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Pharmacokinetics and Safety of Oral Posaconazole in Neutropenic Stem Cell Transplant Recipients

Paul O. Gubbins,[1]* Gopal Krishna,[2] Angela Sansone-Parsons,[2] Scott R. Penzak,[3] Li Dong,[4] Monika Martinho,[2] and Elias J. Anaissie[4]

College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, Arkansas[1]; Schering-Plough Research Institute, Kenilworth, New Jersey[2]; National Institutes of Health, Clinical Pharmacokinetics Laboratory, Clinical Center Pharmacy Department, Bethesda, Maryland[3]; and Myeloma Institute for Research and Therapy, Arkansas Cancer Research Center, University of Arkansas for Medical Sciences, Little Rock, Arkansas[4]

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The pharmacokinetics of posaconazole oral suspension in neutropenic patients undergoing high-dose chemotherapy and stem cell transplantation were evaluated, and the association of plasma posaconazole exposure with the presence and severity of oral mucositis was explored in this nonrandomized, open-label, parallel-group, multiple-dose pharmacokinetic study. Thirty patients were enrolled and received one of three regimens (group I, 200 mg once daily; group II, 400 mg once daily; group III, 200 mg four times daily) for the duration of neutropenia. The mean total exposure for day 1, as shown by the area under the concentration-time curve from 0 to 24 h ($AUC_{0–24}$), was 1.96 mg · h/liter in group I and was 51% higher in group II and in group III. Increases in $AUC_{0–24}$ and maximum plasma concentration (C_{max}) in groups II and III were dose related. The $AUC_{0–24}$ and C_{max} values on day 1 were similar between groups II and III. There was interpatient variability of up to 68% in the pharmacokinetic values for our study population. Steady state was attained by days 5 to 6. Average steady-state plasma posaconazole trough values were 192, 219, and 414 ng/ml in groups I, II, and III, respectively. The $AUC_{0–24}$ and apparent oral clearance increased by increasing dose and dosing frequency. Mucositis appeared to reduce exposure but did not significantly affect mean total posaconazole exposure (AUC and C_{max}) at steady state ($P = 0.1483$). Moreover, this reduction could be overcome by increasing the total dose and dosing frequency. Posaconazole was safe and well tolerated.

With recent additions to the antifungal armamentarium, there are now several effective agents for the prophylaxis and treatment of invasive fungal infections in neutropenic hosts. The selection of an individual agent is still, however, based on its toxicity, pharmacokinetics, and efficacy (14). Posaconazole is a new triazole antifungal compound currently approved in the European Union and in development in the United States. The drug exhibits potent and broad-spectrum in vitro activity against significant fungal pathogens that cause infections in immunocompromised patients, including non-*albicans Candida* species, *Aspergillus* species, and *Fusarium* species (4, 10, 11, 12). Chemically, posaconazole is a highly lipophilic weak base that is structurally related to itraconazole. In addition, posaconazole has physicochemical properties similar to those of both itraconazole and ketoconazole. According to the Biopharmaceutics Classification System of the U.S. Food and Drug Administration Center for Drug Evaluation and Research, posaconazole belongs to biopharmaceutics class II compounds, indicating that it is well absorbed but dissolves slowly (high permeability/low solubility). Posaconazole is administered as an oral suspension.

With increasing azole resistance among stem cell transplant recipients, there is a need to determine the pharmacokinetic profile of oral posaconazole in this population. The single and multiple dose pharmacokinetics of posaconazole (tablet and suspension) in healthy volunteers have demonstrated that oral posaconazole is systemically available and eliminated slowly, with consistent pharmacokinetic values at specific dose levels (1, 3, 5, 9). When administered as a tablet formulation in doses of up to 800 mg/day, posaconazole exhibited linear pharmacokinetics with dose-proportional increases in exposure, as demonstrated by the area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) (3). The median time to peak plasma concentration (T_{max}) was approximately 5 h in healthy volunteers. Steady state was reached by approximately 7 to 10 days of dosing. Exposure to posaconazole was not increased above 800 mg in the rising single-dose study of healthy volunteers (3), probably due to the low aqueous solubility of posaconazole (<1 μg/ml) (1, 3). Because exposure did not increase beyond an oral dose of 800 mg, the administration of posaconazole in split doses was investigated as a means to increase the total amount of drug absorbed. Dose-proportional increases in exposure (AUC from 0 to 12 h [$AUC_{0–12}$] and $AUC_{12–24}$) on day 1 and at steady state (day 14) occurred when posaconazole was given in multiple daily doses, in total doses of up to 800 mg/day (3). With rising multiple doses, posaconazole accumulation was seen with multiple daily doses, and steady-state concentrations in healthy adults were achieved after approximately 10 days (3). More recently, in a study of 18 healthy men studied only under fasting conditions, exposure to posaconazole was 1.7 and 2.6 times higher when administered as 400 mg twice daily and 200 mg four times

