxime and flucloxacillin could only be measured after the intravenous administration; the oral administration did not give any measurable bone concentration. The bone concentrations had a wide intersubject variation (Figures 1 and 2). Each of the 20 patients showed a different pharmacokinetic picture of the combination of the 2 antibiotics.

Table 1. Pharmacokinetic parameters of cefuroxime orally and flucloxacillin i.v. Mean SD

Parameter	Group A n 5		Group C n 5		Groups A + C n 10	
Cefuroxime 500 mg orally						
Cmax µg/mL	4.38	1.75	2.50	1.50	3.4	1.8
t1/2 h	2.28	0.21	2.28	0.38	2.3	0.3
AUC mg/L.h	22.63	10.59	13.70	7.18	18.2	9.7
Bone conc µg/g <sup>a</sup>						
Flucloxacillin 2000 mg i.v.						
AUC mg/L.h	334	88.8	272	127	303	108
AUC1h mg/L.1h	66.1	25.0	80.2	36.1	49.8	26.3
t1/2 h	1.4	0.3	1.3	0.4	1.4	0.4
CL mL/min	105	24.0	180.0	164	142	117
Vss L	10.6	3.4	16.3	3.3	17.6	21.9
Bone conc µg/g	8.6	5.1	6.3	1.5	7.4	3.8
Plasma conc µg/mL (bone removal)	108	44.6	111	44.7	110	42
Bone/plasma	0.08	0.04	0.07	0.04	0.07	0.04
AUC1h/bone	10.5	6.2	14.2	8.0	12.4	7.0

<sup>a</sup>Below quantitation limit.

No statistical significance between groups A and C ( $P > 0.20$ ).

Cmax is the observed maximal plasma concentration.

t1/2 is the half-life of elimination.

AUC is the area under the plasma concentration-time curve extrapolated to infinite time.

AUC 1h is the AUC over a 1-h period.

CL is the total body clearance dose/AUC (bioavailability  $F = 1$ ).

Vss is the volume of distribution in steady-state ( $V_{ss} = \text{dose} \times \text{AUMC}/\text{AUC}^2$ ).

Table 2. Pharmacokinetic parameters of cefuroxime (i.v.) and flucloxacillin orally. Mean SD

Parameter	Group B n 5		Group D n 5		Groups B + D n 10	
Flucloxacillin 500 mg orally						
Cmax µg/mL	12.3	9.7	4.5	1.9	9.4	8.4
t1/2 h	1.8	0.7	2.3	2.2	2.1	1.6
AUC mg/L.h	79.0	93.6	15.1	4.3	29.0	28.6
Bone conc µg/g <sup>a</sup>						
Cefuroxime 1500 mg i.v.						
AUC mg/L.h	267	100 <sup>b</sup>	158	76 <sup>b</sup>	212	101
AUC1h mg/L.1h	64.0	29.4 <sup>b</sup>	33.5	16.5 <sup>b</sup>	72.1	32.2
t1/2 h	2.0	0.6	1.8	0.4	1.9	0.5
CL mL/min	102	27.8 <sup>c</sup>	193	95.0 <sup>c</sup>	147	81.5
Vss L	16.3	3.3	27.9	16.3	22.1	12.7
Bone conc µg/g	14.1	7.4	9.6	2.4	11.9	5.7
Plasma conc µg/mL (bone removal)	97.6	36.2	44.2	18.3	70.9	39.0
Bone/plasma	0.17	0.11	0.26	0.24	0.21	0.18
AUC1h/bone	5.5	3.3	6.3	6.0	5.9	4.6

<sup>a</sup>Below quantitation limit, <sup>b</sup> $P < 0.04$ , <sup>c</sup> $P < 0.05$ .

Cmax is the observed maximal plasma concentration.

Abbreviations, see Table 1.

The calculated pharmacokinetic parameters of intravenous flucloxacillin of the patients in Groups A and C were similar ( $P < 0.20$ ; Table 1); thus the patients in both groups can be treated as one group. The bone concentrations of intravenous cefuroxime in Groups B and D were similar, and both groups were treated as

one group ( $P < 0.13$ ; Table 2). A difference between the number of oral flucloxacillin administrations on the cefuroxime parameters AUC ( $P < 0.045$ ) and total body clearance was found ( $P < 0.05$ ).

The oral co-administration of the second antibiotic had no effect on the bone concentrations of the intra-

venously administered drug (Tables 1 and 2). The mean bone concentration of cefuroxime was higher than that of flucloxacillin ( $P < 0.03$ ), despite the lower dose.

## Discussion

With non-homogeneous matrices, such as bone, it is difficult to make comparisons between the pharmacokinetics of different antibiotics, since the observed levels are not simply related to the degree of penetration; they are also influenced by a number of other factors, such as the type of bone samples and the amount of blood contamination (Leigh et al. 1982). Bone concentrations after oral administration were not studied and reported earlier (Black et al. 1987, Kolyvas et al. 1980, Nelson et al. 1982).

In our study, bone concentrations were measurable only after the intravenous administration of both drugs, where cefuroxime reached a higher bone concentration with a lower dose than flucloxacillin (Table 2). This may be due to the high(er) plasma concentrations obtained after iv administration. The explanation for this observation may be that the plasma concentration was too low after oral administration. There were big variations in the bone concentration of antibiotics in several patients after parenteral administration (Table 1).

Lopiteaux et al. (1978) reported that no linear correlation could be found between the bone and serum concentrations after one and the same antibiotic dosage. They also assumed that the penetration in infected bone is better than in normal bone, due to the increased vascularization.

The bone concentrations of flucloxacillin and cefuroxime after intravenous administration measured in our study are in agreement with previous studies (Parssons et al. 1978, Unsworth et al. 1978, Jung and Mischkowsky 1979, Dornbush et al. 1980, Holm and Larsson 1982, Köndell et al. 1982, Leigh et al. 1982, 1986, Sirot et al. 1982, Brooks and Dent 1984, Hedström et al. 1984, Heimdahl et al. 1988, Wilson et al. 1988).

In our study the bone concentration seemed to be independent of the serum or plasma concentration at the time of bone removal; the ratio bone/plasma concentration and bone/AUC<sub>1h</sub> showed very large variations and a high coefficient of variation. The large inter-individual variation in the total bone concentration could not be related to differences in etiology, location, or the cortical/cancellous bone ratio. Moreover, 1 bone sample gives no information about the bone concentration-time curve and the resulting

AUC<sub>bone</sub>/AUC<sub>plasma</sub> ratio. Lunke et al. (1981) demonstrated in canine cortical bone that cefamandole was distributed in the plasma and interstitial fluid spaces of cortical bone. A direct correlation was observed between the calculated concentration of cefamandole in the interstitial spaces of bone and the simultaneous serum levels in animals in which a steady-state equilibrium had been achieved.

In our study no steady-state plasma concentration was achieved after 1 intravenous administration of the antibiotic. The measured bone concentrations may represent alone or in part the blood concentration of the antibiotic inside the bone. With the exhaustive extraction process, this content is released in the extraction fluid. It is not certain whether the antibiotic has been (covalently) bound to the bone and, if this were the case, whether it is possible to release or hydrolyze it from the bone.

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