

An Open-Label, Multi-Center, Multiple-Application Pharmacokinetic Study of Naftifine HCl Gel 2% in Pediatric Subjects With Tinea Pedis

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ABSTRACT

Background: Tinea pedis is the most common superficial fungal infection. Naftifine hydrochloride is a topical antifungal of the allylamine class, displaying fungicidal activity and clinically significant anti-bacterial and anti-inflammatory effects. Clinical data on topical antifungal therapy using naftifine for tinea pedis in a pediatric population is limited.

Objective: To assess trends in efficacy, tolerability, safety, and to quantify the pharmacokinetics (PK) of topical naftifine hydrochloride gel 2% in pediatric subjects with tinea pedis.

Methods: Twenty-eight subjects (22 pediatric and 6 adult controls) were enrolled and treated in the study. Approximately 2 grams of naftifine hydrochloride gel 2% was applied to each foot (4 grams total) for subjects with tinea pedis. Pharmacokinetic blood and urine samples were collected at various time points throughout the study. Efficacy was assessed based on potassium hydroxide, dermatophyte culture, and signs and symptom results at days 7, 14, and 28. Adverse event information was collected routinely.

Results: The rate and extent of systemic exposure among the pediatric and adult control subjects was low. Adverse events were minimal and were not related to treatment. Positive results were observed as early as day 7; however the proportion of subjects achieving success generally increased over time through day 28 in both treatment groups.

Conclusions: Naftifine hydrochloride gel 2% was found to be well tolerated and safe. Trends in clinical benefit were observed throughout the treatment period; however, continued improvement in efficacy rates were observed during the post-treatment period.

J Drugs Dermatol. 2015;14(7):686-691.

INTRODUCTION

Fungal infections caused by dermatophytes, yeasts, and molds occur globally, affecting millions of people. Although the infection can result from contact with an infected animal, soil, or fomites, most infections are caused by dermatophytes spread through contact with an infected person, or by self-infection by transfer from another body part.[1,2] A fungal infection involving the foot, referred to as tinea pedis, affects up to 15% of the United States population and is estimated to be the second most common skin condition, behind acne. Additionally, approximately half of those infected suffer from reoccurring outbreaks.[2-5] Tinea pedis is more common in adolescents and adult males; however, women and children may come into contact with an infected person or surrounding environments of a contagious nature.[6,7]

The three main types of dermatophytes isolated as the primary cause of tinea pedis are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.[5] *Trichophyton rubrum* accounts for approximately three-fourths of all superficial fungal diseases in a representative sample of the US population.[2,5] Specifically to tinea pedis, *Trichophyton rubrum* accounts for two-thirds of the cases of tinea pedis.[2,5]

Both topical and oral regimens are prescribed for the treatment of tinea infections. Generally, a topical application of an antifungal agent is the most common recommendation by a healthcare provider for the treatment of tinea pedis; however, in some cases oral treatments are warranted.[8] Although oral regimens are an option for treatment, due to the increased risk of undesirable systemic affects, topical treatments tend to be an effective alternative. A commonly prescribed topical treatment for tinea pedis is a two-week once daily application of naftifine hydrochloride gel 2%.

Naftifine hydrochloride is a broad-spectrum antifungal agent of the allylamine class and has been shown to demonstrate better efficacy rates and shorter treatment durations than the azole class.[9-11] Additionally, naftifine hydrochloride has been shown to demonstrate potent fungicidal and fungistatic activity as well as clinically significant anti-inflammatory and anti-bacterial effects.[12-16] In clinical trials, naftifine hydrochloride gel 2% has been shown to be efficacious and in most cases post-treatment improvements have been observed up to four weeks after treatment cessation.[17-19] One possible explanation for this continued post-treatment improvement is bioavailable drug remaining in the deeper layers of the

stratum corneum for extended periods of time beyond the recommended treatment duration.[20]

Clinical data on topical antifungal therapy using naftifine for tinea pedis in a pediatric population is limited. The objective of this manuscript is to present results from a study that quantified the pharmacokinetics (PK) and assessed trends in efficacy, tolerability, and safety of naftifine hydrochloride gel 2% in pediatric subjects with tinea pedis.

