Pharmacokinetics of Dirithromycin in Patients with Mild or Moderate Cirrhosis

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The pharmacokinetics of dirithromycin were determined over a 72-h period following oral administration of a single 500-mg dose to 8 healthy volunteers and to 16 cirrhotic patients (8 patients with class A cirrhosis and 8 patients with class B cirrhosis according to Pugh’s & Child’s classification). Drug levels in plasma and urine were determined by microbiological assay. The mean maximum concentrations of drug in serum obtained 3 to 4 h after administration were 0.29 ± 0.22 mg/liter in volunteers and 0.48 ± 0.21 and 0.52 ± 0.38 mg/liter in patients with class A and class B cirrhosis, respectively. The elimination half-life (t\text{1/2}) was 23.3 ± 7.6 h in healthy subjects and 35.2 ± 11.8 h and 39.5 ± 11.0 h in patients with class A and class B cirrhosis, respectively. The mean area under the concentration-time curve (AUC) and t\text{1/2} were significantly higher in patients with class A and class B cirrhosis than in healthy controls, while total and renal clearances were markedly reduced (P < 0.01). The time to the maximum concentration of drug in serum and the volume of distribution values appeared to be similar in all groups, and the mean recovery in urine at 72 h ranged from 3.7 to 5.7%, without significant differences among groups. These results demonstrate that some dirithromycin kinetic parameters are significantly different in cirrhotic patients in comparison to those in healthy volunteers. However, an increase in the t\text{1/2} or AUC, which is also observed with other semisynthetic macrolides (e.g., azithromycin), does seem to be not clinically relevant if one takes into account both the high therapeutic indices of these antibiotics and the usually short duration of therapy. Therefore, on the limited basis of single-dose administration, no modifications of dirithromycin dosage seem to be required even for patients with class B liver cirrhosis.

Dirithromycin is a new macrolide that has a 14-member lactone ring and that is chemically related to erythromycin lactam. It is identified as (9R)-9-deoxy, 11-deoxy-9,11-\{imino-[(1R)-2-(2-methoxy-ethoxy)ethyldieno]oxy\}erythromycin. Dirithromycin is rapidly and nonenzymatically hydrolyzed in vivo to erythromycin lactam, which is also microbiologically active and which has an antimicrobial spectrum similar to that of erythromycin (3).

Under acid conditions this compound is more stable than natural macrolides, which are poorly soluble in water and which are mostly absorbed in the alkaline intestinal environment. Dirithromycin binds mostly to alpha 1-acid glycoprotein, and the mean plasma protein binding, evaluated after intravenous administration, is as low as 19% (13). The oral bioavailability of dirithromycin ranges from 6 to 14% and may be increased by food and H2 receptor antagonists (13). Following oral administration of 500 mg as a single dose, and after oral administration of 14C-radiolabelled dirithromycin, 81 to 97% of the radioactivity appears in stools (1, 13). In patients with hepatic failure, the pharmacokinetics of some macrolide antibiotics are altered (10). Dirithromycin pharmacokinetics have been studied only in patients with mild cholestatic or parenchymal hepatic insufficiency (6).

The aim of the study described here was to investigate the pharmacokinetics of a single dose of dirithromycin in patients with mild and moderate parenchymal impairment of hepatic function to establish a possible dose modification regimen.

**MATERIALS AND METHODS**

**Patient selection.** Patients enrolled in this study were between 18 and 70 years of age. Ethics Committee approval was obtained, and patients gave written informed consent upon study entry. Control subjects were confirmed to be healthy from their medical histories, prestudy physical examinations, complete blood counts, blood chemistries, and urinalyses. Patients with impaired hepatic function were graded for the severity of their liver disease according to Pugh’s & Child’s Classification System (11). We included in the study only patients with Pugh’s & Child’s grade A and B cirrhosis. The weights of the hepatically impaired patients were within 25% of the range of desirable weights outlined in the 1983 Metropolitan Life Insurance Tables; the weights of healthy control subjects were within 10% of their ideal weights.

**Exclusion criteria.** Exclusion criteria were any condition, including significant underlying disease or concomitant infection, which could preclude completion of the study; anticipated requirement of treatment with systemic antibiotics; history of allergy or hypersensitivity to erythromycin or other macrolide antibiotics; pregnancy or postpartum state, lactation, or failure to use a reliable method of birth control; use of any antimicrobial agents within 1 week prior to enrollment; concurrent therapy with theophylline, carbamazepine, cyclosporine, warfarin, phenytoin, alfentanil, disopyramide, lovastatin or other 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, heparin, lacticase, or neomycin; and Pugh’s & Child’s grade C dysfunction.

