A randomized, open-label, comparative study was conducted in 30 male patients with moderately advanced human immunodeficiency virus (HIV) infection to examine the pharmacokinetics of an investigational intravenous preparation of itraconazole compared with pharmacokinetics after administration of itraconazole capsules. The study also assessed whether adequate plasma concentrations of itraconazole could be rapidly achieved with the intravenous formulation and then maintained after cessation of intravenous therapy with itraconazole capsules. All patients received 200 mg intravenous itraconazole as a 1-hour infusion in 40% hydroxypropyl-β-cyclodextrin (HP-β-CD) vehicle twice daily for 2 days, and then 200 mg intravenously once daily for 5 days. Patients then received itraconazole capsules, either 200 mg twice daily or 200 mg once daily for 28 days. Steady-state plasma concentrations of itraconazole were reached by day 3 with intravenous infusion, a much shorter time than observed with administration of itraconazole capsules. Steady-state concentrations of itraconazole and hydroxyitraconazole were effectively maintained during the rest of the intravenous infusions of itraconazole. Oral follow-up with administration of 200-mg capsules once daily could not maintain the plasma concentrations of itraconazole and hydroxyitraconazole obtained at the end of the intravenous treatment, whereas twice-daily oral administration maintained or increased these concentrations. Mean plasma concentrations of itraconazole and hydroxyitraconazole on day 7 were similar to those on day 36 in the twice-daily group. Mean renal clearance was comparable to mean total body clearance, and approximately 93% to 101% of the HP-β-CD was excreted unchanged in urine within 12 hours of administration. The HP-β-CD was essentially eliminated through the kidney, and little accumulation in the body was observed in this patient population. Adverse events during the intravenous phase were most commonly associated with intravenous administration. Intravenous infusion of itraconazole for 7 days followed by administration of itraconazole capsules twice daily for 28 days is an effective dose regimen in patients with advanced HIV infection.

Journal of Clinical Pharmacology, 1998;38:593–602
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Itraconazole (Sporanox; Janssen Pharmaceutica, Titusville, NJ) is a synthetic, broad-spectrum triazole antifungal agent with activity in vitro and in vivo against a wide variety of pathogenic fungi.1–5

From Novartis Pharmaceuticals, East Hanover, New Jersey (Dr. Zhou); the Division of Infectious Diseases, Indiana University Medical Center, Indianapolis, Indiana (Drs. Goldman and Wheat and Ms. Borum); and Janssen Pharmaceutica, Titusville, New Jersey (Drs. Wu, Lee, Baruch, and Pesco-Koplowitz, Mr. Woestenborghs, and Mr. Hassell). Supported in part by the Janssen Research Foundation and by the Indiana University General Clinical Research Center. Submitted for publication October 29, 1997; accepted in revised form March 23, 1998. Address for reprints: Peter Lee, PhD, Janssen Research Foundation, Titusville, NJ 08560.

The capsule formulation of itraconazole requires an acidic environment and the presence of food for optimum bioavailability, and is indicated for the treatment of histoplasmosis, blastomycosis, onychomycosis, and aspergillosis (Janssen Pharmaceutica: Sporanox capsules package insert, 1995).6,7

An oral solution formulation of itraconazole (Sporanox Oral Solution [SOS]; Janssen Pharmaceutica) in hydroxypropyl-β-cyclodextrin (HP-β-CD) demonstrates significantly greater bioavailability compared with the capsule preparation, does not require gastric acidity for absorption, and is best absorbed in the fasting state (Janssen Pharmaceutica: Sporanox oral solution package insert, 1997).8 This preparation has
shown efficacy in the treatment of oropharyngeal and esophageal candidiasis and has been shown to be a useful agent in the treatment of oropharyngeal candidiasis unresponsive to fluconazole (Janssen Pharmaceutica: Sporanox oral solution package insert, 1997).9–11

For seriously ill patients with fungal infections, the use of oral antifungal medications may not be possible because of difficulty in swallowing, obturation, or vomiting. Achlorhydria and diarrhea also may prevent optimal absorption of orally administered agents. In addition, the ability to reliably achieve and maintain adequate antifungal drug concentrations in patients with serious infections is desirable. For these reasons, an intravenous solution of itraconazole has been developed and is currently under investigation. A pharmacokinetic model has been developed for itraconazole based on data from healthy volunteers who received single intravenous infusions and single and repeated oral administrations of itraconazole.7 Based on this model, an intravenous dose regimen (itraconazole infusion of 200 mg twice daily for 2 days then once daily for 5 days) that produced drug concentrations similar to concentrations obtained with prolonged oral administration (28 days for itraconazole capsules and 14 days for itraconazole oral solution) was identified and verified.

