Pharmacokinetics of Ampicillin and Sulbactam in Patients Undergoing Heart Surgery

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Received 12 March 1990/Accepted 14 June 1991

The pharmacokinetics of ampicillin and sulbactam, a new β-lactamase inhibitor, were investigated in 16 patients undergoing prosthetic cardiac valve insertion. The combination of 2 g of ampicillin and 1 g of sulbactam was administered as perioperative prophylaxis intravenously over 3 to 6 days. Several serum pharmacokinetic parameters were similar for the two drugs after three intravenous doses were given to patients following surgery. The half-lives of elimination of ampicillin and sulbactam were 79 ± 4.9 and 88 ± 5.9 min, the volumes of distribution were 15.6 ± 1.4 and 17.7 ± 1.2 liters/kg, and the total plasma clearances were 144.4 ± 14.5 and 147.2 ± 14.5 ml/min, respectively. The peak concentrations of ampicillin and sulbactam in serum were calculated to be 134.3 ± 1.3 and 58.3 ± 1.2 µg/ml, respectively. Ampicillin and sulbactam rapidly penetrated from the blood into various tissues collected during heart surgery, such as sternum, pericardium, myocardium, and endocardium. The concentrations of ampicillin in tissue ranged from 17.8 ± 9.9 to 50 ± 29.5 µg/g, and those of sulbactam in tissue ranged from 8.8 ± 6.2 to 19.6 ± 10.1 µg/g. The concentrations of ampicillin and sulbactam in serum and tissue also apparently exceeded the MICs against most β-lactamase-producing bacteria usually involved in postoperative wound infections and prosthetic valve endocarditis. The ratio of the two compounds was approximately 2:1 in serum and in the various tissues affected by the operation.

The pharmacokinetics of ampicillin and sulbactam in serum and investigated tissues suggest that the combination of the two β-lactams will be effective in the perioperative prophylaxis of patients undergoing heart surgery.

Experience in cardiac surgery has demonstrated that such surgery carries a significant risk of infection when antibiotics are not administered perioperatively. Infection of sternal wounds, endocarditis, pneumonia, and bacteremia can all occur postoperatively (4). Prophylaxis with antibiotics, usually of the β-lactam group, is therefore almost routine, and this is also the case with the implantation of prosthetic heart valves (2). It has been demonstrated that the efficacy of ampicillin is markedly improved by the addition of sulbactam, a new semisynthetic β-lactamase inhibitor, and this combination seems particularly indicated for use in perioperative prophylaxis in cardiac surgery, because of its favorable tolerance and antibacterial spectrum.

We have therefore evaluated the pharmacokinetics of ampicillin and sulbactam during the perioperative period in patients undergoing heart surgery.

MATERIALS AND METHODS

Patients. Sixteen subjects (seven female and nine male) undergoing heart surgery, mainly insertion of prosthetic heart valves, were included in the study after informed written consent had been given. Their mean age was 59.4 ± 8.57 (45 to 74) years, and they weighed 74.93 ± 9.78 (52 to 91) kg. The patients' inclusion criteria were the absence of infections, no recent antibiotic therapy, lack of pregnancy, and normal hepatic and renal functions. No patient had a history of serious allergic reactions to either penicillin or cephalosporin drugs.

Perioperative prophylaxis. The patients were treated by intravenous infusion of the combination of 2 g of ampicillin and 1 g of sulbactam (UNACID; Pfizer GmbH, Karlsruhe, Germany; 1.5 g, two vials) for 15 min over 3 to 6 days. The infusion was started during anesthesia induction and was carried out three times at 8-h intervals per day. The treatment was administered to nine patients for 4 days and to three patients each for 3 and 6 days. The mean total dose of the combination administered to the 15 patients perioperatively was 12.6 ± 2.94 g.

Sampling. Blood samples were taken before and at various time points (5 min and 4 and 8 h) after the three infusions on the first day of treatment. Serum was separated by centrifugation at 4°C and stored immediately at −70°C. Tissue samples were collected during the surgical procedures and also stored at −70°C.

Sulbactam assay. The concentrations of sulbactam in serum and tissue samples were determined in duplicate by gas chromatography-mass spectrometry (8). The gas chromatography-mass spectrometry system was operated in the selective ion monitoring mode. Prior to the drug analysis, the deep-frozen tissue samples were thoroughly pulverized (Microdismembrator II; Braun, Melsungen, Germany). The tissue samples were weighed and extracted with phosphate buffer (pH 7.0). The resulting homogenates were centrifuged at 4°C, and the supernatant fluids were analyzed by the same assay as the serum samples. 3-β-(Trideuteromethyl)-sulbactam was used as an internal standard.

