

Pharmacokinetics of Itraconazole (Oral Solution) in Two Groups of Human Immunodeficiency Virus-Infected Adults with Oral Candidiasis

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The pharmacokinetics of itraconazole formulated in a hydroxypropyl- β -cyclodextrin oral solution was determined for two groups of human immunodeficiency virus (HIV)-infected adults with oral candidiasis (group A, 12 patients with CD4⁺ T-cell count of >200/mm³ and no AIDS, and group B, 11 patients with CD4⁺ T-cell count of <100/mm³ and AIDS). Patients received 100 mg of itraconazole every 12 h for 14 days. Concentrations of itraconazole and hydroxyitraconazole, the main active metabolite, were measured in plasma and saliva by high-performance liquid chromatography. Pharmacokinetic parameters determined at days 1 and 14 (the area under the concentration-time curve from 0 to 10 h, the maximum concentration of drug in plasma [C_{max}], and the time to C_{max}) were comparable in both groups. Trough levels in plasma (C_{min}) were similar in both groups for the complete duration of the study. An effective concentration of itraconazole in plasma (>250 ng/ml) was reached at day 4. At day 14, C_{min} values of itraconazole were 643 \pm 304 and 592 \pm 401 ng/ml for groups A and B, respectively, and C_{min} values of hydroxyitraconazole were 1,411 \pm 594 and 1,389 \pm 804 ng/ml for groups A and B, respectively. In saliva, only unchanged itraconazole was detected, and mean concentrations were still high (>250 ng/ml) 4 h after the intake, which may contribute to the fast clinical response. In conclusion, the oral solution of itraconazole generates effective levels in plasma and saliva in HIV-infected patients; its relative bioavailability is not modified by the stage of HIV infection.

Itraconazole is a triazole compound with a broad-spectrum antifungal activity (10). Being highly lipophilic, itraconazole is almost insoluble in water, and a unique bead formulation enclosed within a gelatin capsule was developed for oral use. This oral capsule formulation has been used successfully for the treatment of a variety of superficial and systemic fungal infections, including oral and esophageal candidiasis of AIDS patients (10, 11). In two trials of neutropenic patients receiving itraconazole for long-term prophylaxis, the incidence of fatal fungal infections was dramatically reduced among patients maintaining adequate levels of itraconazole in plasma (>250 ng/ml) (2, 13). The response of human immunodeficiency virus (HIV)-related oropharyngeal candidiasis to itraconazole appears to vary with itraconazole MICs; the therapeutic effect may be enhanced by ensuring sufficient levels in plasma for infections due to isolates for which itraconazole MICs are \geq 0.25 μ g/ml (9). In AIDS patients, the bioavailability of itraconazole capsules was shown to be reduced by 50% compared with that in healthy volunteers (12). Hypochlorhydria, a common finding in HIV-infected patients, may be a factor of lower bioavailability, as the absorption of the capsule formulation was shown to be decreased when administered under conditions of low intragastric acidity (7, 14). To improve the absorption of itraconazole, a new formulation was developed in hydroxypropyl- β -cyclodextrin, a carrier adapted to the solubilization of lipophilic molecules (5).

The aims of this study were (i) to evaluate the relative bioavailability of itraconazole from an oral solution in patients at different stages of HIV infection and (ii) to determine the levels of itraconazole and its active metabolite hydroxyitraconazole in saliva.

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Patients and study design. The study population consisted of HIV-infected patients from the Infectious Diseases units of four French university hospitals. The study protocol was approved by the Ethics Committee and was performed in accordance with the Declaration of Helsinki and current European Community guidelines for good clinical practice. Written informed consent was obtained from each patient prior to study participation. Two groups of HIV-infected adults with clinical signs of oral candidiasis were defined. The first group (group A) consisted of patients without AIDS (AIDS-related complex) and a CD4⁺ T-cell count of more than 200 per mm³. The second group (group B), at a more advanced stage of HIV infection, consisted of patients with AIDS (1987 Centers for Disease Control revised case definition) and a CD4⁺ T-cell count of less than 100 per mm³. Each subject was enrolled on the basis of medical history, physical examination, and laboratory tests (hematology, blood chemistry). CD4⁺ T-cell counts were determined by flow cytometry within 2 weeks before each patient's inclusion in the study. Exclusion criteria included treatment with cytochrome P-450 inducers or inhibitors (rifampin, rifabutin, antiepileptics, clarithromycin, or isoniazid), abnormal liver test (alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase level superior to three times the upper limit of the normal range), prothrombin time

