Effect of Mild and Moderate Liver Disease on the Pharmacokinetics of Isavuconazole after Intravenous and Oral Administration of a Single Dose of the Prodrug BAL8557


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Isavuconazole is a promising new antifungal drug with favorable pharmacokinetic properties and excellent activity against a number of fungi. It is administered as a water-soluble prodrug (BAL8557) that is cleaved by plasma esterases to isavuconazole, which is eliminated primarily by hepatic metabolism. The objective of this investigation was to assess the effect of alcohol-related liver disease on the pharmacokinetics of isavuconazole. Subjects were 16 healthy individuals, 16 with mild liver impairment, and 16 with moderate liver impairment who were randomized to receive a single oral or intravenous dose of BAL8557 equivalent to 100 mg isavuconazole. Blood samples were collected for 21 days following drug administration, and plasma concentrations of isavuconazole, BAL8557, and the cleavage product BAL8728 were measured using high-pressure liquid chromatography coupled with tandem mass spectrometry. Following intravenous administration, the half-life of isavuconazole increased from 123 h for healthy volunteers to 224 h and 302 h for subjects with mild and moderate liver impairment, respectively. The systemic clearance of isavuconazole following intravenous administration decreased from 2.73 liters/h for healthy subjects to 1.43 liters/h for subjects with moderate liver impairment (47.6% decrease \([ P < 0.05]\)). A similar decrease (23.5%) was observed after oral administration. These results suggest that a dose adjustment may be needed when isavuconazole is used to treat fungal infections in patients with liver disease.

The treatment of systemic mycoses continues to be a significant therapeutic problem. These infections are increasing in frequency due to the large number of patients who are immunosuppressed as a result of diseases such as human immunodeficiency virus (HIV) infection or treatment with cytotoxic drugs for conditions such as cancer or transplantation. Most systemic fungal infections are caused by opportunistic organisms such as Candida, Aspergillus, and Cryptococcus species. Treatment failure is common due in part to the emergence of organisms resistant to commonly used azole antifungals such as fluconazole and itraconazole. In addition, organ dysfunction and drug interactions limit the usefulness of some of these drugs (5).

A number of new agents are currently in development for the treatment of invasive fungal infections (5). Isavuconazole (formerly known at BAL4815) is a triazole antifungal agent that has a number of favorable therapeutic and pharmacokinetic properties. It is active against all of the major fungi responsible for opportunistic infections as well as against true fungal pathogens such as Histoplasma capsulatum and Blastomyces dermatitidis (2, 3, 4). Importantly, it retains activity against some organisms that are resistant to fluconazole and itraconazole (5). Isavuconazole is administered as a water-soluble prodrug (isavuconazonium [BAL8557]). BAL8557 consists of an [N-(3-acetoxypropyl)-N-methylamino]-carboxymethyl group attached by an ester linkage to isavuconazole. Plasma esterases rapidly and efficiently convert BAL8557 to the active moiety plus an inactive cleavage product (BAL8728). The high degree of water solubility of the prodrug allows for intravenous administration and results in excellent bioavailability after oral administration. In addition, isavuconazole has low clearance, a large volume of distribution, and a long half-life (approaching 100 h) that may permit treatment with an extended dosing interval (7, 8).

In studies with radiolabeled drug administered to rats, more than 80% of the dose was recovered in bile or feces (Basilea Pharmaceutica, unpublished data), whereas in human studies, less than 1% of a dose of isavuconazole was recovered unchanged in the urine (7). These data suggest that the disposition of isavuconazole may be affected by liver disease. The objective of this study was to examine the effect of mild or moderate liver disease due to alcoholic cirrhosis on the disposition of isavuconazole after the administration of a single oral or intravenous dose of the prodrug BAL8557.

MATERIALS AND METHODS

Study design. This was a single-dose, parallel study in which subjects were randomly assigned to receive BAL8557 orally or by intravenous infusion. The study was conducted at a single center according to the principles of the Declaration of Helsinki as amended at Somerset West in 1996 and approved by the Central Ethics Committee of the National Institute of Pharmacy, Hungary. All subjects provided written informed consent.

