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

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Levels in serum and tissue penetration of ornidazole were studied after a single intravenous injection of 1,000 mg given to 14 patients for prophylaxis of surgical infection. They were scheduled for elective colorectal surgery. Adequate levels in blood (=MIC for 90% of Bacteroides fragilis strains tested) were found in all patients throughout the procedure and up to hour 24. Mean-maximal (15 min) and last-determined (24 h) ornidazole levels in serum were 24 ± 5.2 and 6.3 ± 1.4 mg/liter, respectively. β-Phase elimination half-life was 14.1 ± 2.7 h, and clearance and apparent volume of distribution were 47 ± 12 ml/min and 0.9 ± 0.13 liters/kg, respectively. In all patients, adequate levels in tissue were found in the abdominal wall and the epiploic fat at time of incision and in the colonic wall at time of anastomosis. At time of closure, all but one patient had adequate levels in tissue in the abdominal wall and the epiploic fat. No anaerobic nor aerobic infection occurred in the study patients.

The benefit of short-term antimicrobial courses for prevention of postoperative infection has been demonstrated for selected surgical procedures, among them colorectal surgery (4, 11, 23). Antimicrobial agents for prophylaxis should be selected on the basis of their spectrum of activity against pathogens most likely to contaminate the surgical wound (11). Since Bacteroides fragilis and other anaerobic bacteria are among the main pathogens encountered in infections after colorectal surgery, antibiotics with a spectrum of activity extended to these organisms are usually advocated (1). Antibiotic regimens which do not eliminate anaerobic fecal pathogens fail to control postoperative septic complications of colorectal operations (5, 13).

Nitroimidazole derivatives such as metronidazole are commonly used in this situation (3, 8, 12, 22). Ornidazole may be preferred for pharmacokinetic reasons (longer elimination half-life) (24). It seems clear that in surgical prophylaxis, adequate antibiotic concentration in tissue should be achieved in all the potential sites of infection (2). Theoretically, in the tissues involved by postoperative infection, antibiotic activity should be maintained throughout the procedure: from incision to closure. For practical reasons, an ideal antibiotic prophylactic regimen should be as easy to administer as possible, and in colorectal surgery the value of a single-dose administration has been established and can be recommended (7).

This study was designed to determine whether or not a single dose of ornidazole was able to achieve and maintain adequate concentrations in some tissues: abdominal wall, epiploic fat, and colonic wall. Levels ≥ MIC for 90% of B. fragilis strains tested (MIC90) (2 mg/liter of serum or 2 µg/g of tissues) were considered adequate (25).

MATERIALS AND METHODS

This study received the approval of the ethical committee of our institution, and all patients gave their informed consent. Fourteen patients were scheduled for elective rectal or colorectal surgery. They were 10 men and 4 women with a mean age of 66 ± 5 years and a mean weight of 67 ± 8 kg. None had a history of allergic reaction to ornidazole. All patients had normal renal and hepatic function. They had a 2-day mechanical bowel preparation consisting of low-residue diet, purgation, and bowel washouts in the evening. Patients did not present any clinical or laboratory signs of infection and were not receiving any antibiotic therapy before surgery. Before induction of anesthesia, patients were given a single dose of 1,000 mg of ornidazole intravenously (i.v.) administered over 30 min via an arm catheter, at a constant flow rate with an automatic pump. Blood samples were collected from a central venous line (right internal jugular vein) before ornidazole injection and 15 min (maximum concentration), 45 min, and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 (last determined concentration) h after the end of infusion. Different tissue samples were collected during the surgical procedure: abdominal wall and epiploic fat samples at time of surgical incision and at time of closure (end of surgical procedure) and colonic wall samples at time of anastomosis. Simultaneously, additional blood samples were collected. Blood was centrifuged, and serum was separated and stored at −35°C until assay. Tissue samples were rinsed in sterile 10 mM morpholinopropane sulfonate (MOPS) buffer, pH 7.0, to eliminate excess blood within minutes of removal. Tissue samples were also stored at −35°C.

Determinations of ornidazole concentrations were performed by high-performance liquid chromatography with a Perkin-Elmer apparatus coupled to a spectrophotometric detector (LC 75) as previously reported (17). Ornidazole used as test drug was kindly supplied by Roche, Neuilly sur Seine, France. The aqueous reagents, i.e., HClO4 (0.7
mol/liter; Prolabo, Paris, France), NaOH (1 mol/liter; Prolabo), and citrate hydrochloride buffer, pH 4 (Merck), were all prepared with distilled water. Serum samples were added with an equal volume of perchloric acid (0.7 mol/liter). Then, to avoid a secondary degradation, the solution was immediately neutralized (300 μl of sodium hydroxide [1 mol/liter]) and buffered (200 μl of citrate hydrochloride [pH 4] buffer). Then, the solution was vortexed and centrifuged (6 min at 3,000 rpm). Twenty microliters of the solution was injected onto the chromatography column. The A13 was measured. The column used was a μBondapak C18 reversed-phase column (30 by 4.6 cm) maintained in a temperature regulated (25°C) oven (LC 100). The mobile phase consisted of methanol and acetoacetate buffer, pH 4.7 (50/50, vol/vol). Tissue samples were ground at ice-cold temperature (0 to 2°C), and 500 μl of trichloroacetic acid (0.6 mol/liter) was added to 0.5 g of tissue. The solution was vortexed, and 1.5 ml of methanol was added. After centrifugation (10 min at 3,000 rpm), 20 μl of the solution was injected into the chromatography column. In this study, the lower limit of detection was 0.5 μg/ml for plasma samples and 0.5 μg/g for tissue samples, and the percentage of antibiotic recovery was 98%. Recovery was determined by using the method described by Merdjian and co-workers (17). Within-day and between-day repeatability was assayed for three different concentrations of ornidazole (5, 10, and 25 μg/ml), with coefficients of variation of 1.5, 1.5, and 2.3%, respectively, for the within-day variation and 3.9, 2.1, and 2.8%, respectively, for the between-day repeatability assays.

