Penetration of Clindamycin, Cefoxitin, and Metronidazole into Pelvic Peritoneal Fluid of Women Undergoing Diagnostic Laparoscopy

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A single dose of clindamycin, cefoxitin, or metronidazole was administered to each of 30 women. The mean concentration of cefoxitin in pelvic fluid at 1 h exceeded those of the other two drugs (P < 0.007). Cefoxitin concentrations were inferior to those of the other drugs when compared with the published MIC for 90% of Bacteroides fragilis strains.

Although clindamycin, cefoxitin, and metronidazole are widely used and advocated for the prophylaxis and treatment of gynecologic infections, the ability of these drugs to penetrate pelvic peritoneal fluid and adnexa has not been adequately studied. The spectrum of all three agents includes a majority of anaerobic bacterial species. We have undertaken a prospective study to compare the levels of these drugs in pelvic peritoneal fluid following administration of a single intravenous dose to women undergoing elective laparoscopy.

Otherwise healthy women under investigation for primary or secondary infertility were studied. Hepatic function and creatinine concentrations in serum were normal in all instances. None of the patients had a history of antibiotic allergy or had received antimicrobial agents during the preceding 72 h.

Following informed consent, subjects were given a single intravenous dose of clindamycin (600 mg), cefoxitin (1 g), or metronidazole (500 mg) as a 10-min infusion. Each agent was administered to 10 consecutive patients. Laparoscopy was performed through an umbilical incision. When the pouch of Douglas was entered, free peritoneal fluid was aspirated and 5 ml of blood was obtained from a peripheral vein. The time elapsed between the termination of drug infusion and the acquisition of specimens was noted. Serum was separated from blood by centrifugation, and all samples were stored at −70°C until the time of assay.

Clindamycin and cefoxitin concentrations were determined with a standard bioassay which used 6-mm paper disks (Difco Laboratories, Detroit, Mich.), antibiotic medium no. 2 (pH 7.9; Oxoid Ltd., London, England), and Sarcina lutea ATCC 9341 (MIC, 0.06 µg/ml) (1). An anaerobic assay done with GasPak (BBL Microbiology Systems, Cockeysville, Md.) incubation of nonsupplemented anaerobic agar (Difco) and a clinical isolate of Clostridium perfringens (MIC, 0.5 µg/ml) was used for metronidazole (3). A single individual performed all laboratory studies.

Standards were diluted in pooled human serum. Plates were examined after overnight incubation at 36°C. Standard curves were determined in quadruplicate, each with five antibiotic concentrations. Coefficients of variation were ≤5% at minimal and maximal antibiotic concentrations for all four curves. Statistical analyses were done with the Student t test for unpaired means.

Demographic and experimental data are summarized in Table 1. Although the mean body weight of patients given clindamycin was lower than that of patients given metronidazole (P < 0.002), patient age and time elapsed before sample acquisition were similar for the three groups. Mean concentrations of cefoxitin in serum and peritoneal fluid exceeded those of metronidazole (P < 0.013) and clindamycin (P < 0.005). The ability of metronidazole to penetrate (fluid level/serum level) was higher than that of clindamycin (P < 0.012) but was otherwise comparable when drug pairs were analyzed separately. The hemoglobin concentrations of fluid samples were all ≤5% of preoperative blood values, suggesting that antibiotic activity did not represent "contamination" by serum.

Our data should be viewed in terms of the antibiotic concentrations required for the inhibition of bacterial pathogens associated with gynecologic infections. Over 90% of Bacteroides fragilis isolates are inhibited by clindamycin and metronidazole concentrations of 4 and 8 µg/ml, respectively (4). Thus, levels attained in peritoneal fluid in our series may be considered marginally effective for this species. Other pathogens, such as C. perfringens, are somewhat more susceptible in vitro and may be inhibited by documented concentrations of either antibiotic in fluid (4).

Although cefoxitin concentrations were numerically superior to those of the other two antibiotics, relatively high cefoxitin concentrations are required for the inhibition of B. fragilis. Thus, the levels observed in our study (19.5 µg/ml ± a standard error of 3.8 µg/ml) are below the published MIC for 90% of strains of this species (32 µg/ml) (2). It is possible that the use of a larger cefoxitin dose (2 g) would have resulted in somewhat higher concentrations.

A review of the literature (in English) has disclosed no prior publication comparing the penetration of antimicrobial agents into the pelvic peritoneum or adnexa. Only one relevant study concerned with peritoneal levels of cefoxitin was identified. Cefoxitin concentrations of 132 and 8 µg/ml at 20 and 100 min, respectively, were measured following intravenous administration of 2 g to adults (5).

Our study is limited to levels attainable in uninfamed peritoneal fluid at a specific point in time. If clindamycin, cefoxitin, or metronidazole is administered for gynecologic prophylaxis, these data suggest that the single dose used...
TABLE 1. Penetration of clindamycin, cefoxitin, and metronidazole into pelvic peritoneal fluid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient age (yr)</th>
<th>Patient wt (kg)</th>
<th>Time elapsed (min)</th>
<th>Antibiotic level (μg/ml) in:</th>
<th>% Antibiotic in peritoneal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>31.9 ± 1.3</td>
<td>63.1 ± 1.7</td>
<td>58.5 ± 1.8</td>
<td>Serum: 9.4 ± 0.9</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>30.9 ± 1.2</td>
<td>59.7 ± 3.3</td>
<td>56.0 ± 1.3</td>
<td>Serum: 47.9 ± 12.4</td>
<td>19.5 ± 3.8</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>31.6 ± 1.0</td>
<td>54.7 ± 1.5</td>
<td>58.0 ± 1.3</td>
<td>Serum: 10.7 ± 1.9</td>
<td>7.2 ± 7.6</td>
</tr>
</tbody>
</table>

* Data are reported as mean ± standard error.
* Interval between completion of antibiotic infusion and acquisition of samples.

may not provide adequate levels in fluid in the time interval examined. The significance of these findings will require validation by controlled clinical studies.

LITERATURE CITED
ERRATUM

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Volume 34, no. 2, p. 376, column 2, line 5: "lower" should read "higher."
Page 377, Table 1, column 6, row 3: "± 7.6" should read "± 1.6."