ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2003, p. 2788–2795 Vol. 47, No. 9
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.9.2788–2795.2003

Pharmacokinetics, Safety, and Tolerability of Oral Posaconazole Administered in Single and Multiple Doses in Healthy Adults

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Received 16 October 2002/Returned for modification 23 December 2002/Accepted 5 June 2003

The pharmacokinetics, safety, and tolerability of posaconazole, an investigational triazole antifungal, were evaluated following the administration of rising single and multiple oral doses. A total of 103 healthy adults were enrolled in two phase I trials. Each study had a double-blind, placebo-controlled, parallel-group design with a rising single-dose (RSD) or rising multiple-dose (RMD) scheme. In the RSD study, subjects received single doses of posaconazole oral tablets (50 to 1,200 mg) or placebo. In the RMD study, subjects received posaconazole oral tablets (50 to 400 mg) or placebo twice daily for 14 days. By using model-independent methods, the area under the plasma concentration-time curve and the maximum concentration in plasma were determined and used to assess dose proportionality. In the RSD study, the levels of posaconazole in plasma increased proportionally between the 50- and 800-mg dose range, with saturation of absorption occurring above 800 mg. Dose proportionality was also observed in the RMD study. In both studies, the apparent volume of distribution was large (range, 343 to 1,341 liters) and the terminal-phase half-life was long (range, 25 to 31 h). Posaconazole was well tolerated at all dose levels, and the adverse events were not dose dependent. No clinically significant changes in clinical laboratory test values or electrocardiograms were observed. Following the administration of single and twice-daily rising doses, the level of posaconazole exposure increased in a dose-proportional manner. The long elimination-phase half-life of posaconazole supports once- or twice-daily dosing in clinical trials; however, additional studies are required to determine if further division of the dose will enhance exposure.

The evolution of oral triazole antifungal agents began in the 1980s with the introduction of fluconazole and itraconazole for the treatment of systemic fungal infections. In recent years, the patterns of *Candida* infections have changed. Previously, *Candida albicans* was the most prevalent cause of *Candida* infections, whereas in recent times, other *Candida* species, such as *C. glabrata* and *C. krusei*, have become common infection-causing pathogens (6). In addition to this shift in species, fluconazole- and itraconazole-resistant *Candida* strains have emerged, prompting clinicians to search for alternative treatment options. The emergence of new fungal diseases caused by fungi that were previously not thought to be pathogenic has also limited the usefulness of older triazole compounds for the treatment of invasive infections, especially in immunocompromised patients. For example, fusariosis and zygomycosis are increasingly common; however, the treatments for these infections are limited (23). In light of the need for more potent and broad-spectrum therapeutic options, posaconazole (SCH 56592), a novel oral triazole derivative structurally similar to itraconazole (Fig. 1), is in development for the treatment of invasive fungal infections.

Posaconazole has enhanced activity against many old, new, and emerging fungal pathogens (A. Espinel-Ingroff and A. Rezusta, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 375, 2001) compared with the activities of the other azoles and caspofungin (an echinocandin). Numerous in vitro studies demonstrate that posaconazole has a broad spectrum of activity against the majority of yeasts, filamentous fungi, and azole-resistant *Candida* species (1, 3, 14, 18, 19). In addition, posaconazole has excellent in vitro activity against rare and emerging opportunistic fungal pathogens (4, 9, 10, 15, 17), including the difficult-to-treat zygomycetes (21). In a neutropenic mouse model of zygomycosis, posaconazole was shown to significantly reduce the fungal burden in tissue and prolong the survival of mice (22). Compared with fluconazole, which generally demonstrates fungistatic activity (11), in vitro (7) and in vivo (A. H. Groll, D. Mickiene, R. Petraitiene, V. Petraitis, T. Sein, J. Roach, K. Roth, S. C. Piscitelli, and T. J. Walsh, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 385, 2000) evidence suggests that posaconazole is fungicidal against many fungal species. For example, in a neutropenic rabbit model of invasive *Aspergillus* infection, posaconazole therapy eradicated organisms from tissues, also indicating fungicidal activity (Groll et al., 40th ICAAC).

The pharmacokinetics of oral posaconazole have been evaluated in mice, rats, rabbits, dogs, and cynomolgus monkeys (16). A posaconazole suspension was orally bioavailable in all species; following oral administration of a suspension or solution, absolute bioavailability was approximately 50 to 60% in rats and dogs. The terminal-phase half-life ($t_{1/2}$) of posaconazole ranged from 7 to 9 h in mice, rats, and rabbits and was 15 and 23 h in dogs and monkeys, respectively. Dose-related increases were observed in mice (dose range, 20 to 160 mg/kg of body weight), rats (10 to 120 mg/kg), and fed dogs (10 to 120 mg/kg) following administration of a single oral dose; however, posaconazole absorption was saturated at higher doses (>80 mg/kg). The posaconazole exposure in dogs was approximately 3.5-fold greater when posaconazole was administered with food. In the fed dog, multiple doses (8 days) resulted in drug

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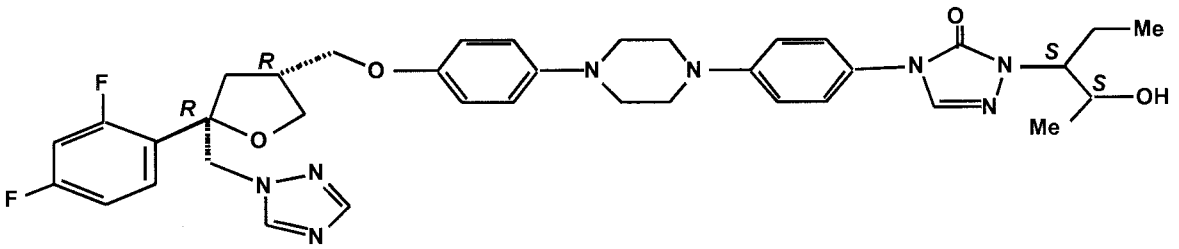

FIG. 1. Chemical structure of posaconazole. Me, methyl.

accumulation, indicated by a 2.6-fold increase in the maximum concentration in plasma (C_{max}). Posaconazole is highly bound (98 to 99%) to plasma proteins (R. Courtney, A. Sansone, P. Statekevich, M. Martinho, W. Richards, and M. Laughlin, Abstr. Am. Soc. Clin. Pharmacol. Ther., abstr. PII-62, 2003).

