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Concentrations in Plasma and Safety of 7 Days of Intravenous Itraconazole Followed by 2 Weeks of Oral Itraconazole Solution in Patients in Intensive Care Units

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Pharmacokinetics and safety of a hydroxy-β-propyl solution of itraconazole were assessed in 16 patients in an intensive care unit. On the first 2 days, four 1-h infusions of 200 mg were given at 0, 8, 24, and 32 h. From day 3 to 7, inclusive, a single 1-h infusion of 200 mg of itraconazole was given daily. The intravenous (i.v.) treatment was directly followed by repeated administrations of an oral solution of itraconazole at a dosage of either 200 mg once daily or 200 mg twice daily (b.i.d.). During i.v. treatment, steady-state concentrations of itraconazole and hydroxy-itraconazole in plasma were reached within 48 and 96 h, respectively. At the end of i.v. treatment, mean (± standard deviation) itraconazole and hydroxy-itraconazole trough concentrations in plasma were 0.344 ± 0.140 and 0.605 ± 0.205 μg/ml, respectively. After the 2-week oral follow-up of 200 mg once daily the mean trough concentration had decreased to 0.245 μg/ml, whereas after 200 mg b.i.d. it increased to 0.369 μg/ml. Diarrhea during oral treatment appeared to be dose related and may be due to the solvent hydroxypropyl-β-cyclodextrin. More severe laboratory abnormalities were noted during the i.v. than the oral treatment phase, probably related to more severe illness in that period of intensive care, but none proved clinically important. These results suggest that plasma itraconazole levels above 0.250 μg/ml may be achieved and maintained with the 1-week i.v. schedule followed by b.i.d. oral administration, whereas the once-daily oral follow-up seems to be a suboptimal treatment.

The triazole derivative itraconazole is an antifungal with complex, nonlinear pharmacologic behavior. Itraconazole acts by impairing the synthesis of the vital fungal cell membrane component ergosterol. Itraconazole capsules demonstrate a broad spectrum of activity against most human fungal pathogens. In noncomparative clinical trials itraconazole was shown to be effective in a wide range of superficial mycoses, including vaginal candidiasis, pityriasis versicolor, and dermatophytoses, as well as in systemic deep fungal infections (e.g., aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis). The safety profile of oral itraconazole has been studied extensively (5, 8).

In contrast to other imidazole drugs, itraconazole is metabolized by side chain hydroxylation to hydroxy-itraconazole. Hydroxy-itraconazole appears in concentrations nearly twice that of the unaltered drug in steady state. Many fungi are susceptible to the parent drug and the hydroxylated metabolite, which contributes importantly to the in vivo activity. This therapeutic activity of hydroxy-itraconazole explains discrepancies between chromatographic and bioassay determinations of serum concentrations and causes difficulties in the determination of susceptibility based on achievable concentrations in blood compared with those based on the MIC and minimal fungicidal concentration (10).

In high-risk patients, such as those with prolonged neutropenia or those requiring intensive care, oral administration of itraconazole may often be impossible, warranting the availability of an intravenous formulation. This has long been hampered by the poor water solubility of itraconazole. The development of a 40% hydroxypropyl-β-cyclodextrin solution, however, may solve the problem of liquid oral and intravenous (i.v.) administration of itraconazole.

A dosage regimen for i.v. administration of itraconazole was developed in order to rapidly reach and maintain concentrations greater than 0.500 μg/ml, based upon data obtained after single i.v. infusion and single and repeated oral administration in healthy volunteers (4, 9). The proposed dosage regimen consists of a 7-day i.v. treatment followed by oral administration. A 2-day i.v. loading scheme has been satisfactorily validated in healthy volunteers (11). In patients with hematological malignancy a 7-day i.v. dosing scheme followed by twice-daily (b.i.d.) administration of 200 mg of oral itraconazole resulted in concentrations in plasma higher than 250 ng/ml. Furthermore, the dosing scheme was generally well tolerated and safe, as no serious drug-related adverse events (AE) were observed (2).