Because individuals infected with human immunodeficiency virus (HIV) are particularly susceptible to opportunistic fungal infections, the validity of any pharmacokinetic parameters for itraconazole must be reevaluated in this special population. An earlier study of itraconazole capsules in patients with acquired immune deficiency syndrome (AIDS) indicated that the pharmacokinetics of a 200-mg dose in these patients12 were similar to the pharmacokinetics of a 100-mg dose in healthy male volunteers.7 This study was undertaken to determine the pharmacokinetics of the intravenous formulation of itraconazole compared with those observed after continuous administration of itraconazole capsules for 28 days (either 200 mg twice daily or 200 mg once daily) in patients with moderately advanced HIV disease.

PATIENTS AND METHODS

Patients

Men and women with HIV infection (reactive screening test with confirmatory HIV antibody test) who were 18 years of age or older were eligible for this study. Patients were required to have a CD4 lymphocyte count <300 cells/μL and a serum creatinine level <2 mg/dL. Patients with significant abnormalities on physical examination or in blood count, biochemical profile, or urinalysis and patients with clinically significant electrocardiographic abnormalities were excluded. A negative drug screen result for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methaqualone, opiates, and phencyclidine also was required, with one exception: those taking dronabinol under a physician’s care could be enrolled despite a positive test result for cannabinoids.

Patients were excluded if they had an acute opportunistic infection or other significant concurrent illness, HIV enteropathy, HIV wasting syndrome, or chronic diarrhea. Patients also were excluded if they had a history of hypersensitivity to imidazole orazole compounds, were unable to swallow capsules, had previous surgery that could affect drug absorption, regularly used chewing tobacco or smoked more than 10 cigarettes per day, or if they had experienced significant blood loss within the previous 30 days. Current or previous (within 15 days) use of rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, digoxin, warfarin, midazolam, triazolam, cisapride, terfenadine, or astemizole; use of H2-blockers, omeprazole, continual antacids, or didanosine; or use of medication known to affect absorption, metabolism, or excretion of imidazole or azole compounds also resulted in ineligibility. Pregnant women and nursing mothers were excluded; women of childbearing potential were required to practice adequate and medically approved contraception throughout the study.

Institutional review board approval was obtained before the study began, and each patient signed written, informed consent before screening.

Thirty male patients were enrolled in the study, 15 in each of the capsule regimens. The median age was 37.5 years (range 20–51). The median CD4 count was 160 cells/μL (range 5–350). The two dose groups were comparable for race, age, and height; however, the average weight was 26 pounds heavier (P = 0.02) for patients in the intravenous itraconazole 200 mg once daily sequence.

Twenty-six patients took medication concurrently with trial medication. This was not unexpected, given that most patients in the study had advanced HIV disease. The most commonly reported concomitant medications were trimethoprim/sulfamethoxazole, zidovudine, stavudine, acenamiphen, and multivitamins.

Study Design

This was an open-label, comparative study conducted in two centers (Indiana University Medical Center, Indianapolis, IN, and Novum, Inc., Pittsburgh, PA). All patients received 200 mg of intravenous itraconazole twice daily for 2 days, followed by 200 mg once daily for 5 days. Patients were random-
IZED BEFORE STUDY ENTRY TO THEN RECEIVE ITRACONAZOLE CAPSULES 200 MG EITHER TWICE DAILY OR ONCE DAILY FOR 28 DAYS. PHYSICAL EXAMINATION, MEDICAL HISTORY, ELECTROCARDIOGRAM, URINE DRUG SCREEN, AND CLINICAL LABORATORY TESTS (HEMATOLOGY, SERUM CHEMISTRY, URINARY) WERE PERFORMED WITHIN 2 WEEKS OF THE FIRST DOSE.