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5 s more than control, serum creatinine level greater than 150 $\mu\text{mol/liter}$, polychemotherapy for lymphoma or Kaposi's sarcoma, and diarrhea (defined as more than three liquid stools per day). Pregnant women and women of child-bearing potential not practicing adequate birth control were also excluded. Subjects were instructed not to take drugs which could alter gastric pH, such as antacids, histamine-2 receptor antagonists, or omeprazole. Patients treated with dideoxyinosine (ddI), a medication which contains antacids, were not excluded from the study; however, ddI was to be administered on an empty stomach.

Patients were treated for oral candidiasis with 100 mg of itraconazole (10-ml oral solution) every 12 h for 14 days (days 1 through 14). The oral solution contained 10 mg of itraconazole/ml in an aqueous hydroxypropyl- β -cyclodextrin solution and was supplied by Janssen Pharmaceutica (Beerse, Belgium). The patients were instructed to ingest the drug at the same time every day, 10 min after breakfast and dinner. Since we wished study circumstances to be as close as possible to daily practice, the participants were allowed to eat nonstandardized meals. With regard to saliva sampling, the intake of solids was not allowed during the first 4 h after drug ingestion, and patients were instructed to refrain from ingesting beverages for 10 min prior to sampling.

Blood samples (6 ml) were collected in heparinized tubes immediately prior to the morning intake of the drug on days 1, 2, 4, 7, 9, 11, 13, and 14. Blood samples were also taken 1, 2, 4, 8, and 10 h after the morning intake on days 1 and 14 and in the morning of day 15. Each blood sample was centrifuged within 1 h of sampling. Plasma was separated and stored at -20°C until analyzed. Nonstimulated whole saliva was collected with a 2-ml syringe under gentle suction. Saliva samples (1 ml) were taken on days 1 and 14 just before and at 2, 4, and 8 h after the first daily administration of itraconazole and then stored at -20°C until analyzed.

Clinical efficacy and safety were observed. At each visit, any change in signs and symptoms of oropharyngeal candidiasis was recorded along with any drug-related side effect. Physical examinations and liver function tests were repeated at the end of treatment. Patients were classified clinically as cured (resolution of signs and symptoms of oropharyngeal candidiasis), clearly improved (substantial reduction of signs and symptoms), or failed (little or no change or clinical progression).

Analytical procedures. Concentrations of itraconazole and hydroxyitraconazole in plasma and saliva were measured by a modified and validated reverse-phase high-performance liquid chromatography method as previously described (15). Quality control was performed with plasma samples (1 ml); over the range of 100 to 2,000 ng/ml, the intra-assay coefficient of variation varied from 2.9 to 6.2% for unchanged itraconazole and from 5.8 to 7.3% for hydroxyitraconazole, and the accuracy varied from 97 to 99% for both compounds. The standard curves were linear from 50 to 2,000 ng/ml. Salivary samples (diluted with 0.5 ml of water) were analyzed with the same analytical batch as for plasma samples, and concentrations were determined by using the plasma calibration curves.

Pharmacokinetic and statistical analyses. Plasma concentrations were expressed as a daily trough concentration in plasma (C_{\min}); a steady-state concentration (C_{ssmin}) was estimated from the mean of C_{\min} values observed during the apparent plateau. To determine the apparent plateau, a statistical analysis was performed to compare trough C_{\min} values at day 15 with those from previous sampling days (days 7, 9, 11, 13, and 14) by using Student's t test for paired data. At days 1 and 14, the peak concentrations in plasma (C_{\max}) and the time to C_{\max} (T_{\max}) were determined by visual inspection of the

individual plasma drug concentration-time data. At days 1 and 14, the areas under the concentration-time curves from 0 to 10 h (AUC_{0-10}) were calculated by using the linear trapezoidal rule. The metabolic ratio was estimated from the ratio of the AUC_{0-10} of hydroxyitraconazole to that of itraconazole.

The comparison between the two groups of patients was performed by one-way analysis of variance and Student's t test for pharmacokinetic parameters (C_{\max} , AUC_{0-10} , and C_{\min}). For concentrations in saliva, at each time point comparisons between groups and between days 1 and 14 for each group were performed by a t test. In all cases, the homogeneity of variances was checked with Fisher's test. A nonparametric test was used for comparing T_{\max} values (Mann-Whitney test). Differences were considered statistically significant if P was <0.05 .

