Pharmacokinetics and Safety of a 7-Day Administration of Intravenous Itraconazole followed by a 14-Day Administration of Itraconazole Oral Solution in Patients with Hematologic Malignancy

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Received 28 July 2000/Returned for modification 27 September 2000/Accepted 4 December 2000

The pharmacokinetics and safety of an intravenous hydroxypropyl- β -cyclodextrin solution of itraconazole administered for 7 days followed by itraconazole oral solution administered at 200 mg once or twice daily for 14 days were assessed in 17 patients with hematologic malignancies. Steady-state plasma itraconazole concentrations were reached by 48 h after the start of intravenous treatment. The mean trough plasma itraconazole concentration at the end of the intravenous treatment was 0.54 ± 0.20 $\mu\text{g/ml}$. This concentration was not maintained during once-daily oral treatment but increased further in the twice-daily treatment group, with a trough itraconazole concentration of 1.12 ± 0.73 $\mu\text{g/ml}$ at the end of oral treatment. As expected in the patient population studied, all patients experienced some adverse events (mainly gastrointestinal). Biochemical and hematologic abnormalities were frequent, but no consistent changes occurred. In conclusion, 7 days of intravenous treatment followed by 14 days of twice-daily oral treatment with itraconazole solution enables plasma itraconazole concentrations of at least 0.5 $\mu\text{g/ml}$ to be reached rapidly and to be maintained. The regimen is well tolerated and has a good safety profile.

Itraconazole is a broad-spectrum antifungal agent effective for the treatment of both systemic fungal infections and superficial mycoses. The drug exhibits dose-dependent pharmacokinetics after the administration of single and multiple doses (6, 7, 14). The active metabolite, hydroxyitraconazole, reaches concentrations in plasma approximately twice those achieved by the parent drug.

Absorption from the capsule formulation of itraconazole can be impaired in patients with epithelial damage (4), but the itraconazole oral solution, which contains hydroxypropyl- β -cyclodextrin, has higher bioavailability in healthy volunteers and in high-risk populations such as patients with hematologic malignancies (1, 2, 5, 9, 12).

However, oral treatment may not be possible for some patients because of their medical condition. For this reason, an intravenous (i.v.) formulation of itraconazole that also contains hydroxypropyl- β -cyclodextrin has been developed for use in high-risk patients who require intensive care or who have had prolonged neutropenia.

A steady-state concentration in plasma of 0.50 $\mu\text{g/ml}$ is considered a desirable target for itraconazole (10). A proposed regimen that enables this target to be reached rapidly consists of treatment with i.v. itraconazole for 7 days (200 mg twice daily for 2 days and then 200 mg once daily for 5 days), followed by treatment with the oral solution (6; 7 K. De Beule, P.

Jacqmin, A. Van Peer, P. Stoffels, and J. Heykants, Abstr. 35th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A75, p. 14, 1995). In a trial involving critically ill patients requiring intensive care (13), this itraconazole regimen resulted in average trough plasma itraconazole concentrations of more than 0.25 $\mu\text{g/ml}$, and the regimen was generally well tolerated. Furthermore, initial results from a clinical trial with patients with hematologic disease showed that this itraconazole regimen is at least as effective as amphotericin B for the empiric treatment of persistent fever (3).

In the present study, we assessed the pharmacokinetics and safety of this proposed dosing regimen in patients with hematologic malignancies.

