

Effect of time interval on tissue concentrations of cephalosporins after tourniquet inflation

Highest levels achieved by administration 20 minutes before inflation

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We studied the effect of different time intervals between antibiotic administration and tourniquet inflation in 62 patients undergoing reconstructive surgery in the lower extremities. The *in vivo* concentrations in soft tissue and bone of 3 cephalosporins

(ceftazidime, ceftriaxone and ceforanide) were determined. Our findings suggest that the highest tissue concentrations were achieved by administration 20 min before tourniquet inflation.

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Among cephalosporins currently used in orthopedic prophylaxis, the second generation ceforanide, and the third generation ceftazidime and ceftriaxone offer a wide antimicrobial cover (O'Gallaghan et al. 1980, Seddon et al. 1980, Daikos et al. 1981), a high concentration in bone tissue (Leigh et al. 1985) and a satisfactory β -lactamase resistance (O'Gallaghan et al. 1980).

We analyzed the effect of a tourniquet on the pharmacokinetics of these antibiotics within the bone and soft tissue and determined the optimal time interval between the intravenous administration of the antibiotics and tourniquet inflation to obtain high local bactericidal concentrations.

Patients and methods

We studied 62 patients (20 men and 42 women) undergoing reconstructive operations in the lower extremities (26 total knee replacements and 36 high tibial osteotomies), with a mean age of 59 (37-78) years. We excluded: (1) patients with hepatic or renal insufficiency, (2) those allergic to any cephalosporins, (3) those with a history of a severe anaphylactic reaction to penicillin and (4) concurrent treatment with other antibiotics, systemic steroids, immunosuppressants or cytotoxics. With the approval of the hospital's Ethics Committee, an informed written consent was obtained from all patients before their participation.

All the operations were performed with a tourniquet placed on the upper thigh and inflated at a pressure constantly maintained at 500 mm Hg. Patients were divided in a random manner into 3 groups. Ceftazidime (2 g, i.v., 30 min infusion) was administered to 26 patients, ceftriaxone (2 g i.v.) to 17 and ceforanide (2 g i.v.) to 19, at different intervals (10 min, 20 min, 2 h and 4 h) before tourniquet inflation (Table 1). The groups of patients receiving antibiotics at 10, 20 min or 2 and 4 h did not differ in their ages, weights or renal function. Therefore the distribution of the drugs and their renal clearance can be assumed to be the same in each of the patient groups. 20 min after the beginning of the operation, small tissue samples were obtained from skin, subcutaneous fat, muscle and bone (lateral femoral or tibial condyle). Specimens were rinsed thoroughly, placed in sterile plastic vials and stored deep-frozen (-70 °C) until

Table 1. Distribution of patients in the study among the different antibiotic and time interval groups (interval between antibiotic administration and tourniquet inflation)

Antibiotic	Time interval				Total
	10 min	20 min	2 h	4 h	
Ceftazidime	8	8	6	4	26
Ceftriaxone	5	6	6	-	17
Ceforanide	7	8	4	-	19
Total					62

Table 2. Antibiotic concentrations ($\mu\text{g/g}$) in lower extremity tissues in relation to the time of intravenous administration. Mean value, SD

Interval between injection and tourniquet inflation	Antibiotic concentrations ($\mu\text{g/g}$)			
	Skin	Fat	Muscle	Bone
<i>Ceftazidime</i>				
10 min	59 13	14 3	45 10	23 2
20 min	67 18	20 4	50 12	27 2
2 h	58 3	18 2	45 3	22 3
4 h	13 3	0.7 0.3	10 0.7	0.4 0.03
<i>Ceforanide</i>				
10 min	21 3	12 1	18 3	15 3
20 min	24 2	15 2	21 2	18 3
2 h	17 4	11 2	15 2	13 1
<i>Ceftriaxone</i>				
10 min	55 5	16 2	42 3	22 2
20 min	54 5	21 1	42 3	22 2
2 h	33 4	13 5	27 5	17 4

antibiotic concentrations were determined. This was carried out using the microbiological agar diffusion method (with *Escherichia Coli* ICB 4004 as the indicator organism).

Statistical analysis was performed using the Student *t*-test for non-paired observations. Differences were considered significant if $P < 0.05$.

Results

The highest concentrations of ceftazidime and ceforanide in skin, fat, muscle, and bone were obtained when the antibiotic was given 20 min before tourniquet inflation, and the lowest when ceftazidime was given 4 h before tourniquet inflation (Table 2). Intermediate values resembling those at 20 min were observed at 10 min and 2 h.

Similar results were obtained after intravenous administration of ceftriaxone, with two exceptions: (a) in skin and muscle specimens, the highest tissue concentrations were achieved using 10 min intervals, but not significantly different from the levels using 20 min intervals, and (b) tissue concentrations in all ceftriaxone specimens using an interval of 2 h were lower than the those obtained using the 10 and 20 min intervals ($P < 0.01$).

Discussion

Data regarding the tissue concentrations of antibiotics in the extremities using a tourniquet are sparse (Leigh et al. 1985, Johnson 1987). Our study suggests that the time interval between the intravenous admin-

istration of antibiotics and tourniquet inflation is critical in achieving appropriate tissue concentrations during the operation.

Among the cephalosporins we selected ceftazidime and ceftriaxone (third generation cephalosporins) and ceforanide (second generation cephalosporin) because they are widely used and have favorable pharmacokinetics (Daikos et al. 1981, Kalager et al. 1984). Thus, with three antibiotics high concentrations were readily achieved in all tissues, especially in muscle and skin, which were not different between the 10 and 20 min interval concentrations. In the case of bone and fat, the tissue concentrations were higher with the 20 min interval. These data indicate that administration of antibiotics 20 min before the surgical procedure results in maximum levels in both soft tissues and bone. Satisfactory results were also observed when ceftazidime and ceforanide were given either 10 min or 2 h before the operation. When ceftriaxone was used, sufficient tissue concentrations were achieved only when the antibiotic was administered between 10 and 20 min before tourniquet inflation.

The tissue concentrations of ceftazidime were slightly higher than those of ceftriaxone and much higher than those of ceforanide at the same time interval. These findings can be explained by ceftazidime's lower rate of protein binding in the plasma (17 percent), compared to ceftriaxone's (80 percent) or to ceforanide's (95 percent), despite its shorter half-life (3-4 times lower than that of ceftriaxone) (O'Gallaghan et al. 1980, Seddon et al. 1980).

Johnson, in 1987, reported that the highest concentrations of cefuroxime in bone and fat tissues were achieved when the antibiotic was administered at

least 10 min before inflation of the tourniquet. Leigh et al. (1985), using a similar protocol, also reported that the highest concentration of ceftazidime in bone tissue was achieved when the antibiotic was administered 20 min before tourniquet inflation. Specifically, their mean bone concentration was 20 $\mu\text{g/g}$, compared to 27 $\mu\text{g/g}$ in our study. This difference may be due to the different doses used (1 g i.v. by Leigh et al. vs 2 g i.v. in our study).

We conclude that, during major orthopedic procedures of the extremities, sufficiently high concentrations of ceftazidime, ceftriaxone and ceforanide in soft and bone tissues can best be achieved when they are administered approximately 20 min before tourniquet inflation.

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