Comparison of Concentrations of Sulbactam-Ampicillin Administered by Bolus Injections or Bolus plus Continuous Infusion in Tissues of Patients Undergoing Colorectal Surgery

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The concentrations of sulbactam and ampicillin were determined in sera and different abdominal tissues of 16 patients who underwent elective colorectal surgery. Patients were randomly allocated to two groups. At the time of induction of anesthesia, patients in group 1 (eight patients) were given 1,000 mg of sulbactam with 2,000 mg of ampicillin by intravenous bolus injection (3 min). This dose was administered again after 2 h by bolus injection by the same route. Patients in group 2 (eight patients) were given the same initial dose of sulbactam-ampicillin by bolus injection (3 min). Then, a continuous infusion of 1,000 mg of sulbactam with 2,000 mg of ampicillin in normal saline was immediately started and was administered over a 4-h period. Blood samples were collected to determine peak (10 min) and trough (end of surgery) antibiotic levels. Serial blood samples were also collected at predetermined periods (at the time of opening and closing of the abdominal cavity and at the time of surgical anastomosis). Abdominal wall fat, epiploic fat, and colonic wall tissue samples were collected simultaneously. Antibiotic concentrations were determined by high-performance liquid chromatography. Similar levels of the drugs in serum were observed for the two regimens of administration, with trough sulbactam levels of 33 ± 16 and 37 ± 22 µg/ml in groups 1 and 2, respectively, and trough ampicillin levels of 72 ± 55 and 79 ± 47 µg/ml in groups 1 and 2, respectively. Similar sulbactam concentrations were observed in abdominal tissues whichever regimen of administration was used; in fatty tissues the sulbactam concentrations ranged from 2.7 to 3.8 µg/g for group 1 and from 1.7 to 4.0 µg/g for group 2, and sulbactam concentrations in the colonic wall were 5.6 ± 7.7 and 6.8 ± 3.2 µg/g in groups 1 and 2, respectively (not significant). Again, no influence of the regimen of administration was observed on tissue ampicillin concentrations; in fatty tissues ampicillin concentrations ranged from 4.1 to 5.4 µg/g for group 1 and from 3.2 to 5.8 µg/g for group 2, and sulbactam concentrations in the colonic wall were 7.0 ± 2.8 and 11.0 ± 4.7 µg/g for groups 1 and 2, respectively (not significant). In most patients, the concentrations of ampicillin-sulbactam were greater than the MIC90 for B. fragilis. No influence of the regimen of administration was observed on the ratio of the two components in the tissues investigated and in sera. In conclusion, a second intraoperative bolus injection or a continuous infusion were equally effective in maintaining sulbactam-ampicillin concentrations in abdominal tissues. The first method of administration can be recommended since it is easier to handle.

Colorectal surgery is a contaminated aseptic type of surgery, and prophylactic antibiotics are widely used prior to and during surgery. The importance of the prophylactic antibiotics in reducing postoperative infections and mortality has been demonstrated (4, 15, 22). Antibiotics are selected on the basis of their ability to eradicate the bacteria most likely to contami-


**MATERIALS AND METHODS**

**Patients and drugs.** This study received the approval of the ethical committee of our institution (Hopital Nord), and all patients gave their informed consent. Fifteen patients were scheduled for elective colorectal surgery. All patients had normal hepatic function (serum bilirubin level, <10 μmol/liter) and renal function (creatinine clearance, >100 ml/min/1.73 m²). None had a history of allergic reaction to β-lactam antibiotics. None presented with any clinical sign (normal body temperature, normal physical examination) or laboratory sign (normal leukocyte count) of infection or had received antibiotic treatment in the preceding 3 weeks. Patients were randomly assigned to one of two groups. Patients in group 1 (five males and three females; mean age, 57 ± 12 years; mean body weight, 65 ± 10 kg) were given 1,000 mg of sulbactam with 2,000 mg of ampicillin by intravenous bolus injection (3 min). This dose was administered again after 2 h. Patients in group 2 (six males and two females; mean age, 59 ± 14 years; mean body weight, 67 ± 11 kg) were given by intravenous bolus injection (3 min) the same initial dose of sulbactam-ampicillin used for group 1 patients, and a continuous infusion of 1,000 mg of sulbactam with 2,000 mg of ampicillin in normal saline was immediately started and administered over a 4-h period.

