Levels of Cefmenoxime in Sera and Peritoneal Tissues of Patients Undergoing Gastrointestinal Surgery

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It is not known whether a prophylactic antibiotic administered prior to surgery reaches adequate levels in the peritoneum, where peritonitis may take place. This study determined levels of cefmenoxime in sera and peritoneal tissues of patients undergoing gastrointestinal surgery. Fifteen patients who underwent elective gastrointestinal surgery received an intravenous drip infusion of cefmenoxime (2 g) over 1 h prior to surgery. In patients who underwent gastrectomy, the level of cefmenoxime in serum was 130.8 ± 6.9 μg/ml at laparotomy and decreased to 5.0 ± 0.7 μg/ml at 4 h. Levels in parietal peritoneal and omental tissues at laparotomy were 35.3 ± 5.2 and 19.2 ± 3.5 μg, respectively, and decreased time dependently. In patients who underwent cholecystectomy, the level of cefmenoxime in serum was 137.9 ± 7.3 μg/ml at laparotomy and decreased to 5.0 ± 1.2 μg/ml at 4 h. Levels in parietal peritoneal and omental tissues were 31.0 ± 8.4 and 13.7 ± 3.3 μg/g, respectively, and decreased time dependently. The level of cefmenoxime in serum correlated with the levels of cefmenoxime in parietal peritoneum (r = 0.64, P < 0.01) and in omentum (r = 0.47, P < 0.02). In patients with appendicitis who received a bolus injection of 2 g of cefmenoxime, the level of drug in inflammatory omental tissue correlated with the level in serum. The levels in peritoneal tissue during surgery lasting up to 2 h were significantly greater than in MIC of cefmenoxime against almost all bacteria reported. A preoperative single dose of 2 g of cefmenoxime probably is effective as a prophylactic for intraoperative contamination.

Prophylactic antibiotics are widely used prior to or during elective gastrointestinal surgery, and the importance of the prophylactic antibiotics in reducing postoperative infections has been demonstrated (3, 4, 10). The aim of a prophylactic administration is to prevent wound infection and peritonitis, both of which may be caused by intraoperative contamination. The basic concept underlying the effective use of prophylactic antibiotics to prevent infectious complications in surgical patients is that an adequate amount of an appropriate antibiotic must be present in the tissue before or during a bacterial challenge (1). The concept has been confirmed and accepted in human studies (4, 10). Further, this concept probably applies to the therapeutic use of antibiotics which are given to patients perioperatively and after surgical drainage for peritonitis or intra-abdominal abscess. However, there is no information on whether the levels of antibiotics are sufficient to be effective in peritoneal tissue, where peritonitis may occur. Therefore, in practice, the use of antibiotics has been based mainly on the experience of each practitioner and on studies with experimental animal models. The current study was conducted during gastrointestinal surgery to determine levels in peritoneal tissue of cefmenoxime given prior to surgery. Cefmenoxime is a semisynthetic cephalosporin with a broad spectrum of activity against many gram-positive and gram-negative bacteria and excellent β-lactamase stability (8, 9). The current study also examined levels of cefmenoxime in serum and compared them with levels in peritoneal tissue.

MATERIALS AND METHODS

The protocol of the study was approved by the Institutional Ethical Committee for Research in Human Subjects (Kyoto University Hospital and Nagahama Red Cross Hospital). Only patients from whom an informed written consent had been obtained were included in the study. Those who had an episode of allergy to the antibiotics were excluded.

Study 1. Fifteen adult patients who underwent elective gastrointestinal surgery were studied under the protocol. Approximately 1 h before surgery, an intravenous drip infusion of cefmenoxime (2 g of cefmenoxime dissolved in 100 ml of saline) was started. The infusion was continuous for 1 h and finished just prior to the beginning of surgery. Tissue samples from parietal peritoneum and greater omentum were taken at laparotomy and at approximately hourly intervals during surgery. Blood samples were obtained at the time of tissue sampling. Tissue samples were quickly frozen and stored at −20°C until prepared for analysis. Blood samples were centrifuged, and serum was separated and frozen at −20°C until analyzed.

