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Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites

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The pharmacokinetics of terbinafine and its inactive metabolites SDZ 86-621 (the N-demethyl form), SDZ 280-027 (the carboxybutyl form), and SDZ 280-047 (N-demethyl-carboxybutyl form) in plasma were characterized for 10 healthy male subjects receiving 250 mg of terbinafine orally once a day for 4 weeks and in the subsequent 8-week washout phase. Terbinafine concentrations were also measured in sebum, hair, nail, and stratum corneum samples. Concentrations of the parent compound and metabolites were determined by validated high-performance liquid chromatography methods. Terbinafine was rapidly absorbed, with peak concentrations in plasma of 1.70 ± 0.77 μg/ml occurring 1.2 ± 0.3 h postdose. Concentrations subsequently exhibited a triphasic decline, with a terminal disposition half-life of 16.5 ± 2.8 days. Terbinafine accumulated approximately twofold over the 4-week dosing phase. The predominant metabolite in plasma samples was SDZ 280-027; specifically, the ratios of metabolite area under the curve to terbinafine area under the curve following the last dose were 1.25, 1.38, and 1.08 for metabolites SDZ 86-621, SDZ 280-027, and SDZ 280-047, respectively. Nonrenal elimination constituted the major route of clearance for terbinafine and all three metabolites, with renal elimination playing a minor additional role in the clearance of metabolite SDZ 280-047. Measurable concentrations of terbinafine were achieved in sebum and hair samples within the first week of administration and by week 3 in stratum corneum and nail samples. Fungicidal concentrations persisted in plasma and peripheral tissue samples for prolonged periods (weeks to months) after administration of the last dose. These pharmacokinetic properties are likely an underlying factor in the shorter treatment times and good clinical cure rates which have been reported for terbinafine in the therapy of onychomycoses and dermatomycoses.

Low cure rates, the necessity for prolonged treatment courses and a high incidence of relapse continue to represent challenges in the treatment of superficial mycoses (6). In this context, the emerging clinical profile of terbinafine, an allylamine antifungal agent, is encouraging (1). Terbinafine is an orally and topically active drug with primarily fungicidal activity against a broad spectrum of fungi, including dermatophyte, filamentous, and dimorphic organisms and some yeasts (1, 10). In vitro comparisons indicate that it is more active than azoles and griseofulvin against dermatophytes and *Aspergillus* species. Clinical trials of oral terbinafine in the treatment of onychomycoses and dermatophyte skin infections (tinea corporis, tinea cruris, and tinea pedis) yielded mycological cure rates of 90% and clinical efficacy rates (mycological cure with resolution of symptoms) of about 80% (1, 12). A duration-finding study of terbinafine in the treatment of onychomycosis (11) supported earlier clinical observations that treatment courses of 250 mg orally once a day could be considerably shortened to 3 to 6 months of therapy compared with the traditional 12-month course currently necessary with other antifungal agents. For dermatomycoses, the recommended oral treatment is 250 mg once a day for 2 to 6 weeks for tinea pedis and for 2 to 4 weeks for tinea corporis, tinea cruris, or cutaneous candidiasis (1). In light of these treatment schedules and the necessity for adequate drug concentrations at peripheral sites of infection, the present study was undertaken to characterize terbinafine pharmacokinetics during multiple-dose administration with a rigorous sampling schedule of plasma, urine, sebum, hair, nails, and stratum corneum during a 4-week dosing phase and an 8-week washout phase following the last dose.