Subjects. The subjects in this investigation were healthy male or female volunteers and individuals with mild liver disease (Child-Pugh class A) or moderate liver disease (Child-Pugh class B) caused by alcoholic cirrhosis. Subjects with...
moderate liver disease were screened and selected initially. Subjects with liver disease were matched to healthy subjects on the basis of age (within ±7 years), sex, body weight (within ±8 kg), and body mass index (within ±4 kg/m²). Screening procedures for all subjects included medical history, vital signs, 12-lead electrocardiogram, physical examination, and serum chemistry. Exclusions included a history or laboratory evidence of chronic disease (other than liver disease), smoking, or a positive screen result for drugs of abuse, hepatitis, or human immunodeficiency virus infection. Subjects taking medications known to induce or inhibit drug metabolism, particularly CYP3A isozymes, were also excluded. To further confirm the assessment of liver function, individuals with liver disease were given a single intravenous dose of lidocaine (1 mg/kg of body weight administered over 3 min) prior to the start of the study and the formation of the metabolite monoethylglycineyleucylidexyle (MEGX) was measured at 15 and 30 min (6).

Safety assessments. Blood was collected for laboratory safety tests, including hematology and biochemistry tests (for assessment of liver and renal function), prior to administration of the dose and on days 1, 2, 3, 10, 16, and 21. Vital signs were measured prior to administration of the dose, at multiple times during the first 4 days after drug administration, and immediately prior to collection of each subsequent pharmacokinetic blood sample. The results of a 12-lead electrocardiogram test were recorded four times on the first study day as well as on study days 2, 3, 4, 10, and 16. Subjects were monitored for adverse events throughout the study. Any observed adverse events were evaluated for intensity (mild, moderate, severe, or life-threatening) and for a likely relationship to the study (unrelated, remote, possible, or probable).

Study procedures and pharmacokinetic sampling. Subjects were randomly assigned to receive a single dose equivalent to 100 mg isavuconazole (180.5 mg BAL8557) orally or by intravenous infusion over 2 h following an overnight fast. A standardized lunch was served 4 h after drug intake. Blood samples (5 ml) were collected from the cubital vein of the forearm (opposite that used for administration of the intravenous BAL8557) prior to administration of the dose and at 0.5, 1, 0.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 14, 16, 21, 28, 36, 43, and 48 h (21 days) after drug administration.

Blood was collected into tubes containing EDTA as an anticoagulant. Citric acid (2 M) and paraoxon (plasma esterase inhibitor) (0.1 M) were added (at 10 μl per ml) to prevent degradation. Blood was centrifuged at 4°C, and the plasma was harvested and stored at −70°C pending analysis.

Analytical methods. Concentrations of isavuconazole, BAL8557, and BAL8728 in plasma were measured using high-pressure liquid chromatography coupled with tandem mass spectrometry operating in the positive electrospray ionization and selected reaction-monitoring modes (7). Isavuconazole levels were measured in all plasma samples; BAL8557 and BAL8728 levels were measured in samples collected during the first 4 h. The interassay precision of the method is between 5 and 10% for all compounds. The validated lower limit of quantification in plasma was 0.005 μg/ml for BAL8557 and isavuconazole and 0.01 μg/ml for the BAL8728 cleavage product.

Analysis of pharmacokinetic data. Pharmacokinetic parameters were calculated by noncompartimental analysis using WinNonLin, version 5.2 (Pharsight Corporation, Mountain View, CA). The elimination rate constant (k) was estimated from the slope of the terminal portion of the plasma concentration-time profile. The elimination half-life (t1/2) was calculated by dividing 0.693 by k. The area under the curve from time 0 until the time of the last measurable plasma concentration (AUC0→t) was calculated using the linear trapezoidal rule. AUC0→∞ values were calculated as the sum of AUC0→t and the extrapolated area (last measurable concentration divided by the elimination rate constant). Total body clearance (CLr) after intravenous administration or oral clearance (CL/F) after oral administration was obtained by dividing the administered dose by AUC0→∞. Peak concentration (Cmax) and time to reach maximum concentration (tmax) values were obtained directly from the plasma concentration-time profile. WinNonLin 5.2 was also used to fit the mean plasma concentration-time profiles for the intravenous data to a three-compartment model (without lag time) by assuming first-order elimination and using 1/2 weighting as illustrated in Fig. 1.