METHODS

Study Design

The data are from a four-week, open-label, multi-center, multiple application study in pediatric subjects (ages 12 years to 17 years, 11 months) with tinea pedis. The study quantified the pharmacokinetic (PK) profile of naftifine hydrochloride gel 2% in pediatric subjects with tinea pedis (both feet affected). Additionally, at small subset of adult PK evaluable subjects with the same condition were obtained to serve as the control.

All subjects stayed at the study center on day 1 (first application) and day 14 (last application). Pharmacokinetic blood samples were collected on days 1 and 14 for 24 hours at: 0 hour (pre-application), and 1, 2, 4, 6, 8, 12, and 24 hours post-application. Pre-application samples were collected on days 1, 3, 7, 11, 12, 13, and 14. Days 11 through 14 samples were used to assess steady state. In addition, samples were collected on days 21 (1-week after the last application), and day 28 (2-weeks after the last application). Pharmacokinetic urine samples were obtained on days 1 and 14 for 24 hours as follows: before on-site treatment application (only on day 1), 0-6, 6-12, and 12-24 hours after on-site application.

Efficacy was assessed based on potassium hydroxide (KOH), dermatophyte culture, signs and symptoms between baseline (first application) and day 7 (1-week into treatment), day 14 (24 hours after last application), and day 28 (2-weeks after the last application and 4 weeks after the start of the study).

The study was conducted according to the ethical guidelines of the Declaration of Helsinki and according to the good clinical practice (GCP) guidelines. Institutional review boards (IRB) and/or ethical committees of all participating sites reviewed the protocol and approved the study before enrolling the first patient. The study was registered with ClinicalTrials.gov (Identification Number: NCT01712360) and was funded by Merz Pharmaceuticals, LLC.

Intervention

The study was conducted under maximal clinical use conditions for both the pediatric subjects and adult control subject. Subjects were instructed to apply 4 grams of naftifine hydrochloride gel 2% to both feet (approximately 2 grams per foot) once a day for two weeks. Subjects applied the assigned study product to the affected areas plus a half-inch margin of healthy skin.

Participants

Participants in the study were recruited from 4 clinical sites from the United States, Dominican Republic, and Honduras. Written and informed consent was obtained from all subjects (as well as by a legal guardian and/or caregiver, if applicable) prior to screening. In order to be included into the study subjects must be male and non-pregnant females' between 12 and 17 years, 11 months of age with a clinical diagnosis (ie, baseline presence of signs and symptoms of erythema, scaling, pruritus, and KOH positive scrapings from the most representative site) of tinea pedis on both feet. For the adult control groups, subjects must have been males or non-pregnant females' ≥18 years of age with tinea pedis. Additionally, subjects must have had an absence of clinically significant disease that could interfere with the interpretation of the results, the ability of the participants to understand the requirements of the study, and willing to comply with them.

Exclusion criteria included any life-threatening condition within the last 90 days of pre-study visit (screening); known hypersensitivity to study medication or any components; uncontrolled diabetes mellitus; hemodialysis or chronic ambulatory peritoneal dialysis; current diagnosis of immunocompromising conditions; onychomycosis; clinically significant abnormal laboratory or physical findings; any severe condition of tinea pedis (incapacitating) including bacterial skin infections such as cellulitis, mucocutaneous candidiasis, dermatophytoses, lymphagitis; or pyoderma; any dermatological disease or condition in the treatment or surrounding area(s) that may prevent application of the study product; participation in another clinical trial or the completion of another clinical study with an investigational drug or device within the past 30 days; received any treatment with the investigational products or any other allylamine or antifungal for any indication within the past 2 months; having received any treatments or medications within 1 month prior to study treatment initiation with the exception of hormonal contraception; anyone who does not use an acceptable form of contraception during the study (if necessary) and; historical or current evidence (physical or laboratory) of anemia. Enrolled subjects who had received antifungal, corticosteroids, or antibacterial therapies prior to randomization were required to undergo a washout period prior to entering the trial.

"Naftifine gel 2% was well tolerated during the 14-day treatment regimen."