For this trial we recruited patients in four centers in Belgium between January and April 1995. Patients who were between 18 and 60 years of age with leukemia, myelodysplastic syndrome, lymphoma, or myeloma and who required antifungal prophylaxis were screened for entry into the study. Inclusion criteria included a life expectancy of at least 21 days and no symptoms or signs of fungal infection. Patients were excluded for the following reasons: pregnancy or breast-feeding; child-bearing potential without reliable birth control; treatment with phenytoin, phenobarbital, rifampin, or rifabutin in the 2 weeks before study entry, terfenadine, astemizole, warfarin, oral midazolam, cisapride, or triazolam at study entry or during the study, or other investigational drugs with the exception of anticancer agents within 1 month before study entry; liver disease (defined as serum aspartate transaminase [AST] or alanine transaminase [ALT] concentrations at least four times the upper normal limit); renal insufficiency (creatinine clear-

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ance less than 30 ml/min); known hypersensitivity to azole antifungals; and human immunodeficiency virus infection. If a patient received cyclosporine or digoxin during the study, the concentrations of these drugs in plasma were monitored.

The trial was performed in accordance with the Declaration of Helsinki and its revisions, ethics committee approval was obtained before the trial, and patients gave their informed consent to participate in the trial.

In this open study, all patients received i.v. itraconazole for 7 days (200 mg twice daily on days 1 and 2 and then 200 mg once daily on days 3 to 7). Patients were then distributed into two treatment groups and received itraconazole oral solution at 200 mg either once or twice daily for 2 weeks.

Blood samples for analysis of itraconazole, hydroxyitraconazole, and hydroxypropyl- β -cyclodextrin were collected immediately before i.v. treatment; at 1, 2, 8, 24, 32, 33, 34, 48, 96, 144, 145, 146, 156, and 168 h after i.v. treatment (where relevant, samples were taken before infusion); at 5 and 24 h after administration of the first oral dose (day 8 of study); and immediately before and 5 h after administration of the morning oral dose on days 13, 17, and 21.

Itraconazole and hydroxyitraconazole concentrations were measured by high-performance liquid chromatography (15), with lower limits of quantification of 0.005 and 0.01 $\mu\text{g/ml}$, respectively. Hydroxypropyl- β -cyclodextrin concentrations were determined in the samples by size-exclusion chromatography with postcolumn complexation (11). The lower limit of quantification was 2.0 $\mu\text{g/ml}$.

The complete urinary output between 144 and 168 h was collected, and a 20-ml aliquot was stored at -20°C until analysis. Hydroxypropyl- β -cyclodextrin concentrations were measured as described above for measurement of itraconazole and hydroxyitraconazole concentrations in plasma samples, with a lower limit of quantification of 20 $\mu\text{g/ml}$.

All adverse events were recorded, regardless of the relationship to the study medication. Any event that was fatal or life-threatening, that was significantly, persistently, or permanently disabling, or that required intervention, hospitalization, or prolongation of hospitalization was considered serious.

Blood samples were taken before entry into the study, just before the first itraconazole infusion, at 24, 48, and 96 h and 7, 14, and 21 days after the itraconazole infusion, and at the end of the study for biochemical and hematologic analyses. Abnormalities were considered severe if the change was code 4 (i.e., the reference value was normal and at least two values or the last value during the study was pathologic) or code 5 (i.e., the reference value was pathologically high [low] and at least two values or the last value during the study was pathologically low [high]). Pathologic limits for most tests were defined by Lippert and Lehman (8).

Descriptive statistics were calculated for the concentrations of itraconazole, hydroxyitraconazole, and hydroxypropyl- β -cyclodextrin in plasma at each sampling time. The metabolic ratio (i.e., the ratio of the trough concentration of hydroxyitraconazole in plasma to the trough concentration of itraconazole in plasma) was calculated at the end of i.v. treatment (day 8) and at the end of oral treatment (day 21). The incidence and type of adverse events were tabulated for each treatment group. Descriptive statistics and pretreatment versus

peri- and posttreatment cross-tabulations were used for all clinical laboratory tests.