* Corresponding author. Mailing address: Department of Pharmacy Practice, College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W. Markham #522, Little Rock, AR 72205. Phone: (501) 686-6683. Fax: (501) 296-1168. E-mail: gubbinspaulo@uams.edu.

daily, respectively, than when administered as 800 mg once daily (5).

Posaconazole oral suspension administered in the fed state, particularly after a high-fat meal, provides optimal oral drug exposure (1). Based on AUC and C_{max} values, relative oral bioavailability estimates were 4-fold and 2.6-fold greater following administration of the posaconazole oral suspension with a high-fat and nonfat meal, respectively (1). The influence of food on the systemic availability of posaconazole tablets is most likely due to a delay in gastric emptying, an increase in gastric secretions, and an enhancement in solubility caused by food that has been shown to increase bioavailability of biopharmaceutical class II weak bases, such as the azole antifungal itraconazole (15). The oral dose of posaconazole found to maximize exposure is 800 mg/day in divided doses (400 mg twice a day) (13).

Collectively, the studies of healthy volunteers indicate that in doses of up to 800 mg/day, posaconazole exhibits linear pharmacokinetics, administration with a high-fat meal significantly increases posaconazole exposure irrespective of dosage form, and systemic availability is optimized with the oral suspension. Moreover, these studies suggest that 800 mg/day as a divided dose is appropriate for the treatment of serious fungal infections.

Neutropenic patients who are at risk for opportunistic fungal infections experience significant gastrointestinal side effects (i.e., anorexia, nausea, vomiting, and diarrhea), most of which are secondary to chemotherapy-induced cytotoxicity to the gastrointestinal mucosa. Consequently, patients often have reduced dietary intake. The purpose of this study was to describe the single- and multiple-dose pharmacokinetics of posaconazole oral suspension in neutropenic patients undergoing high-dose chemotherapy and stem cell transplantation (SCT) who are colonized with a fluconazole-resistant fungus and to explore the association of plasma posaconazole exposure with the presence and severity of oral mucositis. The efficacy of posaconazole in eradicating the fluconazole-resistant *Candida* species was not evaluated.

MATERIALS AND METHODS

Patients. Thirty adult patients (Eastern Cooperative Oncology Group; performance status, 0 to 2; life expectancy, >12 weeks) receiving high-dose chemotherapy and autologous SCT participated in this study at this center. Eligibility was contingent on colonization with a fluconazole-resistant *Candida* species at one or more sites (nares, throat, perirectal area/stool, and urine) within 1 week prior to enrollment.

Once colonization with a fluconazole-resistant fungus was confirmed, patients were confined to the study center prior to the initiation of treatment. Women of childbearing potential were required to have a negative pregnancy test and to use barrier-type contraception from screening until 30 days after the last dose of study medication. Exclusion criteria included current clinically significant fungal infection requiring treatment, previous drug allergy to azoles, renal or hepatic impairment, electrocardiogram (ECG) abnormalities, and concurrent administration of medications known to interact with azoles (e.g., terfenadine, astemizole, cisapride, ebastine, triazolam, midazolam, phenytoin, and barbiturates). Consumption of alcohol and grapefruit/grapefruit juice was prohibited within 48 h prior to and during the confinement period, but caffeine- and xanthine-containing beverages were allowed at the discretion of the investigator.