Outcomes

Pharmacokinetic measurements obtained at various days throughout the study included: 1) AUC_{0-24}: partial area under

the plasma concentration curve within the first 24 hours; 2) C_{max}: the highest observed concentration following a single dose administration; 3) $AUC_{\tau, ss}$: area under the plasma concentration curve within a dosing interval at steady state; 4) $C_{max, ss}$: maximum observed plasma concentration at steady state; 5) t_{max}: time to concentration maximum after single dose; 6) $t_{max, ss}$: time to concentration maximum at steady state; 7) C_{trough}: trough plasma concentration; 8) $t_{trough,max}$: time to maximal trough plasma concentration; 9) $C_{trough, max}$: maximum observed trough plasma concentration; 10) Ae_{0-24}: partial amount of unchanged drug excreted into urine within the first 24 hours after single dose; 11) f_e: fraction of administered drug excreted into the urine after a single dose and during a dosing interval at steady state; 12) CL_R: renal clearance after single dose and multiple doses; 13) $Ae_{\tau, ss}$: amount of unchanged drug excreted into urine during a dosing interval at steady state.

Efficacy measurements included mycology laboratory analysis for the presence of dermatophytes (KOH scraping assessment and fungal culture) and scoring of clinical signs and symptoms (erythema, scaling, and pruritus) severity on a four point scale (0=absent, 1=mild, 2=moderate, 3=marked).

The following efficacy outcomes are based on clinical and mycology data evaluated: complete cure (negative mycology results [KOH and culture] and complete absence [score of 0 for each] of erythema, scaling, and pruritus); mycological (negative KOH and culture results); treatment effectiveness (mycological cure and erythema, scaling, and pruritus scores of 0 or 1); clinical cure (erythema, scaling, and pruritus scores of 0); and clinical success (erythema, scaling, and pruritus scores of 0 or 1). All of the aforementioned endpoint evaluations were performed at day 7 (1-week into treatment), day 14 (end of treatment), and day 28 (2-weeks post-treatment).

Safety assessments included adverse events (AEs), clinical laboratory values, and physical examination findings.

Sample Size

This study was not intended to be confirmatory in nature. Therefore, the sample size is not based on statistical power calculations. It was planned to screen 35 subjects in order to have 28 subjects enrolled to obtain 22 PK evaluable subjects for treatment with naftifine hydrochloride gel 2%.This sample size was determined to be sufficient to address the PK objectives of the study and to be able to detect differences in pharmacokinetics between the pediatric and adult control subjects if they are existent without exposing too large of a number of subjects to undue risk and discomfort. As a result, the planned distribution of subjects needed for a robust pharmacokinetic analysis was 18 PK evaluable pediatric subjects and 4 PK evaluable adult control subjects. The adult cohort is smaller than the pediatric cohort because they served as controls and PK data of adults is already available from former naftifine studies (Data on file, Merz Pharmaceuticals, LLC).

Statistical Analysis

The time courses of the plasma and urine concentrations of naftifine hydrochloride gel 2% was analyzed by non-compartmental analysis. PK variables was described by statistical characteristics (number of observations, arithmetic mean, standard deviation (SD), arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation, median, minimum and maximum) per treatment group and per age group (pediatric and adult).

All efficacy endpoints were described by statistical characteristics for categorical data (n [%]). In addition, a two-sided 90% CI for percentages was computed using the exact method.

Incidences of adverse events during the study period were tabulated and summarized descriptively for both treatment groups. Incidences were calculated for treatment emergent adverse events (TEAEs) on the system organ class level and on the preferred term level and presented by treatment (ie, total and in percent, by intensity and by relationship). Adverse events were also summarized by age cohort.

RESULTS

Participants

A total of 28 subjects were enrolled and treated (22 pediatric and 6 adult subjects). Twenty-one of the 22 pediatric subjects and 4 of the 6 adult subjects completed the study; however, all 22 pediatric

TABLE 1.

