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CLINICAL THERAPEUTICS

Pharmacokinetics, Safety, and Tolerability of Oxfendazole in Healthy Adults in an Open-Label Phase 1 Multiple Ascending Dose and Food Effect Study

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ABSTRACT Neurocysticercosis and trichuriasis are difficult-to-treat parasitic infections that affect more than 1.5 billion people worldwide. Oxfendazole, a potent broad-spectrum benzimidazole anthelmintic approved for use in veterinary medicine, has shown substantial antiparasitic activity against neurocysticercosis and intestinal helminths in preclinical studies. As part of a program to transition oxfendazole from veterinary medicine to human use, phase I multiple ascending dose and food effect studies were conducted. Thirty-six healthy adults were enrolled in an open-label study which evaluated (i) the pharmacokinetics and safety of oxfendazole following multiple ascending doses of oxfendazole oral suspension at 3, 7.5, and 15 mg/kg once daily for 5 days and (ii) the effect of food on oxfendazole pharmacokinetics and safety after a single 3-mg/kg dose administered following an overnight fast or the consumption of a fatty breakfast. Following multiple oral dose administration, the intestinal absorption of oxfendazole was rapid, with the time to maximum concentration of drug in serum (T_{max}) ranging from 1.92 to 2.56 h. A similar half-life of oxfendazole (9.21 to 11.8 h) was observed across all dose groups evaluated, and oxfendazole exhibited significantly less than a dose-proportional increase in exposure. Oxfendazole plasma exposures were higher in female subjects than in male subjects. Following daily administration, oxfendazole reached a steady state in plasma on study day 3, with minimal accumulation. Food delayed the oxfendazole T_{max} by a median of 6.88 h and resulted in a 49.2% increase in the maximum observed drug concentration in plasma (C_{max}) and an 86.4% increase in the area under the concentration-time curve (AUC). Oxfendazole was well tolerated in all study groups, and there were no major safety signals identified in this study. (This study has been registered at ClinicalTrials.gov under identifier NCT03035760.)

KEYWORDS clinical pharmacokinetics, food effect, oxfendazole, soil-transmitted helminthiasis

Soil-transmitted helminthiasis (STH), caused by the roundworm (*Ascaris lumbricoides*), hookworm (*Ancyclostoma duodenale* and *Necator americanus*), or whipworm (*Trichuris trichiura*), is the most common parasitic infection worldwide. Affecting

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approximately 1.5 billion people or 24% of the world's population, STH infections often lead to severe morbidity, especially in young children (1). To reduce the prevalence and intensity of STH infections, the World Health Organization (WHO) advocates mass deworming campaigns (2, 3). A meta-analysis of the results of 20 randomized controlled trials, identified from a search of 168 publications, showed that each of the four drugs studied (albendazole, mebendazole, pyrantel pamoate, levamisole) was efficacious in treating *A. lumbricoides* (87.9 to 96.5% cure rate) but that none of the these anthelmintics had acceptable efficacies against *T. trichiura* (8.6 to 43.6% cure) (4). Thus, a more efficacious treatment for *T. trichiura* is needed.

Cysticercosis, a tissue infection caused by the larval stage of *Taenia solium* (pork tapeworm) following the ingestion of food or water contaminated with *T. solium* eggs, can impact multiple tissues; the most severe form is brain tissue infection, neurocysticercosis. With clinical symptoms including headache, seizure, hydrocephalus, and intracranial hypertension (5), neurocysticercosis is considered the leading cause of adult-onset epilepsy. Highly prevalent in low- and middle-income countries in South and Central America, Sub-Saharan Africa, and South and East Asia, cysticercosis prevalence is rising in developed countries, probably due to growth in immigration (6). Albendazole, the presently approved drug that is preferred for the treatment of neurocysticercosis, requires prolonged treatment, and complete cure is difficult to achieve. A 1- to 2-week treatment with albendazole resolves only 60 to 70% of brain cysts, and fewer than 40% of patients are completely cured (7).

Considering the unsatisfactory efficacy of the current antiparasitic regimens against *T. trichiura* and *T. solium* neurocysticercosis, alternative antiparasitic drugs are needed. In preclinical studies in mouse and pig, albendazole exhibited efficacy against *T. muris* and *T. suis* similar to its efficacy against *T. trichiura* in human, about 40% (4, 8–11). In contrast, in pig, oxfendazole was 100% efficacious in eliminating *T. suis* (12–14), even at low oral doses (12). In preclinical cysticercosis studies, oxfendazole achieved partial cyst clearance in the brain and complete cyst removal from other tissues in pigs infected with *T. solium* with a single oral dose (15–18), a cure rate superior to those of praziquantel and albendazole. Besides its promising efficacy in preclinical models of *T. trichiura* and cysticercosis, oxfendazole exhibited good safety in multiple animal species, including mouse, rat, dog, and cattle (19). Finally, in dogs, sheep, and pigs, oxfendazole had higher drug exposure in plasma and a comparable or longer half-life ($t_{1/2}$) than albendazole (20–23).