PATIENTS WERE ADMITTEN TO THE RESEARCH CENTER THE EVENING BEFORE THE FIRST INTRAVENOUS DOSE ON DAY 1. TWO 1-HOUR INFUSIONS WERE GIVEN ON DAY 1 (TIME 0 AND 12 HOURS) AND ON DAY 2 (24 AND 36 HOURS), FOLLOWED BY ONE INFUSION DAILY ON DAYS 3 THROUGH 7. DURING THE INTRAVENOUS PHASE, BLOOD SAMPLES WERE OBTAINED ON DAY 1 IMMEDIATELY BEFORE ADMINISTRATION (TIME 0), AT THE END OF THE INFUSION, AND 0.25, 0.5, 1, 2, 4, 6, 8, AND 11 HOURS AFTER THE END OF THE INFUSION. ON DAYS 1 THROUGH 6, SAMPLES WERE OBTAINED BEFORE THE START OF EACH 1-HOUR INFUSION, WHICH WERE SCHEDULED AT 12, 24, 36, 48, 72, 96, 120, AND 144 HOURS CALCULATED FROM TIME 0 ON DAY 1. ON DAY 7, SAMPLES WERE OBTAINED BEFORE ADMINISTRATION, AT THE END OF THE 1-HOUR INFUSION, AND 0.25, 0.5, 1, 2, 4, 6, 8, 11, AND 23 HOURS AFTER THE END OF THE INFUSION.

AFTER THE INTRAVENOUS PHASE, PATIENTS RECEIVED ITRACONAZOLE CAPSULES FOR AN ADDITIONAL 28 DAYS AND WERE REQUIRED TO RETURN ONCE A WEEK BEFORE THE MORNING DOSE. PATIENTS RECEIVED A SINGLE, ORAL 200-MG DOSE ON THE MORNING OF DAY 36 AND BLOOD SAMPLES WERE COLLECTED IMMEDIATELY BEFORE AND 0.5, 1, 2, 3, 4, 5, 6, 8, 12, AND 24 HOURS AFTER ADMINISTRATION.

URINE SAMPLES FOR THE DETERMINATION OF HP-B-CD LEVELS WERE COLLECTED DURING THE 12-HOUR INTERVALS BEFORE THE INITIAL INTRAVENOUS DOSE AND ON DAYS 1, 7, AND 36 AFTER ADMINISTRATION.

CLINICAL LABORATORY TESTS FOR BLOOD AND URINE SAMPLES WERE REPEATED BEFORE ADMINISTRATION ON DAYS 1, 3, 8, AND 36, WITH ADDITIONAL SERUM CREATININE LEVELS MEASURED AFTER ADMINISTRATION ON DAYS 1 AND 7. VITAL SIGNS (BLOOD PRESSURE, PULSE, RESPIRATION RATE, AND TEMPERATURE) WERE OBTAINED AT SCREENING; BEFORE, DURING, AND AFTER EACH INTRAVENOUS INFUSION; AND AT THE END OF THE CAPSULE PHASE. BODY WEIGHT WAS MEASURED AT SCREENING AND ON DAYS 6 AND 35, AND AN ELECTROCARDIOGRAM WAS PERFORMED AT SCREENING AND ON DAY 7.

INFORMATION REGARDING ADVERSE EVENTS, INCLUDING ONSET, DURATION, INTENSITY, ACTION TAKEN, DRUG RELATEDNESS, AND OUTCOME, WAS COLLECTED DURING EACH INFUSION, FOR 1 HOUR AFTER INFUSION, AND DAILY DURING ORAL ADMINISTRATION.

**Pharmacokinetic Parameters**

Blood samples were centrifuged within 1 hour at 3,000 rpm for 10 minutes and the plasma pipetted into labeled tubes and stored at or below -20°C. Plasma concentrations of itraconazole and hydroxyitraconazole were determined using a validated high-performance liquid chromatography (HPLC) method. The lower limit of quantification of itraconazole and hydroxyitraconazole in plasma was 5.0 ng/mL. Plasma concentrations of HP-B-CD were determined using a validated size-exclusion chromatograph method with post-column complexation. The detection limit of HP-B-CD in plasma was 1.0 μg/mL.

Urine samples for determination of HP-B-CD levels were mixed, a 20-mL aliquot was removed and labeled, and samples were stored at or below -20°C. The detection limit of HP-B-CD in urine was 10.0 μg/mL using a validated size-exclusion chromatograph method with post-column complexation.

Itraconazole and hydroxyitraconazole, the major active metabolite, were measured in all plasma samples; HP-B-CD concentrations in plasma and urine were measured in samples collected up to day 8. Pharmacokinetic parameters were determined by direct observation or calculation for itraconazole and hydroxyitraconazole using PCNONLIN (Version 4.2, Scientific Consulting, Inc., Cary, NC). Peak plasma concentration (Cmax) and time to peak plasma concentration (tmax) were determined after itraconazole administration on days 1, 7, and 36. Area under the plasma concentration–time curve (AUC) from 0 to 12 hours (AUC0–12) and from 0 to 24 hours (AUC0–24) after administration on days 1, 7, and 36 was calculated using the trapezoidal rule. The average plasma concentration (Cav), defined as AUC0–τ/τ, was determined as follows: day 7, average concentration over the 24-hour period (AUC0–24/24); and day 36, average concentration over the 12-hour period (AUC0–12/12) for the twice daily group and over the 24-hour period (AUC0–24/24) for the once daily group.