In the present study, the itraconazole and hydroxy-itraconazole concentrations in plasma and the safety of this proposed dosage regimen were assessed in critically ill patients in the intensive care unit (ICU).

MATERIALS AND METHODS

Patient selection. All patients admitted to the ICU and eligible for antifungal prophylaxis were screened for entry in the study. Inclusion criteria consisted of an absence of actual signs or symptoms of fungal infection and an estimated minimal life expectancy of 21 days following inclusion in the trial. Patients were excluded in the presence of any of the following criteria: pregnancy or breast-feeding; childbearing potential without adequate birth control; systemic antifungal therapy or prophylaxis within 2 weeks before trial entry; use of terfenadine, astemizole, phenytoin, phenobarbital, rifampin, warfarin, cisapride, oral midazolam, or triazolam; renal insufficiency (measured as a creatinine clearance of <30 ml/min); evidence of liver disease (aspartate transaminase [ASAT] and alanine transaminase [ALAT] four or more times the upper normal limit and bilirubin levels of ≥2.5 mg/dl); use of other trial drugs other than anticancer

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regimens either concurrently or within 1 month prior to trial entry; hypersensitivity to azole antifungals; or human immunodeficiency virus positivity. In case of concomitant treatment with cyclosporin or digoxin, the plasma levels of these drugs were closely monitored.

The study protocol and volunteer information leaflet were approved by the local medical ethics committee. Following written informed consent either by the patient or by next of kin, 16 patients (8 male and 8 female; 15 Caucasian and 1 Oriental) entered the study. The median age was 43 years (range, 18 to 53 years) and the median body weight was 70 kg (range, 50 to 100 kg).

Study drugs. Just before administration, the itraconazole solution for intravenous infusion was prepared by diluting 20 ml of a 10 mg/ml injectable solution of itraconazole containing 40% hydroxypropyl-β-cyclodextrin (batch no. 94K10/F33) with 40 ml of 0.9% NaCl (batch no. 94J05/F35). The pH of the solution was 3.5 to 4. The itraconazole oral solution (batch no. 94D18/F55) consisted of 100 mg of itraconazole per 10 ml of a 40% hydroxypropyl-β-cyclodextrin solution in water and was provided as 100-ml bottles with a 10-ml dosing cup.

Study design. Characteristics, medical histories, and concomitant disorders of patients were recorded at their entry in the trial. Patients were randomly assigned to two different treatment regimens consisting of 7 days of i.v. itraconazole administration followed by different oral dosing regimens, either once daily (group 1; $n = 7$) or b.i.d. (group 2; $n = 9$). i.v. infusions of 200 mg of itraconazole each were administered over a period of 1 h by means of a syringe infusion pump via a separate lumen of a central venous catheter at 0, 8, 24, 32, 48, 72, 96, 120, and 144 h. The catheter was flushed at the completion of the infusion to ensure complete dose delivery. Itraconazole oral solution was administered as 20-ml doses with a minimum interval of 2 h from enteral feeding or oral food intake, either once daily in the morning or b.i.d., in order to assure administration under similar conditions to all patients.

Blood sampling. Blood samples of 6 ml each were collected in heparinized or EDTA tubes for drug analysis (itraconazole and hydroxy-itraconazole) immediately before treatment; at 1, 2, 8 (before the second infusion), 24 (before the third infusion), 32 (before the fourth infusion), 33, 34, 48 (before the fifth infusion), 96 (before seventh infusion), 144 (before the ninth infusion), 145, 146, 156, and 168 h (before the first oral administration); 5 and 24 h after the first oral dose; and just before and 5 h after the morning administrations on days 13, 17, and 21. Blood samples were collected from an arterial line during the i.v. phase of the study. During oral follow-up, venous or arterial blood samples were taken.