**Study design.** This was an open-label, nonrandomized, fixed-dose, inpatient and outpatient study.

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Drug administration and sampling. Twenty-four subjects, including eight healthy volunteers with normal renal and hepatic functions, eight patients with hepatic failure of grade A according to Pugh’s & Child’s classification (11), and eight patients with grade B hepatic dysfunction, entered the study. All subjects received dirithromycin at 500 mg as a single dose in the form of two 250-mg capsules with 150 ml of water. Subjects fasted from midnight on the preceding evening until 3 h after administration of the dirithromycin dose. Smoking and intake of caffeine-containing beverages were not permitted during the fasting period; however, water was freely allowed. Blood samples were collected prior to administration of the study drug and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, and 96 h postdosing and were placed in heparinized tubes. The tubes were then placed on ice and centrifuged.

Microbiological assay. Dirithromycin concentrations in plasma and urine were determined by a validated agar well diffusion technique, according to good laboratory practice standards (8). Antibiotic medium 2 (Difco, Detroit, Mich.) with 1.2% 1 N NaOH (pH 8.0) with a final pH of 8.5 was used, and Micrococcus luteus NCTC 8340 was used as the test organism. Standard concentrations were prepared daily in pooled human plasma for blood samples (range, 0.64 to 0.0025 mg/liter) and in phosphate buffer (pH 8.0) for urine samples (range, 0.64 to 0.01 mg/liter). The test organism was added by the surface layer technique. After administration of the dose at the following intervals: 0 to 6, 6 to 12, 12 to 18, 18 to 24, 24 to 36, 36 to 48, 48 to 72, and 72 to 96 h. Urine volume was recorded. Plasma and urine samples were stored at −80°C until they were assayed.

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\[
y = 0.107x - 3.6
\]

for plasma samples and 

\[
y = 0.07x - 2.3
\]

for urine samples; the correlation coefficient was no less than 0.99. For all samples, intra-assay precisions ranged from 4.5 to 7.5% and interassay precisions at a level of 0.12 mg/liter ranged from 3.5 to 4.7%.

Pharmacokinetic analysis. Pharmacokinetic analysis of concentrations in plasma was performed with a computerized program (Siphar, version 4.0; SIMED) by using a two-compartment model on the basis of the extended-least-squares regression method with the Powell minimization algorithm, with first-order absorption from the dosing site and elimination from the central compartment. The area under the plasma concentration-time curve (AUC) was determined by the trapezoidal rule and was extrapolated to infinity. \( C_{\text{max}} \) and time to \( C_{\text{max}} (T_{\text{max}}) \) were observed values. \( t_{1/2} \) was determined as 0.693/\( \beta \) (where \( \beta \) is the elimination rate constant), \( V \) was obtained by dividing the total clearance (CL) by \( \beta \), and CL was calculated by dividing the dose by the AUC from 0 to 96 h (AUC\(_{0–96}\)) (4). Renal clearance (CL\(_{\text{R}}\)) was calculated by dividing the amount excreted in the urine in the 24-h period by the AUC\(_{0–24}\) for plasma (6). Statistical analysis of the data was performed by one-way analysis of variance and Duncan’s post-hoc test.

RESULTS

Table I summarizes the main characteristics of the 24 subjects, who were subdivided into group I (8 cirrhotic patients with class A hepatic dysfunction), group II (8 cirrhotic patients with class B hepatic dysfunction), and group III (8 healthy volunteers). The mean ages were 55.1 ± 9.1 years for group I, 57.1 ± 8.0 years for group II, and 31.6 ± 5.2 years for group III.

