Comparison of Ceftazidime Concentrations in Bile and Serum

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Biliary excretion of ceftazidime, a new broad-spectrum cephalosporin, was studied in two groups of patients after administration of a 2-g dose intravenously. Group A included 10 patients in whom ceftazidime levels in bile were measured during cholecystectomy. Group B included 10 patients with indwelling biliary tubes in whom ceftazidime levels in bile and serum were simultaneously measured at 0.5, 1, 2, 4, 6, and 8 h after administration of the drug. Although ceftazidime levels were variable, they exceeded the minimal inhibitory concentrations of most biliary tract pathogens in both groups.

Ceftazidime (CAZ) is a new cephalosporin with a broad spectrum of in vitro activity against aerobic and facultative gram-negative bacilli, the latter including Enterobacteriaceae and nonfermenting organisms such as Pseudomonas aeruginosa (4). This spectrum of activity makes CAZ a potentially useful drug for prophylaxis and treatment of biliary tract infections.

The purpose of the present work was to assess levels of CAZ in the bile of patients undergoing biliary tract surgery or of postsurgical patients who had indwelling catheters inserted into their common bile ducts.

MATERIALS AND METHODS

The antibiotic ceftazidime (GR 20263) was kindly provided by Glaxo Group Research Ltd., London, England.

Patients. There were two groups of patients, totaling 19, in this study. None was receiving concurrent antimicrobial therapy. All provided written informed consent to participate in this study, which had been approved by the ethical and investigational committees of this hospital.

Group A included 10 patients about to undergo cholecystectomy (Table 1). The patients were all females (with one exception) whose ages ranged from 36 to 70 years (mean ± standard deviation, 53.1 ± 10.1). The underlying diseases were cholelithiasis in eight cases and hydatid liver cysts in two others. Weights ranged from 54 to 72.8 kg (mean, 64.7 ± 6.5) and heights ranged from 152 to 173 cm (mean, 156.7 ± 5.8). Serum bilirubin ranged from 0.3 to 1.5 mg/dl (normal, ≤1.2 mg/dl) with a mean of 0.6 ± 0.3. Alkaline phosphatase varied from 53 to 401 U/liter (normal, ≤100 U/liter) with a mean of 131 ± 97.5. Results of serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) determinations of group A patients are expressed in Table 1; mean values were, respectively, 37.9 ± 26.9 (normal, ≤45 U/liter) and 44.8 ± 33.3 (normal, ≤45 U/liter). Serum creatinine concentrations ranged from 0.5 to 1.4 mg/dl (mean, 0.95 ± 0.25).

Single samples of gallbladder bile were taken from these patients during cholecystectomy. One patient in group A, who had external bile drainage during the postoperative period, was later included also in group B. In group A patients, the bile sample and simultaneous blood specimen were taken when the gallbladder was surgically approached. Blood samples were taken also at 0.5 and 8 h after CAZ injection.

Group B included 9 patients plus one originally from group A (Table 2). Six patients had undergone surgery for cholecystitis, three for hydatid liver cysts, and one because of traumatic liver injury. All had indwelling biliary tubes, 5 with Kehr tubes, 5 with transcystic catheters. Six were males and four were females; ages ranged from 24 to 87 years (mean, 59.3 ± 15.9). Weights ranged from 53.5 to 75.5 kg (mean, 61.9 ± 6.4), and heights varied from 141 to 170 cm (mean, 159.2 ± 8.9). Serum bilirubin ranged from 0.5 to 8.3 mg/dl (mean, 1.7 ± 2.2). Alkaline phosphatase varied from 39 to 401 U/liter (mean, 171 ± 103); mean SGOT and SGPT were, respectively, 89.7 ± 121 and 163.2 ± 148.6 U/liter. Renal function as measured by levels of serum creatinine varied from 0.8 to 1.8 mg/dl (mean, 1.2 ± 0.2).

