Penetration of Sulbactam-Ampicillin and Clavulanic Acid-Amoxicillin into the Pelvic Peritoneum

ELIZABETH T. HOUANG,1,∗ NIGEL COLLEY,2† AND MICHAEL CHAPMAN2‡

Departments of Microbiology1 and Gynaecology,2 Chelsea Hospital for Women, London, SW3 6LT United Kingdom

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Sixteen patients were given single intravenous injections of ampicillin (0.5 g) with sulbactam (0.5 g), and 15 patients were given amoxicillin (1 g) with clavulanic acid (0.2 g) before elective laparoscopy. At 2 h after dosing, the concentrations of the four compounds in serum and in the peritoneal fluid from the Pouch of Douglas and the ratio of each combination reached levels shown to be effective for antimicrobial activity in vitro.

Sulbactam (penicillanic acid sulphone; Pfizer Ltd.) and clavulanic acid (Beecham Pharmaceuticals) are beta-lactamase inhibitors with very limited antimicrobial activity. Both compounds have been shown to enhance the activity of penicillin G and ampicillin against certain beta-lactamase-producing bacteria in vitro (3). Such antibiotic combinations may be suitable for chemoprophylaxis and the treatment of postoperative infections following gynecological surgery since these compounds are active against penicillinase-producing Staphylococcus aureus and Bacteroides fragilis. The antimicrobial activity of these combinations against anaerobes is particularly important because their etiological role in the postoperative sepsis in gynecology is now recognized (2). In this context, it is important to ascertain the extent of the penetration of these two inhibitors into the pelvic region. We report here the drug levels achieved in the peritoneal fluid in the Pouch of Douglas after a single intravenous (i.v.) dose of the beta-lactamase inhibitors, which were administered in combination with a penicillin.

Penetration of sulbactam with ampicillin. Sixteen patients, aged 24 to 41 years, agreed to take part in this study. The peritoneal fluid in the Pouch of Douglas was collected during laparoscopy, which was performed for sterilization in 10 patients, for investigation of menorrhagia and dysmenorrhoea in 3 patients, and for investigation of infertility in 3 patients. A blood sample was taken before injection of the antibiotic combination for the assay of urea and electrolytes and to test for the presence of antibiotics. A single i.v. dose of sulbactam (500 mg) with ampicillin (500 mg) was given at 30 min and at 1, 1.5, and 2 h before the expected time of aspiration of peritoneal fluid. A second blood sample was taken at the time of the aspiration of peritoneal fluid.

Penetration of clavulanic acid with amoxicillin. A protocol similar to that used above was followed in the study of the penetration of sulbactam with amoxicillin. Fifteen patients, aged 33 to 49 years, underwent laparoscopy for sterilization (8 patients), for investigation of infertility (3 patients), and for investigation of dysmenorrhoea and menorrhagia (4). Similar samples at time intervals of 15 min, 30 min, 1 h, or 2 h were obtained after the single i.v. injection of amoxicillin (1 g) and clavulanic acid (200 mg [1.2 g of Augmentin]).

All samples of serum and peritoneal fluid were stored at −70°C until assay, which was performed within 2 weeks of obtaining the specimens. Peritoneal fluid contaminated with blood was not processed. The details of the microbiological method (agar plate diffusion) used in the assay of the four compounds are shown in Table 1. Human serum (Flow Laboratories, Inc.) was used for the preparations of antibiotic standards and the dilution of all samples. All assays were carried out in triplicate on the same agar plate. Internal controls of predicted levels were included in all assay plates.

Sufficient peritoneal fluid without blood contamination was obtained from 11 of 16 patients in the study of sulbactam with amoxicillin and from 13 of 15 patients in the study of clavulanic acid with amoxicillin. The patients enrolled in the study had the laparoscopy performed as part of a routine list for gynecological surgery. It was therefore difficult to predict the exact time of operation and specimen collection. Tables 2 and 3 show the results of individual patients and the means of intervals at 0.5, 1, 1.5, and 2 h for the sulbactam-amoxicillin study (Table 2) and at 0.25, 0.5, 1, and 2 h for the clavulenic acid-amoxicillin study (Table 3).