The relationships between plasma concentrations of itraconazole and hydroxyitraconazole were based on the metabolic ratio (R), defined as AUC0–r of hydroxyitraconazole to the AUC0–r of itraconazole, where r is 12 hours for the twice-daily regimen and 24 hours for the once-daily regimen.

Plasma and urinary pharmacokinetic parameters of HP-B-CD also were determined by direct observation or calculation using PCNONLIN (Version 4.2, Scientific Consulting, Inc.). Values for Cmax and tmax after itraconazole administration were determined on days 1 and 7 and on days 1, 7, and 36, respectively. The AUC from time 0 to infinity (AUC0–∞) was calculated using trapezoidal summation until the last time with a measurable plasma concentration (t) and extrapolated to infinity by addition of the residual area. Values for AUC0–12 were calculated using trapezoidal summation. Total body clearance (CL) was defined as dose/AUC0–r. Total amount of HP-B-CD excreted in the urine over 12 hours after administration (U0–12) was determined on days 1.
and 7. Total renal clearance (Clr) was defined as U_{0–7}/AUC_{0–12}, and percent renal clearance was defined as Cl/Clr.

Statistical Analyses

SAS statistical software version 6.08 (SAS Institute, Cary, NC) was used to perform the statistical analyses. Baseline characteristics were evaluated with a two-way analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel test for categorical variables. Descriptive statistics of plasma concentrations were calculated for itraconazole and hydroxyitraconazole. Pharmacokinetic parameters were compared using the ratio of the mean for a test group to the mean of a reference group, with 90% confidence interval (CI). A paired t test was used for comparisons of day 7 and day 1 and of day 36 and day 7. Values for AUC, C\text{max}, C\text{av}, Cl, Clr, and percent renal clearance were analyzed using original scale data and natural log transformation data. All statistical tests were interpreted at the 5% significance level (two-tailed).

RESULTS

Of the 30 patients who began the study, 29 completed the intravenous phase and 27 completed both the intravenous and capsule phases. Three patients discontinued the study because of adverse events.

Itraconazole

Plasma concentration–time profile. Figure 1 shows the mean ± standard error (SE) plasma concentration–time profile of itraconazole for the intravenous phase and for both capsule regimens through day 36. For all patients, days 1 through 7 were the intravenous infusion phase. Patients were then divided into two follow-up oral treatment groups: 200 mg twice daily or 200 mg once daily. Only trough plasma concentrations of itraconazole were sampled and determined between day 1 and day 7. The first peak on day 1 for all the patients in the mean concentration–time profile shown in Figure 1 was a result of a 1-hour intravenous infusion of itraconazole. A steady-state itraconazole plasma concentration was achieved on day 3 after intravenous infusion of itraconazole on days 1 and 2, as determined by visual inspection. This was maintained through the end of the intravenous phase (day 7), with a mean itraconazole trough plasma concentration of 915 ng/mL. Only trough plasma concentrations of itraconazole were sampled and determined between day 8 and day 36. The second peak for all the patients shown in the mean itraconazole concentration–time profile was due to a 1-hour intravenous infusion on day 7 (Figure 1).

After intravenous infusion treatment for 7 days, patients were then randomized to two oral dose regimens: 200 mg once daily or 200 mg twice daily.
These two regimens were reflected by two plasma levels of itraconazole. The itraconazole and hydroxyitraconazole plasma concentrations obtained at the end of the intravenous treatment could not be maintained by the oral follow-up treatment of 200 mg once daily, but were maintained or increased with the twice daily oral follow-up treatment (Figures 1 and 2). All but four patients receiving itraconazole capsules twice daily had itraconazole trough concentrations equal to or greater than concentrations measured at the end of the intravenous phase.