Results. Twelve patients were enrolled into each group. All the subjects completed the study except one from group B who was excluded from analysis for poor compliance (proved on residual returned medication). The demographics data and concurrent medications for subjects in the study are shown in Table 1. Both groups were comparable with regard to sex, age, and weight. The CD4 count (mean \pm standard deviation) was 382 ± 96 cells/ mm^3 in group A and 34 ± 27 cells/ mm^3 in group B.

The C_{\min} curves for itraconazole and for hydroxyitraconazole in groups A and B are superimposable (Fig. 1). The mean C_{\min} of unchanged itraconazole became superior to 250 ng/ml on the fourth day of treatment (305 ± 93 ng/ml for group A and 271 ± 199 ng/ml for group B [means \pm standard deviations]). On the same day, the C_{\min} of hydroxyitraconazole (mean \pm standard deviation) reached 771 ± 211 ng/ml in group A and 688 ± 346 ng/ml in group B. The plateaux were reached at day 13 for itraconazole, at day 14 for the metabolite in group A, and at day 9 for both compounds in group B. At the plateau, C_{ssmin} values both for itraconazole and hydroxyitraconazole, were not different in the two groups (Table 2). Pharmacokinetic parameters (AUC_{0-10} , C_{\max} , T_{\max}) were equivalent in both groups (Table 3). AUC_{0-10} values for itraconazole (means \pm standard deviations) were $7,782 \pm 3,144$ ng \cdot h/ml for group A and $6,246 \pm 3,864$ ng \cdot h/ml for group B. The mean plasma metabolic ratio (hydroxyitraconazole/itraconazole) was unchanged from the first to the last day of treatment. There was no statistical difference between the two groups, neither for plasma concentrations nor for pharmacokinetic parameters. The four patients from group B who were treated simultaneously with ddI did not show any difference from the other patients.

No hydroxyitraconazole could be detected in saliva samples. The highest concentrations of unchanged itraconazole in saliva were obtained 2 h after oral intake (Fig. 2). C_{\max} values (means \pm standard deviations) were $2,156 \pm 3,285$ and $7,342 \pm 10,493$ ng/ml for groups A and B, respectively, at day 1 and $1,637 \pm 2,048$ and $4,069 \pm 3,914$ ng/ml at day 14. Four hours after the drug intake, values in saliva (means \pm standard deviations) at day 1 were $680 \pm 1,497$ ng/ml and $1,211 \pm 1,924$ ng/ml. Eight hours after drug intake, four patients showed significant concentrations (840 ng/ml in one patient in group A and 294, 912, and 1,361 ng/ml in three patients in group B). Concerning concentrations of itraconazole in saliva, no significant statistical difference was found between the two groups and between days 1 and 14 for each group. Furthermore, the concentrations in saliva were not related to the concentrations in plasma.

All patients in group A and 9 out of 11 patients in group B were cured at the end of the treatment, and the remaining two in group B were markedly improved. Mean marked improve-

TABLE 1. Demographics of patients in this study

Group ^a and patient no.	Sex ^b	Age (yr)	Wt (kg)	CD4 count (cells/mm ³)	Concurrent medication(s) ^c
A					
1	M	33	52	462	
2	F	36	57	346	Bromazepam
3	M	32	68	480	
4	M	31	63	519	
5	M	26	77	224	AZT, prazepam
6	M	37	68	369	
7	M	26	68	437	
8	M	22	70	504	
9	M	31	61	336	AZT, domperidone
10	F	33	53	264	Zolpidem
11	M	48	70	335	AZT
12	M	38	75	314	AZT, TMP-SMX
Mean ± SD		33 ± 7	65 ± 8	382 ± 96	
B					
1	M	41	74	43	Foscavir, TMP-SMX
2	M	34	55	45	Clonazepam, ddI, mianserin, prednisolone, TMP-SMX
3	M	51	64	58	Atenolol, ddI, pyrimethamine
4	F	33	47	92	Acyclovir, amitriptyline, hydroxyzine, levomepromazine, TMP-SMX
5	M	38	64	7	Oxacillin, fluoxetine, loperamide, TMP-SMX
6	F	36	60	15	Penfluridol, TMP-SMX
7	M	32	65	7	Acetaminophen, AZT, TMP-SMX
8	M	31	62	32	Acyclovir, AZT, ddI, paromomycin, TMP-SMX
9	M	25	70	48	ddI, hydroxyzine
10	M	29	55	5	Leucovorin, TMP-SMX
11	M	43	49	20	TMP-SMX
Mean ± SD		36 ± 7 ^d	60 ± 8 ^d	34 ± 27 ^d	

