Intravenous cefuroxime prophylaxis

Tissue levels after one 3-gram dose in 40 cases of hip fracture

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This study consists of 2 series of patients with cervical hip fracture treated with hemiarthroplasty. In a preliminary study, the method, timing of sample collection, and tissue and serum concentrations were studied in 15 patients. In the main study of another 25 patients, only tissue samples were collected.

In the preliminary study, 3 g of cefuroxime was infused in 15–25 min and serum, muscle, fascia and bone samples were collected at various times. In the main study, 1 dose of 3 g of cefuroxime was infused in 15 min. Skin, muscle, fascia, and bone tissue samples were collected after 30 and 45 min and the concentrations of cefuroxime were measured by high-performance liquid chromatography. In the preliminary study, serum cefuroxime levels were 61 μg/mL and 42 μg/mL at 15–30 and 35–50 min, respectively. Cefuroxime levels in various tissues were only slightly less than those in serum. Blood contamination contributed less than 30 percent to the tissue levels of cefuroxime.

In the main study, mean cefuroxime levels in the tissues were in the range of 39–58 μg/g, and the total range was 5.5–151 μg/g at 30 and 45 min. These concentrations are well above the MIC values of the most common bacteria causing wound and bone infections.

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Cefuroxime has been one of the most popular choices in the antimicrobial prophylaxis in traumatology, orthopedics and general surgery (Hughes et al. 1982, McQueen et al. 1990, Bodoky et al. 1993). We report the tissue concentrations of cefuroxime after one high-dose infusion given during the induction of anesthesia in patients operated for hip fractures.

Material and methods

Surgery

In the preliminary study, 15 patients with hip fractures received an infusion of 3 g of cefuroxime (Zinacef®, Glaxo) in 10–30 min, and blood, fascia, muscle and bone samples were collected during hemiarthroplasty operation at 15–100 min after the beginning of the infusion. These samples, having varying timings, were used to develop the assay method of cefuroxime and also to analyze the contribution of the blood contamination of the tissues to cefuroxime levels in the tissues. Serum cefuroxime was also analyzed only in the preliminary study. Tissue concentration data of the preliminary series were fragmentary and were not included in the main study. Informed consent was obtained.

In the main study, 25 consecutive patients (24 women, 1 man) with hip fracture and coming for hemiarthroplasty were enrolled. The only exclusion criterium was the preoperative use of cefalosporine antibiotics. Their mean age was 81 (59–96) years. Informed consent was obtained. The anterolateral approach was used. During induction of anesthesia, 3 g of cefuroxime was given as a 15-min intravenous infusion. The beginning of the infusion was the zero point for timing. Tissue samples from skin, muscle, fascia and bone distal to the cutting line of the femoral collum were removed 30 and 45 min after the zero point. The samples were stored at –70 °C until analyzed.

The assay of cefuroxime

Cefuroxime sodium salt (Zinacef®) and ceftazidime pentahydrate (Glazidim®) were from Glaxo OY, Espoo, Finland. Acetonitrile used preparing the mobile phase was of high-pressure liquid chromatography (HPLC) grade and purchased from Rathburn (Walkenburg, UK). The following chemicals

were purchased from Merck (Darmstadt, FRG): ammonium dihydrogen orthophosphate, orthophosphoric acid (85%), perchloric acid (70%, PCA), sodium dihydrogen phosphate monohydrate and disodium hydrogen phosphate dihydrate and reagents were of analytical grade.

HPLC assay of cefuroxime. Cefuroxime concentrations were determined by using UV-detection. The system consisted of the Hewlett Packard 1084B instrument (Palo Alto, CA, U.S.A.) and the column was Spherisorb 5 ODS-2 (150 × 4.6 mm, I.D., 5 µm; HPLC Technology, Cheshire, UK) with precolumn (Brounlee Labs, U.S.A.). The wavelength of the detector was 260 nm. The mobile phase consisted of 12% acetonitrile in 0.05 M ammonium phosphate, pH 3.0 and the flow was 1.2 mL/min.

Sample preparation

Serum samples. A series of standards was made by dispensing the stock solution of cefuroxime (1 mg/mL) in blank serum. The standard range was 50–1.25 µg/mL. Serum proteins were precipitated by adding 200 µL of 4% PCA to the standards (200 µL) and the samples (200 µL), and mixing twice for 10 sec on a vortex mixer. The mixture was centrifuged for 15 min at 3000 rpm at 5 °C. A 30 µL aliquot of the filtrated supernatant was injected into the HPLC system. Ceftazidime (20 µg/mL) was used as an internal standard and it was dissolved in 4% PCA solution. A linear regression was obtained for the peak heights of the standards. The peak heights of the samples were compared to the calibration curve to give the concentration of cefuroxime. The correlation coefficient was 0.99 ± 0.0006 (mean ± SD, n 24). The detection limit was 0.2 µg/mL, interassay coefficient of variation (CV %) was 9.9% (at 5 µg/mL, n 16) and intra-assay CV 2.8% (at 10 µg/mL, n 5) and 2.6 % (at 50 µg/mL, n 5). Recovery of cefuroxime was 86% (at 10 µg/mL) and 90% (at 50 µg/mL). The results are not corrected for recovery.

