Comparative pharmacokinetics of ceftriaxone after periincisional and intravenous administration in patients undergoing abdominal surgery

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Abstract

The advantages of the preoperative periincisional infiltration (ppi) of ceftriaxone in the prophylaxis of surgical wound infections over the preoperative intravenous injection (piv) has been demonstrated by comparing the pharmacokinetics of the two routes of antibiotic administration and the clinical results. The study was conducted in 36 patients undergoing abdominal surgery. Eighteen of them received a 2 g ceftriaxone piv (group A) and the rest a similar dose by ppi (group B). The peak time, peak plasma concentration and the bioavailability for the ppi route were respectively 1.19±0.24 h, 96.9±3.8 mg/ml and 0.68±0.07. After piv, a typical bioexponential decline of plasma ceftriaxone levels from 256.7±37.5 mg/ml (0.5 h) to 15.7±7.5 mg/ml (24 h) was observed. Tissue and wound fluid antibiotic levels of patients from group B (range: for tissues 95±1850 mg/g, for fluid 62±1342 mg/ml) were much higher than for group A (range: for tissues 18±150 mg/g, for fluid 35±160 µg/ml). Adequate for chemoprophylaxis antibiotic plasma levels were measured in both patient groups 24 h post operatively (group A: 15.7±7.5 mg/ml, group B: 12.4±4.5 mg/ml). No wound infections or other complications were noted in group B. In contrast, three cases of wound infections and one case of pneumonia were observed in group A.

Keywords: Ceftriaxone ; Pharmacokinetics ; Patients ; Periincisional ; Abdominal surgery

1. Introduction

Recent studies on the prevention of postoperative wound infections advocate the use of prophylactic antibiotics, especially in cases where the risk of contamination is high. To be effective, antibiotic prophylaxis should be started in the preoperative period to ensure adequate antibiotic levels both in plasma and in body tissues (Polk and Lopez-Mayor, 1969; Waterman and Kastan, 1972). It is well recognised that the most important factor in the pathogenesis of wound sepsis is the presence of bacteria in the incision at the time of closure. The studies that established the effectiveness of antimicrobial drugs have generally employed systemically administered agents. The concept of preoperative intraparietal (intracisional) injection of antibiotics was introduced for cefoxitin by Taylor et al. (1982). This technique achieves high local concentrations of the antibiotic combined with adequate serum levels.

This paper reports results of pharmacokinetic studies on ceftriaxone in patients undergoing abdominal surgery. Ceftriaxone, (6R, 7R)-7-[(2)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl]-thio]methyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid disodium salt, is a third genera-
tion cephalosporin which differs from other members of this class of antibacterial compounds because of its unique pharmacokinetics, e.g., remarkably long serum half-life (5.4–8.9 h), due to strong (approximately 90%) serum protein binding (Borner et al., 1985; Scully et al., 1984). Other second and third generation beta-lactam antibiotics (e.g. cefamadole, cefotaxine, cefoperazone, moxalactam) possess half-lives ranging from 0.8 to 2.1 h. Ceftriaxone was also chosen because of its known effectiveness against a wide range of wound pathogens, including obligate anaerobes. Previously published pharmacokinetic studies on ceftriaxone concerned healthy volunteers and subcutaneous administration and also studies on experimental animals.

The purpose of this study was to compare plasma, tissue and wound fluid concentrations of ceftriaxone after a single dose by the preoperative intravenous and preoperative perincisional infiltration routes in order to determine both the local concentration of antibiotic in the wound and the rate and extent of systemic absorption from the time of operation until 24 h postoperatively. The simultaneous measurement of ceftriaxone concentrations in the plasma, the tissue of the wound and the wound fluid after perincisional and intravenous administration of the antibiotic in patients has not yet, to our knowledge, been reported. Perincisional preoperative infiltration of the antibiotic is now a routine administration route for chemotherapy drugs in surgery in our University Hospital.