### TABLE 1. Baseline characteristics of patients and volunteers

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Wt (kg)</th>
<th>Ht (m)</th>
<th>AST concn (U/liter)</th>
<th>ALT concn (U/liter)</th>
<th>Serum phosphatase level (U/liter)</th>
<th>Serum bilirubin concn (mg/dl)</th>
<th>Ammonia concn (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
<td>HCV&lt;sup&gt;a&lt;/sup&gt;-positive cirrhosis</td>
<td>52</td>
<td>1.65</td>
<td>114</td>
<td>123</td>
<td>432</td>
<td>0.6</td>
<td>70</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td>HCV-positive cirrhosis</td>
<td>65</td>
<td>1.55</td>
<td>20</td>
<td>24</td>
<td>348</td>
<td>1.5</td>
<td>159</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td>None</td>
<td>54</td>
<td>1.5</td>
<td>52</td>
<td>24</td>
<td>360</td>
<td>1.2</td>
<td>57</td>
</tr>
</tbody>
</table>

### TABLE 2. Mean concentrations of dirithromycin in plasma after oral administration of 500 mg to patients with impaired hepatic function (groups I and II) and healthy subjects (group III)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD concn (mg/liter) at the following times (h):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>I (n = 8)</td>
<td>0.39 ± 0.10</td>
</tr>
<tr>
<td>II (n = 8)</td>
<td>0.52 ± 0.28</td>
</tr>
<tr>
<td>III (n = 8)</td>
<td>0.17 ± 0.07</td>
</tr>
</tbody>
</table>

<sup>a</sup> F, female; M, male.  
<sup>b</sup> HCV, hepatitis C virus.  
<sup>c</sup> HBV, hepatitis B virus.
The subjects in the three groups were homogeneous with respect to weight, height, blood urea nitrogen levels, and serum creatinine levels. However, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum phosphatase, serum bilirubin, and ammonia levels were significantly higher in patients than in volunteers (P values, at least <0.05). The cirrhotic patients in group I had a mean Pugh’s and Child’s score of 5.7 ± 0.4, and those in group II had a mean score of 7.9 ± 0.6. At the time of investigation, none of the patients had encephalopathy, ascites, a recent history of digestive tract hemorrhage, and/or infection.

Table 2 and Fig. 1 report the mean concentrations in plasma versus time obtained for all three groups of subjects. Peak levels ranged from 0.48 ± 0.21 to 0.52 ± 0.38 mg/liter for cirrhotic patients, whereas the peak level was 0.29 ± 0.22 mg/liter for healthy subjects. Dirithromycin was still detectable in all subjects, albeit at low concentrations (0.01 to 0.03 mg/liter), 72 h after administration.

The values of the principal pharmacokinetic parameters are presented in Table 3. The mean C\text{max} observed for volunteers (0.29 ± 0.22 mg/liter) tended to be lower than those for group I and II patients (0.48 ± 0.21 and 0.52 ± 0.38 mg/liter, respectively), although the difference was not statistically significant. T\text{max} values were similar in all subjects (range, 3.5 ± 0.9 to 3.9 ± 1.4 h), while t\text{1/2} and the AUC from time zero to infinity (AUC\text{0–}) were significantly higher in cirrhotic patients.

CL and CL\text{R} values were significantly lower for patients than for healthy volunteers (P < 0.01). Mean concentrations in urine from 0 to 72 h were similar for all groups and varied from 2.6 and 16.8 mg/liter (Table 4). The mean recovery in urine ranged from 3.7 to 5.7%.

After administration of dirithromycin, one patient in group II and two patients in group III had transitory increased ALT and/or AST values, without clinical signs.

**DISCUSSION**

The pharmacokinetics of macrolide antibiotics usually become modified in patients with hepatic failure because the liver is the major route of elimination of these agents (2, 6, 8, 10). Only a few investigators, however, have suggested a dosage

<table>
<thead>
<tr>
<th>Group</th>
<th>C\text{max} (mg/liter)\text{a}</th>
<th>T\text{max} (h)\text{b}</th>
<th>t\text{1/2} (h)</th>
<th>AUC\text{0–} (mg · h/ml)</th>
<th>V (liters)</th>
<th>CL (ml/min)</th>
<th>CL\text{R} (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 8)</td>
<td>0.48 ± 0.21</td>
<td>3.9 ± 1.4</td>
<td>35.2 ± 11.8\text{e}</td>
<td>8.7 ± 3.3\text{f}</td>
<td>316.5 ± 99.2</td>
<td>116.8 ± 69.4\text{g}</td>
<td>5.8 ± 3.3\text{g}</td>
</tr>
<tr>
<td>II (n = 8)</td>
<td>0.52 ± 0.38</td>
<td>3.5 ± 0.9</td>
<td>39.5 ± 11.0\text{e}</td>
<td>9.4 ± 2.5\text{f}</td>
<td>343.1 ± 196.6</td>
<td>95.3 ± 31.0\text{g}</td>
<td>4.9 ± 3.2\text{g}</td>
</tr>
<tr>
<td>III (n = 8)</td>
<td>0.29 ± 0.22</td>
<td>3.6 ± 1.1</td>
<td>23.3 ± 7.6</td>
<td>3.2 ± 1.9</td>
<td>520.4 ± 452.4</td>
<td>352.1 ± 166.9</td>
<td>12.1 ± 3.4</td>
</tr>
</tbody>
</table>