This study was approved by the University of Arkansas for Medical Sciences Human Research Advisory Committee, and the study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki. We obtained written informed consent from each patient prior to performing any study-related activities. Patients meeting inclusion criteria who consented to participate were enrolled in a nonrandomized sequential manner into groups of escalating doses.

Drug administration. Patients were assigned to one of three posaconazole oral suspension (40 mg/ml) treatment regimens: 200 mg once daily (group I), 400 mg once daily (group II), or 800 mg/day (200 mg four times daily; group III). Enrollment in group II began only after the evaluation of safety and tolerability data from group I, and enrollment into group III proceeded only after the evaluation of safety and tolerability data from group II.

Patients in groups I and II ingested their dose immediately after consuming breakfast (as tolerated); patients in group III were administered each dose with food, four times daily. After each dose was consumed, the dispenser was rinsed once with 50 ml water, which was then administered to the patient. Patients were treated with posaconazole for the duration of their neutropenia and received the final dose only when their neutrophil count reached or exceeded 500 cells/mm^3.

Safety assessment. Evaluation of safety was based on reported adverse events, clinical laboratory test results, vital signs, body weight and physical examination results, ECG findings, and tests for fecal occult blood. Physical examinations were conducted at screening and the conclusion of the study. Vital signs were obtained daily throughout the study. Also performed was a 12-lead electrocardiogram at screening, once between study days 4 and 8, on study day 14, and at the completion of the study. Clinical laboratory tests were conducted at screening, prior to treatment initiation, during treatment, and at the conclusion of the study. Adverse events were evaluated for severity (mild, moderate, severe, or life threatening) using the Common Toxicity Criteria grading system, and the relationship of the adverse events to posaconazole administration (unrelated, possible, probable, or related) was determined. Determinations of clinical significance of laboratory tests that were outside reference ranges were based upon the medical expertise of the treating physician. Mucositis scoring was determined daily throughout the course of therapy.

Sample collection and posaconazole concentration determination. Blood samples (4 ml) for the determination of plasma posaconazole concentrations were collected in heparin-containing tubes immediately prior to dosing (0 h) on day 1 and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h postdose. On the last day of dosing, blood samples were collected at the same time points as those on day 1. Trough (C_{min}) plasma samples were collected each day between day 1 and the last day of dosing.

After collection, the blood samples were kept in an ice bath and centrifuged at 1,500 × *g* and ~4°C for 10 min. Thereafter, the plasma samples were rapidly frozen and stored at −20°C or below until analysis. Plasma posaconazole concentrations were determined using a validated high-performance liquid chromatographic assay with a lower limit of quantitation of 5 ng/ml. The calibration range of the assay was 5.0 to 5,000 ng/ml. The accuracies (percent differences from actual) at low-, medium-, and high-quality control samples were −5.5, −8.0, and −4.4, respectively.

Data analysis. Plasma posaconazole concentrations on day 1 and on the last day of dosing were used for the pharmacokinetic analysis using noncompartmental methods. Values for C_{max}, T_{max}, and C_{min} were the observed values. The AUC_{0-12} and AUC_{0-24} were calculated by the linear trapezoidal method and by using the actual times of plasma sample collection.

Individual accumulation ratios were determined by dividing the AUC_{0-24} on the last day of dosing by the AUC_{0-24} on day 1 for each patient. Steady-state apparent oral clearance (CL/*F*) was calculated as follows: $dose_\tau/AUC_\tau$, where τ represents the dosing interval (24 h for once-daily dosing and 6 h for four-times-daily dosing). Because of a lack of a definitive terminal elimination phase in a large number of patients, it was not possible to reliably estimate the terminal-phase rate constant and, therefore, the terminal-phase half-life, $AUC_{0-\infty}$, and volume of distribution were not calculated.

The plasma posaconazole concentration data were unbalanced. Thus, a two-way analysis of variance was performed. Because the interaction effect between mucositis and dosage was not significant, we tested the two main effects, mucositis (grade 0 versus grades 1 and 2) and dosages (200 mg once daily versus 400 mg once daily versus 200 mg four times daily), based on least-squares means using the PROC GLM procedure (SAS version 8.2). The significant level α (type I error) ≤ 0.05 was chosen a priori. Steady state was confirmed by comparing trough plasma concentration data, using a one-way analysis of variance.