Baseline Demographic Characteristics for All Subjects Receiving Study Treatment at Least Once

	Naftifine Hydrochloride Gel 2%	
	Pediatric (N=22)	Adult (N=6)
Gender, n (%)		
Male	18 (81.8)	4 (66.7)
Female	4 (18.2)	2 (33.3)
Age (years), Mean (SD)	14.7 (1.7)	31.7 (11.2)
Ethnicity, n (%)		
Hispanic or Latino	16 (72.7)	1 (16.7)
Not Hispanic of Latino	6 (27.3)	5 (83.3)
Race, n (%)		
White	6 (27.3)	2 (33.3)
Black or African American	16 (72.7)	3 (50.0)
American Indian or Alaska Native	0	1 (16.7)
Weight (kg), Mean (SD)	65.3 (24.2)	88.0 (18.4)

SD = standard deviation, n = number of observations, N = number of subjects in the treatment group, kg = kilogram

TABLE 2.

Pharmacokinetic Plasma Results for Naftifine Hydrochloride Gel 2%

	Adults	Pediatrics
day 1, Single Dose		
AUC_{0-24} (pg•h/mL) geometric mean and geometric CV	17213.9; 88.1%	15890.1; 211.6%
C_{max} (pg/mL) geometric mean and geometric CV	1741.02; 69.2%	1397.77; 153.8%
t_{max} (h) median (minimum, maximum)	12.0 (8, 24)	23.8 (1, 24)
day 14, Multiple Dose		
$AUC_{\tau,ss}$ (pg•h/mL) geometric mean and geometric CV	72849.8; 71.1%	60038.5; 131.1%
$C_{max,ss}$ (pg/mL) geometric mean and geometric CV	3538.8; 73.3%	3813.38; 153.9%
$t_{max,ss}$ (h) median (minimum, maximum)	5.0 (4, 6)	23.8 (4, 24)
$T_{trough,max}$ (day) median (minimum, maximum)	7.0 (2, 13)	14.0 (2, 21)
$C_{trough,max}$ (pg/mL) geometric mean and geometric CV	3124.7; 101.8%	3485.03; 88.9%

AUC_{0-24} = Area under the concentration curve for 24 hours after dosing,
C_{max}= observed maximum plasma concentration,
CV = coefficient of variation,
t_{max}= time of occurrence of C_{max},
$AUC_{\tau,ss}$= Area under the concentration curve within a dosing interval (τ = 24 hours) at steady state,
C_{max} = observed maximum plasma concentration,
$C_{trough,max}$ = observed maximum trough plasma concentration,
CV = coefficient of variation,
ss=steady state,
t_{max} = time of occurrence of C_{max},
$T_{trough,max}$ = Time of maximal trough plasma concentration

subjects and 5 of the 6 adult subjects (resulting from missing data) were analyzed for PK. Efficacy data was available for all 22 pediatric subjects. All 28 subjects dosed were analyzed for safety.

Among pediatric subjects enrolled, the majority were male (82%), Black or African American (73%), and with a mean (SD) age of 14.7 (1.7) years. For the adult subjects, the majority were male (67%), most were Black or African American (50%) or White (33%) and had a mean (SD) age was 31.7 (11.2) years (Table 1).

Pharmacokinetics – Plasma

Exposure to naftifine increased over the 2-week treatment period with the use of naftifine hydrochloride gel 2%: for pediatric subjects, geometric mean AUC_{0-24} (CV%) was 15890.1 pg*h/mL (211.6%) on day 1 and $AUC_{\tau,ss}$ was 60038.5 pg*h/mL (131.1%) on day 14; for adult control subjects, geometric mean AUC_{0-24} was 17213.9 pg*h/mL (88.1%) on day 1 and $AUC_{\tau,ss}$ was 72849.8 pg*h/mL (71.1%) on day 14. Maximum plasma concentration also increased over the treatment period for both the pediatric and adult subjects. In pediatric subjects, the median time to maximum plasma concentration (t_{max}) was 23.8 hours with a range of 1-24 hours after single application on day 1 and 23.8 hours with a range of 4-24 hours on day 14. In the adult control subjects, the median t_{max} (range) was 12.0 hours (8-24 hours) after a single application on day 1 and 5.0 hours (4-6 hours) on day 14 (Table 2).