Laboratory methods. Blood samples were centrifuged for 10 min at 2,500 rpm ($1{,}000 \times g$) within 2 h after collection. Separated plasma was transferred in plastic (polyethylene or polypropylene) tubes and stored at −20°C until analysis. Itraconazole and hydroxy-itraconazole concentrations were measured by high-performance liquid chromatography (6). The quantification limits were 5.0 and 10.0 ng/ml of plasma for itraconazole and hydroxy-itraconazole, respectively.

Safety. (i) AE. Any undesirable experience occurring during the trial, whether or not considered related to the study drug, was considered an adverse event (AE). An AE that was fatal or life threatening; significantly, persistently, or permanently disabling; required intervention to prevent permanent impairment; or required prolongation of hospitalization was considered a serious AE. All serious AEs were reported within 24 h. The following specifications were given for all AEs: onset and duration; intensity, ranging from mild (not requiring medical treatment) through moderate (requiring medical treatment without interrupting administration of the study drug) to severe (necessitating withdrawal of the study drug); frequency; presumed drug relatedness, and outcome.

(ii) Laboratory safety tests. Blood samples were taken at recruitment into the trial; just before 24, 48, and 96 h; 7, 14, and 21 days after the first itraconazole administration; and at the end of the trial for biochemical (sodium, potassium, chlorides, calcium, inorganic phosphorus, total protein, albumin, glucose, total cholesterol, triglycerides, ureum, creatinine, uric acid, total bilirubin, alkaline phosphatase, ASAT, ALAT, gamma glutamyl transpeptidase, and lactic dehydrogenase) and hematological (hemoglobin, mean corpuscular hemoglobin [MCH], MCH concentration, mean corpuscular volume, hematocrit, erythrocyte count, leukocyte count, leukocyte differential count, and platelet count) analyses. Creatinine clearance tests and urinalysis were performed on days 0, 7, and 14.

Analysis of plasma concentrations and safety. Descriptive analysis was applied at each sampling time for plasma concentrations. Graphical analysis was used to describe and compare i.v. and oral treatment phases. The metabolic ratio, defined as the ratio of the trough concentration of hydroxy-itraconazole to that of itraconazole, was calculated after the 2-day i.v. loading scheme (day 3), at the end of i.v. treatment (day 8), and at the end of oral follow-up (day 21). The type and incidence of AEs were tabulated for each treatment group.

For the clinical laboratory data, descriptive statistics and pretreatment versus within treatment and posttreatment cross-tabulations were performed for all tests. For most hematological and biochemical tests, pathological limits are defined by Lippert and Lehman (12). For enzymes, the upper pathological limit was defined as twice the upper normal value.

RESULTS

Patient and treatment information. During i.v. treatment, three patients dropped out of the trial (one withdrawal of informed consent in group 1 and two deaths in group 2). During the oral treatment phase, two dropouts occurred, both in group 2 (one death and one because of AEs). Primary pathology of all patients is given in Table 1. All except two patients were on mechanical ventilation.

TABLE 1. Primary pathology of the patients in an ICU receiving i.v. treatment followed by oral treatment with itraconazole

Patient	Main pathology at entry in the study	Mechanical ventilation
1	Intoxication, aspiration pneumonia, ARDS	Yes
2	Burns, ventilator-associated pneumonia	Yes
3	Abdominal sepsis following complicated hysterectomy	Yes
4	Pancreatitis with pleural and pericardial fluid effusion	No
5	Pneumococcal sepsis with meningitis and peritonitis	Yes
6	Burns, catheter-related septicemia	No
9	Pneumonia, ischemic cardiomyopathy, and pulmonary edema	Yes
10	Cardiogenic pulmonary edema, valvular disease, infected abdominal wound after liposuction	Yes
11	Neurotrauma, coma	Yes
12	Cardiogenic shock, ventilator-associated pneumonia	Yes
13	Burns, ventilator-associated pneumonia	Yes
14	Carbon monoxide poisoning, coma, cardiogenic shock	Yes
16	Respiratory insufficiency due to nosocomial pneumonia	Yes
17	Lung fibrosis due to inhalation burn injury	Yes
18	Multiple trauma	Yes

As expected in an ICU study population, all patients had concurrent medication, most commonly antimicrobials, stress ulcer prophylaxis with ranitidine, heparin sodium, midazolam, and opiates. No patients took cyclosporin concomitantly; two patients were on digoxin.