2. Materials and methods

2.1. Patients–dosage–sampling

Thirty six patients (selected with weight range 65–80 kg, age 25–35 years old, 20 men and 16 women and with serum creatinin range 52–109 μmol/l) undergoing abdominal surgery (biliary tract 14, vagotomy and pyloroplasty 4, gastrectomy 4, appendicectomy 4, inguinal herniorrhaphy 4, left colectomy 4, small bowel occlusion 2) were randomised into two equal groups (group A and group B). A 2 g dose of ceftriaxone in 20 ml of saline solution was administered intravenously in a single dose to eighteen patients from group A at the moment of inducing anaesthesia. Each of the eighteen patients from group B received a perincisional preoperative infiltration of ceftriaxone (2 g in 20 ml saline injected in a single dose) and anaesthesia was established immediately. Anaesthesia was induced in both groups ten minutes before the start of the operation. Ceftriaxone injection in group B patients was carried out subcutaneously using a 22F spinal needle along the line of the proposed abdominal incision, with a careful attempt being made to perform uniform infiltration along the incision. The wounds were on average 20 cm long: approximately 1 ml of antibiotic solution was injected along each centimetre.

Tissue samples were taken from three different areas of the wound at the end of the operation from both groups. In all patients we placed fine perforated polyethylene tubes in the subcutaneous plane of the wounds and connected them to evacuated bottles (Redovac, Sterimed, Saarbruecken, Germany) for the collection of the “wound fluid” during the period of the following 24 h. Blood samples were taken at 0.50 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h and 24 h. The blood was immediately centrifuged and the plasma separated and stored together with the tissue and the fluid from the wound samples at −20°C until ceftriaxone analysis was performed.

2.2. Sample preparation–instrumentation and liquid chromatographic analysis

Ceftriaxone disodium salt standards were supplied by Roche Hellas. The stock standard solution (1.0 mg/ml) of ceftriaxone in deionized water was freshly prepared every week and stored at −5°C. Ceftriaxone standards (5, 20, 50, 100, 200 μg/ml) in blank plasma and water were prepared and measured every day using a liquid chromatographic technique to obtain standard curves (including day-to-day control). The analysis of ceftriaxone in the biological samples was performed on the basis of the methods described earlier (Trautmann and Haefelfinger, 1981; Dowman et al., 1984). Our modified method, consisted of a deproteinization step for plasma by ethanol (Trautmann and Haefelfinger, 1981) followed by ion-pair reversed-phase high resolution liquid chromatographic separation of the compounds and UV detection at 273 nm. All precautions necessary for analysis efficiency described earlier were taken into account. Plasma and wound fluid samples were treated similarly. The minor alterations in the analytical methodolo-
gy we applied concern the chromatographic conditions and the treatment of the tissue samples. Tissue samples were homogenised with water, centrifuged, the supernatant was filtered through a Minisart® (Sartorious GmbH, Goettingen, Germany) filter (0.2 µm pore size) and the filtrate (or its dilution sample) was injected into the high pressure liquid chromatography (HPLC) system. For quantification of ceftriaxone in the filtrates, water ceftriaxone standards were used. In our practice the published procedure (Dowman et al., 1984) of serum treatment before HPLC analysis was not very efficient. Chromatography was carried out utilising two Spectra Physics (SP) (San Jose, California, USA) eluent delivery systems (SP8810 and SP8800) in conjunction with an SP UV–VIS variable wavelength spectrophotometer (SP8450) interfaced with a Hewlett–Packard (Avondale, PA, USA) (HP3396A) or an SP4270 integrator for monitoring and analysis of the results. The effluent was monitored at 273 nm at a flow-rate of 1.5 ml/min (ambient temperature, 25°C–28°C). All reagents and solvents used for sample treatment were of analytical grade while the reagents of the eluent mixture in chromatography were HPLC grade. Two different columns, each in conjunction with a different eluent mixture, were applied for analysis and showed good performance (two reversed-phase separation systems). The utilisation of two analytical systems was used as a confirmatory method, e.g., to avoid the influence on analytical results resulting from co-elution of compounds in various blood samples (Tsatsakis et al., 1995). System I utilised an

