Pharmacokinetics and Tissue Penetration of a Single Dose of Ceftriaxone (1,000 Milligrams Intravenously) for Antibiotic Prophylaxis in Thoracic Surgery

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The pharmacokinetics and tissue penetration of ceftriaxone after a single intravenous injection of 1,000 mg to 17 patients for antibiotic prophylaxis in thoracic surgery were studied. The patients were scheduled for elective noncardiac thoracic surgery. Adequate levels in serum (higher than or equal to the MIC for 90% of isolates of Staphylococcus aureus, Streptococcus spp., Escherichia coli, Haemophilus influenzae, and Klebsiella pneumoniae) were found for all patients throughout the surgical procedures. Mean maximal (5-min) and final (24-h) ceftriaxone levels in serum were 157 ± 42 and 8.6 ± 4.5 mg/liter, respectively. The beta-phase elimination half-life was 8.6 ± 3 h, the plasma clearance was 18.4 ± 6.25 ml/min, and the apparent volume of distribution at steady state was 0.21 ± 0.07 liters/kg. At the time of the thoracotomy, the ceftriaxone concentrations were 13.5 ± 7.8 μg/g in thoracic wall fat and 27 ± 9 μg/g in lung tissue. At the time of closure, the ceftriaxone concentration was 15 ± 9 μg/g in thoracic wall fat. During the different steps of the surgical procedures, 100% of patients had adequate levels in tissue (higher than or equal to the MIC for 90% of isolates of Streptococcus spp., E. coli, H. influenzae, and K. pneumoniae). For S. aureus, 90 to 100% of patients had adequate tissue ceftriaxone levels.

Noncardiac thoracic surgery is “contaminated-aseptic surgery” in most cases (4, 6, 7, 11). Antibiotic prophylaxis is used against pathogens most likely to contaminate the surgical wound: Escherichia coli, various members of the family Enterobacteriaceae, Streptococcus spp., Haemophilus influenzae, Staphylococcus aureus, and Pseudomonas spp. (4, 6, 7, 11). Bacterial contamination may occur on parietal tissues, in the pleural cavity, or in lung tissues. It seems clear that for surgical prophylaxis, adequate antibiotic concentrations in tissues should be achieved in all the potential sites of infection (1). In tissues with a tendency for postoperative infection, antibiotic activity should be maintained throughout the procedures, from incision to closure. For practical reasons, an ideal antibiotic prophylactic regimen should be as easy to administer as possible; single-dose administration is recommended in many types of surgery (5).

This study was designed to determine whether a single dose of ceftriaxone can result in adequate concentrations being achieved and maintained in thoracic wall fat and lung tissue.

MATERIALS AND METHODS

This study received the approval of the ethical committee of our institution, and all patients gave informed consent. Seventeen patients were scheduled for elective noncardiac thoracic surgery. Patients presented with bronchial cancer, and the following surgical procedures were performed: left or right pneumonectomies (8 patients), left or right inferior lobectomies (5 patients), and left or right superior lobectomies (4 patients). All patients had normal hepatic function (serum bilirubin, <15 μmol/liter; serum albuminemia, >550 μmol/liter) and renal function (creatinine clearance, ≥90 ml/min/1.74 m²). There were 12 men and 5 women, with a mean age of 56 ± 12 years (23 to 82) and a mean weight of 62 ± 12 kg (50 to 83). None had a history of allergic reaction to beta-lactam antibiotics. None presented any clinical sign (normal body temperature, no purulent expectoration) or laboratory sign (normal leukocyte count) of infection or had received antibiotic treatment during the previous 20 days. All patients underwent preoperative preparations, including tobacco prohibition, respiratory physiotherapy, and aerosol treatment with a combination of betamethasone (8 mg), bromexine (4 mg), and hydrophilic gomendis (5 ml) three times a day for at least 3 days.