RESULTS

Table 1 summarizes the demographics of patients in this study. Thirty adult patients, equally split among the genders, undergoing high-dose chemotherapy received posaconazole during the period of neutropenia. The vast majority of patients

TABLE 1. Demographic data

Group	No. of male patients/ no. of female patients	Race (no. of patients)	Mean (SD) of:				
			Age (yr)	Ht (cm)	Wt (kg)	Body mass index (kg/m^2)	Dose (mg/kg of body weight/day)
I	4/4	Caucasian (7) African American (1)	54.4 (8.3)	168.6 (8.3)	81.1 (16.5)	28.3 (4.3)	2.8 (0.8)
II	7/8	Caucasian (14) African American (1)	51.9 (9.6)	163.7 (7.2)	70.3 (14.4)	25.9 (4.2)	5.9 (1.2)
III	4/3	Caucasian (7) African American (0)	51.7 (11.9)	171.3 (8.9)	80.6 (20.4)	27.3 (5.3)	10.5 (3.2)
All	15/15	Caucasian (28) African American (2)	52.5 (9.4)	167.0 (8.3)	75.8 (16.5)	27.0 (4.6)	6.2 (3.3)

were Caucasian, and on average, they were in their sixth decade of life. According to the calculated body mass index, the majority of patients were normal or slightly overweight. Eight patients were assigned to group I (200 mg once daily), 15 to group II (400 mg once daily), and 7 to group III (200 mg four times daily). Although only 28 patients (93%) completed the study (one discontinued due to treatment failure, and one withdrew for personal reasons), all 30 patients were included in the safety analyses. On day 1, samples from 29 patients were included in the pharmacokinetic analysis (plasma samples were not collected from one discontinued patient in group I). On the last day of dosing, samples from 28 patients were included in the AUC calculations (plasma samples were not collected from discontinued patients in groups I and II). Finally, on the last day of dosing, samples from only 28 patients were included in the C_{max} and T_{max} calculations (plasma samples were not collected from discontinued patients in groups I and II).

Pharmacokinetics. The pharmacokinetic values for study day 1 are summarized in Table 2. Posaconazole was systemically available following all three dosing regimens. The AUC_{0-24} values were approximately 51% higher in group II and in group III than in group I (Fig. 1). In groups I and II, the median T_{max} values on day 1 were similar but approximately double that in group III during the first dosing interval. The AUC_{0-24} and C_{max} increased in a dose-related manner, but the increase was less than dose proportional. The AUC_{0-24} and C_{max} values on day 1 were similar between groups II and III. However, because of the lack of sampling between the third and fourth doses in group III, these values may be underestimated for group III. In addition, the degree of interpatient variability in pharmacokinetic parameters in all dosing groups ranged from 38% to 68%.

In group I, plasma posaconazole C_{min} values were not significantly different from day 6 to day 10, indicating that steady state was attained on study day 6. Similarly, for groups II and III, steady state was achieved by study day 5. The average observed steady-state plasma posaconazole C_{min} values were 192, 219, and 414 ng/ml in groups I, II and III, respectively.

The pharmacokinetic values for the last day of dosing are summarized in Table 3. On the last day of dosing (at steady state), C_{max} values increased by increasing the dose and frequency of administration. However, differences in C_{max} were not significantly different between the groups ($P = 0.0697$).

At steady state, total exposure (AUC_{0-24}) increased by increasing the dose and frequency of administration (Fig. 2). AUC_{0-24} values were significantly different between the groups, with values in group III being the highest and those in group I the lowest ($P = 0.0457$) (Table 4). The mean AUC_{0-24} value in group III was approximately 34% and 93% higher than the mean AUC_{0-24} values in groups II and I, respectively. The multiple comparisons analysis (comparison of least-squares means) demonstrated that the AUC_{0-24} in group III was significantly higher than that in group I ($P = 0.0151$). However, the AUC_{0-24} values in groups I and II were not significantly different ($P = 0.0712$). Furthermore, the AUC_{0-24} values in groups II and III were also not significantly different ($P = 0.2381$).