The studies described here are the first to evaluate the pharmacokinetics, safety, and tolerability of oral posaconazole in humans. We summarize herein two independent studies conducted with healthy volunteers that evaluated the single- and multiple-dose pharmacokinetics, safety, and tolerability of posaconazole oral tablets following the administration of escalating oral doses.

MATERIALS AND METHODS

The studies were conducted in accordance with the Declaration of Helsinki and were approved by an accredited institutional review board. All study participants gave written informed consent.

Study subjects. Adult male volunteers aged 18 to 44 (rising single-dose [RSD] study) and adult male and female volunteers aged 19 to 43 (rising multiple-dose [RMD] study) who were in good health on the basis of medical history, physical examination, electrocardiograms (ECGs), and routine laboratory tests and whose weights were within 15% of their ideal body weights on the basis of actuarial tables were eligible for enrollment in the studies. In both studies, all subjects were nonsmokers or light smokers (<10 cigarettes per day) and had not taken any drugs (other than acetaminophen) within 2 weeks or alcohol within 48 h before study drug administration. Subjects with a history of a clinically significant local or systemic infection, recent blood donation, or treatment with a corticosteroid or an investigational drug within 90 days of study initiation were excluded.

Study design and treatment. The studies were randomized, double-blind, placebo-controlled, parallel-group, RSD and RMD studies. Posaconazole tablets (50 and 100 mg) were used in both studies and were of the same formulation. Placebo tablets contained 50 and 100 mg of povidone USP in place of posaconazole at 50 and 100 mg, respectively. All doses were swallowed whole and taken in the morning following a standardized high-fat breakfast. In the RSD study, 54 healthy male subjects were randomly assigned to treatment with posaconazole or placebo in a ratio of 2:1. Study drug was administered as oral tablets in single doses of 50, 100, 200, 400, 800, or 1,200 mg.

In the RMD study, 49 healthy subjects (47 men, 2 women) were randomly assigned to treatment with posaconazole oral tablets or placebo in a ratio of 3:1. Subjects randomized to active drug received posaconazole at 50, 100, 200, or 400 mg every 12 h (BID) for 14 days.

In both studies, the next higher dose was administered only after the lower doses were determined to be safe and well tolerated. Study subjects were confined to the study center the day before dosing and for 48 h following the administration of the final dose in the RSD study and for 48 h following the administration of the morning dose in the RMD study. The subjects in both studies were then monitored as outpatients for an additional 72 h.

Sample collection and assay for pharmacokinetic assessments. In the RSD study, blood samples (10 ml) were collected at 0 h (predosing) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 h postdosing. In the RMD study, on day 1 and day 14, blood samples (6 ml) were collected at 0 h (predosing) and at 2, 4, 5, 6, 8, 10, 12, 16, 17, 18, 20, 22, and 24 h after the administration of the morning dose. On day 14, additional 6-ml blood samples were collected at 36, 48, 72, 96, and 120 h after the administration of the morning dose. Samples for trough posaconazole concentration (C_{min}) determinations were also collected before the administration of the morning dose (0 h) on days 3, 7, 10, 11, 12, and 13.

Plasma from the blood samples collected was assayed for posaconazole concentrations by a validated high-performance liquid chromatographic procedure. The lower limit of quantitation was 5.00 ng/ml. The intraday coefficients of variation (CVs) ranged from 2.9 to 5.8% at high concentrations (4,000 ng/ml; n = 5 to 6) and 4.7 to 12.9% at low concentrations (5 ng/ml; n = 6). The interday CVs were 7.3% at high concentrations (4,000 ng/ml; n = 17) and 9.8% at low concentrations (5 ng/ml; n = 18). The assay was linear, with correlation coefficients of ≥0.9979. All assays were performed at Pharma Bio-Research Laboratories for Bioanalysis, Assen, The Netherlands.

Pharmacokinetic analysis. Plasma posaconazole concentrations were used for the pharmacokinetic analysis by using model-independent methods (8). In both studies, the primary pharmacokinetic endpoints were the area under the concentration-time curve (AUC) and C_{max}. These parameters were used to assess dose proportionality. The pharmacokinetic analysis was performed with Winnonlin* Professional Network Edition software (version 3.1; Pharsight Corporation, Palo Alto, Calif.).

C_{max} and time to C_{max} (T_{max}) were the observed values. The terminal-phase rate constant (k) was calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration-time curve by linear regression. $t_{1/2}$ was calculated as ln(2)/k. The AUCs from time zero (0 h) to the time of recovery of the final sample with a quantifiable concentration (AUC_{tf}) in the RSD study and from 0 to 12 h ($AUC_{0\text{-}12}$), 12 to 24 h ($AUC_{12\text{-}24}$), and 0 to 24 h ($AUC_{0\text{-}24}$) postdosing in the RMD study were calculated by the trapezoidal method. AUC_{tf} was extrapolated to infinity (AUC_I) in the RSD study by using the following equation: $AUC_I = AUC_{tf} + C_{tf}/k$, where C_{tf} is the estimated concentration at the time of recovery of the final sample with a quantifiable concentration.