The three-compartment model was chosen in preference to a two-compartment model based on visual inspection of the residuals, the sum of weighted-square residuals, and predicted versus observed concentrations on both the linear and log/linear scales. The three-compartment model also achieved the lowest values for the Akaike convergence criteria (AIC values). Simulations were performed using the derived macroscale constants for the dose regimen currently being investigated in phase 3 studies (200 mg administered three times daily for 2 days followed by a maintenance dose of 200 mg daily).

Statistical assessment. A two-way analysis of variance was performed to determine the statistical significance of differences in disposition between groups. Factors were subject category (healthy volunteers, patients with mild liver impairment, and patients with moderate liver impairment) and route of administration (oral versus intravenous). Post hoc comparisons were made using the Tukey test with a P value of less than 0.05 for statistical significance.

RESULTS

Subjects. A total of 48 subjects (36 males and 12 females, in groups of 16 healthy subjects, 16 subjects with mild liver impairment, and 16 subjects with moderate liver impairment) were studied. Subjects receiving BAL8557 intravenously were equally divided between males and females, while all subjects receiving oral drug were males. The average ages were 49.7 years for healthy subjects, 55.3 years for subjects with mild liver impairment, and 52.4 years for subjects with moderate liver impairment. There were no differences between groups in body mass index. Child-Pugh scores averaged 5.3 for the subjects with mild hepatic disease compared with 7.4 for subjects with moderate hepatic disease. Subjects with moderate hepatic impairment also had higher bilirubin concentrations (49.5 μmol/liter versus 21.0 μmol/liter) and lower albumin concentrations (3.8 g/dl versus 4.5 g/dl) than individuals with mild hepatic impairment. The relative levels of hepatic function of the three
groups were confirmed by administration of intravenous lidocaine and measurement of the formation of the metabolite MEGX at 15 min and 30 min (Fig. 2). The metabolite concentrations were highest in healthy subjects and lowest in subjects with moderate liver impairment at both time points studied.

**Pharmacokinetics of isavuconazole.** The mean plasma concentrations at each time point for the three groups of subjects are presented in Fig. 3. Subjects with impaired liver function had higher plasma concentrations of isavuconazole at times beyond 8 h after both intravenous and oral administration of BAL8557. Table 1 summarizes the isavuconazole pharmacokinetic parameters for the three groups of subjects. Clearance values were significantly (\(P < 0.05\)) decreased and half-life values were significantly increased for subjects with impaired liver function compared with healthy volunteers. No statistically significant differences between subjects with mild impairment and those with moderate impairment were observed. Peak concentrations following oral administration were lower (\(P < 0.05\)) than the concentrations observed for intravenous administration. The times to reach maximum concentration (\(t_{\text{max}}\)) after oral dosing averaged 2.4, 2.7, and 2.6 h for healthy volunteers, subjects with mild liver impairment, and subjects with moderate liver impairment, respectively. The systemic clearance of isavuconazole following intravenous administration decreased from 2.73 liters/h for healthy subjects to 1.43 liters/h for subjects with moderate liver impairment (47.6% decrease [\(P < 0.05\)]). A similar decrease was observed after oral administration. No differences were noted in the results

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**FIG. 3.** Means (± standard deviations) of plasma concentrations of isavuconazole from 8 h following intravenous (A) or oral (B) administration of BAL8557. Conc, concentration.
with respect to the volume of distribution. The mean pharmacokinetic parameters were used to simulate plasma concentrations of isavuconazole for healthy volunteers as well as for subjects with mild liver disease and subjects with moderate liver disease for both the phase 3 dosing regimen and an adjusted maintenance dose of 100 mg administered once daily (Fig. 4 and 5).

**Pharmacokinetics of BAL8557.** The AUC\(_{0-t}\) values for the prodrug BAL8557 following intravenous administration increased from 0.195 \(\mu g/h/ml\) for healthy volunteers to 0.375 \(\mu g/h/ml\) and 0.433 \(\mu g/h/ml\) for subjects with mild and moderate hepatic impairment, respectively. Similar increases in peak concentrations were observed. BAL8557 was not detected after oral administration.