\text{\textsuperscript{a} Values are means ± standard deviations.}
\text{\textsuperscript{b} Observed value.}
\text{\textsuperscript{c} P < 0.05 versus group III (by analysis of variance).}
\text{\textsuperscript{d} P < 0.01 versus group III (by analysis of variance).}
modification when erythromycin, josamycin, or moxalactam are administered to patients with hepatic disease (5, 9).

For macrolides, with special emphasis on the newer semisynthetic derivatives, the extravascular compartment is of greater importance than the central compartment (6, 10). These antibiotics also have high therapeutic indices and they are usually used for a short duration of therapy, and therefore, an increase in either $t_{1/2B}$ or AUC (e.g., with azithromycin) or a decrease in nonrenal clearance (e.g., with dirithromycin) does not seem to be clinically relevant in patients with hepatic failure (1, 6, 8, 10). For the first time the pharmacokinetics of dirithromycin have been studied in patients with hepatic failure of grade B according to Pugh’s & Child’s Classification (11), and our results demonstrate that the kinetic behavior of the compound differs to some degree in patients with both mild or moderate hepatic impairment in comparison to its behavior in healthy subjects.

Cirrhotic patients have significantly higher AUCs and $t_{1/2B}$ than healthy subjects, and in these patients both the CL and the $CL_R$ are also reduced. This slower elimination rate is probably related to a decreased metabolic capacity of the liver.

However, the possibility that the older ages of the cirrhotic patients compared with those of the healthy subjects (55.1 to 57.1 versus 31.6 years, respectively) may have contributed to the reduced clearance of dirithromycin from plasma cannot be excluded.

As a matter of fact, it is well known that increased age leads to a progressive reduction of renal function. The issue of whether liver function is compromised in the elderly population remains unresolved, and it seems that geriatric patients have reduced hepatic clearance of certain drugs, reflecting a decline in liver volume and blood flow rather than reduced phase I metabolism (12, 14).

Recently, Le Couteur and McLean (7) have suggested that the reduction in hepatic oxygen diffusion may provide one explanation for the reduction of oxygen-dependent metabolism, while the increased hepatocyte volume would also modify oxygen diffusion path lengths (7).

None of the pharmacokinetic parameters studied were significantly different between patients with mild or moderate cirrhosis. Our data are in general agreement with those observed by Labreque et al. (6) after the administration of single or multiple doses of dirithromycin in patients with grade A hepatic disease. Although statistically significant increases in AUC and $t_{1/2B}$ and decreases in $CL_R$ were found by those investigators in their patients with hepatic disease, they concluded that no dosage adjustment would be necessary in patients with mild hepatic insufficiency for a treatment lasting 14 days or less (6).

In our opinion the higher $C_{max}$ observed in our hepatic patients (although not statistically significant) are consistent with the values of the other kinetic parameters evaluated and suggest that, as expected, patients with liver disease, because they are slower metabolizers, may slightly accumulate dirithromycin during a therapeutic course, even increasing its distribution in tissue (6). This is because the kidneys do not function as a vicarious organ during hepatic impairment, as confirmed by the reduction in the $CL_R$ values and by the percent recovery in urine (which were higher but not statistically significantly higher in patients with hepatic disease in comparison to that in healthy volunteers).

However, on the basis of the similar patterns of absorption and elimination observed in the three groups in our study after the administration of a single dose and the great patient intervariability, by taking into account the greater importance of the extravascular compartment in comparison to the vascular one and the high therapeutic indices of the new semisynthetic macrolides, and in consideration of the short duration of treatment, no modifications to the dosage of dirithromycin seem to be required for patients with mild or moderate hepatic impairment.

We should add that the mean half-life of dirithromycin in the plasma of our cirrhotic patients (range, 35.2 to 39.5 h), although longer than that determined for the volunteer group, does not substantially differ from that reported in the literature for healthy subjects (29.6 to 44 h) (1, 13).

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REFERENCES


