Bone and wound fluid concentrations of cephalosporins

Oral cefadroxil and parenteral cefuroxime compared in 52 patients with a trochanteric fracture

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We performed a prospective and randomized study in 52 patients to compare the concentrations in cancellous bone and wound fluid of antibiotics, given orally (cefadroxil) or intravenously (cefuroxime) as prophylaxis in trochanteric fracture surgery.

Oral cefadroxil resulted in adequate antibiotic levels in 22 of 26 patients in wound fluid and cancellous bone, while parenteral cefuroxime resulted in sufficient antibiotic levels in all 26 patients. The concentrations in bone varied greatly between the subjects.

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Prophylactic antibiotics in orthopedic surgery are usually administered intravenously, for fear of either inadequate absorption of oral drugs (Schurman et al. 1978, Burnett et al. 1980, Jones et al. 1985, Garcia et al. 1991) or preoperative complications, such as vomiting and aspiration. Only in a few studies have antibiotic concentrations been determined not only in serum but also in different target tissues by analyzing bone and muscle samples retrieved during surgery (Schurman et al. 1978, 1980, Unsworth et al. 1978, Holm and Larsson 1982, Leigh 1986, Johnson 1987).

In a previous study we have shown that cefadroxil given orally provides adequate serum levels within 2 hours of administration (Nungu et al. 1992).

In this study we measured and compared the concentrations in bone and wound fluid of cefadroxil when given per os and cefuroxime when given intravenously as prophylaxis in trochanteric fracture surgery.

Patients and methods

32 women and 20 men with a trochanteric hip fracture who were allocated to surgery were included. Patients on current antibiotic treatment or with a known allergy to penicillins or cephalosporins were excluded. After giving informed consent, the patients were randomized, using a closed envelope procedure, to prophylaxis with either intravenous cefuroxime (group A) or oral cefadroxil (group B). The mean age was 77 (52–93) years. On admission and 5 days after surgery, creatinine and alanine-aminotransferase (ALAT) were recorded for early identification of possible liver or renal damage. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded on admission, at 6 weeks, and 4 months after surgery to identify possible infectious complications.

The patients in group A received 0.75 g cefuroxime (Zinacef®, Glaxo, Sweden) intravenously at the time of anesthesia induction, followed by another 2 doses at 8 h intervals during the first day. Patients in group B were given 1 g cefadroxil (Cefamox®, Bristol-Myers Squibb, Sweden) dissolved in 100 mL of water, approximately 2 h before surgery, followed by a second similar dose 12 h later. No patient vomited after taking oral cefadroxil.

Operation time, peri- and postoperative bleeding, postoperative temperature and compliance with oral medication were recorded. Intramuscular analgesics (ketobemidon or pethidine) alone or in combination with a sedative were used as premedication. All patients were operated on within 32 h of admission with open or closed reduction, followed by internal fixation with a standard sliding screw device (AO/ASIF dynamic hip screw—DHS). All but one operation were carried out under spinal block. The wound was examined on days 3 and 7, according to the protocol. Any sign of infection or other healing complications was recorded. All patients were fol-

lowed for 4 months after surgery with visits at the out-patient clinic.

During surgery, 2 samples of wound fluid and 1 bone sample were obtained for antibiotic assay. The first fluid sample was aspirated at the start of the operation and the second at the end of the operation, just before closing the wound. During surgery, a piece of cancellous bone measuring about 1 cm^3 was extracted from the inner part of the greater trochanter, with a rongeur inserted through the drill hole made for the lag screw. The bone sample was wiped clean of all surface blood, after which all 3 samples were placed in sterile tubes and immediately transported to the laboratory where the fluid samples were centrifuged for serum isolation, and the bone sample weighed, after which all 3 specimens were frozen pending analysis. At the time of analysis, the serum or wound fluid concentrations were determined by standard techniques (Sutherland and Robinson 1978), using dilution series supplied by Biodisk AB (Stockholm, Sweden), as previously described (Nungu et al. 1992). The method gives a 95 percent confidence limit of 15 percent of the measured value (Jalling et al. 1972). The concentration of antibiotics in the bone pieces was determined by a multiple bone-washing technique where the intact bone piece was immersed in consecutive volumes of saline solution to extract the antibiotic. The total amount of diffusable antibiotic was recorded.

The MIC-90 against methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis*, i.e., the concentration of cefadroxil required to inhibit 90 percent of a standard inoculum of any of the named species, is 2–4 μg/mL (Quintilani 1982, Knapp and Washington 1988, Nungu et al. 1992). The corresponding MIC value for cefuroxime is 1–4 μg/mL.

Statistics

The Student's *t*-test was performed with $P < 0.05$ considered as significant. Mean, standard deviation, range and 90 percent confidence limits were given.