Data from patients 12 and 13 were excluded from analysis because of premature interruption of i.v. treatment. Patients 4, 12, and 13 did not progress into the oral follow-up phase. Data from patient 17, for whom oral follow-up treatment was prematurely discontinued on day 13, were excluded from analysis of the oral follow-up treatment phase.

Plasma drug concentrations during i.v. treatment. Concentrations of itraconazole and hydroxy-itraconazole in plasma during the i.v. treatment are presented in Table 2. At the end of the first 1-h infusion of itraconazole, the peak concentration of itraconazole in plasma was 1.148 ± 0.554 μg/ml (range, 0.504 to 2.210 μg/ml). One hour later plasma itraconazole concentrations had dropped to approximately one-third of the values observed immediately at the end of the infusion. At the end of the last 1-h infusion, the mean peak concentration of itraconazole in plasma was 1.576 μg/ml (range, 0.717 to 3.104 μg/ml). One hour later concentrations in plasma had dropped to 50% of these values.

During the 2-day loading scheme, mean trough itraconazole concentrations gradually increased from 0.137 μg/ml at 8 h to 0.316 μg/ml at 48 h. From 48 h to the end of i.v. administration at 168 h, mean trough itraconazole concentrations fluctuated between 0.316 and 0.349 μg/ml (Table 2). At the end of i.v. treatment, 12 of 14 patients had reached trough plasma drug concentrations greater than 0.250 μg/ml (in 4 patients they were >0.500 μg/ml).

During i.v. treatment, mean trough concentrations of hydroxy-itraconazole in plasma increased gradually from 0.159 ng/ml at 8 h to 0.609 μg/ml at 96 h (Table 2). From 96 h to the end of i.v. administration, mean trough hydroxy-itraconazole

TABLE 2. Concentrations (mean ± SD) of itraconazole and hydroxy-itraconazole in plasma of patients in an ICU[a]

Time after start of therapy	Itraconazole concn (ng/ml)	Hydroxy-itraconazole concn (ng/ml)
Day 1		
0 h	NQ[b]	NQ
1 h	1,148 ± 554	220 ± 122
2 h	377 ± 149	220 ± 81
8 h	137 ± 108	159 ± 63
Day 2		
24 h	168 ± 122	287 ± 140
32 h	287 ± 141	417 ± 170
33 h	1,514 ± 553	544 ± 183
34 h	742 ± 274	567 ± 209
Day 3, 48 h	316 ± 200	525 ± 242
Day 5, 96 h	349 ± 185	609 ± 263
Day 7		
144 h	337 ± 149	658 ± 264
145 h	1,576 ± 734	737 ± 289
146 h	709 ± 340	721 ± 265
156 h	372 ± 134	660 ± 207
Day 8		
168 h	344 ± 140	605 ± 205

[a] During treatment consisting of four 1-h i.v. infusions of 200 mg of itraconazole given over 2 days at 0, 8, 24, and 32 h followed by 5 days of oral doses of 200 mg of itraconazole once daily.
[b] NQ, not quantifiable by high-performance liquid chromatography.

concentrations in plasma fluctuated between 0.605 and 0.658 μg/ml, indicating that steady-state plasma drug concentrations were reached at 96 h with the i.v. dosage scheme investigated. At steady state, the mean metabolic ratio, defined as the ratio between the trough concentration of hydroxy-itraconazole and that of itraconazole, was 1.9 (range, 1.2 to 2.9) (Table 3).