Posaconazole mean CL/F values at steady state also increased by increasing the dose and dosage frequency. In addition, posaconazole accumulated in plasma upon multiple dosing; accumulation ratios of 2.7, 2.4, and 3.9 were determined for groups I, II, and III, respectively.

Oral mucositis scoring was performed in 27 of the 28 patients who completed the study. During the course of the study, 23 (85%) patients developed oral mucositis, which was mild to moderate (grades 1 to 2) in 16/23 (70%) and severe (grades 3 to 4) in 7/23 (30%) patients. Grade 1 to 2 mucositis was present on the last day of dosing in all groups but was most prevalent

TABLE 2. Posaconazole pharmacokinetic data for study day 1 ($n = 29$)

Group (no. of patients)	C_{max} (SD) (ng/ml)	T_{max} (SD) (h)			AUC_{0-12} (SD) (mg · h/liter)	AUC_{0-24} (SD) (mg · h/liter)
		Mean	Median	Range		
I (7)	118 (74)	7.6 (3.0)	8.0	4–12.5	0.96 (0.52)	1.96 (1.1)
II (15)	186 (126.7)	8.2 (5.1)	8.0	3–24	1.4 (1.0)	2.96 (2.0)
III (7)	116.2 (58.5)	4.3 (1.6)	4.5	2–6	1.1 (0.5)	2.95 (1.1)

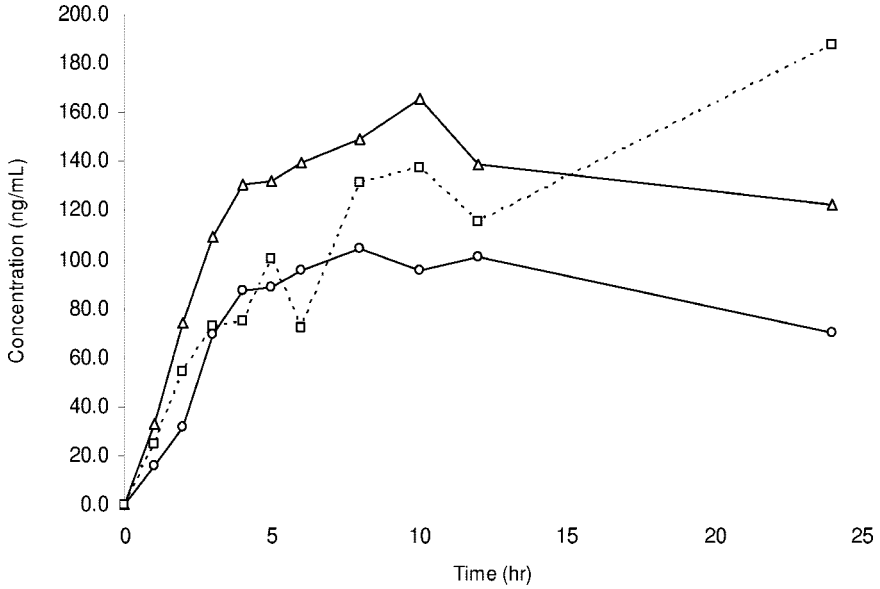

FIG. 1. Plasma posaconazole concentration (ng/ml) versus time (h) for group I (○), group II (△), and group III (□) on study day 1.

in group III (71%). The overall rate of grade 1 to 2 mucositis on the last study day was 47%. In these patients, the mean plasma posaconazole C_{max} was 318.1 ng/ml, compared with 415.4 ng/ml among those without mucositis ($P = 0.1004$). Overall, the mean plasma posaconazole C_{max} on the last day of dosing was not significantly affected when different dose levels were considered with mucositis ($P = 0.3787$). C_{max} values of patients in groups I and II with mild to moderate mucositis were 47% and 49% less than those of patients in groups I and II without mucositis. In group III, mean plasma posaconazole C_{max} values were similar for patients with or without mucositis. For patients with mild to moderate mucositis, the mean posaconazole AUC_{0-24} was not significantly lower (24%) than that for patients without mucositis ($P = 0.1483$). In addition, the mean posaconazole AUC_{0-24} on the last day of dosing was not significantly affected when different dose levels were considered with mucositis ($P = 0.1933$) (Table 4). However, this analysis is limited by the small sample size in the groups. Posaconazole absorption appeared to be reduced in patients in groups I and II with grade 1 to 2 mucositis compared with that of patients in these groups without mucositis. However, this effect was seemingly mitigated by increasing the total dose to 800 mg and administering it in divided doses (200 mg four times daily) (Fig. 3).