![HPLC chromatograms](image-url)

Fig. 1. HPLC chromatograms of a control fortified with ceftriaxone and internal standard (I.S.) plasma (A) and a patient plasma (B) obtained by using system I: peak 1 ($R_t = 5.1$) corresponds to ceftriaxone, peak 2 ($R_t = 7.1$) corresponds to I.S. and peak 3 ($R_t = 4.5$) corresponds to endogenous compound in plasma.
Apex ODS II Su column (Jones Chrom. Ltd., Hengoed, UK) eluted by a mobile phase mixture of acetonitrile (39.4%), water (55.4%), hexadecyl trimethylammonium bromide (HDTMAB) (0.4%), buffer pH 7 (Titrisol, E. Merck, Darmstadt, Germany) (4.8%). The internal standard used for system I was a solution of \( \alpha \)-phthalic acid in ethanol (40 \( \mu \)g/ml). Fig. 1 depicts information from analysis using system I. System II utilised an Apex Phenyl Kpsu (Jones Chrom. Ltd., Hengoed, UK) column eluted by a mobile phase of acetonitrile (38.7%), water (60.4%), HDTMAB (0.4%), 0.01 M triethylamine water solution (0.5%). The internal standard of this system was 1-naphthylacetic acid. Fig. 2 depicts information from the analysis using system II. Each of the fluid and tissue samples was analysed in both chromatographic systems (e.g., in the two SP HPLC instruments simultaneously). In the case of more than 5% variation of the two results, samples were reanalysed (by re-injection or new sample preparation). All data values resulting from the analysis were then normalised to 70 kg body weight.

2.3. Statistical analysis and pharmacokinetics

Differences in terms of concentrations of ceftriaxone in surgical wound tissue at the end of operation and in surgical wound fluid at the end of intervention (24 h postoperatively) obtained by the two routes of administration were tested by two way analysis of variance (ANOVA). The two factors were: group (B versus A) and duration of operation in minutes (40 to 70 min versus 70 to 120 min versus 120 to 180 min). ANOVA was also applied to the data after they were normalised to 70 kg body weight.

Fig. 2. HPLC chromatograms of control fortified with ceftriaxone, 60 \( \mu \)g/ml, and internal standard (I.S.), plasma (A) and a patient plasma (B) obtained by using system II: peak 1 (\( R_f = 10.3 \)) corresponds to ceftriaxone, peak 2 (\( R_f = 7.1 \)) to I.S. and peak 3 (\( R_f = 4.4 \)) to endogenous compound in plasma.
transformed to logarithmic scale; the significance levels were not changed.

The plots of the mean concentration values in the plasma suggested an open two-compartment model for the intravenous administration (Borner et al., 1985) which is expressed by the pharmacokinetic formula \(C(t) = Ae^{-\alpha t} + Be^{-\beta t}\). For the perincisional administration the suggested model was an open one-compartment model (Scully et al., 1984) which is expressed by the pharmacokinetic formula \(C(t) = C_0e^{-\mu t} - Cm\). The estimation of the pharmacokinetic parameters (Table 1) was made by fitting the non-linear models above to the data of the corresponding administration route. A two-stage analysis was used where first the appropriate kinetic model was fitted to the data of each individual and then the estimates of the parameters were calculated as averages of the obtained individual estimates.

The calculations were carried out using the software package SPSS (1992).

The bioavailability for perincisional administration of the antibiotic ceftriaxone was calculated according to the formula \(f = (AUC_{\text{perincisional}})/(AUC_{\text{intravenous}})\), where the area under the curve (AUC) corresponds to the time period from zero to infinity. AUC values were calculated using the trapezoidal rule.