The sulbactam standard curves were prepared with pooled human serum in the range of 0.4 to 80 µg/ml (correlation coefficient, ±0.99994). The intraday coefficient of variation for the serum standard curves was 3.77% in the range of 0.4 to 80 µg/ml. The interday coefficient of variation was <0.1%.
TABLE 1. Serum pharmacokinetic parameters of ampicillin and sulbactam after repeated intravenous administration to 13 patients undergoing heart surgerya

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum concn (µg/ml)</th>
<th>Half-life of elimination (min)</th>
<th>Vol of distribution (liters/70 kg)</th>
<th>Total plasma clearance (ml/min)</th>
<th>Area under the curve (µg - h/ ml) from 0 h to infinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (2 g)</td>
<td>134.3 ± 15.8</td>
<td>79 ± 4.9</td>
<td>15.6 ± 1.4</td>
<td>144.4 ± 14.5</td>
<td>834.8 ± 110.2</td>
</tr>
<tr>
<td>Sulbactam (1 g)</td>
<td>58.3 ± 6.4</td>
<td>88 ± 5.9</td>
<td>17.7 ± 1.2</td>
<td>147.2 ± 14.5</td>
<td>400.5 ± 48.4</td>
</tr>
</tbody>
</table>

a Results are reported as mean ± standard error of the mean. Infusion of 2 g of ampicillin and 1 g of sulbactam was carried out three times for 15 min each time at 8-h intervals during the 24-h period following surgery. Results are from the simultaneous fitting of the three doses by the TOPFIT computer program.

obtained from analyses of aliquots of the same sample (4 µg of sulbactam per ml of serum) on 3 successive days.

**Ampicillin assay.** The concentrations of ampicillin were analyzed in triplicate in the same samples by a microbiological cylinder plate technique with Sarcina lutea ATCC 9341. Ampicillin standards for the serum samples were prepared in pooled noninhibitory human serum and ranged from 0.0125 to 437.4 µg/ml. The intraday and interday coefficients of variation for the serum standards were ≤1.6% in the intermediate range of the reference curves. The supernatant fluids of the tissue samples were diluted with phosphate buffer (pH 7.0) to yield final dilutions of 1/12 and 1/36. One of the samples was spiked with ampicillin. All samples were assayed against an ampicillin standard prepared in phosphate buffer (pH 7.0) at 0.033 and 0.011 µg/ml, with a standard 6 by 6 Latin square. After determination of the relative potencies of the two samples, the percent recovery in the spiked tissue was calculated (mean recovery, 99.6% ± 3.5%; n = 67). The bioassays of ampicillin were not affected by the presence of sulbactam (12).

**Pharmacokinetic analysis.** The TOPFIT computer program (1) was used to derive serum pharmacokinetic parameters for ampicillin and sulbactam in patients after repeated intravenous treatments. The individual datum sets obtained over all 3 days were fitted to a pharmacokinetic one-compartment model with multiple dosing and without a weighting of the analytical data. No accumulation of the drugs was observed. All data reported in Table 1 are based on the fitted curves.

**RESULTS**

The concentrations of ampicillin and sulbactam in serum after intravenous administration to patients undergoing heart surgery are shown in Fig. 1. The pharmacokinetic parameters were calculated from the serum data obtained after three infusions of the drug combination at 8-h intervals over the course of 1 day (Table 1). After a 15-min infusion of 2 g of ampicillin and 1 g of sulbactam, peak concentrations in serum were calculated to be 134.3 ± 15.8 and 58.3 ± 6.4 µg/ml, respectively. The serum half-lives of elimination of ampicillin and sulbactam were both slightly longer than 1 h. The calculated values for volumes of distribution and plasma clearances were similar for ampicillin and sulbactam. The ratio of the area under the concentration-time curve for

![FIG. 1. Concentrations of ampicillin and sulbactam in the serum of patients (n = 16) undergoing heart surgery (mean ± standard deviation). Ampicillin (2 g) and sulbactam (1 g) were infused three times for 15 min each time at 8-h intervals during the 24-h period following surgery.](http://aac.asm.org/Downloaded from http://aac.asm.org)
ampicillin to that for sulbactam was 2.08:1, almost exactly the ratio of the two compounds administered intravenously. The mean concentrations of ampicillin and sulbactam determined in various tissues of these patients after the first infusion are summarized in Table 2. The mean concentrations of ampicillin and sulbactam ranged from 17.8 ± 9.9 to 50 ± 29.5 μg/g and from 8.8 ± 6.2 to 19.6 ± 10.1 μg/g, respectively, in tissues collected from 37 to 62 min (mean times) after administration. The individual concentrations of the two drugs in tissues are shown in Fig. 2 to 5. The results demonstrated that ampicillin and sulbactam penetrated into various tissues taken from patients during heart surgery. The ratio of the two compounds was approximately 2:1 in serum and also in samples of various tissues, such as sternum, pericardium, myocardium, and endocardium. The efficacy of the combination of ampicillin and sulbactam in perioperative prophylaxis could be assessed in 15 of the 16 patients. One patient died of heart failure accompanied by previously diagnosed cardiomyopathy 6 h after the operation. The postoperative recovery of 14 patients was uncomplicated. There was no infection around the wound or peripherally. The body temperatures of these patients were not increased postoperatively. The leucocyte counts of the patients were slightly increased on the second day after the operation but returned to the normal range 2 days later.

Three days after the completion of the ampicillin-sulbactam prophylaxis and 6 days after the operation, infection of the sternum with *Staphylococcus aureus* was observed in a single patient. The infection was preceded by bursting of a circular suture in the area of the sternotomy.