Results

There was no difference between groups regarding sex distribution, age, weight, time elapsed from injury to operation, operation time, and peroperative bleeding (Table 1). No complications or adverse reactions were recorded secondary to the use of antibiotics in either of the 2 groups.

1 patient in the cefuroxime group developed a superficial wound infection, with cultures revealing *Staphylococcus aureus*, within 2 weeks of surgery. The infectious reaction subsided and the wound healed following treatment first with intravenous cefuroxime and then oral cefadroxil. There were no wound infections in the cefadroxil group.

At the beginning of surgery, wound fluid values were above 4 μg/mL in 22 of the patients in each group, i.e., 4 patients from each group had antibiotic concentrations in the wound fluid at the beginning of surgery below those considered to be a satisfactory average MIC-90 value for *Staphylococcus aureus*. In each group, 2 of the patients with low values had a shorter time from the administration of the antibiotic to the sample collection, compared to patients with higher values. Towards the end of surgery—i.e., wound fluid sample 2—all patients in the cefuroxime group had antibiotic concentrations above 4 μg/mL, although the average value for the whole group had decreased slightly compared to sample 1. In the group of patients given antibiotics orally, the same 4 patients who had low values at the beginning of surgery showed values below 4 μg/mL, while the 22 patients with higher values showed almost the same concentrations as at the start of surgery. There was no obvious reason for the low values in these 4 patients.

The antibiotic concentrations in bone were considerably lower than the levels seen in the wound fluid in both groups. In wound fluid, as well as in the bone samples, there was a great variation in concentrations between individuals. Patients given intravenous cefuroxime all had concentrations in cancellous bone exceeding 1 μg/g, of which all but one exceeded 2 μg/g. As for patients given oral cefadroxil, all but one had bone concentrations above 1 μg/g, while 18/26 had values above 2 μg/g. The wound fluid/bone concentration ratio (penetration in bone) for cefuroxime was 5 (90 percent CI of 4 to 7), while the corresponding figure for cefadroxil was about 4 (90 percent CI of 3–5).

Discussion

Our study revealed that oral cefadroxil was well tolerated in all subjects and well absorbed in 22/26 patients. The reason why 4 patients had low concentrations could not be explained. A careful review of the medical records in these patients did not disclose any previous gastric surgery or known gastrointestinal disease that might have affected the ability to absorb drugs. In a recent study by Alvarez Ferrero et al. (1993), oral administration of 500 mg of cefuroxime prior to joint replacement surgery gave no mea-

Table 1. Data for all 52 patients

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	F	93	1	55	64	8	5	40	0	46	35	14.1	40	50
2	M	65	1	81	76	14	25	60	18	13	60	2.4	75	400
3	M	85	1	72	91	9	35	60	35	26	35	2.7	50	225
4	M	69	1	66	213	22	55	85	36	31	75	14.4	35	200
5	F	81	1	65	94	9	30	65	32	16	60	11.8	55	800
6	F	79	1	56	86	19	20	65	3	7	55	9.5	100	200
7	M	82	1	•	108	19	20	55	31	22	50	13.6	60	500
8	M	52	1	71	73	12	25	135	3	5	115	2.0	130	1000
9	M	86	1	63	68	32	45	115	21	20	105	3.1	80	200
10	M	67	1	85	72	16	45	105	23	27	85	2.8	85	350
11	M	82	1	66	106	31	85	195	25	13	175	1.8	145	1200
12	M	84	1	69	88	18	35	75	30	28	65	2.2	55	250
13	F	88	1	66	99	21	15	50	30	28	45	12.2	45	200
14	F	81	1	57	76	15	10	45	72	36	40	8.5	50	300
15	F	77	1	40	95	16	40	110	40	28	95	3.4	90	250
16	M	53	1	85	69	18	10	75	33	12	65	3.2	85	600
17	F	60	1	61	•	11	35	55	16	19	55	8.8	45	150
18	F	73	1	55	89	25	35	55	34	35	45	8.1	40	200
19	F	74	1	62	65	10	15	60	48	34	55	7.7	60	150
20	M	93	1	76	142	19	20	55	37	36	45	8.5	45	250
21	F	86	1	56	165	24	10	60	3	38	45	7.0	65	200
22	F	87	1	69	113	16	40	90	26	16	40	9.4	65	275
23	M	57	1	90	86	10	20	40	20	36	40	12.6	35	150
24	M	79	1	71	74	9	55	120	31	28	100	7.9	65	100
25	F	65	1	54	60	22	50	75	38	36	65	5.5	40	300
26	F	65	1	40	58	20	10	80	43	22	65	6.7	102	150
27	F	70	2	65	76	28	45	80	14	14	70	5.5	105	550
28	M	62	2	69	81	•	85	120	11	13	115	6.7	55	275
29	F	84	2	68	37	8	30	75	20	20	65	4.6	95	300
30	M	80	2	82	103	28	150	185	23	16	140	7.4	40	200
31	M	89	2	55	69	8	85	135	6	12	135	7.5	55	350
32	M	72	2	68	255	13	75	115	20	19	100	7.7	50	100
33	M	72	2	81	75	10	40	70	13	16	70	2.4	35	200
34	F	85	2	70	82	18	85	105	12	11	105	7.9	45	150
35	F	85	2	60	139	9	165	195	14	11	175	4.1	80	300
36	F	82	2	44	50	11	50	75	11	14	60	2.3	35	100
37	F	70	2	58	72	9	105	160	15	14	150	4.0	65	350
38	M	76	2	73	63	18	50	90	8	6	80	2.8	50	100
39	F	86	2	55	55	14	105	135	15	22	135	9.1	50	250
40	M	75	2	69	81	17	45	90	24	22	85	9.2	50	250
41	F	76	2	57	74	20	95	140	2	3	135	1.9	55	300
42	M	81	2	89	98	31	135	200	23	16	185	9.6	65	200
43	F	80	2	68	89	21	115	160	12	7	140	5.9	50	350
44	M	82	2	72	78	21	110	180	14	11	160	1.8	75	450
45	M	84	2	81	91	16	35	50	3	3	55	1.6	25	200
46	F	75	2	65	74	12	220	305	21	17	270	1.3	95	550
47	F	83	2	48	89	10	125	180	25	18	175	5.1	70	50
48	F	84	2	60	122	13	100	160	4	3	145	1.3	60	100
49	F	89	2	61	86	14	65	145	11	11	125	1.3	90	300
50	F	72	2	62	94	11	90	160	19	12	120	3.2	95	400
51	M	79	2	59	86	13	35	50	2	1	35	0.5	25	50
52	F	82	2	60	71	7	90	115	8	9	95	1.3	40	200