Safety. Posaconazole was safe and generally well tolerated. A total of 145 events were reported, the majority of which (95%) were mild or moderate in severity, and 92% were considered unrelated to study drug administration. The most common adverse events were diarrhea ($n = 16$), nausea ($n = 13$), fever ($n = 13$), and vomiting ($n = 8$). Diarrhea occurred in 63%, 47%, and 57% of patients in groups I, II and III, respectively. Similarly, nausea was experienced by 63%, 33%, and 43% of patients in groups I, II and III, respectively. In addition, fever occurred in 38%, 40%, and 57% of patients in groups I, II, and III, respectively. The occurrence of these adverse effects was not associated with an increase in dose. Adverse events that were considered possibly related to posaconazole administration included three adverse events in group I (two nausea, one vomiting), five adverse events in group II (diarrhea, headache, facial flushing, rash, and severe nausea, one patient each), and two adverse events in group III (one gagging, one vomiting). No clinically significant abnormalities in blood chemistries or hematology values attributable to posaconazole were observed. Blood pressure, temperature, pulse rate, and ECG evaluations showed no clinically relevant changes and remained within the normal ranges.

One patient, who discontinued study participation after 4 days of dosing for reasons unrelated to study drug administration, died 18 days after the last dose of posaconazole. The cause of death (progressive pneumonia and multiorgan failure) was considered unrelated to posaconazole administration.

TABLE 3. Summary of posaconazole pharmacokinetic data on last study day ($n = 28$)

Group (no. of patients)	Mean last day (SD)	C_{max} (SD) (ng/ml)	T_{max} (SD) (h)			AUC_{0-24} (SD) (mg · h/liter)	CL/F (SD) (ml/min)
			Mean	Median	Range		
I (7)	14 (6.0)	263 (202)	3.9 (1.7)	4.0	1–6	4.5 (2.9)	990.8 (516.7)
II (14)	9.9 (2.3)	351.7 (165.8)	6.9 (3.1)	7	3–12	6.4 (3.2)	1,506.7 (1201.7)
III (7)	8.1 (1.1)	478.9 (194.2)	10.3 (10)	10.3	1–24	8.7 (3.3)	1,485.5 (873.5)

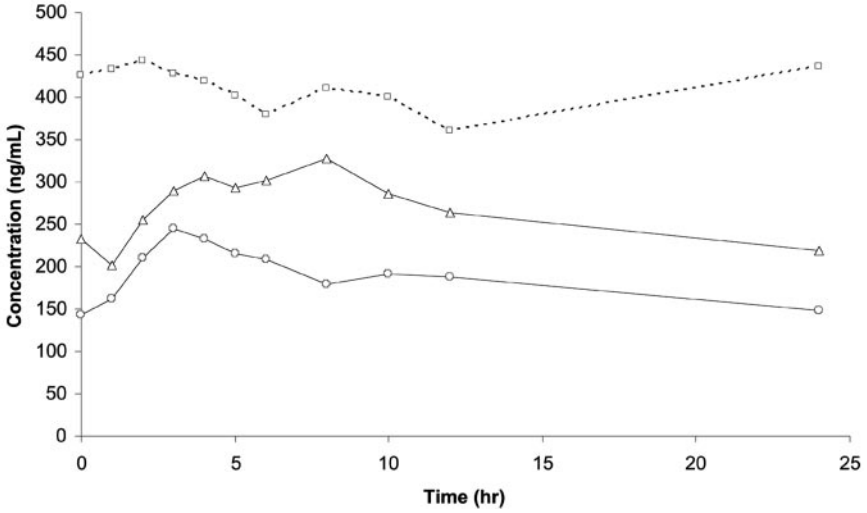

FIG. 2. Plasma posaconazole concentration (ng/ml) versus time (h) for group I (○), group II (△), and group III (□) on the last study day.

