Biliary Excretion of Cefixime: Assessment in Patients Provided with T-Tube Drainage

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The biliary excretion profile of cefixime was studied in 10 patients provided with T-tube drainage of the common bile duct after cholecystectomy. Following a single 200-mg oral dose, the peak concentration of cefixime in bile reached 56.9 ± 70 mg/liter, approximately 20 times as high as the peak concentration in serum, 2.3 ± 0.85 mg/liter. Cefixime levels in bile proved relatively sustained, since a concentration of 4.3 ± 3.7 mg/liter was still found 20 h after dosing. The cumulative amount of cefixime recovered in the 24-h bile drainage averaged 10.0 ± 12.3 mg, which is 5% of the administered dose and positions this β-lactam antibiotic among the most highly bile-excreted cephalosporins. The presented results show that a single 200-mg oral dose of cefixime provided drug levels in bile consistently higher than the MICs for the most frequently recovered members of the family Enterobacteriaceae in biliary tract infections and maintained these levels for over 20 h after dosing. Accordingly, this cephalosporin deserves further clinical trials to assess its usefulness in both prophylaxis and treatment of biliary tract infections.

Cefixime is a new oral cepham antibiotic that inhibits a wide variety of gram-positive and gram-negative bacteria, especially most members of the family Enterobacteriaceae, including strains producing the common plasmid-mediated β-lactamases. Poor activity has been reported against Staphylococcus aureus, enterococci, Pseudomonas aeruginosa, and anaerobes (4, 16). The pharmacokinetic properties of cefixime are characterized mainly by a relatively prolonged elimination half-life and extrarenal clearance processes that appear to be substantial since after intravenous administration, renal clearance accounts for only 40% of total systemic clearance in healthy subjects (7). So far, though, no biologically active metabolites of the drug have been identified in plasma or urine. Accordingly, high biliary excretion may be expected for this cephalosporin. The aim of the present study was to investigate to which extent the extrarenal clearance of cefixime is accounted for by biliary excretion of unchanged drug.

MATERIALS AND METHODS

Patients. Ten adult patients requiring T-tube drainage of the common bile duct after cholecystectomy were investigated. Seven of them were females and three were males, with a mean age of 52.4 years and a mean body weight of 69.8 kg. Nine patients presented with cholecistitis, while one had gallbladder carcinoma. Laboratory data, including kidney and liver function tests, were determined 24 h before cefixime administration. The patients had normal renal function as judged by creatinine clearance (range, 84 to 128 ml/min) obtained from the predictive formula of Cockcroft and Gault (3). Regarding liver function status, all patients had normal serum bilirubin while seven patients exhibited at least two of the following parameters above the normal: aspartate aminotransferase range, 13 to 59 IU/liter (mean, 39; normal, <29); alanine aminotransferase range, 32 to 123 IU/liter (mean, 87; normal, <30); alkaline phosphatase range, 52 to 294 IU/liter (mean, 153; normal, <90). Patients with severe hepatic dysfunction or a history of allergy to a β-lactam antibiotic were not enrolled in the study, nor were those requiring antimicrobial therapy for any infectious process.

The administration of other pharmaceutical agents concomitantly with cefixime was avoided.

Appropriately, informed written consent was obtained from each patient prior to enrollment in the study. The protocol was reviewed and approved by Ethics Committee of the Hospitalo-University Center.

Sampling. For each patient, the study day was at least 1 week after surgical intervention (range, 7 to 16 days; mean, 10.0 ± 2.8 days). Each patient received a single 200-mg dose of cefixime given with 10 ml of water, after an overnight fast. Fasting was continued for a further 3 h.

Concentrations in serum were measured before and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15 h following oral administration.

Fractional bile samples were taken hourly through 15 h after cefixime administration, and the last sample was taken 9 h later to complete the biliary recovery up to 24 h after dosing. Urine was collected in three periods: 0 to 6, 6 to 12, and 12 to 24 h after cefixime administration. Control samples of bile and urine were taken before drug administration. All specimens were stored at −80°C until assay.

Assay. Cefixime concentrations in serum, bile, or urine were determined by high-performance liquid chromatography (HPLC) according to a methodology previously described (10).

(i) Serum. An aliquot of serum (0.5 ml) was mixed thoroughly with an equal volume of acetonitrile in a 7-ml screw-cap glass tube on a vortex mixer (The Vortex Manufacturing Co., Cleveland, Ohio). The tube was then gently shaken by rotation for 10 min (20 rpm). The resulting mixture was centrifuged for 10 min at 1,000 × g. The supernatant was transferred with a Pasteur pipette to another screw-cap glass tube, and seven aliquots of methylene chloride were added.