A Case
B Sex
C Age
D Antibiotics
  1 Cefuroxime intravenously
  2 Cefadroxil orally
E Weight (kg)
F Serum creatinine (mmol/L)
G Hours from trauma to surgery
H Minutes from administration of antibiotics to sample 1
I Minutes from administration of antibiotics to sample 2
J Antibiotic conc in wound at the start of surgery, sample 1 (µg/mL)
K Antibiotic conc in wound at the end of surgery, sample 2 (µg/mL)
L Minutes from administration of antibiotics to bone sampling
M Antibiotic conc in bone (µg/g)
N Operation time (min)
O Bleeding during surgery (mL)

surable levels of antibiotics in the bone, while serum levels were lower than in the present study. Furthermore, the peak concentration of cefuroxime was seen as early as 1 h after antibiotic intake, i.e., earlier than with cefadroxil where the serum peak occurs 2–3 h after oral intake (Nungu et al. 1992). The concentrations of cefadroxil seen in both wound fluid and bone are well in accordance with the study by Quintilani (1982). There are several differences between the study performed by Alvarez Ferrero et al. (1993) and our study that might explain the discrepant results. The type of cephalosporin used was different in these studies, as also were the drug preparation and the dose (500 mg cefuroxime per os, compared to 1000 mg cefadroxil in our study). It might be that the absorption of oral cefuroxime was lower than that of cefadroxil. Such a difference might in part be due to the type of drug preparation—i.e., ordinary tablets—compared to the soluble tablets we used. However, in a previous study which described serum concentrations over time, the serum peak level following oral cefadroxil was seen 2–3 h after administration (Nungu et al. 1992), which is more than 1 h later than the concentration peak seen after oral cefuroxime in the study by Alvarez Ferrero et al. (1993). This difference implies that ordinary cefuroxime tablets are absorbed at least as rapidly as—or even more rapidly than—the soluble tablet used in the present study. The timing of the cefadroxil dose in this study was based on previous experiences with time-concentration curves for the same drug and vehicle (Nungu et al. 1992) and was intended to produce a maximum concentration of antibiotic in the wound during surgery.