Plasma drug concentrations during oral follow-up. Concentrations of itraconazole and hydroxy-itraconazole in plasma during oral follow-up treatment are presented in Table 4. Time courses of mean concentrations in plasma are shown in Fig. 1. With once-daily oral follow-up, mean trough plasma itraconazole concentrations decreased from 0.340 μg/ml at the end of the 1-week i.v. treatment to 0.245 μg/ml at the end of the 2-week oral treatment. With 200 mg of oral solution b.i.d., mean trough plasma itraconazole concentrations increased from 0.369 μg/ml to 0.805 μg/ml. With once-daily 200-mg doses of itraconazole oral solution, mean trough hydroxy-itraconazole concentrations in plasma did not change significantly, ranging from 0.581 μg/ml at the end of 1 week of i.v. treatment to 0.491 μg/ml at the end of 2 weeks of oral treatment (Table 4 and Figure 1). With 200 mg of itraconazole oral solution b.i.d., however, the mean trough plasma hydroxy-itraconazole concentration increased from 658 ng/ml at the end of the 1-week i.v. treatment to 1.234 μg/ml at the end of the 2-week oral treatment. At this time point, the mean metabolic ratio at steady state was 1.7 in the 200 mg once-daily group and 1.5 in the b.i.d. group (Table 3).

TABLE 3. Metabolic ratio (mean ± SD) between hydroxy-itraconazole and itraconazole trough plasma concentrations for patients in an ICU[a]

Subject group	Metabolic ratio at:		
	48 h	168 h	480 h
200 mg once daily	2.02 ± 0.50	1.88 ± 0.50	1.75 ± 0.62
200 mg b.i.d.	1.73 ± 0.85	1.89 ± 0.65	1.47 ± 0.43
Overall	1.87 ± 0.70	1.89 ± 0.54	1.61 ± 0.53

[a] During treatment consisting of four 1-h i.v. infusions of itraconazole (200 mg) given over 2 days at 0, 8, 24, and 32 h and continued with five 1-h infusions of itraconazole (200 mg) given once daily for 5 days followed by repeated administrations of itraconazole oral solution (200 mg) once daily or b.i.d. for 2 weeks.

TABLE 4. Concentrations (mean ± SD) of itraconazole and hydroxy-itraconazole in plasma of patients in an ICU during follow-up treatment[a]

Time after start of therapy	Itraconazole concn (ng/ml)		Hydroxy-itraconazole concn (ng/ml)	
	200 mg once daily	200 mg b.i.d.	200 mg once daily	200 mg b.i.d.
Day 8				
168 h	340 ± 148	369 ± 162	581 ± 149	658 ± 311
173 h	462 ± 244	476 ± 172	666 ± 229	728 ± 291
Day 9				
192 h	325 ± 142	388 ± 174	588 ± 232	704 ± 339
Day 13				
288 h	340 ± 161	417 ± 358	537 ± 425	774 ± 717
293 h	362 ± 148	533 ± 483	576 ± 290	842 ± 799
Day 17				
384 h	215 ± 153	655 ± 532	508 ± 450	1,218 ± 977
389 h	333 ± 194	862 ± 583	594 ± 416	1,267 ± 898
Day 21				
480 h	245 ± 165	805 ± 708	491 ± 419	1,234 ± 1,021
485 h	402 ± 214	1,028 ± 581	640 ± 393	1,451 ± 889

[a] Consisting of either 200 mg of itraconazole once daily or 200 mg of itraconazole b.i.d. as an oral solution after a 7-day i.v. treatment with itraconazole.

