Oral cefadroxil prophylaxis in hip fracture surgery

Serum concentrations studied in 17 patients

Kitugi Samwel Nungu[1], Stellan Bengtsson[2], Claes Olerud[1], Lars Rehnberg[1] and Sune Larsson[3]

Serum concentration-time curves were determined in seventeen 82 (60–90) year-old patients undergoing trochanteric hip fracture surgery after receiving 1 g of cefadroxil per os. All the patients attained a serum level of antibiotic high enough to inhibit the growth of *Staphylococcus aureus* and *S. epidermidis*. When orally administered, cefadroxil should be given within 2 hours before surgery.

Departments of [1]Orthopedics, [2]Clinical Bacteriology, University Hospital, Uppsala, and [3]Orthopedics, Umeå University Hospital, Sweden
Correspondence: Dr. Kitugi Samwel Nungu, Department of Orthopedics, University Hospital, S-751 85 Uppsala, Sweden
Tel +46-18 66 30 00. Fax +46-18 50 94 27

Antibiotic prophylaxis in trochanteric femoral fracture surgery has contributed to the reduction of the postoperative infection rate with *Staphylococcus aureus*, the most commonly identified pathogen, from 10–16 percent in the 1970s to 0–2 percent today (Tengve and Kjellander 1978, Lindberg 1984, Hedström et al. 1987). Parenteral administration has been preferred because the absorption of antibiotics from the gastrointestinal tract varies widely in man (Lindberg 1984). Orally administered antibiotics have been recommended for prophylactic regimens lasting more than 1 day (Tengve and Kjellander 1978, Lindberg 1984, Hedström et al. 1987).

We have evaluated the clinical significance of the interindividual variability in the absorption of cefadroxil from the gastrointestinal tract when used as a prophylactic in elderly patients undergoing trochanteric hip fracture surgery.

Patients and methods

Seventeen consecutive patients with a trochanteric hip fracture treated at the Department of Orthopedics in Uppsala were studied (Table 1). Patients who were

Table 1. Patients' data

Patient	Age	Sex	Weight (kg)	Length (cm)	Op time (min)	Bleeding (mL)	C_1 µg/mL	C_2 µg/mL	C_3 µg/mL
Group A									
1	90	M	65	175	45	200	25	30	27
2	87	F	95	167	80	300	22	27	25
3	79	M	70	180	50	230	28	22	19.5
4	90	F	50	160	60	200	6.2	6.4	4.2
5	78	M	90	172	45	250	11.5	15	13.5
6	84	F	64	161	50	100	33.5	34	34.5
7	85	M	80	178	25	150	21	24	23.5
8	83	F	65	160	50	250	11	9.8	8.5
9	94	F	64	195	25	200	5	7.1	9.2
10	90	M	75	175	50	250	4.5	6	10
Group B									
11	60	F	90	175	45	100	19	16	13
12	80	F	58	165	45	200	6.7	7.2	8.6
13	88	F	58	166	40	150	22	21	19
14	79	F	78	158	75	1,200	11	12	13
15	75	M	82	188	35	100	19	18	16
16	82	F	58	165	50	200	5	6.5	7
17	77	F	65	162	50	200	5.5	5	4.3

C_1, C_2, C_3 = serum cefadroxil concentration after 2 h, 2.5 h, and 3 h, respectively.

unable to take oral medication or who had a known or suspected cephalosporin or penicillin allergy were excluded. The study was approved by the ethics committee of Uppsala University. Informed consent was given by all the patients.

Patients with pain were given a ketobemidon (opiate) injection, 2.5–5 mg s.c., on admission before the application of boot traction. A second dose was given later in 9 cases. As antibiotic prophylaxis, the patients were given orally a single dose of 1 gram of cefadroxil dissolved in 100 mL of water. The used plastic cups were not rinsed afterwards to avoid giving the patients extra fluids.

