Penetration of Sulbactam and Ampicillin into Peritoneal Fluid

R. WISE,1* I. A. DONOVAN,2 J. M. ANDREWS,1 J. DRUMM,2 AND S. BENNETT1

Departments of Medical Microbiology1 and Surgery,2 Dudley Road Hospital, Birmingham B18 7QH, United Kingdom

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Twenty-five patients undergoing elective intraabdominal surgery received either 1 or 2 g of ampicillin together with 1 g of sulbactam intravenously before surgery. The peritoneal levels of the agent were measured. Both compounds penetrated peritoneal fluid readily; the mean percentage of penetration by ampicillin was 92%; that of sulbactam was 96%. After 1 g of each agent, the peritoneal levels of sulbactam were 47% greater than those of ampicillin. Our results suggest that 2 g of ampicillin plus 1 g of sulbactam should provide peritoneal levels that would inhibit most susceptible β-lactamase-producing pathogens encountered in intraabdominal sepsis.

Sulbactam has been shown to be a potent inhibitor of many clinically important β-lactamases (1, 4), such as those commonly found in Staphylococcus aureus, Bacteroides fragilis, and the Enterobacteriaceae (particularly the group III enzymes [3]). In vitro studies have shown that a combination of sulbactam and ampicillin is active against such strains (4). Because this combination may be used in the prevention and treatment of intraabdominal sepsis caused by susceptible pathogens, we have studied the intraperitoneal penetration of these two agents administered together intravenously. We developed a reproducible system for studying the penetration of antibiotics into the peritoneal cavity (5) and have used a modification of this method here.

After the approval of the Dudley Road Hospital ethical committee and informed consent of the participants, 25 patients (mean age, 66 years) undergoing elective gastrointestinal surgery (mainly colorectal and gastric procedures) entered the study. Three patients had slightly raised blood urea counts of up to 9.3 mmol/liter (the laboratory upper limit of normal is 8.3 mmol/liter). Eighteen patients received 1 g of sulbactam plus 1 g of ampicillin; seven patients received 1 g of sulbactam plus 2 g of ampicillin coadministered in sterile water as a bolus intravenous injection over 4 to 5 min at various times before the operation. The time of administration was noted. On opening the peritoneal cavity, we inserted eight preweighed sterile assay disks (6 mm in diameter) under a loop of bowel (usually transverse mesocolon) and left them in place for about 4 min. A blood sample was taken, and the time was noted. The disks were removed and immediately transported in sterile containers to the laboratory, where they were reweighed. If there was no gross bloody contamination of the peritoneal cavity at the end of the operative procedure, a repeat set of blood and disk samples were taken. If the disks were contaminated by >5% blood (as determined by visual comparison with a standard set of disks), they were discarded.

The assays used were based on those described previously (1). Briefly, serum samples were assayed against standards prepared in pooled human serum, and peritoneal standards were prepared in 20% human serum (which has been shown to be equivalent to the protein content of peritoneal fluid). Standards were applied to disks in the same amounts as those found by weighing the test disks. The 95% confidence limits of the serum assays were sulbactam, 19.3%, and ampicillin, 17.9%. Only one disk, contaminated with >5% blood, was discarded. The 25 patients yielded 33 sets of data.

Although there were considerable variations of both serum and peritoneal levels in this group of patients, Fig. 1 and 2 show that sulbactum and ampicillin penetrated the peritoneal fluid rapidly, with levels comparable to those found in serum, as early as 7 min post-administration, consistent with previous studies on the penetration of this combination into blister fluid (1). The level of sulbactam in the peritoneal fluid declined to 10 μg/ml at 2.75 h. A level of ampicillin greater than 10 μg/ml was found for 1.75 h (after 1 g) and for 2.6 h (after 2 g). In the postdistribution phase (taken as >1 h after administration), the serum half-life of ampicillin (1 g) was 0.8 h (correlation coefficient, r = 0.782) and 0.97 h for sulbactum (r = 0.715). The half-lives of the two agents in peritoneal fluid were 0.83 h for 1 g of ampicillin (r = 0.698) and 0.76 h for 1 g of sulbactam (r = 0.763). After a 1-g dose of each,
FIG. 1. Serum (X) and peritoneal (○) levels of sulbactam after the intravenous administration of 1 g.

the serum levels of sulbactam were 34% greater than those of ampicillin, and the peritoneal levels of sulbactam were 47 and 54% greater than those of ampicillin at 1.5 and 3 h, respectively. There were only nine data points available to analyze the 2 g of ampicillin; the serum levels were 3.05 times greater (standard deviation [SD], 1.907), and the peritoneal levels were 2.45 times greater (SD, 1.89) than after 1 g, suggesting that twice the dose was accompanied by an approximately similar rise in serum and peritoneal levels. The half-lives of ampicillin after the 2-g dose were 0.6 and 0.71 h in serum and peritoneal fluid. Increasing the dose of ampicillin had no measurable effect on the serum or peritoneal levels of sulbactam. The mean percentage penetration (peritoneal level times 100 divided by serum level) for both dosage ratios
studied was ampicillin, 92% (SD, 50.3) and sulbactam, 96% (SD, 26.2). In a previously reported study of amoxycillin plus clavulanic acid (6), the percentage of penetration by amoxycillin (84%) was similar to that found with ampicillin, but that of clavulanic acid (66%) was considerably less than that of sulbactam.

In vitro studies (2, 4) suggest that for β-lactamase-producing Enterobacteriaceae, a concentration of approximately 10 μg of sulbactam per ml is required to reduce the minimum inhibitory concentration of ampicillin to less than 10 μg/ml. For S. aureus and B. fragilis, however, concentrations of sulbactam as low as 0.5 to 5 μg/ml should achieve this effect. This study therefore suggests that adequate peritoneal concentrations of sulbactam after a 1-g dose are present for about 2.75 h after administration and that the 2-g dose of ampicillin, which gave levels in excess of 10 μg/ml for 2.6 h, was preferable to the 1-g dose (>10 μg/ml for 1.75 h). We realize that choosing a level of 10 μg/ml for both ampicillin and sulbactam is rather arbitrary, especially when in vitro studies are conducted with levels of inocula greater than those likely to be encountered in surgical prophylaxis (but not necessarily greater than those used for therapy of established infections).

Thus, 1 g of sulbactam plus 2 g of ampicillin should be a dosage sufficient for prophylaxis in gastrointestinal surgery in which little spillage of fecal contents has occurred. In the treatment of established infection, we suggest that this dose be administered three to four times per day in patients with normal renal function, although that regimen should be confirmed by clinical studies.

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LITERATURE CITED