**Pharmacokinetics of BAL8728.** No differences were observed in the disposition of the BAL8728 cleavage product after intravenous administration of BAL8557. Mean AUC\(_{0-t}\) values were 0.606 \(\mu g/h/ml\), 0.685 \(\mu g/h/ml\), and 0.583 \(\mu g/h/ml\) for healthy subjects, subjects with mild liver impairment, and subjects with moderate liver impairment. After oral administration of the drug, BAL8728 was undetectable in samples from healthy subjects. AUC\(_{0-t}\) values increased to a mean of 0.0993 \(\mu g/h/ml\) for subjects with mild liver impairment and 0.251 \(\mu g/h/ml\) for subjects with moderate liver impairment.

**Tolerability.** BAL8557 was well tolerated after both intravenous and oral administration. There were four adverse events observed (right bundle branch block, upper abdominal pain, high blood pressure, and hyperhydrosis), but all were judged to be unrelated to the study treatments. Laboratory findings were unremarkable.

**DISCUSSION**

In this investigation, the effect of liver disease on the pharmacokinetics of isavuconazole was investigated after administration of single doses of the prodrug BAL8557 to healthy subjects, subjects with mild liver impairment, and subjects with moderate liver impairment. All subjects with impaired liver function had alcoholic cirrhosis. Previous studies have established that less than 1% of a dose of BAL8557 is excreted into the urine as unchanged isavuconazole. In addition, administration of rifampin has been found to reduce plasma concentrations of isavuconazole by 40-fold whereas administration of ketoconazole increases concentrations 3-fold (9, 10). These results suggest that hepatic metabolism, likely mediated by CYP3A isozymes, is primarily responsible for the elimination of isavuconazole.

The pharmacokinetic parameters for isavuconazole ob-

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**TABLE 1. Mean values for pharmacokinetic parameters of isavuconazole following intravenous and oral administration (100 mg) of the prodrug BAL8557**

<table>
<thead>
<tr>
<th>Route</th>
<th>Group</th>
<th>Mean (SD) value</th>
<th>C(_{\text{max}}) ((\mu g/ml))</th>
<th>AUC(_{0-t}) (mg/ml/h)</th>
<th>CL(_{\text{f},\text{c}}) (liters/h)</th>
<th>V(_{\text{ss}}) (liters)</th>
<th>Half-life(_b) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Healthy volunteers</td>
<td>1.09 (0.19)</td>
<td>0.039 (0.012)</td>
<td>2.73 (0.76)</td>
<td>422 (96.3)</td>
<td>123 (38.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild impairment</td>
<td>0.98 (0.37)</td>
<td>0.072 (0.056)</td>
<td>1.93 (0.92)</td>
<td>492 (111)</td>
<td>224 (147)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate impairment</td>
<td>0.84 (0.14)</td>
<td>0.101 (0.052)</td>
<td>1.43 (1.23)</td>
<td>471 (121)</td>
<td>302 (131)</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Healthy volunteers</td>
<td>0.84 (0.17)</td>
<td>0.045 (0.011)</td>
<td>2.38 (0.64)</td>
<td>475 (149)</td>
<td>148 (73.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild impairment</td>
<td>0.73 (0.17)</td>
<td>0.098 (0.053)</td>
<td>1.26 (0.55)</td>
<td>485 (212)</td>
<td>292 (117)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate impairment</td>
<td>0.47 (0.12)</td>
<td>0.062 (0.025)</td>
<td>1.82 (0.64)</td>
<td>598 (183)</td>
<td>240 (38.3)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) \(P < 0.05\) for oral versus intravenous administration results.

\(b\) \(P < 0.05\) for moderate and mild impairment group results versus healthy volunteer results.

\(c\) CL represents systemic clearance (CL\(_{\text{s}}\)) for intravenous administration and oral clearance (CL/F) for oral administration.