Total body clearance (CL/F) was calculated as the ratio of the dose to AUC. The apparent volume of distribution (V/F) was calculated as the ratio of CL/F to k.

Statistical analysis. In both studies, the pharmacokinetic parameters for each dose were summarized as means, standard deviations, and CVs. An analysis of variance, with extraction of the effects due to treatment (dose), was performed with log-transformed dose-adjusted (to 1 mg) AUCs and C_{max}s and with the values for the other parameters by using the original scale. Statistically significant differences among the treatment means were considered a measure of a lack of dose proportionality. In addition, to determine if steady state was attained in the RMD study, trough concentrations in plasma on days 10 through 14 were analyzed by an analysis of variance, with extraction of the effects due to subject and day.

Safety analysis. Both studies analyzed safety as a primary variable. The safety evaluations, physical examinations, ECGs, vital sign determinations, routine laboratory tests (complete blood count, blood chemistry, and urinalysis), and special clinical laboratory tests were performed before and at frequent intervals throughout the studies. The special clinical laboratory tests included those used to monitor adrenal function (plasma cortisol levels), testicular function (plasma testosterone levels), and renal function (urine specific gravity and creatinine, sodium, potassium, calcium, *N*-acetylglucosaminidase, and β_2-microglobulin levels).

Volunteers were continuously observed and questioned during the period of confinement for the possible occurrence of adverse events. The investigator(s) assessed the intensity (mild, moderate, severe, or life-threatening) of each adverse event and its relationship to the study drug.

TABLE 1. Demographic characteristics of study subjects

Parameter	RSD study		RMD study	
	Posaconazole (n = 36)[a]	Placebo (n = 18)	Posaconazole (n = 36)	Placebo (n = 12)
Age (yr)	22.7 (18–44)[b]	22.8 (18–41)	24 (19–41)	27 (20–43)
Wt (kg)	78.1 (53.6–103)	75.3 (57.2–101)	75 (51–96)	75 (64–100)
Ht (cm)	184.8 (170–199)	183.2 (174–200)	182 (162–191)	182 (168–198)

[a] One subject did not complete the treatment, and the data for that subject are not included.
[b] The values are presented as means (ranges).

RESULTS

All 54 subjects enrolled in the RSD study completed the study; 36 subjects received posaconazole and 18 received placebo. In the RMD study, 48 of the 49 subjects enrolled completed the study; 37 subjects received posaconazole and 12 received placebo. One subject in the group receiving posaconazole at 200 mg BID prematurely discontinued treatment because of an adverse event determined to be unrelated to study drug (a dental abscess requiring antibiotic treatment). In the active treatment and placebo treatment groups in both the RSD and the RMD studies, subjects were similar with respect to age, weight, and height distribution (Table 1). The mean ages and weights of the study subjects were 23 years (range, 18 to 44 years) and 77 kg (range, 53.6 to 103 kg), respectively, in the RSD study and 25 years (range, 19 to 43 years) and 75 kg (range, 51 to 100 kg), respectively, in the RMD study.

Pharmacokinetic findings. The pharmacokinetic analyses included data for 36 subjects in the RSD study and 36 subjects in the RMD study.

(i) RSD study. The mean plasma posaconazole concentration-time profiles at each dose level are shown in Fig. 2. Posaconazole was well absorbed following oral administration, with mean T_{max}s ranging from 5.8 to 8.8 h across the 50- to 1,200-mg dose range (Table 2). Mean posaconazole C_{max}s ranged from 113 to 1,320 ng/ml for doses between 50 and 800 mg. The plasma posaconazole concentrations increased proportionally (defined as $P > 0.05$) between the 50- and 800-mg dose range, with no pairwise statistically significant differences ($P > 0.233$) among the 50- to 800-mg doses for AUC_I by use of the log-transformed dose-adjusted data (Fig. 2). C_{max}s were also dose proportional ($P > 0.05$) except for doses from 100 to 400 mg ($P = 0.018$), presumably due to variability. The plasma posaconazole concentrations at the 1,200-mg dose level were equal to or lower than those at the 800-mg dose level, suggesting saturation of absorption above the 800-mg dose (Table 2; Fig. 2).

Posaconazole demonstrated dose-independent clearance, with mean CL/F values ranging from 4.1 to 6.6 ml/min/kg across all doses administered. The mean $t_{1/2}$ of posaconazole was approximately 25 h for doses ranging from 200 to 1,200 mg. However, a faster rate of elimination was observed at the lower doses of 50 and 100 mg, with mean $t_{1/2}$s of 16 and 18 h, respectively. The mean apparent V/F of posaconazole was large (range, 431 to 1,341 liters), indicating extensive distribution in tissues.

(ii) RMD study. On day 1, mean C_{max}s following the administration of the first dose were achieved at 5 h postdosing for all posaconazole dose levels, after which the plasma posaconazole concentrations slowly declined for up to 16 h postdosing (Fig. 3). On day 1, mean C_{max}s following administration of the