The results show that, on the average, sulbactam achieved a higher concentration than did amoxicillin in both serum and peritoneal fluid. The ampicillin/sulbactam ratios in peritoneal fluid ranged from 0.46 to 0.64 (mean 0.50), whereas the corresponding ratios in serum were higher (0.57 to 0.94, mean 0.77). Brown et al. (1) investigated the drug levels in serum and blister fluid in healthy male volunteers over the same time intervals after single i.v. injections of similar doses of amoxicillin with sulbactam and found that the mean

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Table 1. Details of the agar plate diffusion technique used for the assay of ampicillin, amoxicillin, sulbactam, and clavulanic acid

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indicator organism</th>
<th>Assay medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin*</td>
<td>Sarcinea lutea strain 9341</td>
<td>Penassay 2 (Difco Laboratories)</td>
</tr>
<tr>
<td>Amoxicillinb</td>
<td>Sarcinea lutea strain 8340</td>
<td>Penassay 2 (Difco)</td>
</tr>
<tr>
<td>Sulbactama</td>
<td>Escherichia coli strain 273 (Pfizer, Inc.)</td>
<td>Brain heart infusion agar (Oxoid Ltd.) plus ampicillin (50 mg/liter)</td>
</tr>
<tr>
<td>Clavulanic acidb</td>
<td>Klebsiella aerogenes NCTC 11228</td>
<td>Nutrient agar (Lab-M, Ltd.) plus benzyl penicillin (2.5 mg/liter)</td>
</tr>
</tbody>
</table>

* Corresponding author.
† Present address: Department of Obstetrics and Gynaecology, University College Hospital, London, United Kingdom.
‡ Present address: Department of Obstetrics and Gynaecology, Guy's Hospital Medical School, London, United Kingdom.

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* Brown et al. (1).
† Method provided by Beecham Pharmaceuticals, Ltd.
ratios were 0.62 and 0.53, respectively. Wise et al. (3) suggested that for ampicillin-resistant strains of *B. fragilis*, *S. aureus*, and *Escherichia coli*, the optimum ratio of ampicillin to sulbactam was about 1:2.

There was ready penetration of both amoxicillin and clavulanic acid into the pelvis. Concentrations of amoxicillin greater than 10 mg/liter were maintained in the peritoneal fluid at least 2 h after dosing. The concentrations of clavulanic acid in peritoneal fluid increased until approximately 1 h after dosing, when the mean concentration was 4.2 ± 1.2 (standard deviation) mg/liter. An average amoxicillin/clavulanic acid ratio of 5.5:3.4 was obtained in both serum and peritoneal fluid, which was similar to the initial proportions of the injected drugs. Wise et al. (4), using paper disks inserted below the transverse mesocolon during abdominal surgery, studied the penetration of amoxicillin and clavulanic acid after a single i.v. injection of amoxicillin (1 g) plus clavulanic acid (0.2 g). They obtained concentrations of both drugs similar to those obtained here and found the ratios of the two drugs (amoxicillin/clavulanic acid) to be 3.8:1 in serum and 5.4:1 in peritoneal fluid.

Clavulanic acid and sulbactam alone have been shown to have little activity against most organisms except some strains of *Neisseria gonorrhoeae* (3). However, in combination with a beta-lactam antibiotic, both inhibitors were highly effective in reducing the MICs of the beta-lactam drug to within the therapeutic range for the majority of beta-lactamase-producing strains. In the presence of sulbactam (10 mg/liter), the MICs of penicillin for *B. fragilis* were reduced from a range of 32 to ≥64 mg/liter to a range of 2 to 4 mg/liter, and those for penicillinase-producing *S. aureus* were reduced from a range of 16 to ≥128 mg/liter to a range of 1 to 2 mg/liter. Similar reductions in the MICs of penicillin were also observed in the presence of clavulanic acid (5 mg/liter) when the same bacterial strains were tested. Our results indicate that antibiotic levels active against these organisms could be achieved in the pelvic peritoneal fluid by using the i.v. regimen studied here. Nevertheless, the clinical efficacy of combinations of beta-lactamase inhibitors with a penicillin in chemoprophylaxis and treatment of postoperative gynecological infection requires evaluation.

In conclusion, after a single i.v. dose of ampicillin (0.5 g) with sulbactam (0.5 g) or amoxicillin (1 g) with clavulanic acid (0.2 g), rapid penetration of the four compounds into the pelvic region was achieved. The concentrations of these drugs in the pelvic peritoneal fluid and the ratio of each combination appeared to reach levels which have been shown to be effective in vitro for antimicrobial activities against anaerobes and penicillinase-producing *S. aureus*.

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**LITERATURE CITED**


