Concentrations of Ceftriaxone (1,000 Milligrams Intravenously) in Abdominal Tissues during Open Prostatectomy

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Ceftriaxone concentrations in abdominal tissues were evaluated at different stages of open prostatectomy. Ceftriaxone was administered as antibiotic prophylaxis, and 15 consecutive patients were given a single dose of ceftriaxone (1,000 mg intravenously in 1 min) 30 min before surgery. Ceftriaxone concentrations in tissue were determined at three stages of the surgical procedure: upon the opening of the abdominal cavity, during the prostatectomy, and upon the closure of the abdominal cavity. Samples of the following tissues or sample were assayed: epiploic and abdominal-wall fat; Retzius’ space, bladder, and prostate tissue; and urine. During the different stages of the surgical procedure, for all patients, and in the different tested tissues, ceftriaxone concentrations greater than or equal to the cutoff point (4 μg/g of tissue) were measured. The highest concentrations were obtained in the bladder (43 ± 18 μg/g) and in the prostate (35 ± 18 μg/g). In fatty tissues, concentrations were between 13 ± 5 and 22 ± 8 μg/g. All patients (15 of 15) had ceftriaxone levels in tissue greater than the MICs for the potential pathogens (Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis). In conclusion, during open prostatectomy and after the use of a single dose of ceftriaxone (1,000 mg), high antibiotic levels were obtained throughout the surgical procedure in the tissues potentially involved in postoperative infection.

The open resection of the prostate is a commonplace operation in older men, and urinary tract infections and other infectious complications are major causes of morbidity. Antibacterial prophylaxis has been available to urologic surgeons for more than 50 years (10). Broad-spectrum cephalosporins and penicillins are most frequently used, and the use of fluoroquinolones has also been evaluated (2). The agent used should cover the broad spectrum of organisms known to cause infection in this particular situation, i.e., following open prostatectomy: Staphylococcus aureus and members of the family Enterobacteriaceae (mainly Escherichia coli). The agent used should be able to reach adequate levels in serum, urine, and tissues potentially involved in postsurgical infections. Prophylactic antibiotics are recommended for patients undergoing open prostatectomy as well as urinary tract stone surgery (13, 14). Ceftriaxone has been used for more than 10 years for prophylaxis of postoperative infections after transurethral resection of the prostate (9, 18). Ceftriaxone is a broad-spectrum cephalosporin with a long half-life and has in vitro activity against staphylococci and gram-negative aerobic bacilli except for Pseudomonas spp. (4, 12). Like that of other beta-lactam antibiotics, ceftriaxone bacterial killing is characterized by a time-dependent activity, and exposure of the bacteria to antibiotic concentrations greater than the MIC for long periods of time seems desirable (4, 12). For prophylaxis of postoperative infections, such adequate antibiotic concentrations should probably be achieved in all potential sites of infection (3, 14, 16). The present study was designed to determine, for patients undergoing open prostatectomy, whether a single (1,000-mg, intravenous)-dose regimen of ceftriaxone could result in the achievement and maintenance of adequate concentrations in abdominal tissues potentially involved in postoperative infection. Obtaining levels in tissues greater than or equal to the MIC at which 90% of methicillin-susceptible staphylococci (4 μg/g of tissue), E. coli (0.5 μg/g), and Klebsiella pneumoniae and Proteus mirabilis (0.06 μg/g) are inhibited was considered a desirable goal (4, 12).

Subjects and study design. The 15 male patients were 67 ± 6 years in age and weighed 74 ± 7 kg (mean ± standard deviation). The study received the approval of the Ethics Committee of our institution (Hôpital Nord), and all patients gave their informed consent. The study was prospective and designed to compare the different rates of penetration of ceftriaxone after a single intravenous dose (1,000 mg) in patients undergoing open prostatectomy. Fifteen consecutive patients were included in the study. Criteria for inclusion as a subject were as follows: no prior history of hepatic or renal disease, no clinical or laboratory signs of infection, no known history of allergy to beta-lactam antibiotics, and the patient’s decision to undergo elective surgery.

Antibiotic administration. Patients were given a single dose of 1,000 mg of ceftriaxone (Roche), administered intravenously by bolus (1-min) injection starting 30 min before the surgical incision.

Blood and tissue sampling. Blood samples (5 ml each) were collected from an arterial catheter and were centrifuged (800 × g for 20 min). Tissue samples were immediately rinsed in normal saline and were pressed in sterile gauze to eliminate contaminating blood. Serum and tissue samples were stored at −80°C until the assay was performed. Simultaneous blood and tissue samples were obtained as follows: from the abdominal opening (epiploic and abdominal-wall fat), during surgery (Retzius’ space, bladder, and prostate tissues and urine), and at the time of abdominal closure (epiploic and abdominal-wall fat).