After naftifine hydrochloride gel 2% maximal use administration (2 grams on each foot), plasma concentrations of naftifine from day 1 (single dose) through day 14 (multiple dose, steady state) in pediatric subjects were similar to those observed in adult subjects. The median time to maximum trough concentration ($t_{trough,max}$) of naftifine was twice as long in pediatric subjects (14.0 days, range, 2-21 days; all subjects had $t_{trough,max}$ between 2 and 15, inclusive, with the exception of one subject for whom there may have been a sample error on day 21) compared with adult subjects (7.0 days, range: 2-13 days; Table 2). Additionally, the geometric mean of maximum naftifine concentration at trough ($C_{trough,max}$) for pediatric and adult control subjects is presented in Table 2. Day 14 plasma concentrations were higher and less variable than day 1 plasma concentrations in both pediatric and adult control subjects. Naftifine continued to be detected in the plasma in most subjects at day 28, when the geometric mean (CV%) was 347.382 pg/mL (80.6%) in the pediatric group and 563.135 pg/mL (91.3%) in the adult control group.

Pharmacokinetics – Urine

In pediatric subjects, mean Ae_{0-24} (range) increased from 380.9 ng (0-1135.4 ng) on day 1 to 823.0 ng (0-2202.3 ng) on day 14;

TABLE 3.

Pharmacokinetic Urine Results for Naftifine Hydrochloride Gel 2%

	Adults	Pediatrics
day 1, Single Dose		
AUC_{0-24} (ng) arithmetic mean and SD	79.9 ± 76.6	380.9 ± 329.8
f_e (%) arithmetic mean and SD	0.0001 ± 0.0001	0.0005 ± 0.0005
CLr (mL/min) geometric mean and geometric CV	0.09; 75.4%	0.28; 227.5%
day 14, Multiple Dose		
$AUC_{\tau,ss}$ (ng) arithmetic mean and SD	974.5 ± 989.1	823.0 ± 679.9
f_e (%) arithmetic mean and SD	0.001 ± 0.001	0.001 ± 0.001
CLr (mL/min) geometric mean and geometric CV	0.16; 33.6%	0.15; 91.9%

Ae_{0-24}=amount of unchanged drug excreted into urine during the 24 hours after dosing,
CLr=renal clearance,
CV=coefficient of variation,
f_e (%)=fraction of administrated drug excreted into urine,
SD=standard deviation

TABLE 4.

Efficacy Responses Rates at Week 1 (1-Week Post-Baseline), Week 2 (End of Treatment), and Week 4 (2-Weeks Post-Treatment) in Pediatric Subjects Using Naftifine Gel 2% (N=22)

Efficacy Variable	Time Point	Response n (%)	90% Exact Confidence Interval for % Response
Complete Cure	Week 1	0 (0.0)	--
	Week 2	1 (4.5)	(0.2, 19.8)
	Week 4	6 (27.3)	(12.6, 46.8)
Mycological Cure	Week 1	7 (31.8)	(16.0, 51.5)
	Week 2	8 (36.4)	(19.6, 56.1)
	Week 4	14 (63.6)	(43.9, 80.4)
Treatment Effectiveness	Week 1	4 (18.2)	(6.5, 36.9)
	Week 2	7 (31.8)	(16.0, 51.5)
	Week 4	12 (54.5)	(35.3, 72.9)
Clinical Cure	Week 1	0 (0.0)	--
	Week 2	1 (4.5)	(0.2, 19.8)
	Week 4	9 (40.9)	(23.3, 60.5)
Clinical Success	Week 1	4 (18.2)	(6.5, 36.9)
	Week 2	16 (72.7)	(53.2, 87.4)
	Week 4	18 (81.8)	(63.1, 93.5)

N= number of subject in the treatment group;
n= number of observations

in adult control subjects, mean Ae_{0-24} (range) increased from 79.9 ng (0-161.9 ng) on day 1 to 974.5 ng (418.5-2456.2 ng) on day 14. The mean fraction of administered drug excreted into the urine (f_e) increased during the treatment period from 0.0005% at day 1 to 0.001% at day 14 for pediatric subjects and from 0.0001% at day 1 to 0.001% at day 14 for adult control subjects. Renal clearance (CLr) decreased during the study period in pediatric subjects and increased in adult control subjects. Geometric mean CLr results for pediatric subjects were 0.2766 mL/min on day 1 and 0.1546 mL/min on day 14 and for adult control subjects were 0.0933 mL/min on day 1 and 0.1646 mL/min on day 14. Overall, renal clearance was relatively low (Table 3).