To perform the pharmacokinetic analysis, ornidazole concentrations in serum were plotted against time and individual pharmacokinetic parameters were determined by assuming a two-compartment open model: β-phase elimination half-life, apparent volume of distribution, plasmatic clearance, and area under the serum concentration-time curve extrapolated to infinity were assessed according to conventional methods (26) with a personal computer program on an Apple Ile computer. The curve fitting of the data was done by the method of residuals according to Wagner (26), the β phase being assessed by linear regression without ponderation.

Evaluation of ornidazole tissue penetration was performed as follows. For each patient, tissue-serum concentration ratios were calculated by using ornidazole concentrations in tissue obtained at different periods during the surgical procedure (abdominal wall and epiploic fat concentrations were obtained during incision and closure, and colonic wall concentrations were obtained at anastomosis). Ornidazole concentrations in serum were concomitantly obtained.

During their hospital stay, patients were carefully followed up for clinical or biological signs of infection. When needed, suspected specimens were obtained, kept at room temperature, and rapidly transported to the laboratory. They were Gram stained and cultured onto conventional solid and liquid media. Specific anaerobic culturing techniques were performed using anaerobic jars.

**RESULTS**

Given in Table 1 are ornidazole levels in serum and pharmacokinetic parameters of the study patients. After 24 h, 100% of patients had ornidazole last-determined levels ≥MIC90 of B. fragilis (2 mg/liter) and only one patient had a level in serum of <4 mg/liter (Fig. 1). Given in Table 2 are ornidazole levels in tissue obtained during the surgical procedures. At time of incision (55 ± 7 min after the end of infusion), ornidazole levels for abdominal wall and epiploic fat were ≥2 μg/g of tissue in 100% of the patients. At time of surgical anastomosis (179 ± 40 min after the end of infusion), ornidazole levels of ≥2 μg/g of tissue in the colonic wall were found in 100% of the patients. At time of closure (230 ± 40 min after the end of infusion), ornidazole levels were ≥2 μg/g of tissue in 100% of the patients for abdominal wall fat and 84% of the patients for epiploic fat. Ornidazole tissue penetration estimated from tissue-serum antibiotic concentration ratios is presented in Table 2.

No case of either anaerobic or aerobic infection was observed in the study patients.

**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 that (ii) the drug must attain and maintain serum and tissue antibiotic concentrations high enough to inhibit the growth of contaminating pathogens (11, 23).

In the present study, ornidazole concentrations in serum and different tissues were compared with the MIC90 for B. fragilis, a pathogen frequently involved in postoperative infections after rectal and colonic surgery. A single dose of 1,000 mg i.v. of ornidazole was given to patients, and after 24 h, 100% of the patients had levels in serum of ≥2 mg/liter. This clearly indicates that adequate concentrations in blood were achieved throughout the surgical procedure. Such a good result is reinforced by the fact that all but one patient had a level in serum of >4 mg/liter (break point for ornidazole). High concentrations were achieved in the colonic wall, and all patients had ornidazole levels >MIC90 for B. fragilis. No patient had a concentration of less than 6 μg/g of tissue, and ornidazole penetration into the colonic wall was greater than 50% of the level in blood. Lower concentrations were achieved in the abdominal wall and epiploic fat, which are poorly vascularized tissues. However, significant concentrations were found, and at incision, 100% of the patients had levels in tissue >MIC90 for B. fragilis. Such adequate levels were maintained throughout the surgical procedure, and in the abdominal wall fat and the epiploic fat, adequate levels in tissue were found in 100 and 84% of the patients, respectively, at closure. Thus, ornidazole tissue elimination is a slow process, and relatively stable concentrations in tissue were observed during the surgical period. This was true even for patients undergoing long (up to 7 h) surgical procedures. The excellent tissue penetration of ornidazole is also evident from the tissue-serum ratios presented in Table 2.

In the study patients, ornidazole achieved better performance than metronidazole given under the same conditions.