^a Group A, patients without AIDS and with CD4⁺ T-cell counts of >200 per mm³; group B, patients with AIDS and with CD4⁺ T-cell counts of <100 per mm³.

^b M, male; F, female.

^c AZT, zidovudine; TMP-SMX, trimethoprim-sulfamethoxazole.

^d Values were not statistically different from those of group A (*t* test).

ment was obtained in 4.2 and 3.2 days, respectively, for groups A and B, and complete cure was obtained in 6.4 and 6.9 days, respectively. No correlation between delays in clinical efficacy and C_{\min} or AUC has been observed. Six patients in group A and seven patients in group B reported mild and mostly transitory adverse gastrointestinal experiences. No significant laboratory abnormality was detected.

This study shows an indistinguishable pharmacokinetic profile of itraconazole in oral solution between these two groups

of HIV-infected patients with markedly different clinical and immune statuses. The bioavailability can be considered comparable in both groups based on the similarity of C_{\min} values and of pharmacokinetics parameters (T_{\max} , C_{\max} , AUC_{0-10}) measured at the 1st and 14th days of the treatment for both itraconazole and hydroxyitraconazole. The C_{ssmin} of itraconazole was reached between days 9 and 15, in agreement with the results obtained by Hardin et al. (3) and Barone et al. (1) with itraconazole capsules in healthy male volunteers. This length of time is longer than the theoretical 4 to 5 days (four to five half-lives), assuming linear kinetics. This phenomenon is due to the complex mechanism of elimination of itraconazole and hydroxyitraconazole that occurs in part, via a first-order process and in part via a saturable process (1). In agreement with other studies (1, 3), the higher-than-proportional accumulation of itraconazole and hydroxyitraconazole during repeated dosing is also demonstrated by the ratios of AUC

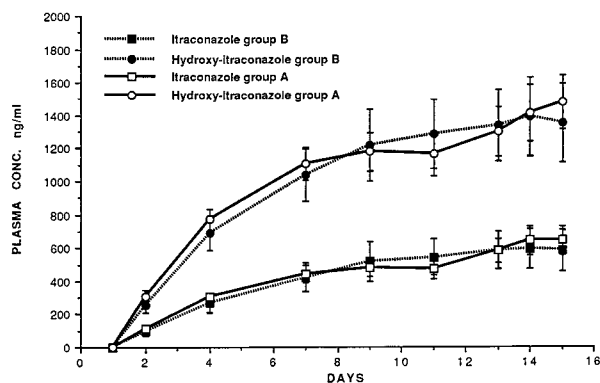


FIG. 1. C_{\min} values (means ± standard errors of the means [error bars]) of itraconazole and hydroxyitraconazole.

TABLE 2. C_{ssmin} values of itraconazole and hydroxyitraconazole^a

Group	C_{ssmin} (day ^b)	
	Itraconazole	Hydroxyitraconazole
A (<i>n</i> = 12)	624 ± 34 (13–15)	1,446 ± 49 (14–15)
B (<i>n</i> = 11)	565 ± 32 (9–15)	1,317 ± 68 (9–15)

^a Values (in nanograms per milliliter) are means ± standard deviations.

^b Period when the plateau is reached.