Trauma may reduce gastrointestinal motility and lead to a reduced ability to absorb drugs given orally. However, the wound fluid and bone concentrations for both groups in the present study are well in accordance with previous studies measuring antibiotic concentrations during joint replacement surgery (Schurman et al. 1978, Unsworth et al. 1978, Holm and Larsson 1982, Leigh 1986). The accuracy achieved when measuring the concentration of antibiotics in bone depends on the type of bone (cortical or cancellous) in the sample, the amount of blood contamination as well as the technique used for extracting the antibiotic from the bone sample. Unsworth et al. (1978) found that blood contamination contributed a maximum of 26 percent when studying flucloxacillin in bone from patients undergoing total hip replacement. The concentration in cortical bone is usually lower than that in cancellous bone, due to the fact that cortical bone is less vascularized and has a higher density (Unsworth et al. 1978, Holm and Larsson 1982). In the present study, we used the immersion technique to extract the antibiotic from the intact bone piece, since we consider this technique more representative of the in vivo situation, where the antibiotic is being extracted from the vascular bed.

The bone concentration in many patients was below or close to the MIC-90 values for common strains of *Staphylococcus aureus*, i.e., the most frequent organism causing post-operative wound infections. It is important to remember that the inhibitory effect described by the MIC-90 value is just one of several factors which may affect the clinical efficacy of a certain antibiotic (Hamilton-Miller 1987). Even low concentrations of cephalosporins can have a lytic effect on certain bacteria, including *Staphylococcus aureus*, as well as stimulate leucocyte activity (McDonald et al. 1981).

Oral cephadroxil provides adequate antibiotic concentrations against the commonly identified bacteria in the surgical wound and the exposed bone in most patients, while parenteral cefuroxime seems to be a better guarantee for sufficient antibiotic levels in trauma patients.

References

Alvarez Ferrero M M, Vree T B, Baars A M, Slooff T J J H. Plasma and bone concentrations of cefuroxime and flucloxacillin. Oral versus parenteral administration in 20 arthroplasties. Acta Orthop Scand 1993; 64 (5): 525–9.

Burnett J W, Gustillo R B, Williams D N, Kind A C. Prophylactic antibiotics in hip fractures. A double-blind prospective study. J Bone Joint Surg (Am) 1980; 62: 457–62.

Garcia S, Lozano M L, Gatell J M, Soriano E, Ramon R, Sanmiguel J G. Prophylaxis against infection. Single-dose cefonicid compared with multiple-dose cefamandole. J Bone Joint Surg (Am) 1991; 73: 1044–8.

Hamilton-Miller J M. Microbial investigations of cephalosporins. Drugs (Suppl 2) 1987; 34: 23–43.

Holm S, Larsson S-E. The penetration of flucloxacillin into cortical and cancellous bone during arthroplasty of the knee. Int Orthop (SICOT) 1982; 6: 243–7.

Jalling M, Malmborg A S, Boreus L O. Evaluation of a micromethod for determination of antibiotic concentrations in plasma. Eur J Clin Pharmacol 1972; 4 (3): 150–7.

Johnson DP. Antibiotic prophylaxis with cefuroxime in arthroplasty of the knee. J Bone Joint Surg (Br) 1987; 69 (5): 787–9.

Jones S, DiPiro J T, Nix D E, Bhatti N A. Cephalosporins for prophylaxis in operative repair of femoral fractures: Levels in serum, muscle, and hematoma. J Bone Joint Surg (Am) 1985; 67: 921–4.

Knapp C C, Washington J A. In vitro activities of LY 163892, cefaclor and cefuroxime. Antimicrob Agents Chemother1988; 32 (1): 131–3.

Leigh D A. Serum and bone concentrations of cefuroxime in patients undergoing knee arthroplasty. J Antimicrob Chemother 1986; 18 (5): 609–11.

McDonald P J, Wetherall B L, Pruul H. Postantibiotic leukocyte enhancement: increased susceptibility of bacteria pretreated with antibiotics to activity of leukocytes. Rev Infect Dis 1981; 3: 33–44.

Nungu K S, Bengtsson S, Olerud C, Rehnberg L, Larsson S. Oral cephadroxil prophylaxis in hip fracture surgery. Acta Orthop Scand 1992; 63 (1): 4–6.

Quintilani, R. A review of the penetration of cefadroxil into human tissue. J Antimicrob Chemother 1982; 10 (Suppl B): 33–8.

Schurman D J, Hirshman H P, Kajiyama G, Moser K, Burton D S. Cefazolin concentrations in bone and synovial fluid. J Bone Joint Surg (Am) 1978; 60 (3): 359–62.

Schurman D J, Hirshman H P, Burton D S. Cefalotin and cefamandole penetration into bone, synovial fluid, and wound drainage fluid. J Bone Joint Surg (Am) 1980; 62 (6): 981–5.

Sutherland R, Robinson G N. In: Laboratory Methods in Antimicrobiological Chemotherapy (Eds. Reeves D S, Phillips J, Williams J D, Wise R). Churchill Livingstone, Edinburgh 1978; 171.

Unsworth P F, Heatley F W, Phillips I. Flucloxacillin in bone. J Clin Pathol 1978; 31: 705–11.