Study 2. Eight adult patients who underwent appendectomy were studied. From 30 min to 1 h before surgery, a bolus injection of cefmenoxime (2 g of cefmenoxime dissolved in 20 ml of saline) was given through the intravenous catheter for the fluid infusion. Tissue samples were obtained from the inflammatory omental cap surrounding the appendix, and blood samples were obtained simultaneously. Sampling was performed only one time for each patient. Tissue and blood samples were processed as described for study 1.

Assays and statistics. Cefmenoxime concentrations in serum and tissue were determined by the agar well diffusion method (2) using Escherichia coli NIHJ JC-2 as the test organism. Cefmenoxime concentrations in serum were analyzed together with standards prepared in normal serum. The best-fitting curve for the standards was calculated by

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polynomial regression by using the following equation: $y = a + bx + cx^2$, where $x$ is the logarithm of the concentration of the standards (1.25, 2.5, 5.0, 10.0, 20.0, and 40.0 $\mu$g/ml) and $y$ is the corresponding mean zone diameter. High-concentration samples were diluted with normal serum so that the resulting zone sizes were within the range of the standard curve concentrations. The sensitivity of the method was 0.5 $\mu$g/ml in serum. The coefficients of variation (including day-to-day variation) were 10.0% at 2.5 $\mu$g/ml and 9.8% at 20 $\mu$g/ml.

Tissue samples were thawed, blotted dry, and weighed. Phosphate buffer (0.1 M, pH 7.4) was added at four times the sample weight. The sample was homogenized on ice and centrifuged (2,500 × g) at 4°C for 20 min. The supernatant was used for analysis. Since it was not possible to obtain no-drug tissue for preparation of standards, the antibiotic concentrations in tissues were determined with standards prepared in phosphate buffer (0.1 M, pH 7.4) in the range of 0.625 to 20.0 $\mu$g/ml. The sensitivity of the method in tissue sample was 1.3 $\mu$g/g. Under similar assay conditions, the recoveries of the antibiotic from mouse liver and kidney were tested. The results were 110 and 101%, respectively.

Data were expressed as the mean ± standard error of the mean. Linear dependences between cefmenoxime concentrations in serum and tissues in study 1 and between time and logarithm of serum or tissue concentrations in study 2 were tested by linear regression analysis.

**RESULTS**

**Study 1.** Eight patients who underwent gastrectomy (six males and two females; age, 59.0 ± 4.1 years; body weight, 51.7 ± 3.3 kg) and seven patients who underwent biliary tract surgery (one male and six females; age, 56.9 ± 5.6 years; body weight, 53.0 ± 2.0 kg) were recruited to participate in the study. Gastrectomy was performed for gastric cancer in five patients and for intractable peptic ulcer in three patients. Biliary tract surgery included cholecystectomy for cholelithiasis in three patients and cholecystectomy plus choledochotomy in 4 patients. The patients showed no evidence for intra-abdominal infection before surgery as assessed by leukocyte count and abdominal computerized tomography findings, which were confirmed at surgery.

In patients who underwent gastrectomy (Fig. 1), the level of cefmenoxime in serum was 130.8 ± 6.9 $\mu$g/ml at laparotomy and declined gradually to 38.8 ± 3.7 $\mu$g/ml at 1 h, 21.5 ± 3.2 $\mu$g/ml at 2 h, and 5.0 ± 0.7 $\mu$g/ml at 4 h. Levels in parietal peritoneal and omental tissue were 35.3 ± 5.2 and 19.2 ± 3.5 $\mu$g/g, respectively, at laparotomy and decreased time dependently.

In patients who underwent biliary tract surgery (Fig. 2), the level of cefmenoxime in serum was 137.9 ± 7.3 $\mu$g/ml at laparotomy and declined gradually to 32.4 ± 3.7 $\mu$g/ml at 1 h, 10.0 ± 0.3 $\mu$g/ml at 2 h, and 5.0 ± 1.2 $\mu$g/ml at 4 h. Levels in parietal peritoneal and omental tissue were 31.0 ± 8.4 and 13.7 ± 3.3 $\mu$g/g, respectively, and decreased time dependently.