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MATERIALS AND METHODS

Study design. This was an open-label study of 10 healthy male subjects aged 28.3 ± 8.8 years (mean ± standard deviation) and weighing 77.1 ± 11.3 kg who were enrolled following written informed consent. The study protocol was approved by a local medical ethics committee and was performed in accordance with the Declaration of Helsinki and current European Community and U.S. Food and Drug Administration guidelines for good clinical practice. The study consisted of two consecutive periods. In period I (study days 1 and 2), subjects received a single, fasting oral administration of terbinafine as one 250-mg tablet of Lamisil (lot no. X 001 0289; Sandoz Pharma Ltd., Basel, Switzerland). Over the subsequent 48 h, 20 serial blood samples and 2 24-h urine collections were obtained to characterize single-dose pharmacokinetics. Period II was divided into two phases, a multiple-dose phase (study days 3 to 30) and a washout phase following the last dose (study days 31 to 90). During the dosing phase, subjects received 250 mg of terbinafine orally once a day for 28 consecutive days. Morning predose blood samples and 24-h urine collections were obtained approximately every 4 days, and an intensive 24-h plasma profile (14 blood samples) was performed on study day 16. At the last dose administration and during the subsequent washout phase, intensive blood sampling and three 24-h urine collections were performed over study days 30 to 33. Thereafter, morning blood samples and 24-h urine collections were obtained approximately every 4 days up to day 56 for urine and up to day 90 for plasma. Peripheral tissue and body fluid samples were obtained throughout the duration of this study. Specifically, sebum, hair, nail, and stratum corneum samples were obtained prior to dosing on study day 1 and at approximately 6-day intervals thereafter (2-week intervals for nails) up to study day 90.

Clinical evaluation and confinement. Prior to study initiation, subjects were evaluated for general good health on the basis of medical history, physical examination, electrocardiogram, hepatitis and human immunodeficiency virus

TABLE 1. Pharmacokinetic parameters of terbinafine and metabolites in plasma[a]

Substance	Study day	$t_{1/2a}$ or $t_{1/2f}$ (h)[b]	T_{max} (h)	C_{max} (μg/ml)	AUC_τ (μg · h/ml)	$t_{1/2\lambda1}$ (h)[b]	$t_{1/2\lambda2}$ (h)[b]	$t_{1/2}$ (days)
Single-dose terbinafine	1	0.35 ± 0.08	1.5 ± 0.0	1.34 ± 0.45	4.74 ± 2.07[c]	1.3 ± 0.3	12.6 ± 4.7	—[d]
Multiple dose								
Terbinafine	16	0.28 ± 0.11	1.2 ± 0.4	1.62 ± 0.85	8.87 ± 4.59	1.4 ± 0.6	14.5 ± 2.8	—
Terbinafine	30	0.28 ± 0.08	1.2 ± 0.3	1.70 ± 0.77	10.48 ± 6.20	1.7 ± 0.5	28.7 ± 14.7	16.5 ± 2.8
SDZ 86-621	30	0.29 ± 0.09	1.5 ± 0.5	1.60 ± 0.42	12.59 ± 5.34	2.8 ± 2.5	26.3 ± 19.1	8.5 ± 5.6
SDZ 280-027	30	1.01 ± 0.08	3.2 ± 1.9	1.03 ± 0.69	17.60 ± 13.62	DC[e]	26.9 ± 8.4	32.4 ± 20.1
SDZ 280-047	30	0.86 ± 0.45	4.0 ± 4.7	0.79 ± 0.53	13.64 ± 10.08	DC	34.3 ± 18.0	30.3 ± 14.7

[a] Data are means ± standard deviations of the means.
[b] Half-life subscript designations are as follows: a, absorption; f, metabolite formation; and λ1 and λ2, first and second disposition phases, respectively.
[c] Value for $AUC_{0\text{-}Tz}$.
[d] Because of restricted blood sampling duration and the assay quantification limit, the terminal phase was not observed.
[e] DC, disposition phase difficult to characterize.

tests, and routine biochemical, hematologic, and urinalysis tests. Laboratory chemistries and electrocardiogram evaluations were repeated on study days 16, 30, and 58. Subjects were confined to the study center from at least 10 h before to 24 to 48 h after dosing on study days 1, 16, and 30. They returned to the study center for scheduled body fluid and tissue sampling.