Safety. (i) AEs. AEs were reported for 11 of 16 patients during i.v. treatment, for 4 of 6 patients during once-daily oral treatment, and for 6 of 7 patients during b.i.d. oral treatment. Most were not considered drug related but rather due to underlying disease in critically ill patients, e.g., in the case of hemodynamic instability (4 of 16 patients during i.v. treatment, 1 of 6 patients during once-daily oral treatment, and 1 of 7 patients during b.i.d. oral treatment). Gastrointestinal symptoms were frequently reported. There appeared to be a dose-dependent correlation mainly between diarrhea and oral dose, as an unspecified gastrointestinal AE was reported for only 1 of 16 patients during i.v. treatment compared to 2 of 6 patients (1 diarrhea and 1 vomiting) during once-daily oral treatment and 5 of 7 patients (5 diarrhea, 1 dyspepsia, 1 nausea, and 1 abdominal pain) during b.i.d. oral treatment.

One case of albuminuria during i.v. treatment (≥3 g/liter) and three cases of severe gastrointestinal symptoms (two with diarrhea alone and one with abdominal pain, diarrhea, and nausea) during b.i.d. oral treatment were reported as severe AEs. Deaths were due either to a combination of respiratory insufficiency, cardiac failure, and cardiopulmonary resuscitation (patient 12) or of septic shock and adult respiratory distress syndrome (ARDS) (patient 13) or to ARDS alone (patient 15). Other serious AEs consisted of respiratory depression during i.v. treatment (patient 15) and diarrhea and nausea during b.i.d. oral treatment (patient 17). No abnormal-

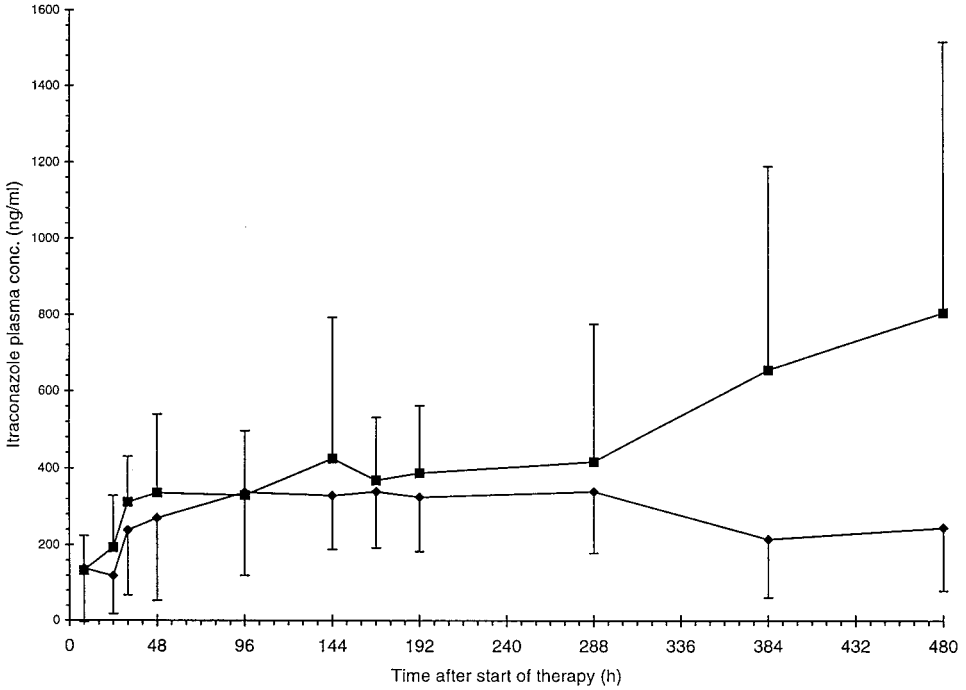

FIG. 1. Mean plasma itraconazole concentrations for patients in an ICU during treatment consisting of four 1-h i.v. infusions of itraconazole (200 mg) given over 2 days at 0, 8, 24, and 32 h and continued with five 1-h infusions of itraconazole (200 mg) given once daily for 5 days followed by repeated administrations of itraconazole oral solution (200 mg) once daily or b.i.d. for 2 weeks. Symbols: ◆, itraconazole, once-daily oral group; ■, itraconazole, b.i.d. oral group.

ities of creatinine clearance were noted (at entry, mean creatinine clearance was 105.5 ml/min [SD, 65.7]; at day 7 mean creatinine clearance was 120.5 ml/min [SD, 78.4]).