**Pharmacokinetic parameters.** Table I shows the pharmacokinetic parameters of itraconazole, based on original scale data, for both treatment groups during the intravenous and capsule phases. After multiple intravenous infusions (day 7), the C\text{max} of itraconazole was increased by 47% compared with results after a single intravenous dose on day 1. A C\text{max} of 1,941 ng/mL was reached 1 hour (median) after the intravenous infusion on day 1, whereas a C\text{max} of 2,856 ng/mL occurred 1 hour (median) after the intravenous infusion on day 7. After the first 1-hour infusion on day 1, most of the patients (28 of 30) reached C\text{max} immediately after the infusion. However, in two patients C\text{max} occurred 12 hours after initiation of the infusion. This may have been caused by a mistake in blood sampling after initiation of the second intravenous infusion on day 1 instead of before the infusion, as scheduled. At endpoint (day 36), C\text{max} was 889 ng/mL for the once-daily group compared with 2,010 ng/mL for the twice-daily group. At day 36, t\text{max} was comparable between the two groups (4.20 versus 3.92 hours).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intravenous Phase</th>
<th>Capsule Phase (Day 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (n = 30)</td>
<td>Day 7 (n = 29)</td>
</tr>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>9,141 ± 546</td>
<td>2,856 ± 866</td>
</tr>
<tr>
<td>t\text{max} (hrs)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C\text{av} (ng/mL)</td>
<td>—</td>
<td>1,275 ± 373</td>
</tr>
<tr>
<td>AUC\text{0-12} (ng-hr/mL)</td>
<td>6,511 ± 1,864</td>
<td>—</td>
</tr>
<tr>
<td>AUC\text{0-24} (ng-hr/mL)</td>
<td>—</td>
<td>30,605 ± 8,961</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± standard deviation, except for t\text{max}, which is median only. QD, once daily; BID, twice daily; C\text{max}, maximum plasma concentration; t\text{max}, time to C\text{max}; C\text{av}, average plasma concentration; AUC\text{0-12} and AUC\text{0-24}, area under the concentration–time curve from 0 to 12 and 0 to 24 hours, respectively.
for the once-daily and twice-daily groups, respectively).

Table II shows the ratios of pharmacokinetic parameters of itraconazole from day 36 to those from day 7, based on log-transformed scale data, for both the once-daily and twice-daily capsule regimens. For patients who received itraconazole capsules once daily, values for $C_{\text{max}}$ and $C_{\text{av}}$ on day 36 were significantly decreased ($P < 0.001$) from the end of the intravenous phase (day 7). For those who received itraconazole capsules twice daily, $C_{\text{max}}$ on day 36 was significantly lower ($P = 0.02$) than $C_{\text{max}}$ after intravenous administration on day 7. However, $C_{\text{av}}$ for day 36 was not significantly different from that for day 7.

### Hydroxyitraconazole

*Concentration–time profile.* Figure 2 depicts the mean ± SE plasma concentration–time profile of hydroxyitraconazole for the intravenous phase and for both capsule regimens through day 36. Concentrations of hydroxyitraconazole reached steady state on day 6 after intravenous infusion of itraconazole 200 mg twice daily for 2 days and 200 mg once daily for 3 days. The mean trough plasma concentration of hydroxyitraconazole was 1,760 ng/mL at the end of the intravenous phase (Figure 2).

At study endpoint (day 36), mean trough plasma concentration of hydroxyitraconazole was 933 ng/mL for the once-daily group and 2,397 ng/mL for the twice-daily group (Figure 2).

**Pharmacokinetic parameters.** Pharmacokinetic parameters for hydroxyitraconazole are summarized in Table III. On day 7, the mean $C_{\text{max}}$ of hydroxyitraconazole increased more than 300% from the value obtained after a single dose on day 1. The metabolic ratio (R) also doubled from day 1 to day 7. At the end of the capsule phase, $C_{\text{max}}$ was 1,114 ng/mL for patients in the once-daily group compared with 2,614 ng/mL for patients in the twice-daily group.

Table IV shows the ratios of pharmacokinetic parameters of hydroxyitraconazole from day 36 to those from day 7, based on log-transformed scale data, for both the once-daily and twice-daily capsule groups. For those receiving itraconazole capsules once daily, $C_{\text{max}}$ and $C_{\text{av}}$ of hydroxyitraconazole

### Table II Ratios of Pharmacokinetic Parameters of Itraconazole on Day 36 to those on Day 7

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Day 36</th>
<th>Day 7</th>
<th>$P^{\dagger}$</th>
<th>Ratio of Day 36 to Day 7 (%)</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QD Capsule Group (n = 15)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{m}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BID Capsule Group (n = 12)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{av}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Date analyzed on Log scale, but statistics transformed back to original scale.

$^{\dagger}$ From the paired t test, testing a zero difference between groups (two-sided).

QD, once daily; $C_{\text{max}}$, maximum plasma concentration; $C_{\text{av}}$, average plasma concentration; BID, twice daily.