**Specimen collection.** Blood samples (10 ml each) were collected from a central venous catheter before surgery, 10 min after the beginning of surgery (peak level), and at the end of surgery (trough level). Blood samples were kept on ice and were centrifuged in a refrigerated centrifuge within 30 min of collection. Sera were placed in polypropylene tubes. Several samples of the selected tissues were collected during surgery. Abdominal wall fat and epiploic fat were obtained at the times of opening and closure of the abdominal cavity; colonic wall and epiploic fat samples were obtained at the time of surgical anastomosis. The exact time of sample collection was registered, and a corresponding blood sample was taken. Tissue sample sizes were 1 cm³ or larger. To remove the attached blood, tissue samples were rinsed in sterile saline and were cleaned with dry, sterile gauze. Tissue samples were placed in sterile polypropylene tubes. Serum and tissue samples were assayed immediately following surgery.

**Specimen preparation procedures.** For determination of sulbactam levels in serum, 1 ml of the sample was mixed with 0.5 ml of 5% propylene glycol and 5 ml of water. After mixing and centrifugation the sample was then treated in the same way that the sulbactam samples were. The aqueous phase (50 μl) was injected into the HPLC system.

**TABLE 1. Concentrations of sulbactam and ampicillin in serum**

<table>
<thead>
<tr>
<th>Concen</th>
<th>Group 1</th>
<th>Sulbactam concn (μg/ml)</th>
<th>Ampicillin concn (μg/ml)</th>
<th>Sulbactam concn/ampicillin concn ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (10 min)</td>
<td>142 ± 9</td>
<td>267 ± 155</td>
<td>0.5 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Trough (end of surgery)</td>
<td>33 ± 16</td>
<td>72 ± 52</td>
<td>0.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>109 ± 8</td>
<td>207 ± 85</td>
<td>0.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 ± 22</td>
<td>79 ± 47</td>
<td>0.5 ± 0.2</td>
<td></td>
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</tbody>
</table>

* Values are means ± standard deviations.

**Evaluation of sulbactam:ampicillin ratios.** Samples of specific tissues were analyzed according to collection time: opening and closure of the abdominal cavity and surgical anastomosis of the colon. For each defined period, the ratios of the concentrations of the two compounds (sulbactam and ampicillin) were obtained for the different tissue samples and the corresponding serum samples. The mean ± the standard deviation ratio was calculated for both groups. Antibiotic concentrations in tissues were also compared to the MICs at which 50% (MIC₅₀) and 90% (MIC₉₀) of Bacteroides fragilis isolates are inhibited (2 and 8 μg/mliter for sulbactam and ampicillin, respectively), assuming a 1:2 sulbactam-to-ampicillin ratio.

**Clinical evaluation.** All patients were closely monitored during their hospital stays and for up to 30 days for clinical or laboratory signs of infection.

**Statistical analysis.** Statistical analysis was performed by Student’s t test for unpaired values and the chi-square test. A P value of less than 0.05 was considered significant.

**RESULTS**

**Concentrations in serum.** The sulbactam and ampicillin concentrations in serum are presented in Table 1. No significant differences in concentrations in serum were observed, whichever drug regimen used. At the end of surgery both methods of drug administration achieved high levels of sulbactam and ampicillin in the two groups.

**Antibiotic concentrations in tissues.** The sulbactam and ampicillin concentrations in tissues at various periods during surgery are presented in Table 2. Stable concentrations of antibiotics were observed in fatty tissues when the concentrations at the surgical opening and closure periods are compared. This was observed after administration of a second bolus dose or the use of the continuous infusion during surgery. No significant differences were observed between the two groups. Sulbactam and ampicillin concentrations were higher in the colonic wall than in fatty tissues. The mode of antibiotic administration during surgery had no influence on the concentrations achieved in colonic wall samples.

**Sulbactam-to-ampicillin concentration ratios.** The sulbactam-to-ampicillin concentration ratios are presented in Tables 1 and 3. For group 1, they ranged from 0.33 to 0.70 in tissues and from 0.44 to 0.67 in serum. For group 2, the ratios ranged from 0.41 to 0.69 in tissues and from 0.46 to 0.67 in serum. The ratios were not significantly modified by the method of administration of antibiotics during surgery.