The mixture was allowed to equilibrate for 10 min and then gently shaken by rotation for 10 min (20 rpm). After centrif-
Ugation (10 min at 1,000 \times g), a 50-, 20-, or 5-\mu l aliquot of the upper aqueous layer was injected into the column.

(ii) Urine and bile. All urine and bile samples were centrifuged, diluted (1:20 and 1:10, respectively), and injected into the chromatograph.

Chromatography was performed on a reversed-phase analytical column (150 by 4.6 mm) filled with 5-\mu m-diameter octadecylsilane-coated silica particles. The mobile phase consisted of 17% acetonitril in 10 mM sodium hydrogen phosphate and was adjusted to pH 2.2 with phosphoric acid.

The flow rate was set at 1 ml/min, and the A220 was measured. The detection limit was 0.05, 1, and 0.5 \mu g/ml in serum, urine, and bile, respectively. For each of the three kinds of biological samples, the within- and between-day reproducibilities were characterized by a coefficient of variation lower than 8.5% at both low and high cefixime concentrations (in serum, 0.1 and 2 \mu g/ml; in urine, 5 and 100 \mu g/ml; in bile, 2 and 50 \mu g/ml). The linearity of the detector response was assessed for concentrations ranging from the detection limit to 100, 500, and 200 \mu g/ml for serum, urine, and bile, respectively (n = 6 for each concentration included). The coefficients of correlation between the concentrations and peak areas were, respectively, 0.997, 0.989, and 0.987.

**Kinetic analysis.** Pharmacokinetic parameters for cefixime were determined by noncompartmental methods (9). The peak concentrations in serum or bile and times of their appearance were determined following visual inspection of the data. Values for the elimination rate constant (\beta) were estimated by linear regression of the semilogarithmic plot of the last four concentrations in serum versus time. The elimination half-life was calculated from (\ln 2)/\beta. The area under the serum concentration-time curve (AUC\_ser) was calculated by the linear trapezoidal method and extrapolated to infinity by dividing the last measurable concentration by \beta. The apparent total clearance of cefixime (CL\_T/F) was obtained from the equation CL\_T/F = dose/AUC\_ser, where F is the bioavailability factor. Renal clearance and biliary clearance (CL\_b) were estimated as \frac{Au/AUC\_ser}{Ab/AUC\_ser}, where Au and Ab represent the amount of unchanged drug excreted in the urine and in the bile, respectively.

**RESULTS**

Figure 1 shows the comparative profile of the serum and biliary concentration-time curves after oral administration of 200 mg of cefixime. The mean \pm standard deviation peak concentration in bile reached 56.9 \pm 70.9 \mu g/liter, while that in serum was 2.3 \pm 0.85 \mu g/liter (Table 1).

A mean drug concentration of 4.3 \pm 3.7 \mu g/liter was still observed in bile 20 h after dosing. The CL\_T/F of cefixime was 195.0 \pm 88.5 ml/min, and the terminal elimination half-life

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (mean \pm SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (\mu g/liter)</td>
<td>2.3 \pm 0.85</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>5.1 \pm 2.6</td>
</tr>
<tr>
<td>AUC_ser (\mu g \cdot h/liter)</td>
<td>20.1 \pm 7.8</td>
</tr>
<tr>
<td>t_1/2b (h)</td>
<td>3.45 \pm 0.75</td>
</tr>
<tr>
<td>CL_T/F (ml/min)</td>
<td>195 \pm 88</td>
</tr>
<tr>
<td>Ab_24 (% of dose)</td>
<td>26.7 \pm 13.1</td>
</tr>
<tr>
<td>Ab_24 (% of dose)</td>
<td>5.0 \pm 6.2</td>
</tr>
</tbody>
</table>

* C\_max peak concentration in serum; T\_max, time of peak occurrence; t\_1/2b, serum drug elimination half-life; AUC\_ser, 24-h urinary recovery; Ab\_24, 24-h biliary recovery.
greatly compounds antimicrobial chemotherapy are in organisms.