Ceftriaxone assay. Ceftriaxone concentrations in serum and tissues were assayed by high-performance liquid chromatog-
raphy (15, 20), with a normal-phase technique and an NH bonded-phase column (length, 100 mm; 5-μm internal diameter; Spherisorb C18; Waters). The mobile phase was a combination of acetonitrile (50 ml; Merck Laboratories), hexadecyltrimethylammonium bromide (0.4 g; Fluka Laboratories), buffer (pH 7.0, 5 ml; Titrisol; Merck), and high-performance liquid chromatography-grade water (45 ml). The internal standard was probenecid (Théraplix Laboratories). The bonded-phase column was connected to a UV spectrophotometer (254 nm). For the determination of tissue ceftriaxone concentrations, tissue pretreatment was necessary. An aliquot of tissue (100 mg) was crushed for 30 s at room temperature in 1 ml of isotonic saline solution with an Ultra-Turrax T25 homogenizer (Bioblock) and centrifuged, and the ceftriaxone assay was performed on the supernatant. To 0.1 ml of the sample, 0.3 ml of water was added, and the mixture was vortexed. Two microliters of internal standard (200 μg/ml) was added in methanol, and the mixture was vigorously vortexed for 5 min. The mixture was centrifuged, and 25 μl of the supernatant was injected into the high-performance liquid chromatography column. The lower limits of detection were 0.5 μg/ml for plasma samples and 0.5 μg/g for tissue samples. Ceftriaxone recovery was calculated for fatty tissues. Extraction was performed on serum and on water at four concentrations (25, 50, 100, and 200 μg/ml). The recoveries were 98% at 25 μg/ml, 94% at 50 μg/ml, 98% at 100 μg/ml, and 91% at 200 μg/ml. Human serum was the biological matrix used for preparing high-performance liquid chromatography standards for ceftriaxone for the assay of tissue homogenates. Within-day reproducibilities were assayed at concentrations of 1 and 400 μg/liter, with coefficients of variation of 4.2 and 4.0%, respectively. Between-day repeatabilities (3 days) were assayed at the same concentrations, and coefficients of variation were 3.0 and 6.0% for 1 and 400 μg/liter, respectively.

The evaluation of ceftriaxone penetration in tissue was performed as follows. For each patient, ratios of concentrations in tissue to concentrations in serum were calculated by using ceftriaxone concentrations in tissue obtained at different periods during the surgical procedure. Serum ceftriaxone concentrations were obtained concomitantly.

Results were as follows. Figure 1 shows ceftriaxone concentrations in the different tissues studied at the various stages of the surgical procedures. Concentrations of ceftriaxone in the fatty tissues were between 12 ± 4 and 22 ± 8 μg/g. Higher concentrations were found in the bladder (43 ± 18 to 37 ± 18 μg/g), in the Retzius’ space (19 ± 14 to 34 ± 14 μg/g), and in the prostate 35 ± 18 μg/g (Fig. 1). The level of ceftriaxone penetration into abdominal and epiploic fat at the closure period increased twofold relative to that at the opening period (Table 1). The level of penetration into the Retzius’ space tissues was similar to that into fatty tissues, and the level of penetration into the bladder and the prostate was two to three times higher (Table 1). Tissue concentrations were compared with the MICs at which 90% of the potential pathogens are inhibited in order to predict the potential clinical efficacy of ceftriaxone concentrations achieved with the single 1,000-mg administration. In all tissues studied and at the different steps of surgical procedures, all patients had tissue ceftriaxone levels greater than the MIC at which 90% of the potential pathogens are inhibited. Patients were carefully followed up until hospital discharge, and none of them presented any clinical or laboratory signs of postoperative infection.

Previous studies (5, 6, 11, 14, 15, 19, 21) have established the basic principles of antibiotic prophylaxis in surgical procedures, and the main points of these studies are (i) that the

**FIG. 1.** Ceftriaxone concentrations in serum and tissues at various stages of surgical procedure. Patients were given a single 1,000-mg intravenous injection at the time of administration of anesthesia. Abdominal opening, prostatectomy, and abdominal closure were performed 30 ± 3, 64 ± 10, and 173 ± 12 min after the end of ceftriaxone injection, respectively.