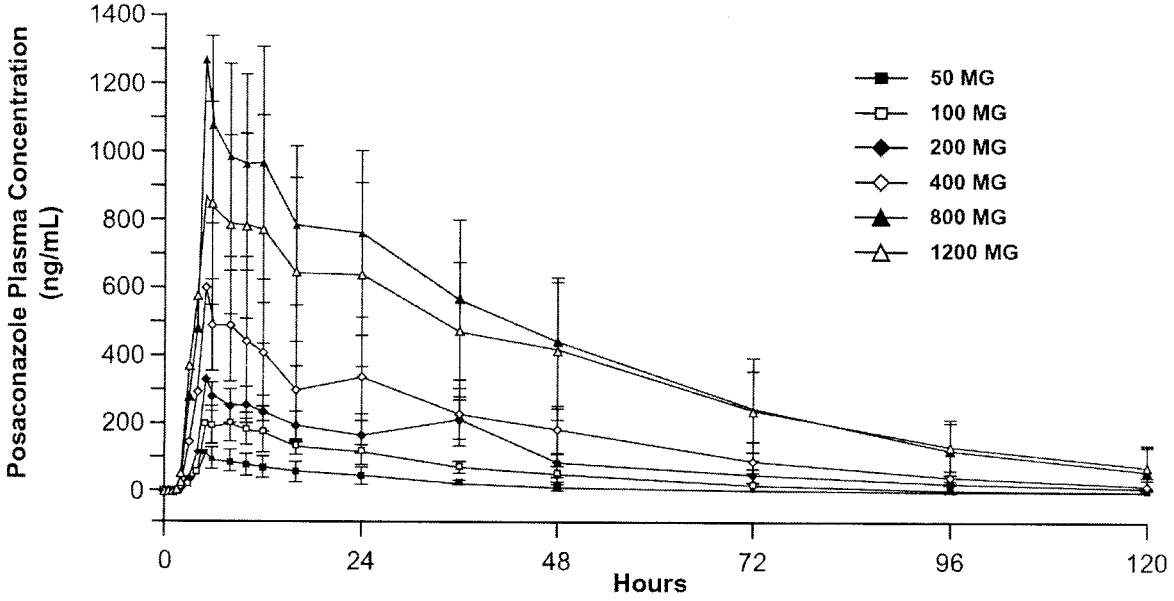

FIG. 2. Mean concentrations of posaconazole in plasma over time after administration of a single dose.

TABLE 2. Pharmacokinetic parameters for posaconazole in plasma after administration of a single dose (RSD study)

Posaconazole dose (mg)[a]	C_{max} (ng/ml)	T_{max} (h)	AUC_{tf} (ng · h/ml)	AUC_I (ng · h/ml)	$t_{1/2}$ (h)	CL/*F* (ml/min)	*V*/*F* (liters)
50	113 (46)[b]	6.3 (51)	2,317 (50)	2,501 (45)	15.9 (18)	389 (40)	511 (32)
100	235 (26)	7.3 (36)	6,101 (28)	6,357 (27)	18.3 (13)	275 (21)	431 (20)
200	332 (21)	5.8 (35)	10,354 (30)	10,896 (31)	24.5 (22)	341 (40)	674 (18)
400	611 (31)	6.3 (44)	19,401 (33)	20,264 (33)	24.1 (24)	363 (35)	781 (49)
800	1,320 (26)	6.2 (46)	46,984 (40)	49,841 (43)	24.4 (33)	320 (48)	594 (19)
1,200	933 (28)	8.8 (85)	41,755 (42)	45,260 (44)	28.5 (26)	585 (73)	1,341 (58)

[a] Each dose group contained six subjects.
[b] The values in parentheses are CVs (in percent).

second dose were attained by approximately 8 h after the administration of the second dose (at ~20 h after the administration of the first dose) and did not decline appreciably thereafter, suggesting that accumulation of the drug occurred with repeated daily dosing (Fig. 3).

Steady-state concentrations were achieved by day 10 of dosing (the first sample collected for evaluation of C_{min}), with no statistically significant increase in C_{min}s observed between days 10 and 14 ($P > 0.155$). The plasma posaconazole pharmacokinetic parameters after 14 days of multiple twice-daily dosing are summarized in Table 3. On day 14, peak concentrations were attained from 4 to 6 h after the administration of the morning dose and from 9 to 11 h after the administration of the evening dose. Following the administration of the final dose on day 14, quantifiable concentrations in plasma were detected for up to 120 h postdosing for all dose levels (Fig. 4). Posaconazole exhibited dose-proportional increases in exposure ($AUC_{0\text{-}12}$ and $AUC_{12\text{-}24}$) on day 1 (for $AUC_{0\text{-}12}$, $P = 0.138$; for $AUC_{12\text{-}24}$, $P = 0.073$) and at steady state (day 14) (for $AUC_{0\text{-}12}$, $P = 0.197$; for $AUC_{12\text{-}24}$, $P = 0.148$). The C_{max} after the administration of the morning dose was dose proportional on day 1 and at steady state ($P = 0.085$ and $P = 0.246$, respectively), but the C_{max} after the administration of the second daily dose was not dose proportional (for day 1, $P = 0.030$; for steady state, $P = 0.044$). Figure 5 shows the concentration-time profile of posaconazole following twice-daily dosing for 14 days.

Over the 50- to 400-mg BID dose range, the mean $t_{1/2}$ (range, 19 to 31 h) and mean apparent *V*/*F* (range, 343 to 486 liters) were similar to those observed in the RSD study. The accumulation values based on $AUC_{0\text{-}12}$ ratios ($AUC_{0\text{-}12}$ on day 14/$AUC_{0\text{-}12}$ on day 1) were between 6.6- and 8.3-fold (Table 3).

Safety and tolerability. The safety analyses included data for 54 subjects in the RSD study and 49 subjects in the RMD study. Posaconazole was well tolerated in both studies. No subjects reported serious adverse events or discontinued the studies prematurely because of drug-related adverse events. However, in the RMD study, one subject assigned to posaconazole treatment discontinued early because of a severe dental abscess determined to be unrelated to the study medication.