### Table III Pharmacokinetic Parameters of Hydroxyitraconazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intravenous Phase</th>
<th>Capsule Phase (Day 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (n = 30)</td>
<td>Day 7 (n = 29)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>464 ± 150</td>
<td>1,906 ± 612</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hrs)</td>
<td>3.63 ± 2.84</td>
<td>8.53 ± 6.36</td>
</tr>
<tr>
<td>$C_{\text{av}}$ (ng/mL)</td>
<td>1,769 ± 553</td>
<td>955 ± 596</td>
</tr>
<tr>
<td>AUC$_{0-12}$ (ng.hr/mL)</td>
<td>4,578 ± 1,588</td>
<td>—</td>
</tr>
<tr>
<td>AUC$_{0-24}$ (ng.hr/mL)</td>
<td>—</td>
<td>42,445 ± 13,282</td>
</tr>
<tr>
<td>R</td>
<td>0.72 ± 0.18</td>
<td>1.39 ± 0.16</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± standard deviation. QD, once daily; BID, twice daily; $C_{\text{max}}$, maximum plasma concentration; $t_{\text{max}}$, time to $C_{\text{max}}$; $C_{\text{av}}$, average plasma concentration; AUC$_{0-12}$ and AUC$_{0-24}$, area under the concentration–time curve from 0 to 12 and 0 to 24 hours, respectively; ratio of AUC$_{0-\tau}$ of hydroxyitraconazole to AUC$_{0-\tau}$ of itraconazole, where $\tau$ = 12 hours for the BID dose regimen and 24 hours for the QD dose regimen.
Table IV  Ratios of Pharmacokinetic Parameters of Hydroxyitraconazole on Day 36 to those on Day 7

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Day 36</th>
<th>Day 7</th>
<th>P†</th>
<th>Ratio of Day 36 to Day 7 (%)</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD Capsule Group (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>926</td>
<td>1,625</td>
<td>0.001</td>
<td>57</td>
<td>45–72</td>
</tr>
<tr>
<td>$C_{\text{av}}$ (ng/mL)</td>
<td>775</td>
<td>1,507</td>
<td>&lt;0.001</td>
<td>51</td>
<td>39–68</td>
</tr>
<tr>
<td>R‡</td>
<td>1.72</td>
<td>1.35</td>
<td>&lt;0.001</td>
<td>127</td>
<td>121–135</td>
</tr>
<tr>
<td>BID Capsule Group (n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2,032</td>
<td>2,089</td>
<td>0.9</td>
<td>97</td>
<td>63–151</td>
</tr>
<tr>
<td>$C_{\text{av}}$ (ng/mL)</td>
<td>1,810</td>
<td>1,955</td>
<td>0.7</td>
<td>93</td>
<td>59–145</td>
</tr>
<tr>
<td>R§</td>
<td>1.63</td>
<td>1.41</td>
<td>0.003</td>
<td>116</td>
<td>108–124</td>
</tr>
</tbody>
</table>

* Data analyzed on Log scale. But statistics transformed back to original scale.
† From the paired t test, testing a zero difference between groups (two-sided).
‡ Ratio of AUC_{0-24} of hydroxyitraconazole to AUC_{0-24} of itraconazole.
§ Ratio of AUC_{0-12} of hydroxyitraconazole to AUC_{0-12} of itraconazole group.

were significantly lower ($P = 0.001$) at the end of the capsule phase (day 36) than at the end of the intravenous phase (day 7). Metabolic ratios also were significantly increased ($P < 0.001$) by approximately 30% from day 7 to day 36. For those receiving itraconazole capsules twice daily, $C_{\text{max}}$ and $C_{\text{av}}$ of hydroxyitraconazole were not significantly different on day 36 from those on day 7. Although the metabolic ratio was statistically significantly increased by 15% from day 7 to day 36 ($P = 0.003$), this increase was not considered to be clinically significant.

Plasma and Urine Concentrations of HP-β-CD

Figure 3 displays the mean ± SE plasma concentration–time profile of HP-β-CD during intravenous treatment. There were two peaks shown in Figure 3: one for the first intravenous infusion on day 1 and another for the last intravenous infusion on day 7. Only trough plasma concentrations of HP-β-CD were sampled and determined between day 1 and day 7. Most patients had nondetectable plasma concentrations of HP-β-CD 12 and 24 hours after intravenous administration of itraconazole. Approximately 93% to 101% of HP-β-CD was excreted in urine within 12 hours of administration. Pharmacokinetic parameters for day 7 were within ± 10% of those for day 1 (Table V). Although differences in $C_{\text{max}}$, AUC_{0-24} and Cl were statistically significant ($P < 0.01$), these differences were not considered to be clinically significant.