(ii) Important abnormalities in individual patients. As could be expected in critically ill patients in ICUs, all 16 patients had important biochemical abnormalities during the trial. Of these, 14 had to be considered severe during i.v. treatment, most likely the most critical phase of illness (Table 5). Similarly, during oral treatment, severe laboratory abnormalities were seen in the once-daily (three of six patients) and the b.i.d. (five of seven patients) groups.

DISCUSSION

Treatment or prophylaxis of deep fungal infections is often required in hematological patients and patients in ICUs. Particularly in intensive care, i.v. infusion may be the only possible route of administration. Itraconazole has been shown to be effective against deep fungal infection. At present, the only possibility for i.v. administration of itraconazole appears to be the use of a 40% hydroxypropyl-β-cyclodextrin solution. To reach as quickly as possible and maintain plasma itraconazole concentrations of 0.500 μg/ml, a 7-day i.v. treatment with itraconazole followed by 2 weeks of oral administration has been proposed.

The predefined therapeutic concentration is supported by the MIC of itraconazole against *Aspergillus* sp., reported by Espinell-Ingroff et al. to be about 0.130 μg/ml (7) and by Dupont and Drouhet to range from <90 to 0.360 ng/ml (6). The efficacy of i.v. administration of itraconazole solubilized in hydroxypropyl-β-cyclodextrin was confirmed in a rat model with *Aspergillus fumigatus* pneumonia (13). For *Candida* infections, it is substantiated by an analysis of clinical data correlating itraconazole MICs, determined by the M27-T methodology (14), with outcome, mainly in AIDS patients receiving

TABLE 5. Summary of clinical laboratory parameters for which a code 4 (change from normal value to pathological value) or code 5 (change from pathologically low to pathologically high value) was noted

Parameter	Change during indicated treatment phase[a]		
	i.v. (n = 14 of 16 paired)	Oral once daily (n = 3 of 6 paired)	Oral b.i.d. (n = 5 of 7 b.i.d.)
Calcium	3 ↑		
Chloride	2 ↑		1 ↓
Phosphorus	1 ↑, 1 ↓		2 ↑
Potassium	3 ↓		1 ↑ (code 5)
Total protein	2 ↓		
Albumin	8 ↓		1 ↓
Glucose	1 ↑	1 ↑	1 ↑
Total bilirubin	3 ↑		
Alkaline phosphatase	2 ↑		
Gamma glutamyl transpeptidase	1 ↑		1 ↑
Lactic dehydrogenase	1 ↑		
ASAT	1 ↑	1 ↑	1 ↑
ALAT	2 ↑		
Creatinine	2 ↑		
Hemoglobin	1 ↓		
MCH	1 ↓		
Erythrocyte count	1 ↓		
Hematocrit	1 ↓		
Leukocyte count	1 ↑ then ↓	2 ↑	1 ↑
Platelet count	1 ↑, 3 ↓		1 ↑, 1 ↓
Urea			1 ↑
Triglycerides			2 ↑

[a] ↑, increase; ↓, decrease. The numbers indicate the number of patients in whom the change occurred.

almost identical treatment with itraconazole oral solution at a dosage of 200 mg/day for oropharyngeal candidiasis. The average plasma itraconazole level in this analysis of 264 patient-episode-isolate events was 550 ng/ml. With a cutoff point of 0.5 μg/ml, higher success rates were observed for patients infected by isolates for which the MICs were 0.250 to 0.500 μg/ml (50% if the itraconazole level was <0.500 μg/ml versus 76% if the level was >0.500 μg/ml) and >1.0 μg/ml (44 versus 65% for the two levels of itraconazole, respectively). With low MICs (<0.125 μg/ml), the outcome seemed independent of the itraconazole level achieved. Tentative interpretive breakpoints of ≤0.125 μg/ml as itraconazole susceptible and ≥1.0 μg/ml as itraconazole resistant were proposed; because infections due to isolates for which the itraconazole MICs are 0.250 to 0.500 μg/ml responded more often if higher plasma itraconazole levels were ensured, the subcommittee proposed placing these isolates in the category "susceptible—dose dependent" (16).