(i) RSD study. Of the 54 subjects enrolled in the RSD study, 27 (50%; 18 posaconazole-treated subjects and 9 placebo-treated subjects) reported at least one adverse event. The overall incidence of adverse events among subjects receiving

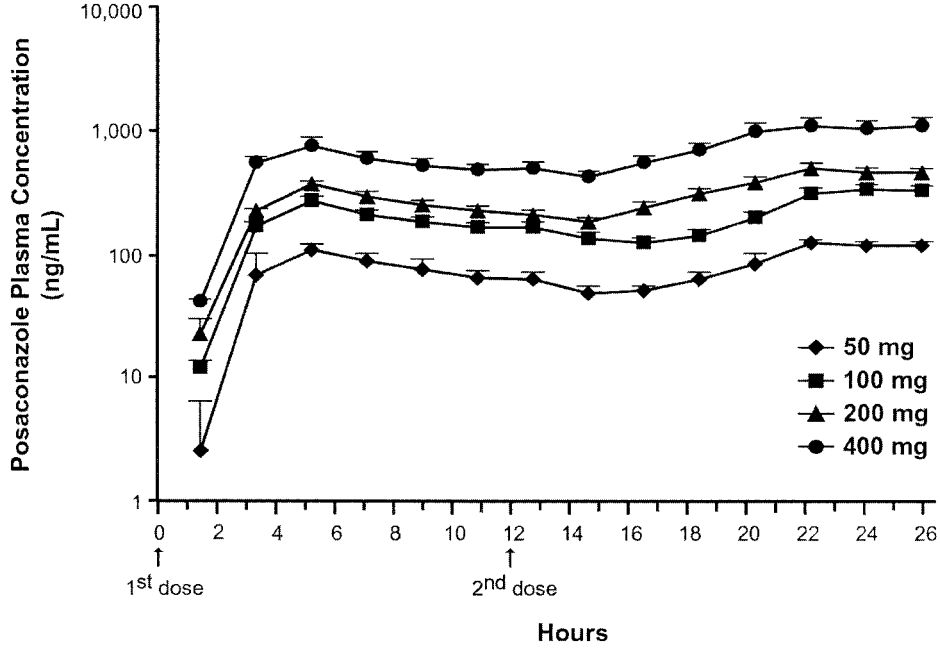

FIG. 3. Mean concentrations of posaconazole (multiple doses) in plasma by dose on day 1 of twice-daily administration.

TABLE 3. Pharmacokinetic parameters for posaconazole in plasma on day 14 after BID dosing (RMD study)[a]

Posaconazole dose (mg)[b]	$C_{max}1$ (ng/ml)	$T_{max}1$ (h)	$C_{max}2$ (ng/ml)	$T_{max}2$ (h)	AUC_{0-12} (ng · h/ml)	AUC_{12-24} (ng · h/ml)	AUC_{0-24} (ng · h/ml)	$t_{1/2}$ (h)	CL/*F* (liters/h)	*V*/*F* (liters)	Accumulation ratio[c]
50	457 (38)[d]	5 (12)	371 (30)	9 (34)	4,454 (37)	3,841 (36)	8,295 (36)	19.2 (16)	13.5 (34)	365 (29)	6.6 (29)
100	1,141 (37)	6 (40)	1,045 (42)	11 (16)	11,571 (40)	10,206 (40)	21,778 (40)	24.1 (20)	10.3 (32)	343 (24)	6.9 (27)
200	1,753 (27)	4 (12)	1,358 (27)	10 (19)	16,801 (26)	14,305 (27)	31,106 (26)	23.9 (26)	13.9 (34)	467 (32)	7.6 (37)
400	4,150 (20)	5 (12)	3,239 (19)	9 (32)	39,206 (20)	33,899 (21)	73,105 (20)	31.0 (46)	11.5 (25)	486 (34)	8.3 (32)

[a] $C_{max}1$ and $T_{max}1$, values after the administration of the first dose; $C_{max}2$ and $T_{max}2$, values after the administration of the second dose.
[b] Each dose group contained nine subjects.
[c] Accumulation ratio, AUC_{0-12} on day 14 to AUC_{0-12} on day 1.
[d] The values in parentheses are CVs (percent).

posaconazole was identical to that among subjects in the placebo group (50% in each group). The incidence of any of the adverse events did not increase with increasing dose. Regardless of causality, the most common adverse events (which occurred in ≥10% of subjects) reported among those receiving posaconazole were headache, somnolence, dizziness, and fatigue. The types of adverse events were similar between the posaconazole- and placebo-treated groups; however, only subjects receiving posaconazole reported fatigue (overall incidence, 11%).

(ii) RMD study. Of the 49 subjects enrolled in the RMD study, 42 (86%; 31 posaconazole-treated subjects and 11 placebo-treated subjects) reported at least one adverse event. The majority of the adverse events were mild and of short duration (<12 h); eight adverse events were rated as moderate, with only headache being possibly related to study drug administration. The single previously mentioned non-drug-related adverse event (a dental abscess) was rated as severe. The overall incidence of adverse events among subjects receiving posaconazole was lower than that observed among the subjects in the RMD study (posaconazole-treated group, 84%; placebo-treated group, 92%). In general, the types of adverse events were similar between the posaconazole- and placebo-treated groups. In contrast to the RSD study, fatigue was reported more frequently by the placebo-treated subjects (25%) than by the posaconazole-treated subjects (14%). Regardless of causality, the most common adverse events (occurring in ≥10% of the subjects) reported by the posaconazole-treated subjects were headache, dry mouth, somnolence, dizziness, fatigue, and constipation. Although a larger number of subjects receiving the higher doses of posaconazole reported dry mouth ($n = 0$ in the 50-mg BID group; $n = 1$ in the 100-mg BID group; $n = 3$ in the 200-mg BID group; $n = 8$ in the 400-mg BID group), subjects administered placebo ($n = 2$) also reported this event.

