Preincisional Single-Dose Ceftriaxone for the Prophylaxis of Surgical Wound Infection

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BACKGROUND: Preincisional intraparietal injection of antibiotics is used for the prophylaxis of postoperative surgical infections. Whether topically injected antibiotics remain primarily in the surgical wound or are systemically absorbed is uncertain, however.

PATIENTS AND METHODS: The pharmacokinetics of preincisional injection of 2 g ceftriaxone were studied in 20 patients who have undergone abdominal surgery, with determination of serum, wound tissue, and wound fluid antibiotic concentrations.

RESULTS: Preincisional injection of ceftriaxone resulted in high antibiotic concentrations in the wound tissue and wound fluid. The highest plasma concentrations were achieved at 1.50 hours (99.47 ± 14.67 µg/mL). Plasma concentrations exceeded the minimal inhibitory concentrations of most aerobic gram-positive and gram-negative organisms with the exception of Pseudomonas aeruginosa, Acinetobacter species, and Streptococcus faecalis for 24 hours (10.42 ± 4.12). No local or general complications arose in any of the patients.


The concept of "preincisional-intracutaneous" injection of antibiotics was introduced by Taylor et al in 1982. This technique achieves high local concentrations of the antibiotic combined with adequate serum levels.

The aim of this study was threefold: to determine the actual levels of antibiotic in the serum, surgical wound edges, and fluid from the surgical wound during the operation and 24 hours postoperatively; to compare the found values with the already reported pharmacokinetic data of IV and intramuscular (IM) injections of ceftriaxone in healthy volunteers and to evaluate the effectiveness of the intraparietal administration.

Ceftriaxone was chosen because of its known effectiveness against a wide range of wound pathogens, including obligate anaerobes, at concentrations likely to be present locally. The simultaneous measurement of serum, wound tissue edges, and wound fluid antibiotic concentrations after preincisional administration of ceftriaxone in patients undergoing abdominal surgery has not been reported, to our knowledge.

PATIENTS AND METHODS

Twenty patients undergoing abdominal surgery were studied. The operations were: cholecystectomy (10); inguinal herniorrhaphy (1); vagotomy and pyloroplasty (2); small-bowel occlusion (1); gastrectomy for lymphoma (2); colectomy (1); and appendectomy (3).

The patients’ ages ranged from 28 to 74 years. Each patient received a local injection of ceftriaxone (2 g in 20 mL saline) immediately after anesthesia was established (ie, 10 minutes before the start of the operation). Injection was carried out using a 22-Fr spinal needle subcutaneously (and often, in thin patients, intramuscularly) along the line of the proposed abdominal incision, with a careful attempt being made to perform uniform infiltration along the incision. The wounds were an average of 20 cm long, thus approximately 1 mL of antibiotic solution was injected along each centimeter. Tissue samples were taken from three areas of the wound at the end of the operation. In all patients, fine perforated polyethylene tubes were placed in the subcutaneous plane of the wounds and connected to evacuated bottles (Redovac, Sterimed, Saarbruecken, Germany) for the collection of the wound fluid during a period of 24 hours after the operation.

Blood samples were taken at 30 minutes and at 1, 1.5, 2, 3, 4, 5, 6, 12, and 24 hours.

The blood was immediately centrifuged, and the serum separated and stored at −20°C until high-pressure liquid chromatography (HPLC) analysis was performed.

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TABLE I

Plasma Concentrations of Ceftriaxone During Operation and Postoperatively (During a 24-Hour Period) in 20 Patients Undergoing Abdominal Surgery

<table>
<thead>
<tr>
<th>Time (h) After 2-g Preincisional Injection of Ceftriaxone Solution</th>
<th>Plasma Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>82.50 ± 10.87</td>
</tr>
<tr>
<td>1.0</td>
<td>96.13 ± 22.54</td>
</tr>
<tr>
<td>1.5</td>
<td>99.47 ± 14.67</td>
</tr>
<tr>
<td>2.0</td>
<td>88.60 ± 21.72</td>
</tr>
<tr>
<td>3.0</td>
<td>84.93 ± 18.53</td>
</tr>
<tr>
<td>4.0</td>
<td>74.79 ± 18.11</td>
</tr>
<tr>
<td>5.0</td>
<td>68.27 ± 20.15</td>
</tr>
<tr>
<td>6.0</td>
<td>55.07 ± 17.56</td>
</tr>
<tr>
<td>12.0</td>
<td>32.15 ± 11.57</td>
</tr>
<tr>
<td>24.0</td>
<td>10.42 ± 4.12</td>
</tr>
</tbody>
</table>

Data reported as mean ± standard deviation.
*Sampling time deviation: ± 0.05 hour.

Laboratory Methods

Plasma samples and wound fluid were prepared (using a method described earlier) with protein precipitation with ethanol. Tissues were homogenized with water, the homogenate was centrifuged, the supernatant was filtered through a Minisart filter with 0.2-mm pore size (Sartorius GmbH, Goettingen, Germany), and the filtrate was injected to the HPLC system. For the quantification of the ceftriaxone in tissues, water ceftriaxone standards were used.

The reversed-phase HPLC analysis was performed by using an APEX ODS II SU column (Jones Chromatography Ltd., Hengoed, United Kingdom) with ultraviolet detection at 273 mm. The mobile phase was a system solution containing acetonitrile (39.4%), water (55.2%), hexadecyltrimethylammonium bromide (0.4%), and Titrisol buffer (E. Merck, Darmstadt, Germany) pH 7 (5%). The internal standard used was phthalic acid. In the above-mentioned conditions, the ceftriaxone and phthalic acid signal appeared in the chromatogram with a retention time of 5.11 and 7.12, respectively.