Safety

All 30 patients were included in the safety analyses. Overall, 24 of 30 (80%) patients reported adverse events during the course of the study. Adverse events that occurred in at least 5% of the patients and were at least possibly related to study drug included application site reaction, nausea, vein disorder, headache, diarrhea, abdominal pain, and rash. Most adverse events reported during the intravenous phase were specific to intravenous administration, such as application site reaction and vein disorder (described as irritation, inflammation, swelling, hardness, pain, and redness). Four patients also reported nausea and three reported mild diarrhea during the intravenous phase.

Adverse events with onset during the capsule phase occurred in eight (53%) patients taking the capsule once daily and eight (57%) taking the capsule twice daily. Adverse events that occurred in two or more patients in either group were nausea (three patients in the once-daily group) and headache (two patients in the twice daily group).

Three patients assigned to the twice-daily capsule group withdrew from the study because of an adverse event. One patient discontinued on day 3 during the intravenous phase (suicide attempt), one patient discontinued on day 11 (rash), and one patient discontinued on day 35 (concurrent illness and progressive multifocal leukoencephalopathy). Only the rash, which resolved 3 days after discontinuation, was considered to be related to study drug. Six patients (20%) were reported to have thrombocytopenia at baseline; during intravenous treatment this number increased to 13 of 30 patients (43%). The higher incidence of thrombocytopenia might be related to the intravenous formulation. No clinically significant changes from baseline or differences between groups were found in vital signs or electrocardiographic results.
DISCUSSION

This study demonstrates that steady-state concentrations of itraconazole and its active metabolite, hydroxyitraconazole, are effectively maintained by twice-daily administration of 200-mg oral itraconazole capsules after multiple intravenous infusions of itraconazole over a period of 7 days. Patients in the twice-daily capsule group had itraconazole and hydroxyitraconazole trough concentrations that were maintained or increased relative to the end of the intravenous period.

Steady-state plasma concentration of itraconazole

Table V Pharmacokinetic Parameters of Hydroxypropyl-β-cyclodextrin Day 1 and Day 7 after Intravenous Administration

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (µg/mL)</td>
<td>30</td>
<td>562 ± 99</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng.hr/mL)</td>
<td>30</td>
<td>1,323 ± 233</td>
</tr>
<tr>
<td>t_{1/2} (hrs)</td>
<td>30</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>U_{0-12} (g)</td>
<td>26</td>
<td>8.09 ± 1.48</td>
</tr>
<tr>
<td>Cl (mL/min)</td>
<td>30</td>
<td>104 ± 19</td>
</tr>
<tr>
<td>Cl_{l} (mL/min)</td>
<td>26</td>
<td>108 ± 28</td>
</tr>
<tr>
<td>% Renal Clearance</td>
<td>26</td>
<td>101 ± 19</td>
</tr>
</tbody>
</table>

C_{max}, maximum plasma concentration; AUC_{0-∞}, area under the plasma concentration-time curve extrapolated to infinity; t_{1/2}, half-life; U_{0-12}, amount excreted in urine from 0 to 12 hours; Cl, apparent total clearance; Cl_{l}, renal clearance.

was reached by day 3, and were maintained throughout the intravenous infusion period (days 3–7). At the end of the intravenous phase (day 8), the mean trough concentration of itraconazole was 915 ng/mL. During the capsule phase of the study, steady-state plasma concentrations of itraconazole at end of the intravenous phase were maintained or increased in the group taking the 200-mg oral capsule twice daily; concentrations were not maintained, however, in the group taking the 200-mg oral capsule once daily.

Steady-state plasma concentrations of hydroxyitraconazole were reached by day 6 of the intravenous regimen. At day 8, mean trough concentration of hydroxyitraconazole was 1,760 ng/mL. Mean trough concentrations of hydroxyitraconazole on day 36 were 933 and 2,397 ng/mL for the once- and twice-daily dose regimens, respectively.

In an earlier study, a similar dose regimen of 1-hour intravenous infusions of 200 mg itraconazole twice daily for 2 days followed by 1-hour infusions of itraconazole 200 mg once daily for 5 days was studied in patients in an intensive care unit and in patients with hematologic malignancy (Janssen Pharmaceutica, Titusville, NJ: data on file). Steady-state plasma concentrations were reached by 48 hours after infusion for itraconazole and 96 hours after infusion for hydroxyitraconazole. At the end of treatment, trough plasma concentrations of itraconazole and hydroxyitraconazole were 344 and 605 ng/mL, respectively, in the patients in the intensive care unit, and 535 and 1,123 ng/mL, respectively, in
the patients with hematologic malignancy (Janssen Pharmaceutica, Titusville, NJ: data on file).