Group A comprised 10 patients, with a mean age of 86 years, who were operated on the day after admission (Table 1). They received their cefadroxil prophylaxis dose at 6 a.m. (which is the routine time for dispensing medication on the ward). A ketobemidon i.m. injection was given to 8/10 patients as premedication about 2.5 hours after taking cefadroxil. The premedication was augmented with a sedative in 6/10 patients immediately before they underwent spinal anesthesia: viz., approximately 4 hours after receiving cefadroxil. Group B, comprising 7 patients with a mean age of 77 years, were operated on as emergency cases on the day of admission (Table 1). The oral cefadroxil dose was given simultaneously (± 4 min) with the ketobemidon premedication injection. The spinal anesthesia was given approximately 35 minutes later. Two cases, 1 in each group, were operated on under general anesthesia.

All the patients swallowed and retained the medication. None of them had diarrhea or showed an adverse reaction to cefadroxil. The operations were performed on an extension table using the AO/ASIF dynamic hip screw (DHS) technique. Patients Nos. 9 and 10 in Group A and No. 6 in Group B required an extra liter of i.v. fluids to stabilize their blood pressures, whereas 600 mL of transfusion blood was needed by patient No. 4 in Group A. Serum creatinine was determined and recorded on the day of admission and 4 and 5 days after the operation.

Antibiotic assay. Venous blood samples (2–5 mL) for antibiotic assay were collected in series at intervals of 1 hour for all the patients. A new venous puncture was made for every sample. We desisted from taking a sample whenever we failed for some reason to collect the sample at the appointed time. The last sample (after 12 hours) was taken immediately before the second dose of cefadroxil was given. The samples were stored in a refrigerator at + 8 °C for not more than 12 h before they were sent to the laboratory, where the serum was frozen after centrifugation.

The cefadroxil concentrations were measured by standard techniques (Sutherland et al. 1978) using a dilution series prepared by Biodisk AB (Stockholm, Sweden). In brief, duplicate samples of patient serum were assayed on PDM agar plates (Biodisk AB) inoculated with a strain of *Sarcina lutea* using one standard concentration series for each plate. Inhibition zones were read after 16 hours, a standard curve prepared, and the serum concentration calculated. This gives a 95 percent confidence limit of ± 15 percent of the measured value (Jalling et al. 1972).

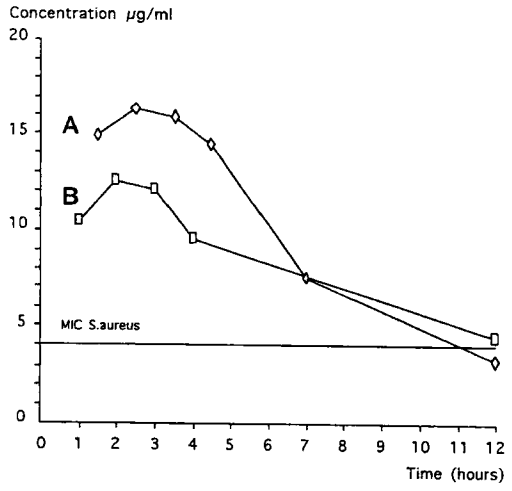

Figure 1. Mean cefadroxil serum concentration vs time curve for Groups A and B patients.

Determination of staphylococcal MIC. The minimal inhibitory concentration (MIC) of cephadroxil was determined for five strains of *S. aureus* and five strains of *S. epidermidis,* all sensitive to methicillin. The strains were from ambulatory and admitted patients from different departments.

Statistics. The Mann-Whitney test for unpaired data, the Wilcoxon paired ranking-sum test for data in two groups, and the Spearman test for rank correlation were used.

Results

The peak serum concentration of cefadroxil occurred after 2–2.5 hours irrespective of when the antibiotic was taken in relation to the opiate premedication and spinal anesthesia (Figure 1). The results show a wide scatter and variability among individuals. The average operation time for each group was 50 min and the average blood loss was respectively 200 mL and 160 mL for the patients in Groups A and B (Table 1).

The median MIC was less than 4 μg/mL (for *Staphylococcus aureus* 2, 2, 4, 4, 4 μg/mL, and for *S. epidermidis* 0.5, 2, 4, 4, 8 μg/mL) and did not differ between the species. The MIC value of 8 μg/mL was for a strain from a patient with rheumatoid arthritis who was receiving steroid and cytostatic treatment and whose scratch wound had become infected while admitted in the ward. All the patients attained serum concentration values equivalent to or well above this value (4 μg/mL) 2 hours after taking cefadroxil. No changes were recorded in serum creatinine levels between the two readings.