Body fluid and tissue sampling techniques. Blood samples were collected in heparinized glass tubes, and plasma was separated by centrifugation at 4°C within 15 min of collection. Urine samples were collected in glass bottles, and a 20-ml portion was saved after the total volume was measured. Samples of sebaceous gland secretions (sebum samples) were obtained indirectly by collecting skin surface lipids on a standardized piece of absorbent weighing paper which was covered by an aluminum foil patch taped to the forehead for 3 h. Beard shavings of 2-day growth were obtained with an electric razor. Nail samples consisted of clippings from the free border of five fingernails. The stratum corneum (10 to 15 mg) was scraped with a curette down to the stratum lucidum from preidentified quadrants on the sole. Plasma and urine samples were stored at −20°C; all other samples were stored at −70°C until analyzed.

Bioanalytical methods. The concentrations of terbinafine and its N-demethyl (SDZ 86-621), carboxybutyl (SDZ 280-027), and N-demethyl-carboxybutyl (SDZ 280-047) metabolites in plasma, urine, and tissue samples were determined by validated and sensitive high-performance liquid chromatography methods (3, 14). Standard curves were constructed independently for each biological matrix and analyte. Assay linearity was demonstrated from the respective quantification limit up to 2,000 ng/ml, the highest standard concentration used. The within-day coefficient of variation and the bias of quality control samples never exceeded 18%. The concentrations of the unchanged parent drug from all plasma samples were determined, whereas concentrations of the three metabolites in plasma samples were determined following the last dose administration only. The assay quantification limit was 0.02 μg/ml for terbinafine and SDZ 86-621 and 0.1 μg/ml for the two carboxymetabolites. In urine samples, the concentrations of the parent drug and three metabolites were determined after the enzymatic hydrolysis of samples; the limit of quantification was 0.04 μg/ml for all compounds. Only the terbinafine concentration was determined in tissue samples, which were either solubilized in NaOH solution and subsequently extracted with an organic solvent (hair, nail, and stratum corneum samples) or extracted directly (sebum samples) prior to determination. The quantification limit was 0.5 μg/g (original units, 5 ng per 10-mg sample) for all matrices.

Pharmacokinetic evaluation. The concentration-time data were analyzed by standard model-independent methods. The maximum concentration in plasma and the time of its occurrence were designated C_{max} and T_{max}, respectively. Following single-dose administration, the area under the curve ($AUC_{0\text{-}Tz}$) was calculated by trapezoidal summation to the last sampling timepoint (T_z) with a quantifiable concentration; the $AUC_{0\text{-}Tz}$ was not extrapolated (see Results). During multiple-dose administration, the area under the curve over the dosing interval (AUC_τ) for each analyte was calculated over a dosing interval from 0 to 24 h by trapezoidal summation. The apparent total body clearance of terbinafine on study day 30 was calculated as dose/AUC_τ. The renal clearance (CL_R) of terbinafine and metabolites on study day 30 was calculated as Ae_τ/AUC_τ, where Ae_τ is the amount of the substance excreted in urine over a dosing interval. The method of residuals (7) was used to resolve the concentration profiles into the various exponential components. The half-lives of terbinafine absorption; of metabolite formation; and of the initial, second, and terminal ($t_{1/2}$) disposition phases were calculated by dividing ln(2) by the appropriate rate constant (k_a, k_f, λ_1, λ_2, and λ_z, respectively). The accumulation ratio is the ratio of the AUC from 0 to 24 h from the single-dose administration on study day 1 over the AUC_τ from study day 30.

RESULTS

Clinical observations. Terbinafine was well tolerated during multiple-dose administration. No clinically relevant or drug-related changes in electrocardiogram or laboratory chemistry profiles occurred over the course of this study. A single adverse event occurred: mycoplasma urethritis of moderate severity on study day 45 (14 days after the last terbinafine dose), which responded to appropriate therapy.