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Table 4 presents data for the patients who achieved ampicillin plus sulbactam concentrations in tissues greater than the MIC for B. fragilis. For most patients concentrations in the fatty tissues greater than the MIC₅₀ were achieved, but only in the colonic wall were concentrations greater than the MIC₉₀ for B. fragilis achieved.

No patient had any signs of postoperative infection during the 30-day follow-up period.
TABLE 2. Concentrations of sulbactam and ampicillin in abdominal tissues and serum of patients undergoing colorectal surgery at different periods of the surgical procedure

<table>
<thead>
<tr>
<th>Group and drug&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Opening&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Surgical anastomosis&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Closure&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal wall fat (µg/g)</td>
<td>Epiploic fat (µg/g)</td>
<td>Serum (µg/ml)</td>
</tr>
<tr>
<td>Group 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulbactam</td>
<td>3.1 ± 3.8</td>
<td>3.1 ± 2.7</td>
<td>47 ± 18</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>5.1 ± 2.5</td>
<td>5.3 ± 3.1</td>
<td>88 ± 29</td>
</tr>
<tr>
<td>Group 2&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulbactam</td>
<td>4.0 ± 4.2</td>
<td>3.4 ± 2.3</td>
<td>55 ± 23</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>5.8 ± 1.1</td>
<td>5.7 ± 3.3</td>
<td>120 ± 47</td>
</tr>
</tbody>
</table>

<sup>a</sup> Bolus and infusion doses were 1,000 mg for sulbactam and 2,000 mg for ampicillin.
<sup>b</sup> For groups 1 and 2, the opening times in relation to the start of antibiotic administration were 35 ± 6 and 36 ± 7 min, respectively.
<sup>c</sup> For groups 1 and 2, the surgical anastomosis times in relation to the start of antibiotic administration were 124 ± 12 and 117 ± 13 min, respectively.
<sup>d</sup> For groups 1 and 2, the closure times in relation to the start of antibiotic administration were 184 ± 11 and 175 ± 16 min, respectively.
<sup>e</sup> P < 0.02 compared with concentrations in fatty tissues.

DISCUSSION

This study shows that the intraoperative administration of sulbactam-ampicillin as two sequential bolus injections or by bolus injection plus a continuous infusion during surgery had no significant influence on antibiotic penetration into tissue. Previous studies have established the basic principles of antibiotic prophylaxis in surgical procedures, and the main points are that (i) the antibiotic must reach the tissues involved before surgery allows bacterial contamination, and (ii) the drug must attain and maintain concentrations in serum and tissues high enough to inhibit the growth of contaminating pathogens (7, 9, 15, 22). This study addressed the tissue penetration of a β-lactam-β-lactamase inhibitor combination, with the drugs being administered as two sequential bolus injections or one bolus injection immediately followed by a continuous infusion during the intraoperative period. The absolute concentrations of the drugs in tissues, the time course of these concentrations, and the extent of penetration are of interest. Penetration was evaluated by measuring the concentration in tissue-to-concentration in plasma ratios at specific collection times. The data for sulbactam and ampicillin are in agreement with results reported previously (11, 13, 14). Specific differences between tissues were observed. The extent of sulbactam and ampicillin penetration into fat was 4 to 8% of the levels in serum, significantly lower than the penetration into the colonic wall (10 to 20%; P < 0.02). This is in agreement with a study on the penetration of tazobactam-piperacillin into fat, which was 10% of the levels in plasma (16), but is at variance with a study with clavulanic acid-amoxicillin, in which the former drug had a higher level of penetration (30%) than the latter drug (10 to 20%) (17). The exact mechanisms that cause these important findings deserve further investigations. The level of penetration of sulbactam and ampicillin into the colonic wall was higher than that into fatty tissues. This might be explained by the fact that the blood flow to the gastrointestinal tract is higher than that to the fat. From these data, it is clear that no single mechanism governs the extent of penetration of antibiotics into tissues. Further investigations are needed to more clearly define the relationship among blood flow, water content, and the physicochemical properties of the agents.