DISCUSSION

This study evaluated the pharmacokinetics, safety, and tolerability of oral posaconazole suspension in neutropenic SCT recipients following the administration of increasing single and multiple doses of posaconazole. This therapy was given as prophylaxis in this high-risk patient population throughout their period of neutropenia and mucositis. Posaconazole was found to be systemically available, safe, and well tolerated.

Following a single dose in healthy volunteers, posaconazole concentrations increased dose proportionally up to 800 mg (3). In addition, with multiple-dose administration of 50 mg to 400 mg of posaconazole to healthy adult volunteers, linear pharmacokinetics were observed following twice-daily administration (3). However, in contrast to studies of healthy volunteers, our results show that with total doses of 800 mg/day or less, there was a dose-related but less than dose-proportional increase in C_{max} and AUC_{0-24}. In this study, the AUC_{0-24} was highest in group III, and although it differed significantly from that of group I, it was similar to the total exposure observed in group II. In addition, there was interpatient variability of up to 68% in the posaconazole pharmacokinetic values in our study population. There are many possible reasons for these findings. First, all prior pharmacokinetic data have been from healthy volunteers. Patients in our study had received cytotoxic chemotherapy, which produces cytotoxicity in the rapidly dividing cells of the intestinal mucosa and produces various degrees of mucositis and gastric motility dysfunction. Consequently, unlike healthy volunteers, these patients experience anorexia, nausea, vomiting, odynophagia, and dysphagia, all of which often limit nutritional intake.

TABLE 4. Effect of dosage and mucositis on posaconazole AUC_{0-24} on the last study day

Comparison group	No. of patients	Posaconazole AUC_{0-24} (mg · h/liter)				*P* value[a]
		Mean	Median	SD	Range	
Mucositis grades						
0	13	7.3	8.0	3.2	2.2–11.9	0.1483
1–2	14	5.9	4.9	3.5	1.3–11.9	
Dosage groups						
I	7	4.5	3.7	2.9	1.8–10.0	0.0457*
II	13	6.5	5.8	3.2	1.3–10.5	
III	7	8.6	10.1	3.3	3.9–11.9	
Dosage groups/ mucositis grades						
I/0	5	5.1	3.7	3.1	2.2–10.0	0.1933
I/1–2	2	2.8	2.8	1.4	1.8–3.8	
II/0	6	8.8	9.5	1.7	5.8–10.5	
II/1–2	7	4.5	4.3	2.9	1.3–10.1	
III/0	2	7.9	7.9	5.7	3.9–11.9	
III/1–2	5	8.9	10.1	2.8	4.6–11.9	

[a] *, $P \leq 0.05$.

The presence of food and its composition are important determinants of oral drug absorption. A single-dose study of healthy volunteers showed that systemic exposure to posaconazole increased 4 and 2.6 times when the dose was administered with a high-fat and nonfat meal, respectively, relative to that in fasted subjects (1). A high-fat meal enhances solubilization of poorly soluble drug by increasing luminal volume and bile and pancreatic secretions (6). The high-fat meal also delays gastric emptying as a function of caloric density (calories/ml) (6). Food intake and caloric content have also been shown to enhance posaconazole absorption, with optimal absorption following a high-fat meal (1, 2). Because of the high rates of nausea, vomiting, and oral mucositis in our study, patients may have received inadequate food intake and caloric content. However, these two parameters were not accurately measured in this study. It is also likely that mucositis, which is rarely limited to the oral cavity and usually involves the lower gastrointestinal tract, interfered with the absorption of the drug. Interestingly, C_{max} values for group I (200 mg once daily) were comparable to values observed for healthy volunteers receiving the same dose under fasting conditions (118 ng/ml versus 132 ng/ml, respectively) (1). Another possible reason contributing to the lower AUC_{0-24} in our study compared with that of