Pharmacokinetics of terbinafine in plasma. The pharmacokinetic parameters are summarized in Table 1, and the concentration-time profiles following the last dose are shown in Fig. 1. Terbinafine was rapidly absorbed, reaching peak concentrations approximately 1 h postdosing. The C_{max} increased on average by 20% between days 1 and 16; thereafter, it increased only slightly, by 3% to day 30. Because of the limited sampling duration (48 h) and the decline of concentrations below the assay quantification limit, the terminal disposition phase was not characterizable following single-dose administration on study days 1 and 2; hence, the $AUC_{0\text{-}Tz}$ was not extrapolated to infinity. The AUC_τ increased by 17% on average between days 16 and 30. The accumulation ratio of terbinafine (R) administered once a day for 28 days was 2.3 ± 0.5. A biphasic decline in concentrations was apparent following single-dose administration and from the 24-h sampling period on day 16. Extended sampling during the washout phase after the last dose on day 30 revealed a third disposition phase with a $t_{1/2}$ of 16.5 days on average. Predose trough concentrations continued to rise slowly over the study's duration, as depicted in the lower curve of Fig. 2. Linear regression analysis of the trough values over time did not reject a zero slope when values from study days 21 to 31 were included. However, the failure to detect a nonzero slope may have been due to intersubject variability in these observations. In view of the long terminal disposition phase, steady state is unlikely to have been attained in this study. It is estimated, however, that following dosing for 28 days (approximately two half-lives) about 70% of steady state was achieved. The apparent total body clearance of terbinafine calculated on the basis of day 30 data was 503 ± 223 ml/min. This value must be viewed as a rough estimate which likely overestimates the true steady-state clearance slightly. Inasmuch as no intact terbinafine was measurable in urine samples, biotransformation represents the primary elimination route.

Pharmacokinetics of metabolites in plasma. As is evident from Fig. 1, the plasma profile of the N-demethyl metabolite SDZ 86-621 paralleled that of the parent compound. Its T_{max} and C_{max} were roughly similar to those of terbinafine, while the area ratio (geometric mean ratio of metabolite AUC_τ to terbinafine AUC_τ) on study day 30 of 1.25 indicated that systemic exposure to the metabolite was slightly higher than that to terbinafine. The predominant metabolite during multiple dosing was SDZ 280-027. Its peak concentrations were about