### 3. Results

Typical chromatograms obtained from patient and control plasma by using systems I and II of mobile and steady phase are shown in Figs. 1 and 2, respectively. The resolution factors with the nearest peak in both chromatograms are very good. The detection limits of both systems (I, II) were found to be 0.3 and 0.4 µg/ml respectively. The average coefficient of variation for the day-to-day variation of freshly prepared plasma standards \((n = 10)\) was very satisfactory \((3.6\%, \text{range } 2.1-8.5)\). The calibration curve of ceftriaxone assay generated the line \(y = 5.12x - 1.31\) with a correlation coefficient \((r)\) of 0.9981 and a 0.1261 mg/ml value for the standard error of estimated slope.

The results of HPLC analysis of biological samples are presented in Tables 2 and 3 and individual’s plots are shown in Fig. 3. With respect to the estimates of the half-time of drug elimination, we note that the perincisional administration reaches this point at a slightly longer time than the intravenous (no significant difference in \(t_{1/2}\) is shown).

The bioavailability calculated for the perincisional route, \(f = 0.73 \pm 0.07\) is noticeably lower than that known from the literature for the same dose subcutaneously injected into healthy volunteers \((f = 0.96 \pm 0.20)\) (Borner et al., 1985). The difference can be attributed to the different mode of drug administration.

### Table 1
Pharmacokinetic parameters of ceftriaxone derived from clinical data\(^a\) (plasma drug levels) using the two-stage estimation method

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intravenous(^a)</th>
<th>Perincisional(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) (µg/ml)</td>
<td>280.3 ± 23.4</td>
<td>–</td>
</tr>
<tr>
<td>(a) (1/h)</td>
<td>2.10 ± 0.22</td>
<td>–</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>0.39 ± 0.04</td>
<td>–</td>
</tr>
<tr>
<td>(B) (µg/ml)</td>
<td>174.4 ± 8.9</td>
<td>134.0 ± 8.7</td>
</tr>
<tr>
<td>(β) (1/h)</td>
<td>0.13 ± 0.01</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>5.88 ± 0.48</td>
<td>5.93 ± 0.63</td>
</tr>
<tr>
<td>(C_e) (µg/ml)</td>
<td>–</td>
<td>143.2 ± 42.0</td>
</tr>
<tr>
<td>(K_e) (1/h)</td>
<td>–</td>
<td>2.21 ± 0.44</td>
</tr>
<tr>
<td>Plasma peak (µg/ml)</td>
<td>454.6 ± 23.9</td>
<td>98.0 ± 4.2</td>
</tr>
<tr>
<td>Peak time</td>
<td>0</td>
<td>1.32 ± 0.12</td>
</tr>
<tr>
<td>AUC(_{\text{day}}) (µg·h/l)</td>
<td>1547.0 ± 56.6</td>
<td>1024.6 ± 96.6</td>
</tr>
<tr>
<td>Bioavailability ((f))(^c)</td>
<td>–</td>
<td>0.73 ± 0.07</td>
</tr>
</tbody>
</table>

\(^a\) Clinical data normalised to 70 kg body weight.

\(^b\) An open two-compartment model was justified for intravenous administration described by the model equation, \(C(t) = Ae^{-\alpha t} + Be^{-\beta t}\).

\(^c\) For the perincisional administration a model equation, \(C(t) = Be^{-\mu t} - Cm\) was justified. Expressing first order absorption and monoexponential decline.

\(^d\) Bioavailability \(f = (AUC_{\text{perincisional}})/(AUC_{\text{intravenous}})\).

