Prospective study of preincisional single-dose ceftriaxone in reducing postoperative wound infection in high risk of infection patients

I. PETRAKIS, N. VRACHASSOTAKIS, A. TSATSAKIS, G. CHALKIADAKIS

Departments of General Surgery and Toxicology, University Hospital of Herakleion, University of Crete - (Greece)

Abstract. – Background-Aims: The risk of wound contamination in high risk of infection patients after abdominal operations is well recognised. 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 systematically absorbed is uncertain, however.

Patients and Methods: The pharmacokinetic of preincisional injection of 2 g Ceftriaxone were studied in 50 high risk of infection patients (diabetic, oncologic, immunocompromised and obese) 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 fluid. The highest plasma concentrations were achieved at 1½ hours (118.40 SD 38.43 µg/ml). Plasma concentrations exceeded the minimal inhibitory concentrations of most aerobic gram positive and gram negative organisms with the exception of Pseudomonas aeruginosa, Acinobacter species, and Streptococcus faecalis for 24 hours (10.10 SD 4.00 µg/ml). No longer or general complications were arose in any of the patients.

Conclusion: Our results suggest that preincisional administration of ceftriaxone for prophylaxis of the wound sepsis in high risk of infection patients is very effective.

Key-Words:
- Ceftriaxone, Preincisional Intraparietal, Infection, Surgery.

Introduction

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. Recent studies on the prevention of postoperative wound infections advocate the use of prophylactic antibiotics, especially in cases of oncologic, immunocompromised, obese and diabetic patients where the risk of contamination is high, while other studies reveal a high index of surgical wound infection after surgery in such patients. An appropriate antibiotic administrated intravenously in a single dose prior to surgery (preoperative prophylaxis) ensures high blood levels of the antibiotic at the time of wound closure and reduces wound infection, as well as other septic complications.

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

However, the purpose of this study was threefold: to determine the actual levels of antibiotic in the high risk of infection patients (diabetic, oncologic, immunocompromised and obese) 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 intravenous (IV) and intramuscular (IM) injections of ceftriaxone in healthy volunteers, and to evaluate the effectiveness of the intraparietal administration, in a prospective controlled study.

Ceftriaxone an antibiotic with long half life, was chosen because of its known effectiveness against a wide rage of wound pathogens, including obligate anaerobes, at concentrations likely to be present locally. The simultaneous administration of ceftriaxone in high risk of infection patients was examined.
measurement of serum, wound tissue edges, and wound fluid antibiotic concentration of ceftriaxone in the high risk of infection patients undergoing abdominal surgery has not been reported, to our knowledge.

Patients and Methods

Fifty patients with high risk of wound infection (diabetic oncologic, immunocompromised and obese) undergoing abdominal surgery were studied. The operations were cholecystectomy (7 patients), vagotomy and pyloroplasty (4 patients), vertical gastroplasty (3 patients), small bowel occlusion (4 patients), oesophageal cancer (9 patients), colorectal cancer (2 patients), appendectomy (3 patients), gastric cancer (4 patients), gastrectomy (2 patient), pancreatic (4 patients), hepatic and biliary tract neoplasias (5 patients) ovarian neoplasias (2 patient) and hysterectomy (1 patient).

The patients' ages ranged from 34 to 77 years. Each patient received a local injection of ceftriaxone (2 g in 20 ml normal saline) 10 minutes before the start of the operation. Injection was carried out using a 22-Fr spinal cord 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 centimetre. 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 evaluated bottles (Redovac, Sterimed, Saarbrucken, 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 1/2, 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.

Laboratory Methods

Plasma samples and wound fluid were prepared (using the method described earlier) with protein precipitation with ethanol. Tissues were homogenised with water, the homogenate was centrifuged, the supernatant was filtered through a Minisart filter with 0.2 mm pore size (Sartorious GmH, Göttingen, 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 nm. The mobile phase was a system solution containing acetonitrile (39.4%), water (55.2%), hexadeceyltrimethylammonium 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.

Statistical Analysis

The data are reported as mean values and standard deviations (SD), of ceftriaxone concentration in fluids and tissues and were performed using a statistical software package (Statgraphics, STSC Inc, Rockville, Maryland).