**TABLE 1. Ornidazole levels in serum and pharmacokinetic parameters after i.v. injection**

<table>
<thead>
<tr>
<th>Measurement or parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum (15-min) level (mg/liter)</td>
<td>24 ± 5.2</td>
<td>33.3–18.2</td>
</tr>
<tr>
<td>Last-determined (24-h) level (mg/liter)</td>
<td>6.3 ± 1.4</td>
<td>7.7–3.2</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>14.1 ± 2.7</td>
<td>19.8–10.2</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>47 ± 12</td>
<td>66–34</td>
</tr>
<tr>
<td>V1 (liter/kg)</td>
<td>0.9 ± 0.13</td>
<td>1.05–0.59</td>
</tr>
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* A 1,000-mg dose of ornidazole was administered to each of 14 surgical patients over a 30-min period.

* B 1/2; β-Phase elimination half-life; CL, clearance; V1, apparent volume of distribution.
FIG. 1. Ornidazole levels in serum were plotted against time. After 24 h, all patients had levels in serum ≥MIC₉₀ for B. fragilis. Incision, anastomosis, and closure of the abdomen were performed 0.9, 2.9, and 3.8 h, respectively, after the end of oridazole infusion.

in a similar group of patients. The latter drug had a shorter elimination half-life (9.5 ± 2.3 h) and a lower penetration into the abdominal wall and the epiploic fat (only 40 to 60% of patients had levels in tissue >MIC₉₀ for B. fragilis) (M. Condomines, C. Martin, J. P. Brun, B. Bruguerolle, and P. de Micco, Program Abstr. 6th Mediterranean Congr. Chemother., p. 185, 1988).

In the present study, no case of anaerobic and aerobic infection was observed. This could be related to an adequate antibiotic concentration in tissue, exceeding the MICs for the bacteria involved. However, what constitutes an optimal antibiotic concentration in tissue is poorly understood (2). It is often defined as a concentration above the MICs for the bacteria, but many examples of effective prophylaxis with antibiotic concentrations in tissue below the MIC and failures of prophylaxis with concentrations above the MIC exist (15, 20, 21). Subminimal concentrations of antibiotics do produce morphological damage to bacteria, thus decreasing the growth rate and favorably influencing the outcome of infection (16, 27, 28). Clearly, many factors influence the control of operative infections: discipline of the surgical team, meticulous surgical technique, proper preparation for surgery, status of the immune system of the patient, etc. Thus, the selection of antibiotics with an adequate tissue penetration is an important goal to achieve, and clearly oridazole fulfills this condition in colorectal surgery, but other factors should be controlled too.

No major modification was seen in oridazole pharmacokinetics in the study patients (24). Results were similar to those reported for healthy volunteers, and in view of the present study, the single dose used (1,000 mg i.v.) can be recommended (24). It represents an easy and convenient technique of administration.

Prophylaxis directed only against anaerobic pathogens has been recommended in colorectal surgery (8, 10, 14, 18). In the present study, no case of postoperative infection was observed. But no firm and definite conclusion can be drawn since only a relatively small number of patients was studied. In view of the literature published on the subject, the most common pathogens encountered postoperatively in colorectal surgery are Escherichia coli and B. fragilis (5, 9, 13, 23). There is strong evidence that an effective prophylaxis requires the use of drugs effective against both anaerobes and aerobes (9). The addition of an antibiotic from the cephalo-

| TABLE 2. Ornidazole tissue penetration estimated from tissue/serum antibiotic concentration ratios at different periods of the surgical procedurea |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Period of surgery (time [min]) | Serumb (µg/ml) | Abdominal wall fatb (µg/g) | A/S | Epiploic fatb (µg/g) | E/S | Colonic walla (µg/g) | C/S |
| Incision (55 ± 7) | 19.7 ± 4.5 | 4.4 ± 1.3 | 0.23 ± 0.06 | 4.7 ± 1.2 | 0.25 ± 0.06 | 8.7 ± 1.8 | 0.58 ± 0.14 |
| Anastomosis (179 ± 40) | 15.4 ± 3.3 | 3.6 ± 1 | 0.26 ± 0.06 | 3.4 ± 1.1 | 0.25 ± 0.08 | | |
| Closure (230 ± 40) | 14 ± 2.7 | | | | | | |

a All data are means ± standard deviations.
b Concentration of oridazole in serum or tissue.
c A/S, Abdominal wall fat/serum ratio; E/S, epiploic fat/serum ratio; C/S, colonic wall/serum ratio.
sporin group should be considered in combination with ornidazole (18, 19).

The emergence of antimicrobial agent-resistant bacteria related to the use of prophylactic ornidazole could be reason for concern. Data suggest that prolonged (>48 h) postoperative prophylaxis is responsible for modification of susceptibility to antimicrobial agents (6), but no deleterious effect caused by an appropriate short-course prophylactic regimen has been reported. This should preclude the use of multiple-dose antibiotic regimens, and a 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 i.v. ornidazole is given before colorectal surgery, levels >MIC50 for B. fragilis can be achieved and maintained in serum and tissue throughout the surgical procedure. Reasons for this could be a long plasma elimination half-life and an excellent penetration into lipidic tissues. This probably explains the lack of postoperative infection observed in the study patients.

LITERATURE CITED