Laboratory safety tests, vital signs, and ECG results. No consistent or clinically significant changes in baseline values were observed by routine or special laboratory safety tests (tests for serum cortisol and testosterone levels) in either study, although there was a trend toward reduced testosterone levels at day 14 in those treated with higher doses of posaconazole. In the RSD study, there were no clinically significant differences between the posaconazole- and placebo-treated

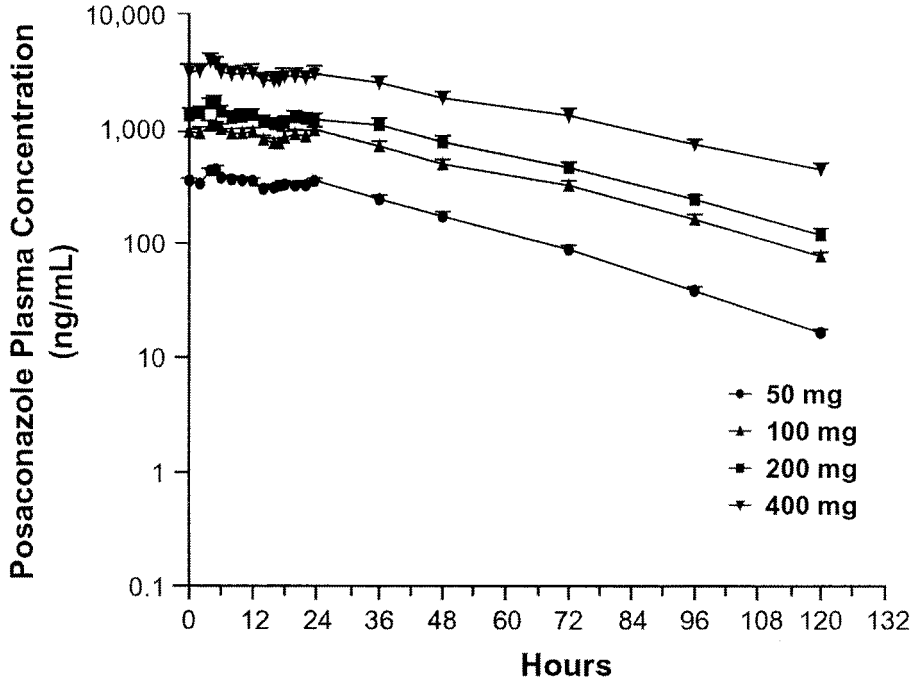

FIG. 4. Mean concentration of posaconazole in plasma by dose on day 14 of twice-daily administration.

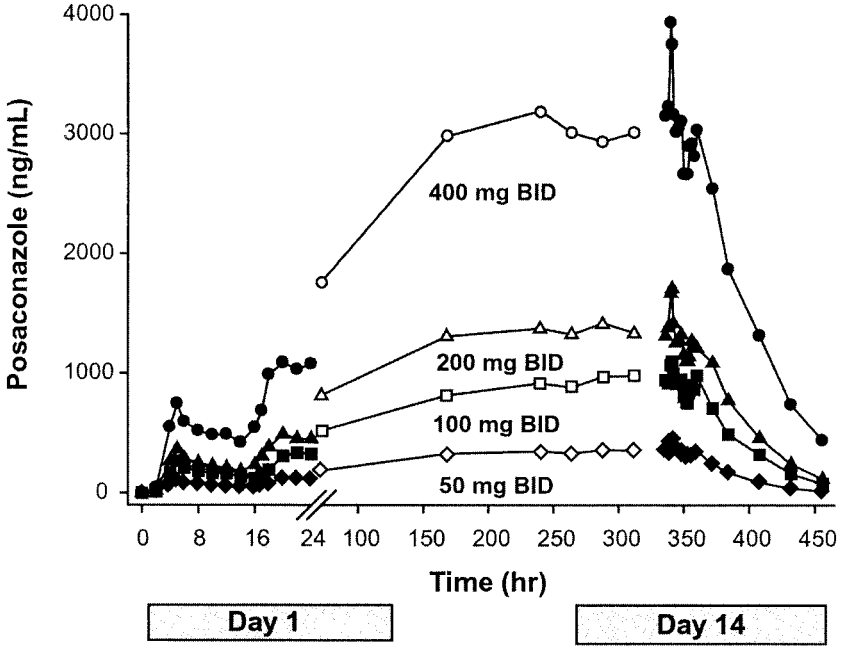

FIG. 5. Mean concentrations of posaconazole in plasma after twice-daily administration over the 14-day study period.

groups in the results of special urine tests. A few isolated cases of elevated alanine aminotransferase levels, either with or without accompanying increases in the levels of other liver enzymes (aspartate aminotransferase and γ-glutamyltransferase), were observed in both studies. These elevations were mild to moderate and were observed in subjects administered placebo ($n = 2$) as well as those administered posaconazole ($n = 3$). Two subjects (one in the placebo-treated group and one in the 400-mg BID dose group) had World Health Organization grade 2 increases in alanine aminotransferase levels. The changes in liver enzyme levels in all subjects with increased levels returned to the baseline levels within 2 weeks of the completion of treatment.

No clinically relevant changes in vital signs were observed in the posaconazole-treated subjects in either the RSD study or the RMD study. Similarly, there were no clinically relevant changes in ECG results for posaconazole-treated subjects (in both the RSD study and the RMD study) in comparison with their baseline values or compared with those for the placebo-treated subjects. Two subjects who received single 100- or 200-mg doses (RSD study) had mild transient prolongation of their corrected QT interval (<10% above the baseline); however, these changes were considered to be within normal diurnal variation and not clinically relevant.