During the intravenous period in our study, mean metabolic ratio (R) increased from 0.7 on day 1 to 1.4 on day 7, and further increased to 1.7 on day 36 during the capsule phase. The exact mechanism for this phenomenon is unknown. It might be related to the nonlinear pharmacokinetics of itraconazole.

For the oral follow-up treatment phase, all demographic parameters (race, age, and height) were comparable between groups except for weight. The patients assigned to receive the 200-mg capsules once daily had a significantly higher average body weight (difference in means = 26 pounds) than those assigned to receive the capsules twice daily. It has been reported that body weight accounts for most of the variability in volume of distribution and for some of the variability in hepatic clearance. 

Presumably, a slightly higher itraconazole concentration might be obtained if the patients in the once-daily group had an average body weight comparable to that of the twice-daily group. However, no body weight adjustment was performed in the pharmacokinetic analysis of this study.

Of the patients in our study, 26 took other medication concurrently with trial medication. The most commonly reported concomitant medications were trimethoprim/sulfamethoxazole, zidovudine, stavudine, aceterminophen, and multivitamins. Because imidazole agents (e.g., ketoconazole, fluconazole, and itraconazole) are well-known inhibitors of cytochrome P-450 isozymes, an extensive literature search has been performed on any potential interactions between itraconazole and the medications taken in this study.

Zidovudine is widely used in patients with HIV infection and is often administered with other drugs, including antymyctic agents. Zidovudine is mostly metabolized by uridine diphosphoglucuronosyltransferase to an inactive 5'-O-glucuronide. No interaction was observed between zidovudine and itraconazole. Therefore, no effect of zidovudine on the concentration levels of itraconazole was expected when both drugs were coadministered.

Stavudine (d4T) is an antiretroviral thymidine analog used to treat patients with advanced HIV infection who are unable to tolerate or who no longer benefit from other nucleoside analog therapy. Stavudine is primarily excreted unchanged in urine, and no metabolites have been identified yet. Lack of any interaction between itraconazole and stavudine could be reasonably expected.

In vitro studies have shown that there was no interaction between sulphanmethoxazole and ketoconazole (CYP 3A and 2C inhibitor), a compound that is similar to itraconazole. No evidence has shown that trimethoprim/sulfamethoxazole might interact with itraconazole. Acetaminophen is a known substrate of CYP 1A2 and 2E1, and itraconazole is a known inhibitor of CYP 3A4 and 2C. It is unlikely that an interaction between acetaminophen and itraconazole exists.

HP-β-CD is a chemically modified cylinder-shaped oligosaccharide derived from starch. It is highly soluble in water and can form inclusion complexes with many poorly soluble drugs. It is used as a delivery vehicle for itraconazole in this study. Renal clearance of HP-β-CD in patients with advanced HIV infection (108 mL/min on day 1 and 104 mL/min on day 7) was similar to that in healthy volunteers (108 mL/min) (Janssen Pharmaceutica, Titusville, NJ: data on file). The safety of HP-β-CD as the solubilization vehicle for this itraconazole intravenous formulation was confirmed in that approximately 93% to 101% of HP-β-CD was excreted unchanged in urine within 12 hours of administration in this patient population. The HP-β-CD was essentially eliminated through the kidney, and little accumulation in the body was observed.

Itraconazole was well tolerated in this population. adverse events during the intravenous phase were most commonly associated with intravenous administration, were mild in nature, and required no special treatment. Three patients discontinued the study because of adverse events, only one of which (rash) was considered to be possibly related to study drug. The increased incidence of thrombocytopenia during the intravenous phase might be a result of the intravenous administration.

We found that a regimen of intravenous itraconazole infusion for 7 days followed by itraconazole capsules twice daily for 28 days is well tolerated and can provide safe and effective treatment for a wide range of systemic mycoses, an area of particular concern in patients with HIV infection. Steady-state concentrations of itraconazole and hydroxyitraconazole can be achieved rapidly with intravenous administration of itraconazole, and these concentrations can be effectively maintained with oral administration of itraconazole capsules twice daily. However, the concentrations achieved at the end of the intravenous phase could not be maintained with the oral follow-up regimen of itraconazole capsules once daily for 28 days. From the standpoint of pharmacokinetic parameters, the 200-mg twice daily capsule follow-up regimen appears to be superior to the 200-mg once daily follow-up regimen. Additionally, an intravenous formulation of itraconazole may be useful in patients with moderately severe to severe disease, for whom use of oral triazole compounds as initial treatment generally has been avoided.
REFERENCES