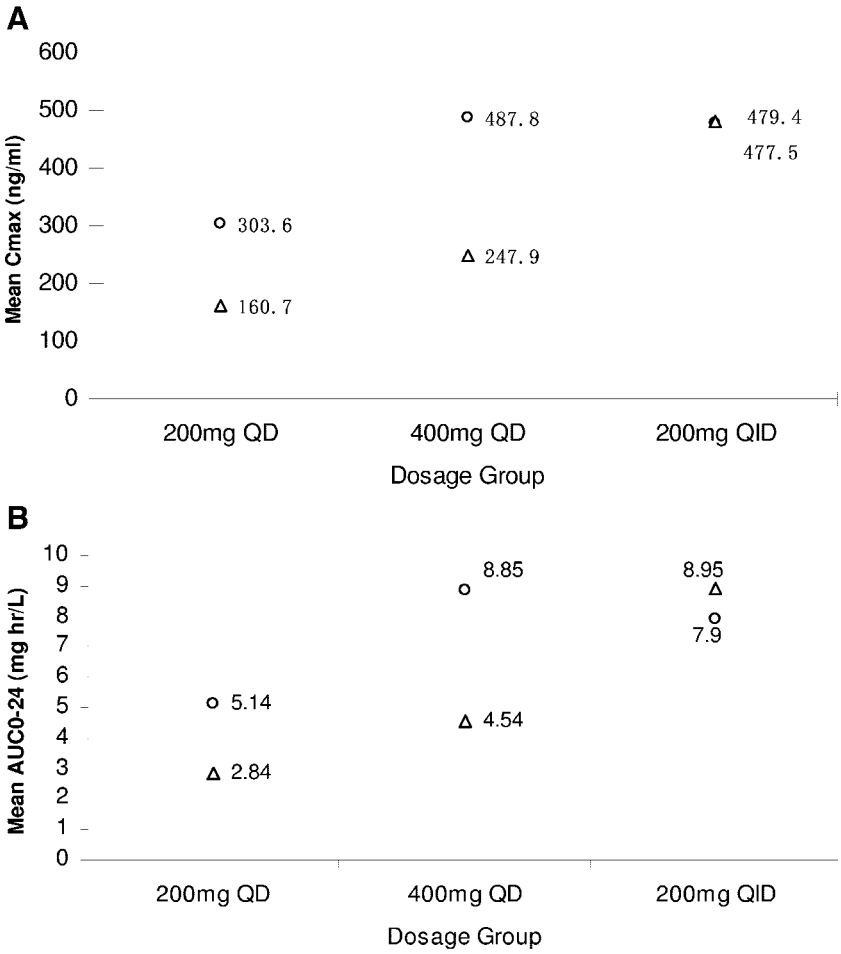

FIG. 3. Effect of mucositis (grade 0, ○; grades 1 to 2, △) on (A) maximum plasma posaconazole concentration (C_{max}) and (B) total posaconazole exposure (AUC_{0-24}) on the last study day. C_{max} values overlapped for group III: grade 0, 477.5 ng/ml; grades 1 to 2, 479.4 ng/ml. QD, once a day; QID, four times a day.

healthy volunteers is the lack of sampling between 12 and 24 h postdose. Sampling at 16 h was included in the study design but was subsequently dropped because of inconvenience to study patients.

There were no breakthrough infections in our small study. We acknowledge that the steady-state plasma concentrations observed in this pharmacokinetic study with total daily dosing of 800 mg in four divided doses are below what is seen in the in vitro setting and that breakthrough infections due to certain strains of yeasts and molds may be a concern. However, only data from larger studies designed to assess breakthrough infections can address that concern. Additionally, given the long elimination half-life of approximately 35 h and the large apparent volume of distribution observed for posaconazole, it is likely that posaconazole concentrates and accumulates in tissues that are the site of infection at levels above those observed in the plasma (7–9).

Our study indicates that posaconazole oral suspension was systemically available, with a dose-related increase in exposure observed following once-daily dosing. The exposure observed in patients from this study was lower than that in healthy volunteers from previous studies given equivalent doses, presumably due to general poor food intake as a result of underlying disease and gastric dysfunction in neutropenic patient populations. The mean posaconazole steady-state exposure (AUC) was not significantly affected when different dose levels were considered with mucositis. However, posaconazole absorption appeared to be reduced in the presence of mild to moderate mucositis. This reduction in absorption can be overcome by increasing the total dose and administering it in divided doses. Posaconazole was safe and well tolerated in the neutropenic oncology patients.

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