DISCUSSION

The studies described here are the first to evaluate the pharmacokinetics, safety, and tolerability of oral posaconazole in humans following the administration of increasing single and multiple doses. In both studies, posaconazole was found to be orally bioavailable and slowly eliminated and displayed dose-proportional (AUC) pharmacokinetics up to a total dose of 800 mg/day. No further increases in concentrations in plasma were observed with the 1,200-mg dose, suggesting that absorption was saturated above 800 mg. It is unknown why this saturation occurred, but it is primarily thought to be due to the poor solubility of posaconazole ($pK_a = 8$; melting range = 164 to 165°C).

Because the saturation of absorption was observed at doses greater than 800 mg, we hypothesized that splitting the dose may increase the total amount of drug absorbed. Thus, we designed and conducted the RMD study. Data from these two trials indicate that posaconazole has an extensive V/F, approximately 10-fold greater than that of total body water (~42 liters), indicating that posaconazole is widely distributed into tissues. Similar estimates of $t_{1/2}$ of 25 h were observed in the RSD and RMD studies. On the basis of this $t_{1/2}$, the predicted level of accumulation following BID dosing is fourfold. However, accumulation, expressed as the ratio of the $AUC_{0\text{-}12}$ on day 14 to the $AUC_{0\text{-}12}$ on day 1, was six- to eightfold in the RMD study. The reason for the difference in accumulation between the actual and predicted values upon multiple dosing is unknown.

Following the administration of all dose levels in both studies, posaconazole was slowly eliminated with a long $t_{1/2}$, typically ranging from 25 h following the administration of a single dose and up to 31 h following the administration of multiple doses. This implies that twice-daily dosing would be an appropriate clinical dosage regimen for the treatment of serious fungal infections; however, additional studies are required to determine if further division of the dose would enhance exposure.

The results from these studies of the pharmacokinetics of posaconazole in humans corroborate those findings reported from preclinical investigations with animals, in which dose-related increases in exposure were observed in all species, although a saturation of absorption was observed at higher

doses (16). Similar to humans, $t_{1/2}$s were prolonged in dogs and monkeys (15 and 23 h, respectively), and as in the multiple-dose study with humans, significant accumulation was detected in all animal species evaluated following multiple once-daily oral dosing.

The pharmacokinetic properties of the currently marketed azole and triazole antifungal agents vary greatly. It is well recognized that the capsule formulation of itraconazole is associated with highly erratic absorption and unpredictable concentrations in plasma (5, 12). However, the itraconazole solution appears to have more reliable pharmacokinetics (5) when it is given on an empty stomach (2). In comparison with posaconazole, fluconazole has a less variable pharmacokinetic profile (i.e., food does not affect its bioavailability); however, fluconazole has reduced microbiological activity against some non-*albicans Candida* species and no activity against *Aspergillus* species and some rare fungi (18). The pharmacokinetics of voriconazole, a new triazole, have been described recently (20). In contrast to posaconazole, voriconazole exhibits nonlinear pharmacokinetics when it is administered at the recommended clinical doses (i.e., disproportional increases in C_{max} and AUC with increasing dose), possibly due to saturable first-pass metabolism. Furthermore, the interindividual variability of voriconazole pharmacokinetics is high (AUC variability range, 74 to 100%, depending on the dose and the route of elimination), and the mean $t_{1/2}$ of voriconazole (6 to 12 h) is shorter than that of posaconazole (13).

Posaconazole was well tolerated in both the single-dose and the multiple-dose trials. The most commonly reported adverse events were mild to moderate and nonspecific and included headache, somnolence, dizziness, and fatigue. There also was no suggestion that posaconazole caused cardiac adverse events, including clinically significant ECG findings or QT prolongation. Although there were more reports of dry mouth in subjects receiving the higher doses of posaconazole, the rates of adverse events did not appear to be dose dependent over the range of doses studied (i.e., 50- to 1,200-mg single doses and from 50 to 400 mg BID for 14 days). Although this study was a small phase I trial, the safety and tolerability of posaconazole will ultimately be determined in large phase III clinical trials and by postmarketing surveillance.

Although the present studies were small and conducted with healthy subjects, the findings suggest that posaconazole may have a clinical safety and tolerability advantage over other antifungal agents. Amphotericin B and flucytosine are associated with renal and hematologic toxicities. Voriconazole has been associated with ocular toxicity, elevated liver enzyme levels by liver function tests (LFTs), and rash (13; VFEND package insert; Pfizer Inc., 2002). Visual disturbances following voriconazole administration are significant, with approximately 30% of subjects experiencing altered or enhanced visual perception, blurred vision, color vision change, and/or photophobia (13; VFEND package insert; Pfizer Inc., 2002). In addition, LFT abnormalities with voriconazole appear to be directly related to increased doses (K. K. C. Tan, N. Brayshaw, and M. Oakes, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-18, 2001). Following 14 days of dosing with posaconazole, there was no evidence that posaconazole was associated with nephrotoxicity, hepatotoxicity, skin reactions, or visual toxicity. Although LFT abnormalities were reported, the number of reports was very small and the frequencies were similar between the placebo groups and the treatment groups. Thus, it is impossible to distinguish the reason for these elevations. Posaconazole may prove to be a better-tolerated alternative to some currently available antifungals if this lack of toxicity is confirmed in ongoing clinical trials.

In conclusion, posaconazole was well tolerated by healthy human adults following the administration of single oral doses and multiple twice-daily doses. Posaconazole was orally bioavailable, demonstrated dose-proportional pharmacokinetics, and was characterized by a large V/F. The long $t_{1/2}$ observed with posaconazole supports once- or twice-daily dosing in clinical trials; however, additional studies are required to determine if divided dosing will further enhance the exposure to posaconazole.