In patients who received drip infusion of 2 g of cefmenoxime, levels of cefmenoxime in serum correlated with both the parietal peritoneal level ($r = 0.64$, $P < 0.01$) and the omental level ($r = 0.47$, $P < 0.02$) of cefmenoxime (Fig. 3). The tissue/serum ratios were 24.9% ± 3.3% for parietal peritoneum and 12.7% ± 2.0% for omentum at laparotomy. These ratios increased slightly at 1 h to 33.1% ± 3.5% for parietal peritoneum and 21.7% ± 4.4% for omentum. No postoperative infection was observed in these patients.

**Study 2.** Eight patients were included in the study (five males and three females; age, 43.8 ± 4.7 years; body weight, 59.9 ± 2.6 kg). The patients showed signs of appendicitis and had a mean leukocyte count of 12,800 ± 1,640×10^3/mm³. Levels of cefmenoxime in serum and omentum are shown as a function of time in Fig. 4. The level of drug in inflammatory omentum tissue correlated with the level in serum, and both declined time dependently. No postoperative infection was observed in these patients.
DISCUSSION

Levels of cefmenoxime in serum and peritoneal tissue were studied during abdominal surgery in humans following the administration of drug by a drip infusion or a bolus injection. The results of our study showed that the levels of antibiotic in parietal peritoneum and omentum during gastrointestinal surgery correlated highly with the level in serum. At laparotomy following a drip infusion of 2 g of cefmenoxime, the tissue/serum ratio was 25% for parietal peritoneum and 13% for omentum. The ratios increased slightly 1 h after dosing. The level in omental tissue was lower than that in parietal peritoneum, probably because omental tissue contains more fat, suggesting that disposition of an antibiotic to adipose tissue may be relatively lower than that to parietal peritoneum. These data are important, because for an antibiotic to be effective as a prophylactic agent, it should be present at the site of infection before bacterial contamination occurs.

In patients with appendicitis, cefmenoxime was administered by an intravenous bolus injection. By this method, the peak concentration in serum may occur just after the injection and decline gradually thereafter. On the other hand, the level in omental tissue should increase after injection and attain a peak after that of the level in serum. Of interest, however, within the range of the current study, the time-related phase of the level in omental tissue was similar to that of the level in serum and the two correlated with each other, suggesting that the disposition of cefmenoxime to peritoneal tissues might be rapid. The current results demonstrated that by either a drip infusion or a bolus injection, the level of drug in peritoneal tissue correlated highly with the level in serum. Thus, the first goal of antibiotic administration can be to achieve a high level in serum.

It has been reported that the MIC of cefmenoxime was under 1 μg/ml against almost all bacteria isolated from patients with clinical infections (5, 7). The current study demonstrated that levels in peritoneal tissue during surgery were greater than 1 μg/ml for up to 2 h. Concentrations in tissue homogenate represent a mixture of levels in intracellular and interstitial fluids, and tissue homogenates underestimate the concentrations of β-lactams because of poor intracellular penetration. Thus, the actual levels of antibiotic in interstitial fluids might be higher than the values obtained in this study. From this point of view, a preoperative single dose of cefmenoxime (2 g, either by a drip infusion or by a bolus injection) probably is effective as a prophylactic against intraoperative contamination. However, for postoperative infectious complication, the duration of the surgical procedure has been cited as another important factor. Kaiser et al. (6) reported more infectious complications in patients with operations exceeding 4 h. The current results showed that the levels of drug in tissue exceeded MICs for up to 2 h but declined time dependently. Thus, physicians may have to consider an additional dose of an intraoperative antibiotic with longer surgical procedures.

In summary, the levels of cefmenoxime in peritoneal tissue were sufficient as a prophylactic during surgery of up to 2 h when the drug was administered prior to surgery. The levels in cefmenoxime in tissue correlated highly with the levels in serum. Thus, it is most likely unnecessary to monitor levels of drug in tissue. The optimal use and timing of prophylactic antibiotics may reduce the number of postoperative infections induced by contamination during surgery.

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