In the present study, the extent of penetration of both compounds (sulbactam and ampicillin) was maintained throughout the surgical procedure thanks to the intraoperative administration of the antibiotics. In clinical practice, when intermittent antibiotic dosing is used, antibiotic levels in serum and tissues will gradually decrease. The bacteria will often be exposed to low concentrations of the antibiotic during the dosing interval and infection may start in the tissues potentially affected by postoperative infection. This emphasizes the need for repeated administration of drugs with shorter half lives (7, 15, 17, 22), such as sulbactam and ampicillin (8, 12). If the intraoperative administration is not performed, decreased concentrations of both compounds, sulbactam and ampicillin, would probably be measured in fatty tissues and colonic wall, with an increased risk of postoperative infection. To maintain active concentrations of antibiotics, one can consider either the administration of a second intraoperative bolus injection or continuous administration during surgery. The administration of an intraoperative bolus dose (after 2 h, which corresponds to two half-lives for most antibiotics used) is recommended, but objective data are lacking (7, 15, 22). β-Lactam antibiotics can also be administered by continuous infusion (6), and in the present

TABLE 3. Sulbactam concentration/ampicillin concentration ratios at different periods of the surgical procedure in patients undergoing colorectal surgery

<table>
<thead>
<tr>
<th>Group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Opening</th>
<th>Surgical anastomosis</th>
<th>Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal wall fat</td>
<td>Epiploic fat</td>
<td>Serum</td>
</tr>
<tr>
<td>Group 1</td>
<td>1.2 ± 2.1</td>
<td>0.60 ± 0.60</td>
<td>0.52 ± 0.11</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.80 ± 0.90</td>
<td>0.70 ± 0.70</td>
<td>0.67 ± 0.11</td>
</tr>
</tbody>
</table>

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the use of a continuous infusion started immediately after injection of a second bolus dose after 2 h (two half-lives) or by After the administration of a first bolus injection 30 min prior to maintenance of a constant antibiotic levels in tissue during surgery. Intraoperative administration of sulbactam-ampicillin is able to follow-up period. Laboratory signs of postoperative infection during the 30-day view, in the present study no patient exhibited any clinical or clinical use.

Current practice with β-lactam–β-lactamase inhibitor combinations is to maintain an optimal ratio between the two components (1:2 sulbactam to ampicillin) (3). Because of their similar pharmacokinetics these two components theoretically maintain a 1:2 ratio at the site of potential infection over the entire period of surgery. In the present study, ratios close to 1:2 were obtained in the tissues studied, but it has been suggested that the efficacy of sulbactam-ampicillin is more dependent upon the maintenance of both sulbactam and ampicillin levels above a minimum critical concentration than on the maintenance of a constant 1:2 ratio (2). With both regimens of antibiotic administration used in the present study, the levels of sulbactam and ampicillin were maintained in the studied tissues until the end of surgery. Will these concentrations be active against the most common pathogens encountered during surgery? It can be speculated that a desirable goal is to achieve antibiotic levels above the MIC for the potential pathogen. This also means maintaining such levels until the end of the surgical procedure (7, 19). At the time of closure of the abdomen, sulbactam concentrations in the fatty tissues reached an average of 2 μg/g. At this concentration of sulbactam, the ampicillin MIC for plasmid-mediated β-lactamase-producing strains of E. coli can be as high as 16 μg/ml (1). Given the average level of ampicillin achieved in the same tissues (Table 2), some patients can be at risk of postoperative infection. This finding was observed whatever the regimen of antibiotic administration used. With regard to B. fragilis, in most patients, antibiotic levels greater than the MIC50 were achieved in the fatty tissues up to the end of surgery, but only in the colonic wall were antibiotic concentrations greater than the MIC90 for this organism achieved. From a clinical point of view, in the present study no patient exhibited any clinical or laboratory signs of postoperative infection during the 30-day follow-up period.

In conclusion, the results of this study indicate that the intraoperative administration of sulbactam-ampicillin is able to maintain constant antibiotic levels in tissue during surgery. After the administration of a first bolus injection 30 min prior to surgery, antibiotic levels can be maintained either by the injection of a second bolus dose after 2 h (two half-lives) or by the use of a continuous infusion started immediately after administration of the first bolus dose and administered over 4 h.

REFERENCES