REFERENCES

1. **Barchiesi, F., A. M. Schimizzi, F. Caselli, D. Giannini, V. Camiletti, B. Fileni, A. Giacometti, L. F. Di Francesco, and G. Scalise.** 2001. Activity of the new antifungal triazole, posaconazole, against *Cryptococcus neoformans.* J. Antimicrob. Chemother. **48:**769–773.
2. **Barone, J. A., B. L. Moskovitz, J. Guarnieri, A. E. Hassell, J. L. Colaizzi, R. H. Bierman, and L. Jessen.** 1998. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy **18:**295–301.
3. **Cacciapuoti, A., D. Loebenberg, E. Corcoran, F. Menzel, Jr., E. L. Moss, Jr., C. Norris, M. Michalski, K. Raynor, J. Halpern, C. Mendrick, B. Arnold, B. Antonacci, R. Parmegiani, T. Yarosh-Tomaine, G. H. Miller, and R. S. Hare.** 2000. In vitro and in vivo activities of SCH 56592 (posaconazole), a new triazole antifungal agent, against *Aspergillus* and *Candida.* Antimicrob. Agents Chemother. **44:**2017–2022.
4. **Carrillo, A. J., and J. Guarro.** 2001. In vitro activities of four novel triazoles against *Scedosporium* spp. Antimicrob. Agents Chemother. **45:**2151–2153.
5. **De Beule, K., and J. Van Gestel.** 2001. Pharmacology of itraconazole. Drugs **61**(Suppl. 1)**:**27–37.
6. **Diekema, D. J., M. A. Pfaller, R. N. Jones, G. V. Doern, P. L. Winokur, A. C. Gales, H. S. Sader, K. Kugler, and M. Beach.** 1999. Survey of bloodstream infections due to gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin. Infect. Dis. **29:**595–607.
7. **Espinel-Ingroff, A.** 1998. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J. Clin. Microbiol. **36:**2950–2956.
8. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics. Marcel Dekker, Inc., New York, N.Y.
9. **Gonzalez, G. M., D. A. Sutton, E. Thompson, R. Tijerina, and M. G. Rinaldi.** 2001. In vitro activities of approved and investigational antifungal agents against 44 clinical isolates of basidiomycetous fungi. Antimicrob. Agents Chemother. **45:**633–635.
10. **Gonzalez, G. M., R. Tijerina, L. K. Najvar, R. Bocanegra, M. Rinaldi, D. Loebenberg, and J. R. Graybill.** 2002. In vitro and in vivo activities of posaconazole against *Coccidioides immitis*. Antimicrob. Agents Chemother. **46:**1352–1356.
11. **Groll, A. H., S. C. Piscitelli, and T. J. Walsh.** 2001. Antifungal pharmacodynamics: concentration-effect relationships in vitro and in vivo. Pharmacotherapy **21:**133S–148S.
12. **Hoffman, H. L., E. J. Ernst, and M. E. Klepser.** 2000. Novel triazole antifungal agents. Expert Opin. Investig. Drugs **9:**593–605.
13. **Hoffman, H. L., and R. C. Rathbun.** 2002. Review of the safety and efficacy of voriconazole. Expert Opin. Investig. Drugs **11:**409–429.
14. **Manavathu, E. K., J. L. Cutright, D. Loebenberg, and P. H. Chandrasekar.** 2000. A comparative study of the in vitro susceptibilities of clinical and laboratory-selected resistant isolates of *Aspergillus* spp. to amphotericin B, itraconazole, voriconazole and posaconazole (SCH 56592). J. Antimicrob. Chemother. **46:**229–234.
15. **Meletiadis, J., J. F. Meis, J. W. Mouton, J. L. Rodriquez-Tudela, J. P. Donnelly, and P. E. Verweij.** 2002. In vitro activities of new and conventional antifungal agents against clinical *Scedosporium* isolates. Antimicrob. Agents Chemother. **46:**62–68.
16. **Nomeir, A. A., P. Kumari, M. J. Hilbert, S. Gupta, D. Loebenberg, A. Cacciapuoti, R. Hare, G. H. Miller, C. C. Lin, and M. N. Cayen.** 2000. Pharmacokinetics of SCH 56592, a new azole broad-spectrum antifungal agent, in mice, rats, rabbits, dogs, and cynomolgus monkeys. Antimicrob. Agents Chemother. **44:**727–731.

17. **Perfect, J. R., G. M. Cox, R. K. Dodge, and W. A. Schell.** 1996. In vitro and in vivo efficacies of the azole SCH56592 against *Cryptococcus neoformans*. Antimicrob. Agents Chemother. **40:**1910–1913.
18. **Pfaller, M. A., S. A. Messer, R. J. Hollis, and R. N. Jones.** 2001. In vitro activities of posaconazole (Sch 56592) compared with those of itraconazole and fluconazole against 3,685 clinical isolates of *Candida* spp. and *Cryptococcus neoformans.* Antimicrob. Agents Chemother. **45:**2862–2864.
19. **Pfaller, M. A., S. A. Messer, R. J. Hollis, and R. N. Jones.** 2002. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob. Agents Chemother. **46:** 1032–1037.
20. **Purkins, L., N. Wood, P. Ghahramani, K. Greenhalgh, M. J. Allen, and D. Kleinermans.** 2002. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob. Agents Chemother. **46:**2546–2553.
21. **Sun, Q. N., A. W. Fothergill, D. I. McCarthy, M. G. Rinaldi, and J. R. Graybill.** 2002. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob. Agents Chemother. **46:**1581–1582.
22. **Sun, Q. N., L. K. Najvar, R. Bocanegra, D. Loebenberg, and J. R. Graybill.** 2002. In vivo activity of posaconazole against *Mucor* spp. in an immunosuppressed-mouse model. Antimicrob. Agents Chemother. **46:**2310–2312.
23. **Walsh, T. J., and A. H. Groll.** 1999. Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. Transplant. Infect. Dis. **1:**247–261.