The statistical analysis (mean values and standard deviations of ceftriaxone concentration in fluids and tissues)

![Graph](image.png)

**Figure.** Plasma concentration (µg/mL) of ceftriaxone within 24 hours. Values were fitted on a curve obtained from a biexponential pharmacokinetic formula (Cp[t] = Be⁻ᵃᵗ + Cpeᵇᵉᵗ, G.E. Chalkiadakis, MD, unpublished data, 1995) based on an open one-compartment model.

and graphics were performed using a statistical software package (Statgraphics 4.0 for DOS, STSC Inc., Rockville, Maryland).

RESULTS

There were no complications following injection nor did any wound infections occur. The mean plasma concentrations are shown in Table I and the Figure. The concentrations of ceftriaxone in fluid from the wound and the tissue from the wound are shown in Table II. The results show that preincisional injection of ceftriaxone gives desirable serum levels with peak plasma concentration of 99.47 ± 14.67 µg/mL found after 1.5 ± 0.05 hours, and a mean plasma concentration of 10.42 ± 4.12 µg/mL after 24 hours.

Tissue concentrations measured at the end of the operation were higher than the corresponding plasma concentrations. These high tissue levels of ceftriaxone were maintained for the length of the operation and were constantly higher than the highest levels achieved in the serum. The wound fluid concentration was also higher than the highest plasma concentrations of ceftriaxone.

COMMENTS

Wound infection remains an important postoperative complication with significant clinical and economic consequences.10 Moylan,11 from the United States, estimated its occurrence in 7% to

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TABLE II

Concentrations of Ceftriaxone in Surgical Wound Tissue Measured at the End of Each Operation* and in Fluid From the Surgical Wound

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound tissue (µg/g)</td>
<td>1.282 ± 044</td>
</tr>
<tr>
<td></td>
<td>657 ± 320</td>
</tr>
<tr>
<td></td>
<td>255 ± 209</td>
</tr>
<tr>
<td>Range</td>
<td>830–1,850</td>
</tr>
<tr>
<td></td>
<td>355–1,130</td>
</tr>
<tr>
<td></td>
<td>95–620</td>
</tr>
<tr>
<td>Fluid from wound† (µg/mL)</td>
<td>859 ± 345</td>
</tr>
<tr>
<td></td>
<td>431 ± 279</td>
</tr>
<tr>
<td></td>
<td>117 ± 45</td>
</tr>
<tr>
<td>Range</td>
<td>420–1,342</td>
</tr>
<tr>
<td></td>
<td>145–851</td>
</tr>
<tr>
<td></td>
<td>62–173</td>
</tr>
</tbody>
</table>

Data reported as mean ± standard deviation.
*Operation time period range: A = from 40 to 70 minutes; B = from 70 to 120 minutes; C = from 120 to 180 minutes.
†The fluid was collected and measured 24 hours postoperatively.
8% of all operations. After surgery of the gastrointestinal tract, wound infections are nearly always caused by intestinal organisms being released and disseminated into the incision during the operation. From a study of 1,000 general surgical operations, Davidson et al.3 clearly showed that the most important factor in the pathogenesis of wound sepsis was the presence of bacteria at the time of wound closure.

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 would be destroyed immediately. Failure to maintain adequate serum and tissue levels throughout the surgical procedure increases the likelihood of the infection.12 Polk and Lopez-Mayor13 have emphasized that wound levels, not blood or serum levels, appear to determine the efficacy of agents for prophylaxis of operative wound infection. We would propose that these very high tissue levels are only achieved by a preoperative intracranial injection.

Phylactic antibiotics are generally administered systemically prior to operation.10 Under experimental conditions, antibiotics have been shown to be effective only if given within 4 hours of inoculating bacteria into a wound.5 The concentration of an appropriate antibiotic in the wound itself, rather than in the serum, is the critical factor in determining the efficacy of agents used for the prophylaxis of surgical wound infections.14

We have shown that high concentrations of antibiotic are present in the wound throughout the operation if a preincisional injection of an antibiotic is given and are likely to kill any sensitive bacteria that contaminate the wound (Table II).

The mean plasma concentrations of ceftriaxone (Table I) are comparable with results of previous studies when the antibiotic was given intravenously or intramuscularly.6,8 But the fact that with this technique we have achieved good plasma concentrations of ceftriaxone means the antibiotic returns to the wound by the systemic route as well, and we consider that we have a higher concentration of the drug in the surgical wound compared to both IV and IM administration.

At 6 to 12 hours, concentrations of free drug are above the minimum inhibitory concentrations (Table I) for staphylococci and streptococci (excluding Pseudomonas aeruginosa, Acinetobacter species, and Streptococcus faecalis) and for organisms such as Escherichia coli and Klebsiella, Proteus, and Haemophilus species.6 Indeed, the ceftriaxone concentrations in serum present at 24 hours (10.42 ± 4.12 μg/mL) exceed the minimal bactericidal concentrations of most streptococcal species, Haemophilus influenzae, and many of the Enterobacteriaceae, including β-lactamase–producing strains.6

For these reasons, we feel that preincisional injection of ceftriaxone can protect against septic complications occurring in other sites. Preincisional injection of ceftriaxone should therefore be beneficial in two ways; very high wound levels will prevent wound sepsis, and good serum levels will minimize systemic complications for 24 hours.

This is an interesting study of the pharmacokinetics of drug delivery of ceftriaxone injected subcutaneously prior to an abdominal incision. The idea never caught on very widely but is sound, especially if one is reminded that wound levels of drug determine the efficacy of prophylaxis.

REFERENCES