Seventeen patients (9 men, 8 women; 16 Caucasians, 1 Asian) received treatment and entered either the once-daily treatment group ($n = 6$) or the twice-daily treatment group ($n = 11$). Eight patients had acute myeloid leukemia, three had acute lymphocytic leukemia, two each had chronic myeloid leukemia and high-grade non-Hodgkin's lymphoma, and one each had multiple myeloma and nonspecified leukemia. Their median age was 41 years (range, 19 to 60 years), and their median body weight was 66.5 kg (range, 51 to 102 kg). All patients took concurrent medication, most frequently erythrocyte or platelet transfusions, furosemide, phytonadione, allopurinol, ranitidine, chlorhexidine, and nystatin. No statistically significant differences in patient characteristics were found between the two groups.

Data for two patients in the twice-daily treatment group who withdrew during i.v. treatment were not used in the pharmacokinetic analysis. Five patients withdrew from the twice-daily group and two withdrew from the once-daily group during oral treatment. Furthermore, data for one patient in the once-daily group who received rifampin were not used. Some concentrations in plasma were not used in the analysis because they were inconsistent with the known pharmacokinetic profile of itraconazole and were clearly outliers.

The trough plasma itraconazole and hydroxyitraconazole concentrations during the i.v. and oral treatments are shown in Table 1. The mean plasma itraconazole concentrations were $1.84 \pm 0.53 \mu\text{g/ml}$ at the end of the first 1-h infusion and $2.25 \pm 0.74 \mu\text{g/ml}$ after the last infusion on day 7.

During the loading period (0 to 48 h), the mean trough plasma itraconazole concentration increased gradually and remained stable until the end of the i.v. treatment period (Table 1). The mean trough plasma hydroxyitraconazole concentrations increased gradually throughout the i.v. treatment period (Table 1).

In the once-daily oral treatment group, mean trough concentrations of itraconazole decreased from the end of i.v. treatment to the end of oral treatment. In contrast, in patients treated with oral itraconazole twice daily, mean trough concentrations gradually increased, reaching a maximum at day 21 (Table 1). Hydroxyitraconazole concentrations during oral treatment evolved similarly to the itraconazole concentrations (Table 1).

At the steady state of the i.v. treatment (168 h), the metabolic ratio on the basis of the trough concentrations in plasma was 2.2 ± 0.5 . Metabolic ratios were similar at the end of the once-daily and twice-daily oral treatments (2.2 ± 0.5 and 2.2 ± 0.9 , respectively).

Mean peak plasma hydroxypropyl- β -cyclodextrin concentrations at the end of each infusion were comparable throughout the i.v. period, ranging from 437 ± 117 to $488 \pm 139 \mu\text{g/ml}$. Trough plasma hydroxypropyl- β -cyclodextrin concentrations at the end of the 2-day loading period (i.e., at 48 h) ranged from below the lower limit of quantification to 36.6 $\mu\text{g/ml}$. In the following 5 days, only 4 of 15 patients had quantifiable trough concentrations in plasma, none of which exceeded 8.2 $\mu\text{g/ml}$. On average, $84.5\% \pm 23.5\%$ of the hydroxypropyl- β -cyclodextrin dose was excreted in the urine during a dosing interval.