At the time of induction of anesthesia, patients were given a single dose of 1,000 mg of ceftriaxone (Rocephine; Roche Laboratories) administered intravenously over 1 min. No other antibiotic was given to patients. Blood samples were collected from a central venous catheter before ceftriaxone injection and 5 (maximum concentration), 15, 30, 60, and 120 min and 4, 8, 24, and 48 (last determined concentration) h after the injection. Different tissue samples were collected during the surgical procedures: thoracic wall fat at the time of surgical incision and thoracic closure and healthy lung tissue at the time of extraction of the lobe or the lung. Simultaneously, additional blood samples were obtained. Blood samples were centrifuged, and serum was separated and stored at −35°C until assay. Tissue samples were rinsed in sterile 10 mM morpholino propane sulfonate buffer (pH 7.0) to eliminate excess blood within minutes of removal. Tissue samples were also stored at −35°C.

Ceftriaxone concentrations were determined by high-performance liquid chromatography (HPLC) (19), with a normal-phase technique and an NH-bonded-phase column (Spherisorb C18 Waters; 100 mm; 5-μm internal diameter). The mobile phase was a combination of acetonitrile (50 ml)
(Merck Laboratories), hexadecyl-trimethylammonium bromide (0.4g) (Fluka Laboratories), buffer (pH 7.0) (titrisol) (5 ml) (Merck), and HPLC-grade water (45 ml). The internal standard was Probencid (Theraplix Laboratories). The bonded-phase column was connected to a UV spectrophotometer detector (254 nm).

For the determination of tissue ceftriaxone concentrations, tissue pretreatment was necessary. An aliquot of tissue (100 mg) was crushed in 1 ml of isotonic saline solution 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) in methanol was added, and the mixture was vigorously vortexed for 5 min. The mixture was centrifuged, and 25 μl of the supernatant was injected into the HPLC column. The formula of Roncoroni et al. was used to subtract, for the tissues, any blood contamination (17). The formulas used were the following: $C_1 = (Hb_{\text{supernatant}}/Hb_{\text{blood}}) \times F \times C_3 \times [100 - \text{hematocrit (hematocrit expressed in percentage)}/100]$ and $C_4 = C_3 - C_1$, where $C_1$ is blood concentration in the tissue, $C_2$ is blood ceftriaxone concentration, $C_3$ is experimental tissue ceftriaxone concentration, $C_4$ is true tissue ceftriaxone concentration, $F$ is the dilution factor for the tissue in normal saline, and Hb is hemoglobin.

The lower limits of detection were 0.5 μg/ml for plasma samples and 0.5 μg/g for tissue samples, and the percent recovery with ceftriaxone was 98% ± 5%. Within-day and between-day reproducibilities were assayed over a concentration range of 1 to 400 μg/liter, with coefficients of variation of 3 and 6%, respectively.

Tissue or serum ceftriaxone levels greater than or equal to the MIC for 90% of isolates (MIC90) of $S.\, aureus$ (4 mg/liter of serum or 4 μg/g of tissue), $E.\, coli$ and $Klebsiella\, pneumoniae$ (0.1 mg/liter or 0.1 μg/g), $Streptococcus$ spp. (0.05 mg/liter or 0.05 μg/g), and $H.\, influenzae$ (0.003 mg/liter or 0.003 μg/g) were considered satisfactory (2, 9).

To perform the pharmacokinetic analysis, we plotted ceftriaxone concentrations in serum against time and determined individual pharmacokinetic parameters by a compartmental analysis. A two-compartment open model was used for 15 patients. For the other two patients, a three-compartment model was chosen. The beta-phase elimination half-life, plasma clearance, volume of distribution at steady state, and area under the serum concentration-time curve extrapolated to infinity were assessed by conventional methods (20). An initial estimation of the parameters was performed with the nonlinear least-squares method. Results of the goodness-of-fit test were confirmed with the correlation coefficient test, the Kolmogorov-Smirnov test, the chi-square test, and the run test. The number of exponents in the pharmacokinetic model was determined automatically with a computer on the basis of the time and the concentrations entered into the computer program (program written for an IBM 9781 computer).