Results

There were no complications following injection nor did any wound infection 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 demonstrate that preincisional injection of ceftriaxone gives desirable serum levels with peak plasma concentration of 98.30 SD 14.10 µg/ml found after 1 1/2 SD 1/2 hours and a mean plasma concentration of 10.10 SD 4.00 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 plasma concentration ceftriaxone.
Discussion

Wound infection remains an important postoperative complication with significant clinical and economic consequence\(^\text{15}\), mostly in high-risk patients, as are the diabetics the obese, the oncologic (and the immunocompromised)\(^\text{4-9,16,17}\). Moylan\(^\text{18}\) estimated its occurrences in the United States in 7% to 8% of all operations, while Lumley et al after intravenously administration of the same antibiotic reports an incidence of 7.9% of wound contamination after colorectal surgery\(^\text{19}\). 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\(^\text{10}\). From the study of 1,000 general surgical operations, Davidson et al\(^\text{3}\), clearly showed that the most important factor in the pathogenesis of wound sepsis was the presence of bacteria at the time of wound closure. Delgado-Rodriguez et al\(^\text{20}\) found that obese or immunocompromised patients undergoing abdominal surgery showed a statistically significant association with postoperative pneumonia risk after wound infection.

The goal of surgical prophylaxis is to ensure that a satisfactory tissue concentration of a drug with a reasonable spectrum activity against expected organisms is achieved and maintained during the period of potential

<table>
<thead>
<tr>
<th>Time(^*) (hrs) after 2 g preincisional injection of ceftriaxone solution</th>
<th>Plasma concentration ((\mu g/ml))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>0.5</td>
<td>98.90 ± 17.53</td>
</tr>
<tr>
<td>1</td>
<td>110.40 ± 34.21</td>
</tr>
<tr>
<td>1.5</td>
<td>118.40 ± 38.43</td>
</tr>
<tr>
<td>2</td>
<td>104.30 ± 30.70</td>
</tr>
<tr>
<td>3</td>
<td>89.93 ± 28.42</td>
</tr>
<tr>
<td>4</td>
<td>80.30 ± 22.88</td>
</tr>
<tr>
<td>5</td>
<td>73.27 ± 28.78</td>
</tr>
<tr>
<td>6</td>
<td>62.07 ± 21.25</td>
</tr>
<tr>
<td>12</td>
<td>36.15 ± 14.70</td>
</tr>
<tr>
<td>24</td>
<td>18.42 ± 6.10</td>
</tr>
</tbody>
</table>

Data report as mean ± standard deviation. *Sampling time deviation: ± ½ hour.
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 infection. Polk and Lopez-Mayor have emphasized that wounds levels, not blood or serum levels, appear to determine the efficacy of agents for prophylaxis of operative wound infection. These very high tissue levels could only achieved by a preoperative intraincisional injection.

Prophylactic antibiotics are generally administered systemically prior to operation. Under experimental conditions, antibiotics have been shown to be effective only if given within 4 hours of inoculating bacteria into a wound. 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 infection.

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. The mean plasma concentrations of ceftriaxone (Table I) are comparable with results of previous studies when the antibiotic was given intravenously or intra-muscularly. 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, intravenously and intramuscular 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, A. cynobacter species, and Streptococcus faecalis) and for organisms such as E. coli and K. lebsiella, Proteus, and H. aeremophilus species. Indeed, the ceftriaxone concentrations in serum present at 24 hours (10.10 SD 4.00 µg/ml) exceed the minimal bactericidal concentrations of most streptococcal species, H. aeremophilus influenzae, and many of the Enterobacteriaceae, including β-lactamase-producing strains.

In conclusion, the results of the present study suggest that preincisional injection of ceftriaxone in all the high infection risk patients, as are the diabetics, could protect them against septic complications occurring in other sites. Preincisional injection of ceftriaxone should be beneficial in two ways; very high wound levels will prevent wound sepsis, and good serum levels will minimise systemic complications for 24 hours.

### References


### Table II. Concentration of Ceftriaxone in surgical wound tissue measured at the end of each operation* and in the fluid from the surgical wound.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Wound Tissue (µg/ml), (range)</td>
<td>1.581 ± 0.488, (890-2.020)</td>
</tr>
<tr>
<td>Fluid from the Woundº</td>
<td>1.119 ± 0.405, (470-1.540)</td>
</tr>
</tbody>
</table>

Data report as mean ± standard deviation.

*Operation time period range: A = from 40 to 70 min; B = from 70 to 120 min; C = from 120 to 180 min.

ºThe fluid was collected and measured 24 hours postoperatively.