Tissue samples. Frozen samples of fascia, muscle and skin were weighed and then melted and homogenized in the 0.05 M phosphate buffer, pH 6.0 (1:10) in ice. After centrifugation, the supernatant was used as a sample for protein precipitation and handled by the same procedure as the serum sample.

The bone samples were further frozen in the small volume of liquid nitrogen, and then crushed by a hammer between 2 metal plates. Phosphate buffer (0.05 M, pH 6.0) 1:10 w/v was added and the suspensions were extracted by gentle shaking at 4 °C for 5 h. After centrifugation, the supernatant was handled by the same procedure as the serum samples.

The assay of blood and tissue hemoglobin levels

The hemoglobin content of the whole blood and the tissue homogenates were assayed photometrically at 540 nm (Ultrospec III, Pharmacia, Uppsala, Sweden), after converting to cyanmethemoglobin, according to van Kampen and Zijlstra (1961).

Results

The preliminary study

Serum levels of cefuroxime were 61 ± 9.2 µg/mL (n 15) and 42 ± 13 µg/mL (n 15) at 15–30 and 35–50 min, respectively. Cefuroxime levels in various tissues were only slightly less than those in serum. Blood contamination contributed less than 30 percent of cefuroxime when calculated on the basis of the hemoglobin content of the tissue samples.

The main study

Cefuroxime was found in all samples. Tissue levels were similar at 30 and 45 min. There were surprisingly small differences between the cefuroxime concentrations in various tissues. The lowest level was found in the bone at 30 min (5.5 µg/g) and the highest in the skin at 45 min (151 µg/g). A linear correlation between the patient's weight and the cefuroxime concentration was seen, with large variations (Table 1).

Discussion

Antimicrobial prophylaxis in surgery, particularly its timing and dosing and the choice of the drug, has been much studied and discussed (Boyd et al. 1973, Burnett 1980, Ritter et al 1989, Classen et al. 1992). Cefuroxime has been one of the most popular choices in this field, as also in traumatology and orthopedics (Hughes et al. 1982, McQueen et al., 1990, Bodoky et al. 1993). Its antimicrobial spectrum is suitable covering the most important bacteria causing wound and bone infections.

Although serum levels of cefuroxime were measured only in the preliminary study, it is obvious, and in accordance with the published data (Hughes et al. 1982), that tissue cefuroxime levels are lower than those in serum. However, the protein-binding of cefuroxime is low (around 30 percent) and therefore this water-soluble, poorly lipophilic compound is easily distributed to the water compartment of the tissues (Kucers and Bennett 1988).

Table 1. Concentrations of cefuroxime (μg/g) in skin, muscle, fascia and bone at 30 and 45 min after the 15-min intravenous infusion of 3 g of cefuroxime.

Patient	Tissue concentration, μg/g								Patient weight, kg
	Skin		Fascia		Muscle		Bone		
	30	45	30	45	30	45	30	45	
1	29	26	21	35	32	33	60	93	42
2	32	50	21	24	31	33	45	43	71
3	41	44	19	29	48	39	8	16	60
4	53	46	47	45	33	25	26	39	74
5	29	46	28	30	25	25	16	27	39
6	52	36	49	64	71	51	55	41	56
7	53	87	47	84	93	53	89	36	82
8	9	16	16	32	29	44	13	20	65
9	16	40	90	35	41	27	16	41	58
10	31	56	54	63	44	29	20	93	60
11	16	19	8	6	37	34	67	54	–
12	35	29	41	36	50	44	42	61	40
13	11	17	30	40	25	40	23	57	60
14	67	120	66	62	42	24	58	47	51
15	33	36	53	356	20	29	6	65	54
16	79	76	30	46	61	59	65	71	52
17	125	98	76	72	50	51	62	52	45
18	67	50	71	41	26	30	41	35	67
19	91	151	92	79	56	69	84	75	45
20	55	63	49	53	47	36	23	27	50
21	56	35	48	46	74	46	49	67	46
22	95	91	54	28	52	53	29	16	47
23	73	74	55	44	36	41	39	32	63
24	16	92	73	28	18	31	57	70	56
25	31	44	59	44	24	22	28	37	100
Mean	48	58	48	44	42	39	41	49	58
SD	29	34	23	18	18	12	23	22	
SE	5.8	6.7	4.5	3.7	3.7	2.5	4.7	4.4	
N	25	25	25	25	25	25	25	25	24

A single intravenous infusion of 3 g of cefuroxime during the induction of anesthesia seems to give adequate tissue concentrations in all relevant tissues during the operation, since the average MIC values of the bacteria usually involved in wound and bone infections are 1–4 μg/mL (Kuckers and Bennett 1988).

The half-time of cefuroxime is 70 min in serum, according to product information. Tissue samples were not collected after 45 min to avoid unnecessary lengthening of the operation time. Thus, the concentrations during long operations can only be estimated.

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