### Table 2
Plasma concentrations of ceftriaxone\(^a\) during operation and postoperatively (in a 24 hour time-period) in 36 patients undergoing abdominal surgery

<table>
<thead>
<tr>
<th>Time(^c) (h)</th>
<th>Concentration in plasma (mean ± standard deviation, µg/ml)</th>
<th>Group A (intravenous)</th>
<th>Group B (perincisional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>–</td>
<td>–</td>
<td>256.7 ± 37.5</td>
</tr>
<tr>
<td>1.00</td>
<td>197.7 ± 32.2</td>
<td>96.1 ± 21.8</td>
<td></td>
</tr>
<tr>
<td>1.50</td>
<td>156.8 ± 19.7</td>
<td>99.5 ± 14.2</td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>139.2 ± 16.6</td>
<td>88.6 ± 20.9</td>
<td></td>
</tr>
<tr>
<td>3.00</td>
<td>122.7 ± 22.3</td>
<td>84.9 ± 17.9</td>
<td></td>
</tr>
<tr>
<td>4.00</td>
<td>108.4 ± 18.2</td>
<td>74.8 ± 16.9</td>
<td></td>
</tr>
<tr>
<td>5.00</td>
<td>90.8 ± 19.1</td>
<td>68.3 ± 19.5</td>
<td></td>
</tr>
<tr>
<td>6.00</td>
<td>84.7 ± 13.0</td>
<td>55.1 ± 16.3</td>
<td></td>
</tr>
<tr>
<td>12.00</td>
<td>30.4 ± 7.9</td>
<td>32.2 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>24.00</td>
<td>15.7 ± 7.5</td>
<td>12.4 ± 4.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Individual results normalised to 70 kg body weight.

\(^c\) Sampling time deviation: ±0.05 h.
Table 3
Concentrations of ceftriaxone µg/g in surgical wound tissue (i) measured at the end of each operation, and in fluid from surgical wound (ii)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Periincisional (route B)</th>
<th>Intravenous (route A)</th>
<th>Source of Variation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Route</td>
<td>Period</td>
</tr>
<tr>
<td>(i) Wound tissue</td>
<td>a 1282.6 (404.3)</td>
<td>96.7 (38.8)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>b 657.0 (320.2) 540.0 (355–1130)</td>
<td>79.2 (51.6) 70.0 (25–150)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c 255.0 (209.8) 180.0 (95–620)</td>
<td>34.3 (16.9) 28.0 (18–65)</td>
<td></td>
</tr>
<tr>
<td>(ii) Fluid from the wound</td>
<td>a 859.6 (345.2) 850.0 (420–1342)</td>
<td>108.3 (34.3) 105.0 (70–160)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>b 431.8 (279.9) 309.0 (145–851)</td>
<td>95.8 (32.3) 92.5 (60–150)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c 117.4 (45.0) 114.0 (62–173)</td>
<td>51.0 (16.5) 46.0 (35–80)</td>
<td></td>
</tr>
</tbody>
</table>

Top row: means and standard deviations in brackets.
Bottom row: medians and ranges in brackets.
* Operation time-period range: from 40 to 70, from 70 to 120 and from 120 to 180 min a; b; c respectively.
** The fluid was collected and measured 24 h postoperatively.
*** P-values for main effects and interaction of two-way ANOVA.

The mean plasma concentrations and their standard deviations over the various time points are shown in Table 2. The kinetic behaviour of the concentrations following intravenous infusion of a 2 g dose start from a mean level of 256.7±37.5 µg/ml at 0.5 h and decline to 15.7±7.5 µg/ml at 24 h. Similarly, the periincisional administration of a 2 g dose starts from a mean concentration level of 82.5±11.6 µg/ml at 0.5 h increases to a maximum level of 99.5±14.2 at 1.5 h and declines thereafter to 12.4±4.5 µg/ml at 24 h. Both administration routes approach similar levels at about 12 h after injection.