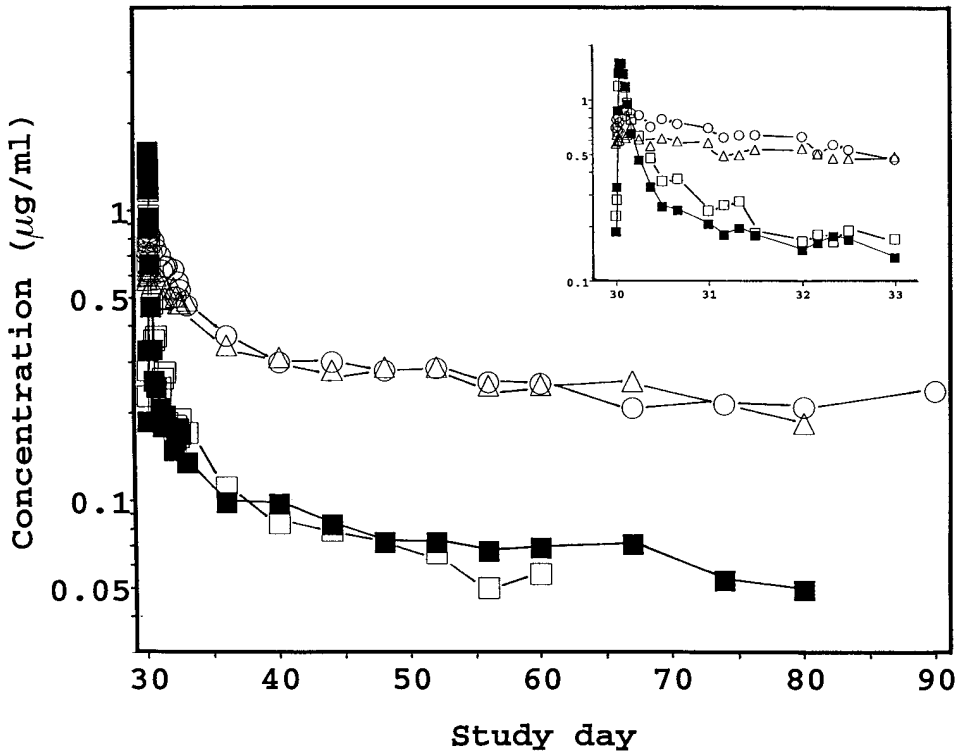

FIG. 1. Mean concentration-time plasma profiles of terbinafine (■) and metabolites SDZ 86-621 (□), SDZ 280-027 (○), and SDZ 280-047 (△) following administration of the last dose. The inset shows the initial portions of curves to study day 33.

one-third of those of the parent compound and occurred later. Systemic exposure exhibited wide intersubject variability, with an average area ratio on study day 30 of 1.38. Metabolite SDZ 280-047 yielded a profile similar to that of SDZ 280-027, with a later T_{max} and C_{max} compared with those of the parent compound. Systemic exposure was also highly variable between subjects, with a magnitude similar to that of terbinafine on average (area ratio of 1.08). The $t_{1/2}$ of each carboxymetabolite was approximately twice as long as that of the parent compound. During the washout phase, the amount of each intact metabolite excreted in urine (Ae/day) declined in parallel with the respective concurrent concentrations in plasma. Urinary recovery of intact metabolites on study day 30 indicated that renal elimination plays no role in the clearance of SDZ 86-621 (CL_R = 0 ml/min) or SDZ 280-027 (CL_R = 3 ± 3 ml/min), whereas it represents a minor elimination route for SDZ 280-047 (CL_R = 23 ± 14 ml/min).

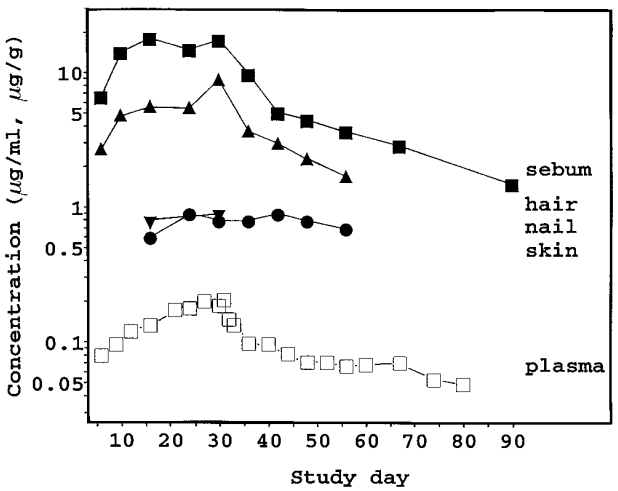

FIG. 2. Mean concentrations of terbinafine in plasma, stratum corneum (skin), nail, hair, and sebum samples during multiple-dose administration (study days 3 to 30) and in the subsequent washout phase (study days 31 to 90). For plasma samples, only morning predose concentrations are graphed during the dosing phase. The assay quantification limits were 0.02 μg/ml for plasma samples and 0.5 μg/g for samples from all other matrices.

Terbinafine concentrations in body fluids and tissues. The terbinafine concentrations from peripheral matrices are compared graphically in Fig. 2. Of the tissues sampled, terbinafine concentrations were highest in sebum and hair samples. From these matrices, terbinafine was measurable at all sampling timepoints during dosing and reached maximum values on study day 30. Following the last dose, quantifiable concentrations persisted in hair samples to day 56 and in sebum samples to day 90. The decline in concentrations during the washout phase indicated a slow redistribution from the peripheral sites back to the central plasma compartment. Redistribution half-lives were 14.5 ± 8.5 and 15.0 ± 5.5 days for sebum and hair samples, respectively. Concentrations were quantifiable in stratum corneum and nail samples between study days 16 and 30 (when the highest values were reached). Prior to this and during the washout phase, concentrations were detectable but below the validated assay quantification limit (0.5 μg/g); therefore, they are not shown in Fig. 2.