Efficacy Response Rates

Among pediatric subjects (N=22), while positive results were observed as early as day 7 for most efficacy measures (ie, treatment effectiveness, mycological cure, and clinical success), the proportion of subjects achieving each efficacy endpoint generally increased over time through day 28 (2 weeks post-treatment). Efficacy rates at day 28 were as follows: complete cure (27.3%), treatment effectiveness (54.5%), mycological cure (63.6%), clinical success (81.8%), and clinical cure (40.9%; Table 4).

In regards to five evaluable adult control subjects, no subjects achieved complete cure during the 28-day study period; one subject (20%) achieved effective treatment at day 28; one subject (20%) achieved mycological cure at 28; four subjects (80%) achieved clinical success at day 28; and one subject (20%) achieved clinical cure at day 28.

Safety

Naftifine gel 2% was well tolerated during the 14-day treatment regimen. Two out of twenty-two (9%) pediatric subjects and one out of six (17%) adult subject experienced treatment emergent adverse events (TEAE) during the study. None of these events was a serious adverse event, led to dose reduction or discontinuation from the study, or was considered treatment-related which is defined as a causal relationship between the investigational product and an adverse event that is at least a reasonable possibility. All TEAEs were resolved by the end of the study.

DISCUSSION

After multiple applications of naftifine hydrochloride gel 2% under maximal use conditions where approximately 4 grams total (2 grams to each foot) were applied for the treatment of tinea pedis in pediatric patients (ages 12 to 17 years, 11 months) and adult controls, the rate and extent of systemic exposure was low. These findings are especially important given that topical regimens can reduce the spread of active ingredients into the bloodstream, thus minimizing systemic exposure and undue risks for side effects.

Naftifine hydrochloride gel 2% was found to be efficacious for tinea pedis in pediatric subjects in this study. A larger proportion of pediatric subjects responded to naftifine hydrochloride gel 2% with positive results for all efficacy measures, when compared with the adult subjects. The study was underpowered for efficacy, especially with respect to the adult subjects (N=6), who were included as a comparison group, rather than the main focus of the study. While positive results were observed as early as day 7 for some efficacy measures, the proportion of subjects achieving each efficacy endpoint (i.e. complete cure, effective treatment, mycological cure, clinical success, and clinical cure) generally increased over time through day 28. The trends in these findings are consistent with the results obtained from the randomized, multicenter, double-blind, vehicle-controlled clinical trials using naftifine hydrochloride gel 2% for the treatment of tinea pedis in a population between the ages of 12 and 70 years old.[19]

The continued post-treatment improvement in clinical signs and symptoms observed is consistent with naftifine's well-established residual post-treatment therapeutic activity. One possible reason for this observed prolonged treatment response may result from bio-available drug remaining in the stratum corneum for extended periods of time after treatment cessation; thus, continuously exposing dermatophytes to naftifine.[20]

The safety evaluation demonstrated an excellent safety profile with topically applied naftifine gel 2% in both the pediatric and

adult control subjects. Naftifine hydrochloride gel 2% was well tolerated during the 14-day treatment period. Only two pediatric subjects (9%) and one adult subject (17%) experienced a treatment emergent adverse event and in all cases these adverse events were found to be unrelated to treatment and resolved prior to the end of the study.

"One possible reason for this observed prolonged treatment response may result from bio-available drug remaining in the stratum corneum for extended periods of time after treatment cessation; thus, continuously exposing dermatophytes to naftifine."

Overall, as demonstrated in this maximal use pharmacokinetic study, as well as previous clinical trials,[19] naftifine hydrochloride gel 2% was found to be safe, well tolerated, and efficacious for the treatment of tinea pedis in a pediatric and adult population.

ACKNOWLEDGMENT

This research was supported and funded by Merz Pharmaceuticals, LLC

DISCLOSURES

Amit Verma, Babajide Olayinka, and Alan B. Fleischer are all employees of Merz North America, Inc.

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