<table>
<thead>
<tr>
<th>Tissue or sample examined</th>
<th>Ceftriaxone concn ratio measured during:</th>
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<tbody>
<tr>
<td></td>
<td>Abdominal opening</td>
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<tr>
<td>Abdominal-wall fat</td>
<td>0.11 ± 0.06</td>
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<tr>
<td>Epiploic fat</td>
<td>0.12 ± 0.07</td>
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<tr>
<td>Retzius’ space</td>
<td>0.20 ± 0.18</td>
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<tr>
<td>Bladder</td>
<td>0.37 ± 0.25</td>
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<tr>
<td>Urine</td>
<td>3 ± 2.8</td>
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<tr>
<td>Prostate</td>
<td>0.38 ± 0.18</td>
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* Patients were given a single 1,000-mg intravenous injection at the time of administration of anesthesia. Abdominal opening, prostatectomy, and abdominal closure were performed at 30 ± 3, 64 ± 10, and 173 ± 12 min after the end of ceftriaxone injection, respectively. Values are means ± standard deviations.
antibiotic must be present in the involved tissues before surgery allows bacterial contamination and (ii) that the drug must attain and maintain concentrations in plasma and tissues high enough to inhibit the growth of contaminating pathogens (5, 6, 15, 21). The present study confirms the effective penetration of ceftriaxone into human abdominal tissues during open prostatectomy. Concentrations in abdominal-wall and epiploic fat and Retzius’ space, bladder, and prostate tissues were high and greater than or equal to the MIC at which 90% of the usually susceptible pathogens are inhibited. Effective penetration of ceftriaxone into the prostate has already been demonstrated after a single injection of 2,000 mg (1). With the 46 patients studied, Adam and Naber concluded that ceftriaxone not only had a long serum half-life compared with those of other comparable cephalosporins but also had prolonged concentrations in tissue, which justified a single preoperative dose of 2,000 mg (1). The present study shows that a single preoperative dose of 1,000 mg is followed by high ceftriaxone concentrations achieved in the tissues potentially involved in postoperative infection. Interestingly, high levels of ceftriaxone in the abdominal-wall fat (a poorly vascularized tissue) were achieved at times of abdominal opening and closure as well. Similar findings were observed when ceftriaxone was used for antibiotic prophylaxis in thoracic surgery (15). This is of great clinical interest, since abdominal-wall infections are among the most severe complications after open prostatectomy.

Achieving and maintaining sufficient antibiotic concentrations in tissues to avoid the risk of postoperative infection are important goals when antibiotics with a time-dependent efficacy, such as ceftriaxone, are being used. Optimal concentrations should be maintained throughout the surgical procedure (3, 5, 6, 14, 15, 17, 19). With ceftriaxone, efficacy is directly related to the time during which its concentration in target tissues exceeds the MIC for the offending organisms. Little gain in the rate or extent of killing is obtained by increasing concentrations above that level.

In the present study, ceftriaxone concentrations in tissue homogenate (drug plus binding proteins) were compared with MICs measured in broth (no binding proteins). For a more accurate estimation of the potential bactericidal activity of ceftriaxone, MICs in tissue homogenates should have been determined. However, at least with a conventional evaluation, as done in the present study, a high level of bacteriological safety can be expected with ceftriaxone used in open prostatectomy.

One point more to be considered is the duration of the prophylaxis: should multidose or single-dose prophylaxis be employed? The results from the present study indicate that adequate tissue penetration was achieved after the use of a single 1,000-mg dose of ceftriaxone. With the use of multidose prophylaxis, the emergence of antimicrobial agent-resistant bacteria related to the use of prophylactic ceftriaxone could be reason for concern. Data suggest that prolonged (>48 h) postoperative prophylaxis is responsible for modification of susceptibility to antimicrobial agents (7, 8), but no deleterious effect caused by an appropriate short-course prophylactic regimen has been reported. Such data should preclude the use of multiple-dose antibiotic regimens, and a consistent effort should be made to use short-course or single-dose prophylaxis whenever possible. In urologic surgery, a single dose of antibiotic for prophylaxis has been shown to offer at least the same advantages as multiple-dose therapy in terms of clinical efficacy. In addition, the single-dose therapy selected for both the resistant strains and the numerous microbial associations in lesser proportions (8).

In conclusion, the use of ceftriaxone (1,000 mg intravenously) 30 min before open prostatectomy allowed the achievement and maintenance, throughout the operative procedures, of elevated antibiotic concentrations in tissues in all patients in the present study. Further studies are needed to draw definite conclusions on the potential clinical applications of these findings, but data from the present study are in favor of a single-dose regimen of ceftriaxone (1,000 mg) for patients undergoing open prostatectomy.

REFERENCES