TABLE 3. Pharmacokinetic parameters in plasma^a

Group and parameter	Itraconazole		Hydroxyitraconazole	
	Day 1	Day 14	Day 1	Day 14
Group A (n = 12)				
T _{max} (h)	3.8 ± 2.3	3.9 ± 2.2	4.3 ± 2.0	4.5 ± 2.4
C _{max} (ng/ml)	122 ± 68 (79–165)	953 ± 382 (710–1,196)	240 ± 100 (177–303)	1,659 ± 658 (1,241–2,077)
C _{min} (ng/ml)		643 ± 304 (450–836)		1,411 ± 594 (1,034–1,788)
AUC _{0–10} (ng · h/ml)	720 ± 345 (500–939)	7,782 ± 3,144 (5,785–9,775)	1,698 ± 712 (1,246–2,150)	15,110 ± 5,780 (11,438–18,782)
Metabolic ratio ^b			2.42 ± 0.49	1.95 ± 0.25
Group B (n = 11)				
T _{max} (h)	3.1 ± 2.2 ^c	4.9 ± 2.6 ^c	4.4 ± 2.1 ^c	6.3 ± 3.8 ^c
C _{max} (ng/ml)	124 ± 65 ^d (81–167)	697 ± 391 ^d (435–959)	217 ± 79 ^d (164–270)	1,464 ± 826 ^d (911–2,017)
C _{min} (ng/ml)		592 ± 401 ^d (324–860)		1,389 ± 804 ^d (851–1,927)
AUC _{0–10} (ng · h/ml)	821 ± 406 ^d (549–1,093)	6,246 ± 3,864 ^d (3,664–8,836)	1,618 ± 632 ^d (1,195–2,041)	13,740 ± 8,040 ^d (8,353–19,127)
Metabolic ratio			2.14 ± 0.30	2.32 ± 0.51

^a Values are means ± standard deviations; 95% confidence intervals are shown in parentheses.

^b Metabolic ratio, AUC_{0–10} for hydroxyitraconazole/AUC_{0–10} for itraconazole.

^c Values were not statistically different from those of group A (Wilcoxon test).

^d Values were not statistically different from those of group A (analysis of variance and *t* test).

between days 1 and 14. The metabolic capacity to form hydroxyitraconazole, the main active metabolite, does not seem to be modified by the stage of HIV disease. This fact is attested by the similarity of the plasma metabolic ratios in the two groups of patients, which are comparable with previous values obtained with healthy volunteers (4).

Potentially effective concentrations in plasma of unchanged itraconazole (>250 ng/ml [2]) were achieved as early as the 4th day of treatment. At day 14, the AUC_{0–10} was markedly superior to 1,000 ng · h/ml, which is a level proposed as a satisfactory outcome (8). If we compare our group B with another group of AIDS patients treated at the same daily dose (200 mg) with the capsule formulation (4), the C_{ssmin} is increased by 111% with the oral solution, clearly suggesting a better bioavailability. The previously described gastric secretory failure in AIDS patients (6) could have hindered the solubilization of itraconazole from capsules. This could explain the decreased absorption in patients treated with the capsule formulation compared with the oral solution.

Concentrations in saliva were high compared to those in plasma; however, the former were not related to the latter. The level of plasma protein binding of itraconazole is very high (99.6%); therefore, we expected to find in saliva small amounts of itraconazole from plasma origin. Furthermore, we detected

only unchanged itraconazole without any traces of its metabolite hydroxyitraconazole in saliva samples. These data suggest a topical uptake of itraconazole on the buccal mucosa. The wide variability of concentrations in saliva could be partly explained by local conditions and variable ingestion of beverages.

In conclusion, this study demonstrates that the relative bioavailability of the oral solution of itraconazole is good and produces effective levels in plasma in HIV-infected patients. Bioavailability and pharmacokinetics are not affected by the degree of immunodeficiency. High concentrations of unchanged itraconazole in saliva along with a quick clinical response suggest the contribution of a topical effect of the oral solution in the treatment of oropharyngeal candidiasis.

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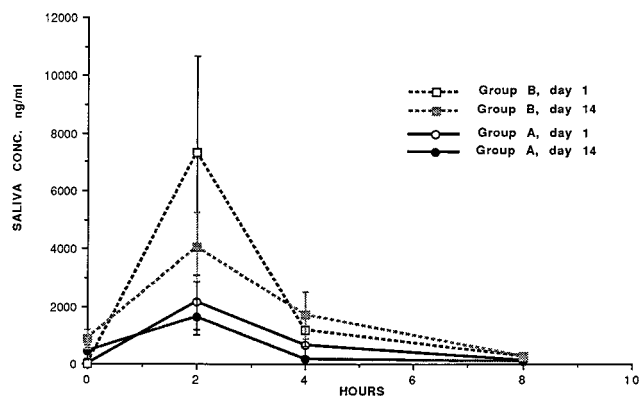


FIG. 2. Concentrations (means ± standard errors of the means [error bars]) of itraconazole in saliva.

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