No adverse drug reactions were noted in any patient during the perioperative prophylaxis.

## DISCUSSION

Infections after heart surgery represent a substantial risk that can compromise the quality of the surgical procedure and finally the success of the operation (9). In the choice of an antibiotic for perioperative prophylaxis, not only the antimicrobial spectrum and tolerance but also the pharmacokinetic properties of the drug are important. The total distribution of the active substance, excretion, and concentrations in various tissues in the area of the operation are all significant. The serum pharmacokinetics of ampicillin and sulbactam were similar after three intravenous combination doses to patients undergoing heart surgery (Fig. 1 and Table 1). The volumes of distribution were ca. 15.6 and 17.7 liters for ampicillin and sulbactam, respectively, suggesting that both drugs are widely distributed in extracellular fluid and tissues. Analyses of the samples indicated that ampicillin and sulbactam did indeed rapidly penetrate from the blood into the various tissues collected during heart surgery (Table 2 and Fig. 2 to 5). It is noteworthy that ampicillin and sulbactam were able to pass not only into cardiac tissue, such as the pericardium, myocardium, and endocardium (Fig. 3, 4, and 5), but also into the sternum within a few minutes (Fig. 2). The ratio of the two substances in the intravenous dose was 2:1, and this ratio was largely maintained in serum and in the various tissues affected by the

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Time after infusion (mean min ± SD)</th>
<th>Conc (μg/g) of:</th>
<th>Ampicillin</th>
<th>Sulbactam</th>
</tr>
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<tbody>
<tr>
<td>Sternum</td>
<td>37.5 ± 22.3</td>
<td>17.8 ± 9.9</td>
<td>8.8 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Pericardium</td>
<td>38.4 ± 21.9</td>
<td>50 ± 29.5</td>
<td>19.6 ± 10.1</td>
<td></td>
</tr>
<tr>
<td>Myocardium</td>
<td>45.8 ± 24.1</td>
<td>32.8 ± 20.3</td>
<td>15.2 ± 10</td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>61.7 ± 27.4</td>
<td>24.2 ± 12.4</td>
<td>10.2 ± 5.7</td>
<td></td>
</tr>
</tbody>
</table>

*a* Ampicillin (2 g) and sulbactam (1 g) were infused for 15 min. Sternum, pericardium, and myocardium tissue samples were evaluated for 16 patients; endocardium tissue samples (cardiac valves included) were evaluated for 15 patients.

![FIG. 2. Concentrations of ampicillin and sulbactam in the sternum of patients (n = 16) undergoing heart surgery. Infusion was as described in the legend to Fig. 1.](http://aac.asm.org/)
operation. This finding is of the utmost importance, as the presence of sulbactam is necessary to inhibit the degradation of ampicillin by β-lactamases. Sufficiently high concentrations of sulbactam must be present at the site of infection together with ampicillin. Analyses of ampicillin and sulbactam in samples taken from 16 patients during heart surgery revealed concentrations in serum and tissue that are effective even against aerobic and anaerobic bacteria that produce β-lactamases. The bacteria involved in postoperative infections following heart surgery, such as *S. aureus*, *S. epidermidis*, or streptococci (4, 7), are inhibited by ampicillin-sulbactam (MICs for 90% of strains) in the range of 0.5 to 4 μg of ampicillin per ml (6). These MICs were substantially exceeded by the concentrations of ampicillin in the various tissues and serum from all 16 heart surgery patients investigated. On the basis of our pharmacokinetic data, both compounds attained therapeutically effective concentrations in serum, in the various cardiac tissues, and even in the sternum. Although no adverse reactions related to ampicillin-sulbactam were observed during the 3 to 6 days of

FIG. 3. Concentrations of ampicillin and sulbactam in the pericardium of patients (*n* = 16) undergoing heart surgery. Infusion was as described in the legend to Fig. 1.

FIG. 4. Concentrations of ampicillin and sulbactam in the myocardium of patients (*n* = 16) undergoing heart surgery. Infusion was as described in the legend to Fig. 1.
prophylaxis, the group of 15 patients was too small to assess the tolerance of the combination in patients undergoing heart surgery. In addition, our assessment of the pharmacokinetic data is supported by the efficacy in a larger number of patients of 2 g of ampicillin and 1 g of sulbactam against systemic infections involving some tissues investigated in the present study. Thus, the observed penetration of ampicillin and sulbactam into the sternum provides an explanation for the successful treatment with this combination of patients suffering from bone infections (11). Other clinical studies have clearly demonstrated the efficacy of ampicillin-sulbactam in the prophylaxis of infectious complications in several types of surgical procedures, such as gastrointestinal, gynecological, or breast surgery (3, 5, 10). In conclusion, the pharmacokinetic data and clinical results strongly suggest that the combination of ampicillin and sulbactam is generally effective in perioperative prophylaxis for patients undergoing heart surgery and should provide adequate protection.

ACKNOWLEDGMENT

We acknowledge the support of G. Pfaff, R + D Laboratories, Pfizer/Mack, Illertissen, Germany, in statistical evaluations.

REFERENCES