Simultaneous blood and bile specimens were taken at 0.5, 1, 2, 4, 6 and 8 h after CAZ injection. All studies were performed in the first 15 days after biliary tract surgery (mean, 5.9 ± 4.0 days).

CAZ injection and assays. All patients received a single 2-g dose of CAZ dissolved in 50 ml of 5% dextrose in water, infused intravenously over 15 min. All blood and bile specimens were immediately transported to the microbiology laboratory. The specimens

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with underlying obstructing and nonobstructing biliary tract diseases (3, 6). Cephalosporins have been used frequently in the prophylaxis and treatment of biliary tract infections, owing to their low toxicity and their excretion into unobstructed bile (1, 2, 5, 7–16). Cephalosporins with a narrow spectrum of activity are of limited value in many biliary tract infections (2, 16). There are, however, a number of cephalosporins with broad spectrums of activity against many Enterobacteriaceae, including organisms resistant to aminoglycosides (4, 19). CAZ, one of the broad-spectrum agents, combines a high degree of activity against nonfermenting aerobic gram-negative rods, e.g., P. aeruginosa (including P. aeruginosa resistant to aminoglycosides and to other cephalosporins) (4, 19). Our study shows adequate excretion of CAZ into bile, with drug concentrations which are well over the minimal inhibitory concentrations of most biliary tract pathogens. Levels showed a wide range of individual variations which could not always be explained by factors such as dose, bile sampling time, gallbladder function, and bilirubin levels. Other authors have also observed these individual variations (2, 7, 9, 10, 14, 15). Wittmann et al. obtained similar results in a group of four patients with indwelling T tubes (18). Even 8 h after a single g-dose, detectable levels were found in most patients. These data and preliminary clinical trials justify further studies to define the role of CAZ as a single agent in prophylaxis and treatment of biliary tract infections. Finally, it is important to remember that diffusion of antibiotics into obstructed bile is very poor; therefore, biliary excretion may not be an essential consideration in the selection of antimicrobial agents for prophylaxis or treatment of biliary tract sepsis in patients with bile obstruction (6).

**DISCUSSION**

Biliary tract infections are a well known cause of morbidity and mortality, especially in patients

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**TABLE 1. Group A CAZ concentrations in serum and bile**

<table>
<thead>
<tr>
<th>Patient no. (underlying disease)*</th>
<th>Bilirubin (mg/dl)</th>
<th>Alkaline phosphatase (U/liter)</th>
<th>SGOT (U/liter)</th>
<th>SGPT (U/liter)</th>
<th>Creatinine (mg/dl)</th>
<th>CAZ dose (mg/kg)</th>
<th>Min after end of infusion</th>
<th>CAZ concns in serum/bile (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (C)</td>
<td>0.3</td>
<td>65</td>
<td>9</td>
<td>9</td>
<td>1.0</td>
<td>2.75</td>
<td>25</td>
<td>70.2/7.5</td>
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<tr>
<td>9 (C)</td>
<td>0.8</td>
<td>93</td>
<td>39</td>
<td>92</td>
<td>1.1</td>
<td>31.2</td>
<td>45</td>
<td>108.0/58.0</td>
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<tr>
<td>10 (C)</td>
<td>1.1</td>
<td>94</td>
<td>65</td>
<td>100</td>
<td>0.5</td>
<td>27.7</td>
<td>55</td>
<td>54.7/7.8</td>
</tr>
<tr>
<td>4 (C)</td>
<td>0.7</td>
<td>107</td>
<td>39</td>
<td>80</td>
<td>0.9</td>
<td>27.4</td>
<td>60</td>
<td>74.7/17.0</td>
</tr>
<tr>
<td>5 (C)</td>
<td>0.4</td>
<td>127</td>
<td>20</td>
<td>32</td>
<td>0.9</td>
<td>35.7</td>
<td>60</td>
<td>70.1/6.6</td>
</tr>
<tr>
<td>6 (H)</td>
<td>1.5</td>
<td>401</td>
<td>68</td>
<td>ND</td>
<td>1.4</td>
<td>33.3</td>
<td>60</td>
<td>94.3/6.8</td>
</tr>
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<td>7 (C)</td>
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<td>77</td>
<td>7</td>
<td>7</td>
<td>0.8</td>
<td>32.7</td>
<td>65</td>
<td>96.2/24.5</td>
</tr>
<tr>
<td>2 (C)</td>
<td>0.4</td>
<td>96</td>
<td>22</td>
<td>ND</td>
<td>1.3</td>
<td>29.1</td>
<td>85</td>
<td>72.6/25.0</td>
</tr>
<tr>
<td>8 (H)</td>
<td>0.4</td>
<td>197</td>
<td>46</td>
<td>69</td>
<td>0.9</td>
<td>30.3</td>
<td>160</td>
<td>51.6/48.0</td>
</tr>
</tbody>
</table>