TABLE 1. Trough plasma itraconazole and hydroxyitraconazole concentrations

Drug, treatment, and time point	No. of patients	Concn ($\mu\text{g/ml}$ [mean $\pm$ SD])	Range ($\mu\text{g/ml}$)	No. (%) of patients with concn <0.5 $\mu\text{g/ml}$
Intraconazole				
i.v. treatment				
Day 1, 8 h	14	0.19 ± 0.08	0.10–0.36	14 (100)
Day 2, 24 h	13	0.27 ± 0.09	0.12–0.45	13 (100)
Day 2, 32 h	13	0.55 ± 0.20	0.24–0.87	6 (46)
Day 3, 48 h	10	0.50 ± 0.20	0.24–0.81	6 (60)
Day 5, 96 h	12	0.51 ± 0.16	0.28–0.78	6 (50)
Day 7, 144 h	15	0.53 ± 0.22	0.22–1.00	9 (60)
Day 8, 168 h	15	0.54 ± 0.20	0.23–0.94	8 (53)
Oral treatment, 200 mg once daily				
Day 8, 168 h	5	0.63 ± 0.24	0.23–0.84	1 (20)
Day 9, 192 h	5	0.56 ± 0.31	0.25–1.07	2 (40)
Day 13, 288 h	4	0.36 ± 0.32	0.09–0.78	3 (75)
Day 17, 384 h	5	0.36 ± 0.28	0.07–0.70	3 (60)
Day 21, 480 h	3	0.24 ± 0.15	0.13–0.77	2 (67)
Oral treatment, 200 mg twice daily				
Day 8, 168 h	5	0.43 ± 0.09	0.29–0.53	4 (80)
Day 9, 192 h	5	0.57 ± 0.16	0.31–0.72	1 (20)
Day 13, 288 h	5	0.85 ± 0.45	0.45–1.51	1 (20)
Day 17, 384 h	5	0.83 ± 0.43	0.41–1.33	2 (40)
Day 21, 480 h	4	1.12 ± 0.73	0.58–2.19	0 (0)
Hydroxyitraconazole				
i.v. treatment				
Day 1, 8 h	15	0.29 ± 0.10	0.15–0.46	
Day 2, 24 h	15	0.48 ± 0.16	0.21–0.81	
Day 2, 32 h	15	0.69 ± 0.23	0.27–1.14	
Day 3, 48 h	15	0.78 ± 0.21	0.38–1.23	
Day 5, 96 h	15	0.99 ± 0.25	0.64–1.41	
Day 7, 144 h	15	1.07 ± 0.34	0.62–1.98	
Day 8, 168 h	15	1.12 ± 0.35	0.56–1.89	
Oral treatment, 200 mg once daily				
Day 8, 168 h	5	1.24 ± 0.47	0.56–1.89	
Day 9, 192 h	5	1.05 ± 0.41	0.37–1.44	
Day 13, 288 h	4	0.71 ± 0.67	0.13–1.47	
Day 17, 384 h	5	0.84 ± 0.66	0.10–1.48	
Day 21, 480 h	3	0.75 ± 0.70	0.32–1.31	
Oral treatment, 200 mg twice daily				
Day 8, 168 h	5	0.95 ± 0.24	0.70–1.27	
Day 9, 192 h	5	1.10 ± 0.24	0.87–1.44	
Day 13, 288 h	5	1.53 ± 0.79	1.03–2.93	
Day 17, 384 h	5	1.62 ± 0.91	1.10–3.23	
Day 21, 480 h	4	2.06 ± 0.70	1.39–3.04	

During i.v. treatment, 13 of 17 patients (76%) reported adverse events. During oral treatment, all six patients in the once-daily group and eight of nine patients in the twice-daily group reported adverse events. The most frequently reported events were constipation (seven patients during i.v. treatment and one patient during once-daily oral treatment), fever (six patients during i.v. treatment and three patients each during once-daily and twice-daily oral treatments), diarrhea (one patient each during i.v. and once-daily oral treatments and three patients during twice-daily oral treatment), and bacterial infection (three patients during i.v. treatment and two patients during twice-daily oral treatment).

Serious adverse events were reported in two patients during i.v. treatment (one patient had constipation and bacterial in-

fection; the other had constipation, fever, hypotension, pain, and pneumonitis) and in two patients during twice-daily oral treatment (both had pneumonitis).

The two patients who were withdrawn from the study during i.v. itraconazole treatment both reported fever. One of these patients also had pneumonitis and died from pneumonia 2 weeks after withdrawal, but this was unrelated to a study medication. Patients were withdrawn during oral treatment for fever (one patient in the once-daily treatment group and two patients in the twice-daily treatment group), pneumonitis (two patients in the twice-daily treatment group), colitis (one patient in the once-daily treatment group), and abdominal pain and diarrhea (one patient in the twice-daily treatment group).