The mean and median concentrations of ceftriaxone in “the fluid from the wound” and in the “tissue from the wound” obtained by both drug routes are shown in Table 3(i) and (ii), respectively. The analysis of variance indicates that for each case (tissue or fluid) there are significant differences between the two drug routes and between the three time periods (40–70 min, 70–120 min and 120–180 min). Periincisional mean levels of concentration are significantly higher than corresponding intravenous mean levels and both decline fast as time progresses. The significant interaction in the case of “fluid from the wound” indicates that the noted difference in the rates of decrease of concentration levels with time between the two drug routes is significant; the periincisional route is associated with a faster decline than the intravenous route. A similar difference is noted for the case of “tissue from the wound”, but it does not reach statistical significance (Table 3(i)).

Ceftriaxone plasma levels following intravenous administration are significantly higher than those recorded for periincisional administration at all times (Table 2). The corresponding concentrations in wound tissue during the first three hours after administration (Table 3(i)) show a reverse relationship, i.e., the periincisional concentrations are significantly higher than the intravenous ones. Similarly, the fluid from the wound concentrations (Table 3(ii)) shows higher levels for periincisional than intravenous administration.

Comparing the tissue concentrations (Table 3(i)) with the corresponding (first three hours after administration) plasma concentrations (Table 2), we note first that for periincisional administration the former (means 255.0; 657.0; 1228.6 µg/ml for a,b,c operation time-period) are much higher than the latter (means 84.9–99.5 µg/ml, Table 2). Indeed the tissue concentration levels are higher than the maximum plasma level (98.0 µg/ml) Table 1. The opposite is noted for the intravenous administration, i.e., the tissue concentrations are generally lower (means 34.3; 79.2; 96.7 µg/ml for a,b,c, operation time-period) than the corresponding plasma concentrations (122.7–256.7 µg/ml, Table 2). Similarly, the fluid from the wound concentrations following periincisional administration (Table 3(ii)) are higher than the plasma concentrations (Table 2) while again for intravenous administration the fluid concentrations are lower than the plasma concentrations.

There were no complications following periinci-
sional injection nor did any wound infections occur in group B. In contrast, in group A we had three cases of wound infections and one case of pneumonia.

4. Discussion

The production of wound infection depends upon many factors. A study of 1000 general surgical operations clearly showed that the most important factor in the pathogenesis of wound sepsis was the presence of bacteria at the time of wound closure (Davidson et al., 1971). The goal of surgical prophylaxis is to ensure that a satisfactory tissue concentration of a drug with a reasonable spectrum of activity against expected organisms is achieved and maintained during the period of potential bacterial contamination of the wound, so that organisms introduced into the wound during the operation will be destroyed immediately. It has been emphasised that wound levels, not blood or serum levels, appear to determine the efficacy of agents for prophylaxis of operative wound infection (Polk and Lopez-Mayor, 1969; Chalkiadakis et al., 1995). We would propose
that these very high tissue levels are only achieved by a preoperative perincisional infiltration. The aim of our study was to confirm whether or not the perincisional route of drug administration in patients undergoing abdominal surgery is beneficial in comparison to the intravenous route in relation to chemoprophylaxis.

The pharmacokinetic data of this study were in general agreement with earlier reports for ceftriaxone conducted in healthy volunteers (with the exception of the bioavailability value). The values of the coefficients $A$, $\alpha$, $t_{\alpha/2}$, $B$, $\beta$, $t_{\beta/2}$, $K_a$ and $C_p^\infty$ are quite similar and do not differ significantly from those published previously (Borner et al., 1985; Scully et al., 1984).

Perincisional administration of ceftriaxone, as would be expected, yields significantly higher drug concentrations in the tissue of the abdominal wall than those obtained after intravenous administration. Both methods provide adequate plasma and wound tissue levels at the time of wound closure (Table 3(i)). It has already been mentioned that wound tissue levels are much higher for preoperative perincisional infiltration in comparison to the preoperative intravenous injection route of drug administration. Such very high wound levels will prevent wound sepsis while simultaneously not provoking systemic complications. Perincisional administration of ceftriaxone resulted also in very high antibiotic concentrations in the wound fluid compared with intravenous administration (Table 3(ii)); the wound fluid concentration is regarded to be a critical factor in determining the efficacy of agents used for prophylaxis of surgical wound infections (Matushek and Rosin, 1991). With respect to the plasma concentrations of ceftriaxone (Table 2) it was noted that half-an-hour into the operation the concentration levels obtained from perincisional administration are significantly lower than those obtained with intravenous injection and they remain so until twelve hours after the start of the operation where both administrations reach similar levels.