The purpose of the present study was to determine whether the proposed regimen would result in the target concentrations being reached in critically ill patients. Itraconazole peak concentrations in plasma after i.v. dosing were transient, with fast distribution of itraconazole in the tissues. i.v. treatment resulted in steady-state mean itraconazole trough concentrations ranging from 0.316 to 0.349 μg/ml within 48 h. From 96 h to the end of i.v. administration at 168 h, mean plasma hydroxy-itraconazole concentrations fluctuated between 0.605 and 0.658 μg/ml, indicating that steady state was reached within 96 h with the investigated i.v. dosage scheme.

With once-daily administration of 200 mg of an oral solution, mean trough itraconazole concentrations in plasma decreased from 0.340 μg/ml at the end of 1 week of i.v. treatment to 0.245 μg/ml at the end of the 2-week oral treatment course. On the other hand, with b.i.d. oral solution administrations, mean trough plasma itraconazole concentrations significantly increased from 0.369 to 0.805 ng/ml. These results indicate that 200-mg b.i.d. oral follow-up is preferable in order to maintain or even increase itraconazole concentrations. Overall variability of itraconazole trough concentrations was higher after oral than after i.v. administration.

The mean plasma itraconazole levels in patients in the ICU appeared to be lower than those in patients with hematological malignancies (2) and healthy volunteers (11). In the latter, itraconazole trough concentrations at steady state during i.v. infusion varied between 0.503 and 0.535 μg/ml compared to 0.316 to 0.349 μg/ml in patients in the ICU. The same pattern was observed during oral follow-up, with lower concentrations in patients in the ICU. Since the metabolic ratio of hydroxy-itraconazole and itraconazole in this population is not different from that in healthy volunteers or other patients, the difference in plasma itraconazole levels is probably not due to alterations in metabolism. Hence, it may be attributed to larger volumes of distribution, as has been observed in several types of critically ill patients with pathophysiologic changes, e.g., following thermal injury, peritonitis, or congestive heart failure. Altered aminoglycoside and glycopeptide pharmacokinetics in the critically ill has also been attributed to large interpatient variability in volumes of distribution (1, 3, 15, 17). No relationship between creatinine clearance and the metabolic ratio was observed.

There appeared to be a dose-related incidence of gastrointestinal AEs, mainly diarrhea, during oral treatment. More severe laboratory abnormalities were observed during the first 7 days, i.e., the i.v. treatment phase, but this was to be expected in the more critical phase of ICU stay. No clinically consistent laboratory abnormalities were noted. Even though diarrhea was the most commonly observed AE, this could probably be attributed to the solvent hydroxypropyl-β-cyclodextrin. Diarrhea was serious enough to terminate the trial medication for only one patient on b.i.d. oral itraconazole solution. Moreover, diarrhea is not uncommon in this population, due, e.g., to infectious pathology (*Clostridium difficile* colitis) or hyperosmolar enteral nutrition.

In conclusion, in a mixed medical-surgical ICU population, a 7-day i.v. dosing scheme of itraconazole followed by once-daily or b.i.d. oral administration of 200 mg of a hydroxypropyl-β-cyclodextrin-based solution resulted in lower concentrations of itraconazole and hydroxy-itraconazole in plasma than was anticipated from previous trials with a similar design in healthy volunteers and patients with hematological malignancy. This dosing scheme is generally well tolerated and safe. Further oral-dose escalation may be limited by the dose-related diarrhea observed. Whether this dosing regimen is effective in the prophylaxis or treatment of fungal infections in patients in ICUs remains to be established in clinical trials.

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