* Underlying disease is indicated in parentheses: C, cholelithiasis; and H, hydatid liver disease.

ND, Not determined.

were assayed immediately or stored at −20°C and assayed within 14 days. CAZ levels were measured by the agar-well microbiological diffusion procedure as described elsewhere (17), with Proteus morganii NCTC 235 as the indicator organism. All single specimens were assayed in triplicate.

**RESULTS**

Concentrations of CAZ in serum and bile of group A patients are shown in Table 1. Levels of CAZ in bile, 25 to 160 min after intravenous CAZ infusion ranged from 6.6 to 58 µg/ml (mean, 22.4 ± 17). Levels of CAZ in serum, measured at these same times, ranged from 51.6 to 108 µg/ml (mean, 77.4 ± 17). Levels of CAZ in serum 15 min and 8 h after the end of the infusion were also measured; their mean values were 144.5 ± 13.9 and 8.7 ± 4.4 µg/ml, respectively.

Concentrations of CAZ, measured simultaneously in serum and bile of group B patients at 0.5, 1, 2, 4, 6, and 8 h are shown in Table 2. Maximum levels of CAZ appeared in bile between 1 and 2 h after intravenous infusion. Mean levels at 1 and 2 h were 34.1 ± 24.8 and 31.1 ± 21.6 µg/ml, respectively. Mean CAZ levels in serum at 1 and 2 h were 103.5 ± 34.5 and 62.0 ± 22.0 µg/ml, respectively. At 8 h after intravenous infusion, all but one patient still had detectable levels of CAZ in bile (mean, 6.9 ± 6.3). At 8 h, levels of CAZ in serum ranged from 1.4 to 20.8 µg/ml (mean, 9.8 ± 7.8). Considerable individual variations of CAZ levels in bile were observed. Patient 5 in group B had common biliary tract obstruction.

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* ND, Not determined.
TABLE 2. Group B CAZ concentrations in serum and bile

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CAZ dose (mg/kg)</th>
<th>Creatinine (mg/dl)</th>
<th>Biliubin (mg/dl)</th>
<th>SCFT (U/liter)</th>
<th>SGPT (U/liter)</th>
<th>Albumin phosphate (mg/dl)</th>
<th>Bilirubin (mg/dl)</th>
<th>Alkaline phosphatase (U/liter)</th>
<th>CAZ concentration in serum/bile (mg/liter)</th>
<th>CAZ concentration in bile (mg/liter)</th>
<th>CAZ concentrations in serum/bile at h after end of infusion:</th>
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<td>ND</td>
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<td>106</td>
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<td>44.1</td>
<td>1</td>
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<td>17</td>
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</table>

Means = SD 1.7±2.2 171±108 89.7±141 126±148.2±12.2 8.2±3.2 122±22 10.2±34.3 6.2±22.0 32.3±19.8 18.9±15.7 8.8±7.8 6.3±4.3

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LITERATURE CITED