The mean plasma ceftriaxone concentrations after intravenous administration are comparable with the results of previous studies (Bricaire et al., 1988; Scully et al., 1984; Borner et al., 1985; Patel et al., 1981; Stoeckel, 1981). Bricaire et al. (1988) have found similar mean plasma concentrations after 2 g intravenous administration of the drug in eight patients suffering from infectious diseases. In the same study, the results of the mean plasma concentrations of ceftriaxone after 2 g subcutaneous administration to four healthy volunteers and to eight infected patients appear to differ from our results. This discrepancy must be attributed to differences between the routes of administration of these two studies resulting in different pharmacokinetics of the drug.

The study of Borner et al. (1985) concerning a subcutaneous injection of a 0.5 g ceftriaxone dose in ten healthy volunteers showed that the maximum mean serum peak concentration was $37.1 \pm 5.6$ mg/l and was reached after $138 \pm 49$ min ($2.3 \pm 0.8$ h). Moreover 24 h later mean concentrations of $6.6 \pm 1.6$ mg/l were found. In the same study after intravenous injection 2 g of ceftriaxone the mean plasma concentrations declined from $258.0 \pm 38.4$ mg/l at 0 h to $11.6 \pm 4.2$ mg/l 24 h later. These results are comparable with ours.

Between 6 and 12 h, concentrations of free drug (protein binding is about 95%) in plasma for both preoperative perincisional infiltration and preoperative intravenous injection, are above the minimum inhibitory concentrations (Table 2) for *staphylococci* and *streptococci* and for organisms such as *Escherichia coli* and *Klebsiella*, *Proteus Haemophilus* species (excluding *Pseudomonas aeruginosa*, *Acinetobacter* species *Streptococcus faecalis* and *Bacteroids fragilis*) based on data reported by Neu, 1982. In addition, the ceftriaxone concentrations in plasma present at 24 h postoperatively for both preoperative intravenous injection and preoperative perincisional infiltration ($15.7 \pm 7.5$ in group A and $12.5 \pm 4.5$ in group B) also exceed the minimal bactericidal concentrations of most streptococcal and staphylococcal species, *Haemophilus influenza* and many of the *Enterobacteriaceae* including beta-lactamase producing strains whilst of course considering the existing protein binding (Scully et al., 1984 and Neu, 1982).

For the strains of *Citrobacter freundic*, *Enterobacter cloacae*, *Serratia marcescens* and *Klebsiella*, *Proteus* and *Providencia* species higher concentrations of ceftriaxone are required (Neu, 1982; Neu et al., 1981). With regard to this the concentrations of ceftriaxone measured in tissues ($255–1282.6$ $\mu g/ml$) using the preoperative perincisional infiltration route are adequate for chemoprophylaxis from these species, and this should be considered an advantage.
of perincisional administration in comparison to intravenous.

We had no complications due to the perincisional administration of 2 g of ceftriaxone (group B) and no wound infection or general septic complications. In contrast, in group A (intravenous administration) we noted two wound infections and one case of pneumonia. This significant difference can be explained due to the higher wound tissue concentrations of the drug in group B. The prophylactic administration of ceftriaxone by preoperative perincisional infiltration is a very safe and easy method. Furthermore, it is not time consuming, remaining, during the critical period, at high tissue levels (higher than those achieved by intravenous administration) while at the same time attaining effective plasma levels.

Acknowledgments

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