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**FIG. 4.** Simulated isavuconazole concentrations in samples from healthy patients and samples from patients with mild or moderate liver disease receiving the phase 3 dosing regimen (200 mg administered once daily) without dose adjustment.
served with healthy subjects were in general agreement with previously reported data (7). Clearance was low, the half-life was long (more than 100 h in subjects with normal liver function), and oral bioavailability was high. As indicated in Table 1, systemic clearance after intravenous administration declined from 2.73 liters/h for healthy subjects to 1.93 liters/h for subjects with mild liver impairment (29.3% decrease). A further decrease to 1.43 liters/h was observed for patients with moderate liver impairment (47.6% lower than in healthy subjects). Similar results were observed after oral administration, with oral clearance decreasing from 2.38 liters/h for healthy volunteers to 1.28 liters/h for subjects with mild liver impairment. The decline in clearance after intravenous dosing was accompanied by a corresponding increase in the half-life of isavuconazole, which averaged 123, 224, and 302 h for healthy subjects, subjects with mild liver disease, and subjects with moderate liver disease, respectively. The volume of distribution was not significantly affected by the presence of liver disease.

Differences in peak concentrations related to impaired liver function after intravenous dosing were minimal (Table 1). After oral administration, peak concentrations depend on the volume of distribution as well as on the rate and extent of availability of the drug. Although the presence of liver disease did not have a statistically significant effect on $C_{\text{max}}$ values, peak concentrations were lower after oral administration than after intravenous administration (Table 1) ($P < 0.05$). There was no difference in $t_{\text{max}}$ values for subjects with liver disease, suggesting that the rate of absorption after oral administration of the drug to subjects with liver disease was not significantly lower. The lower peak concentrations seen with subjects with moderate liver disease after oral administration compared with the results seen after intravenous administration (43.9%) may simply have been due to the fact that the mean AUC value was approximately 40% lower after oral dosing for this group. Firm conclusions are difficult to draw, however, since this was not a crossover design and there were only eight subjects in each group.

The significant increase in the terminal half-life from 123 h for healthy subjects to 224 h and 302 h for subjects with mild and moderate liver impairment, respectively, would be expected to lead to different levels of accumulation with chronic daily dosing. In the ongoing phase 3 studies examining systemic candidiasis and aspergillosis, a loading regimen of 200 mg administered three times daily for the first 2 days followed by daily maintenance doses of 200 mg are currently under investigation. Based on the simulations presented in Fig. 4, this regimen is expected to result in substantial accumulation for patients with mild or moderate liver disease. Trough concentrations are predicted to be 3 to 4 µg/ml for subjects with mild liver impairment and 4 to 5 µg/ml for subjects with moderate liver impairment, values substantially higher than the values of 2 to 3 µg/ml expected for subjects with normal liver function. This strongly suggests that a dose adjustment is required for subjects with impaired liver function. The same loading regimen with a reduction in the maintenance dose to 100 mg administered daily should produce plasma concentrations for subjects with mild or moderate liver disease that are similar to those determined for patients without liver disease (Fig. 5). Due to the excellent oral bioavailability of BAL8557, the same dose adjustment should be appropriate for both oral and intravenous dosing. This approach is, however, subject to regulatory approval.

The prodrug BAL8557 and the cleavage product BAL8728 disappear rapidly from the circulatory system and were measured for only 4 h after administration of BAL8557. After intravenous dosing, the AUC for the prodrug was consistently less than 1% relative to the isavuconazole level, suggesting that liver disease does not impair the extent of conversion of the prodrug to an active species. The prodrug was not detectable in samples collected after oral administration. The BAL8728 cleavage product was not detectable in healthy volunteers after oral administration but accumulated in patients with liver disease. Again, these concentrations were a small fraction of those observed for isavuconazole and were unlikely to be of clinical significance.

Conclusions. The results of this study indicate that liver disease has a significant effect on the disposition of the active compound isavuconazole. Clearance was reduced by approxi-
mately 50% in patients with moderate hepatic impairment compared with healthy subjects after both intravenous and oral administration. A corresponding increase in half-life values was observed. Whether or not a change in clearance and plasma concentrations of this magnitude is clinically meaningful is not known at this time. However, standard recommendations include the suggestion that doses be reduced when a greater than twofold change in drug exposure related to liver disease is observed (1). Given the magnitude of the increase in half-life values, a 50% decrease in the maintenance dose of BAL8557 is recommended for patients with mild or moderate liver disease. Larger changes in drug disposition in patients with severe liver disease are likely; such changes would require a larger dose adjustment. Changes in the disposition of the prodrug BAL8557 and cleavage product BAL8728 with liver disease appear to be minor. Overall, isavuconazole was well tolerated in all subjects investigated in the present study.

ACKNOWLEDGMENT

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REFERENCES