All patients had important abnormalities at some point dur-

TABLE 2. Severe laboratory abnormalities

Abnormality	No. of patients in the following treatment groups ^a :		
	Intravenous (n = 17)	Oral once daily (n = 6)	Oral twice daily (n = 5)
Biochemistry			
Calcium	6 ↓	1 ↓	1 ↓
Chloride	3 ↑, 1 ↓	1 ↑ ^b	
Phosphorus	2 ↓, 1	2 ↓	
Potassium		1 ↓	1 ↓
Total protein	4 ↓		2 ↓
Albumin	1 ↓	1 ↓	
Glucose	3 ↑		2 ↑
Total cholesterol		1 ↓	
Triglycerides			1 ↑
Total bilirubin	1 ↑		3 ↑
Gamma-glutamyl-transferase	3 ↑		1 ↑
AST	1 ↑		
ALT	2 ↑	1 ↑	
Urea	3 ↑, 1 ↓		1 ↑
Uric acid		2 ↓	1 ↓
Hematology			
Hemoglobin	3 ↓	1 ↓	
Erythrocyte count	3 ↓	1 ↓	
Hematocrit	3 ↓		
Leukocyte count	7 ↓ ^c , 1 ↑, 1 ↑ + ↓	3 ↓	
Platelet count	2 ↓	2 ↓	

^a Data are numbers of patients with code 4 or code 5 changes. ↑, increase; ↓, decrease.

^b Code 5 abnormality.

^c Five patients had code 5 abnormalities.

ing the study. Severe abnormalities are detailed in Table 2. During i.v. treatment, 16 of 17 patients (94%) had at least one code 4 abnormality and 5 (29%) had a code 5 abnormality. In the oral treatment period, five of six patients (83%) in the once-daily treatment group and four of five patients (80%) in the twice-daily treatment group had at least one code 4 abnormality. One patient had a code 5 abnormality during once-daily oral treatment. No consistent changes in laboratory variables were observed.

The i.v. dosing regimen used in the trial described here was suitable for rapid achievement of a target mean steady-state trough plasma itraconazole concentration in the region of 0.50 µg/ml (10). This trough concentration could be maintained and increased by follow-up treatment with itraconazole oral solution at 200 mg twice daily. The once-daily oral regimen failed to maintain trough plasma itraconazole concentrations above 0.50 µg/ml. The results suggest that i.v. and oral hydroxypropyl-β-cyclodextrin solutions of itraconazole can be used to treat patients with hematologic malignancies. This has been confirmed in a recent randomized trial with patients with hematologic disease. The trial showed that i.v. itraconazole treatment followed by oral itraconazole treatment had efficacy equivalent to that of amphotericin B and safety better than that of amphotericin B for the empiric treatment of persistent fever of unknown origin (3).

Overall, the plasma itraconazole and hydroxyitraconazole concentrations in our study were consistent with those found by use of a similar regimen with healthy volunteers but were

higher than those found in a corresponding study involving patients receiving intensive care, perhaps because of the larger volumes of distribution in critically ill patients (13). The metabolic ratios were slightly higher in our study population than those found in critically ill patients (13), which could imply slower rates of metabolism in patients with hematologic malignancies, but the significance of this difference is not clear.

All patients experienced at least one adverse event during the study. Nine patients withdrew from the trial because of adverse events; one of these patients died from pneumonia 2 weeks after leaving the trial, although this was considered to be unrelated to a study treatment. The adverse events and abnormalities in laboratory variables were expected given the patient population.

We conclude that for patients with hematologic malignancies, a regimen consisting of 7 days of i.v. treatment followed by 14 days of twice-daily oral treatment with a solution containing 200 mg of itraconazole in 40% hydroxypropyl-β-cyclodextrin leads rapidly to and maintains a trough plasma itraconazole concentration of at least 0.50 µg/ml. The regimen is well tolerated and is associated with no safety risks.

This work was supported by Janssen Research Foundation, Beerse, Belgium.

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