All the patients have been followed up for 6 months, and none of them has shown signs of wound infection.

Discussion

In fracture surgery a parenteral route of prophylactic antibiotic administration has been used because of its momentaneous serum concentration peak values and because antibiotics are variably absorbed after oral administration (Lindberg 1984). However, studies (Quintiliani 1982, Bergan 1987, Hamilton-Miller 1987) have shown that later, 1 hour or 2 hours after the oral dose, the pharmacokinetics are similar for both routes, i.e., the concentration of antibiotic is high enough to prevent infection.

The choice of cefadroxil, an oral cephalosporin, for the study was motivated by such factors as the soluble 1-gram tablet is easy to store, handle, and administer; it is designed for an empty, fasting stomach; and cefadroxil has a long half-life when compared with other antibiotics, including cephalosporins. Cefuroxime, recommended by Lindberg (1984) and Hedström et al. (1987), is four times more expensive than cefadroxil.

The serum concentration-time curves of our patient Groups A and B resembled the one obtained in healthy younger individuals (Quintiliani 1982, Bergan 1987), and the rate of absorption was not affected by the traumatic condition of our patients. However, the degree of absorption was apparently affected, whereas with adequate serum cefadroxil concentrations, this was of no clinical or statistical significance. Our results confirmed that cefadroxil was well absorbed and tolerated irrespective of preoperative factors and age.

Despite interindividual variability in cefadroxil absorption, our patients achieved serum concentration levels equivalent to, or several times greater than, the MICs for common pathogens, such as *Staphylococcus aureus, S. epidermidis,* and group A streptococci (Quintiliani 1982, Bergan 1987, Hamilton-Miller 1987, McEniry 1987). Commonly occurring *Staphylococcus aureus* and *S. epidermidis* are methicillin-sensitive.

We have confirmed that these strains from ambulatory patients or patients who have been confined to the hospital for rather short periods of time are sensitive to the bactericidal effect of cefadroxil at concentrations equal to or less than 4 μg/mL (Quintiliani 1982, Hamilton-Miller 1987).

Cefadroxil has favorable pharmacokinetic properties; further, it is negligibly biotransformed into a less active metabolite, has a long half-life, and is less bound by serum protein. This ensures availability of effective amounts of antibiotic in the hematoma should such be formed within 12 hours of administration (dosage 1 g × 2). Bowers et al. (1973) found that hematomas are easily and effectively penetrated when bathed in rather high serum concentrations of drugs during the first 36 hours.

Acknowledgements

This study was partly funded by Bristol Myers-Squibb, Sweden.

References

Bergan T. Pharmacokinetic properties of the cephalosporins. *Drugs* (Suppl 2), 1987; 34: 89–104.

Bowers H W, Wilson F C, Green W B. Antibiotic prophylaxis in experimental bone infections. *J Bone Joint Surg* (Am) 1973; 55: 795–807.

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

Hedström S Å, Lidgren L, Sernbo I, Törholm C, Önnerfält R. Cefuroxime prophylaxis in trochanteric hip fracture operations. *Acta Orthop Scand* 1987; 58 (4): 361–4.

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

Lindberg L. Antibiotic prophylaxis in postoperative infections in orthopaedic surgery. In: *Antibiotics and surgery workshop* National Board of Health and Welfare, Sweden 1984: 59–65.

McEniry D W, Gorbach S L. Cephalosporins in surgery. Prophylaxis and therapy. *Drugs* (Suppl 2)1987; 34 : 216–39.

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

Sutherland R, Robinson G N. Penicillin. In: *Laboratory methods in antimicrobiological chemotherapy.* (Eds. Reevers D S, Phillips J, Williams J D, Wise R) Churchill Livingstone, Edinburgh 1978: 171.

Tengve B, Kjellander J. Antibiotic prophylaxis in operations on trochanteric femoral fractures. *J Bone Joint Surg* (Am) 1978; 60 (1): 97–9.