The cumulative amount of unchanged drug recovered in the 24-h bile drainage averaged 10.0 ± 12.3 mg (i.e., 5% of the dose), and the CL\(_B\) was found to vary greatly between the subjects, ranging from 0.85 to 27.3 ml/min (mean, 8.3 ± 8.8 ml/min). The relative contribution of the CL\(_B\) process to the CL\(_{TP}\) of cefixime, as determined by the ratio CL\(_B\)/CL\(_{TP}\) × 100, was only 5.0% ± 6.1%.

Of note, there was no significant correlation between the amount of cefixime recovered in the 24-h bile drainage and the 24-h cumulative volume of bile secreted: r = 0.33 as provided by Spearman’s range correlation test (5). No correlation was found between the bile excreted amount of drug and any of the liver function tests.

**DISCUSSION**

Bioavailability parameters for a single 200-mg oral dose of cefixime are similar to those reported in the literature. Indeed, the mean values for peak concentration, time of peak concentration, and AU\(C_{o-m}\) found by Kees et al. (11) and Nakashima et al. (15) in healthy subjects were, respectively, 2.95 and 2.08 mg/liter, 3.45 and 4.04 h, and 20.9 and 15.0 mg·h/liter and appear to be good agreement with the values recorded in our study (Table 1).

The 24-h biliary recovery of cefixime, being 5% of the dose, ranks among the highest compared with those of the other cephalosporins that we previously investigated, following cefpiramide and ceftriaxone (1). However, all the patients investigated in our study had a certain degree of liver dysfunction. The available data in humans (20, 21) suggest that the biliary excretion of antibiotics is impaired in patients with liver disease, most likely through decreasing drug uptake into hepatocytes or transfer from the liver cell into the bile. Accordingly, the mean amount of cefixime ultimately recovered in the bile drainage most likely represents an underestimation of the actual biliary excretion for this drug.

Carrier-mediated transport systems and binding to intracellular hepatic proteins (14) appear to be important in the biliary excretion of compounds which are concentrated in bile (i.e., bile-to-plasma drug concentration ratio > 1.0). In vitro experiments previously showed that almost all \(\beta\)-lactam antibiotics use a common carrier system responsible for their uptake into isolated rat hepatocytes (18). Whether such a mechanism also underlies the relatively high biliary excretion of cefixime in humans is unknown yet.

In healthy subjects, only 40% of cefixime total clearance is accounted for by renal clearance after intravenous administration (7). So, given the relatively low contribution of CL\(_B\) to the CL\(_{TP}\) of the drug found in the present study, the extrarenal clearance processes of cefixime remain unclear.

The results of this study indicate that the usual 200-mg dose of cefixime provides concentrations in serum and bile that might render the drug useful for both prophylaxis and treatment of biliary tract infections (BTI) by susceptible organisms. While high antibiotic levels in serum, wounds, and tissues surrounding the gallbladder seem to be sufficient in prophylaxis (12), it has been shown that elevated concentrations are needed in both serum and bile to optimize antimicrobial chemotherapy of acute cholangitis (8). Furthermore, even if bile duct obstruction tends to reduce greatly the biliary excretion of drugs, only highly bile-excreted compounds may be expected to produce, in this setting, concentrations in bile that could be sufficient to inhibit the causative pathogens, as previously shown for mezlocillin (2).

*Escherichia coli* is widely recognized as the most frequent organism in BTI (13, 17). Cefixime exhibits sustained therapeutic concentrations against this pathogen in both serum and bile. Indeed, the mean drug level in bile at time 20 h is eight times the MIC for 90% of strains tested (0.5 \(\mu\)g/ml) for *E. coli*, while concentrations in serum remain above that MIC for about 12 h. There are some limitations, however, in the use of this drug in BTI. Indeed, cefixime is ineffective against enterococci and exhibits poor activity against anaerobes, especially *Bacteroides* spp., which are resistant (MIC for 90% of strains tested, >128 \(\mu\)g/ml). However, the pathogenicity of enterococci in BTI is unclear, as these organisms are nearly always part of mixed infections.

Regarding anaerobes, an antimicrobial agent providing coverage of both *Bacteroides fragilis* and members of the *Enterobacteriaceae* should probably be preferred to cefixime in the management of those BTI in which a mixture of aerobic and anaerobic organisms is likely to be involved, namely, cholangitis in the elderly or patients with previous bile duct-bowel anastomoses (6).

Even though some clinical reports have proved encouraging (19), the usefulness of cefixime in BTI should be substantiated by further clinical trials to better delineate the role of this cephalosporin in the management of BTI.

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BILIARY EXCRETION PROFILE OF CEFIXIME