DISCUSSION

Terbinafine is the first orally active antifungal agent with a primarily fungicidal action. As an allylamine derivative, it is

structurally unrelated to other commonly used antifungal agents, such as azoles, polyenes, and morpholines (6). It has demonstrated encouraging mycological and clinical profiles with the potential to shorten the course of treatment in some superficial mycoses (1). This multiple-dose pharmacokinetic study was performed to characterize the pharmacokinetics of terbinafine and its major metabolites in plasma over a typical treatment duration. An additional objective was to quantify the concentrations of terbinafine achievable at peripheral sites of clinical relevance in the treatment of onychomycoses and dermatomycoses.

The single-dose plasma pharmacokinetics of terbinafine in this investigation were in good agreement with those of earlier studies in which rapid absorption and a biphasic decline in concentrations with a presumed $t_{1/2}$ of about 25 h were reported (1, 8, 9). Because of the limited duration of blood sampling and the assay limit of quantification, a third disposition phase was not observed in these early single-dose studies. Only in subsequent multiple-dose investigations in which plasma washout kinetics were followed was a third disposition phase with a half-life of about 20 to 28 days clearly identifiable (4, 13). The average $t_{1/2}$ of 17 days in the present investigation is in line with these results. It is likely that this disposition phase is governed by the slow return of terbinafine to the central plasma compartment from peripheral tissue and adipose distribution sites (13).

As expected for a highly lipophilic compound, the total body clearance of terbinafine is via biotransformation, with essentially no intact drug measurable in urine samples. Fifteen metabolites of terbinafine have been identified; however, none of them is mycologically active (2). The three major metabolites measurable in human plasma samples during multiple dosing were characterized in this investigation. All three are reportedly further biotransformed prior to elimination (2), which is consistent with the finding in the present study that negligible or minor amounts of these metabolite were detectable in urine samples during multiple dosing.

The present study demonstrates that terbinafine distributes extensively to peripheral body fluids and tissues. The concentrations in sebum and hair samples were severalfold higher than simultaneous concentrations in plasma samples. This is in agreement with a previous investigation employing a similar dosing schedule (4). In the present study terbinafine levels in stratum corneum samples (about 1 μg/ml) were lower than those previously reported (about 10 μg/ml), which may have been due in part to intersubject variability and to the different sampling sites investigated (i.e., sole versus back [4]). The levels in nail clippings were generally quantifiable by week 3 of multiple dosing, which is in agreement with the results of Finlay (5), who speculates that the early presence of terbinafine in distal nails indicates that it enters the nail plate across the whole nail bed and not primarily via the proximal growing nail matrix, the presumed entry route for other antifungal agents. These tissue concentrations can be put in clinical perspective by referring to the in vitro MIC ranges of 0.001 to 0.01 μg/ml for dermatophytes, 0.05 to 1.56 μg/ml for *Aspergillus* species, and ≤0.05 to 2.0 μg/ml for dimorphic fungi (1, 10). The validated assay quantification limits were generally much higher than the in vitro MICs against susceptible fungal pathogens. Therefore, the duration over which concentrations were measurable, as shown in Fig. 2, is a minimal estimate of the duration of fungicidal concentrations at peripheral sites.

High terbinafine concentrations in tissue samples combined with its slow rate of redistribution back to the central plasma compartment indicate that fungicidal concentrations are maintained for weeks to months after a course of treatment. It is likely that these pharmacokinetic properties are an underlying factor in the reduced treatment times and good clinical cure rates which have been reported for terbinafine in the therapy of onychomycoses and dermatomycoses (1, 11, 12).

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