During their hospital stay, patients were carefully monitored for clinical or biological signs of infection. When needed, specimens were obtained (thoracic wound samples, bronchial secretions, drainage tube secretions), kept at room temperature, and rapidly transported to the laboratory. They were Gram stained and cultured in conventional liquid media.
RESULTS

Figure 1 shows serum ceftriaxone levels during the 48 h of the study. Up to 24 h, all patients had ceftriaxone levels higher than or equal to the MIC$_{90}$ for *S. aureus*. The maximum level (at 5 min) was 157 ± 42 mg/liter (mean ± standard deviation) (range, 109 to 262 mg/liter), the last determined level (at 24 h) was 8.6 ± 4.5 mg/liter (range, 2.4 to 15.3 mg/liter), the beta-phase elimination half-life was 8.6 ± 3.0 h (range, 4.6 to 14.4 h), the plasma clearance was 18.4 ± 6.3 ml/min (range, 11.5 to 35.8 ml/min), and the volume of distribution at steady state was 0.21 ± 0.05 liters/kg (range, 0.13 to 0.31 liters/kg). As shown in Fig. 2, at the time of incision (15 ± 10 min after injection), the ceftriaxone level in thoracic wall fat was 13.5 ± 7.8 µg/g. At time of extraction of the lobe or the lung (72 ± 21 min after injection), the ceftriaxone level was 27 ± 9 µg/g in lung tissue. At the time of closure (120 ± 30 min after injection), the ceftriaxone level was 15 ± 9 µg/g in thoracic wall fat. All patients had tissue ceftriaxone concentrations higher than or equal to the MIC$_{90}$ for *S. aureus*, *Streptococcus* spp., *E. coli*, and *K. pneumoniae*, and *H. influenzae* in lung tissue and thoracic wall fat, except that 94 and 90% of patients had such concentrations for *S. aureus* in thoracic wall fat at opening and closure, respectively. No patient developed thoracic wall sepsis or bronchopneumonia during the postoperative period. No remote infectious complication was observed.

DISCUSSION

Previous studies have established the basic principles of antibiotic prophylaxis in surgical procedures, and the main points are that (i) the antibiotic must be present in the involved tissues before surgery allows bacterial contamination and (ii) the drug must attain and maintain concentrations in serum and tissue high enough to inhibit the growth of contaminating pathogens (8, 18).

In the present study, ceftriaxone concentrations in serum and thoracic tissues were compared with the MIC$_{90}$s for *E. coli*, *K. pneumoniae*, *Streptococcus* spp., *H. influenzae*, and *S. aureus*, all being pathogens frequently incriminated in infections occurring after thoracic surgery. A single dose of 1,000 mg of ceftriaxone was given to patients, and after 24 h, 86.7% of patients had levels in serum of ≥4 mg/liter. This result clearly indicates that adequate concentrations in serum were achieved throughout the surgical procedures. High concentrations were achieved in thoracic wall fat, and all patients had ceftriaxone levels higher than or equal to the MIC$_{90}$ for *S. aureus* in lung tissue. In the present study, no infection was observed. This result could be related to an adequate antibiotic concentrations in tissues, exceeding the MICs for the bacteria involved. However, prevention of postoperative bronchopneumonia after noncardiac thoracic surgery seems to depend on several factors, among them high-quality analgesia, which allows effective physiotherapy. Therefore, what constitutes an optimal antibiotic con-
centration in tissue is poorly understood (1). It is often defined as a concentration above the MIC for the bacteria, but many examples of effective prophylaxis with antibiotic concentrations below the MIC and failures of prophylaxis with concentrations above the MIC exist for tissue (10, 13, 15). Concentrations of antibiotic below the MIC do produce morphological damage to bacteria, thus decreasing the growth rate and favorably influencing the outcome of an infection (12, 21, 22). It is clear that many factors influence the control of postoperative infections: the discipline of the surgical team, meticulous surgical techniques, proper preparation for surgery, and status of the immune system of the patient, etc.

No major modification in ceftriaxone pharmacokinetics in the study patients was seen. Results were similar to those reported for healthy volunteers, and in view of the present study, the single dose used (1,000 mg intravenously) can be recommended (14, 16). This type of administration is easy and convenient.

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 a modification of susceptibility to antimicrobial agents (3), but no deleterious effect of an appropriate short-course prophylactic regimen has been reported. Such data should preclude the use of multiple-dose antibiotic regimens, and continuous effort should be made to use short-course or single-dose prophylaxis whenever possible.

In conclusion, when a single dose of 1,000 mg of ceftriaxone is given before noncardiac thoracic surgery, adequate levels in serum and tissue can be achieved throughout the surgical procedures. The reasons for this result could be a long plasma elimination half-life and an excellent penetration into lipidal tissue.

REFERENCES