To facilitate the transition of oxfendazole to human use, we previously completed a first-in-human (FIH) single-dose escalation study in healthy adults (ClinicalTrials.gov registration no. NCT02234570) (24). In that study, oxfendazole was rapidly absorbed with a mean plasma half-life of 8.5 to 11 h, and the maximum observed plasma concentration (C_{max}) of oxfendazole ranged from 944 to 6,770 ng/ml across the doses evaluated (0.5 to 60 mg/kg). All doses were well tolerated, and there were no serious adverse events (SAEs). Although a single dose of oxfendazole might be sufficient to treat some helminths, *Trichuris* infection and neurocysticercosis appear to be more difficult to treat, potentially requiring more extended treatment. Therefore, the present study was conducted to evaluate drug pharmacokinetics and safety following the administration of multiple ascending doses of oxfendazole. Because food effects on benzimidazole pharmacokinetics in human have been observed for albendazole (25) and mebendazole (26), evaluation of food effects on the single-dose pharmacokinetics of oxfendazole was also included in this study.

RESULTS

Subjects. In total, 24 subjects were enrolled in the multiple ascending dose evaluation, and 12 subjects were enrolled in the food effect evaluation. Table 1 summarizes the demographics and baseline characteristics of all participants by dose group and dosing condition. Overall, the majority of participants were white, and about two-thirds of the participants were male. The average age of all participants was 29.2 years (range, 19.0 to 44.0 years). Mean height, body weight, and body mass index (BMI) were

TABLE 1 Summary of demographics and baseline characteristics of study participants[a]

Characteristic	Value for:					
	Group 1 (3 mg/kg)	Group 2 (7.5 mg/kg)	Group 3 (15 mg/kg)	Group 4A (3 mg/kg, fasted → fed)	Group 4B (3 mg/kg, fed → fasted)	All subjects
n	8	8	8	6	6	36
Age (yr)	29.3 ± 9.1 (21.0–44.0)	27.1 ± 6.1 (19.0–33.0)	30.1 ± 4.4 (21.0–35.0)	27.7 ± 5.6 (22.0–34.0)	32.2 ± 9.4 (23.0–44.0)	29.2 ± 6.9 (19.0–44.0)
Height (cm)	178.0 ± 10.3 (163.5–195.6)	173.5 ± 7.1 (165.0–184.0)	170.8 ± 8.6 (160.0–184.0)	173.9 ± 6.9 (166.0–184.5)	174.1 ± 13.2 (158.5–196.0)	174.1 ± 9.1 (158.5–196.0)
Weight (kg)	88.9 ± 10.7 (76.8–103.0)	78.4 ± 14.0 (56.8–97.0)	76.9 ± 16.3 (58.6–104.0)	82.6 ± 11.9 (69.8–105.0)	86.3 ± 13.2 (73.2–105.0)	82.4 ± 13.6 (56.8–105.0)
BMI (kg/m^2)	28.1 ± 2.6 (25.0–32.6)	26.2 ± 5.3 (18.3–34.8)	26.3 ± 5.3 (21.1–34.3)	27.3 ± 4.0 (23.9–34.0)	28.6 ± 4.0 (24.2–33.9)	27.2 ± 4.2 (18.3–34.8)
Sex						
Male	7 (88)	5 (63)	4 (50)	5 (83)	4 (67)	25 (69)
Female	1 (13)	3 (38)	4 (50)	1 (17)	2 (33)	11 (31)
Ethnicity						
Not Hispanic or Latino	7 (88)	8 (100)	7 (88)	4 (67)	6 (100)	32 (89)
Hispanic or Latino	1 (13)	0 (0)	1 (13)	2 (33)	0 (0)	4 (11)
Race						
Asian	1 (13)	1 (13)	1 (13)	1 (17)	0 (0)	4 (11)
Black or African-American	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	1 (3)
White	7 (88)	6 (75)	6 (75)	4 (67)	6 (100)	29 (81)
Multiracial	0 (0)	0 (0)	1 (13)	1 (17)	0 (0)	2 (6)

[a]Continuous variables are summarized as means ± SD (range); categorical variables are summarized as number (percentage) of patients.

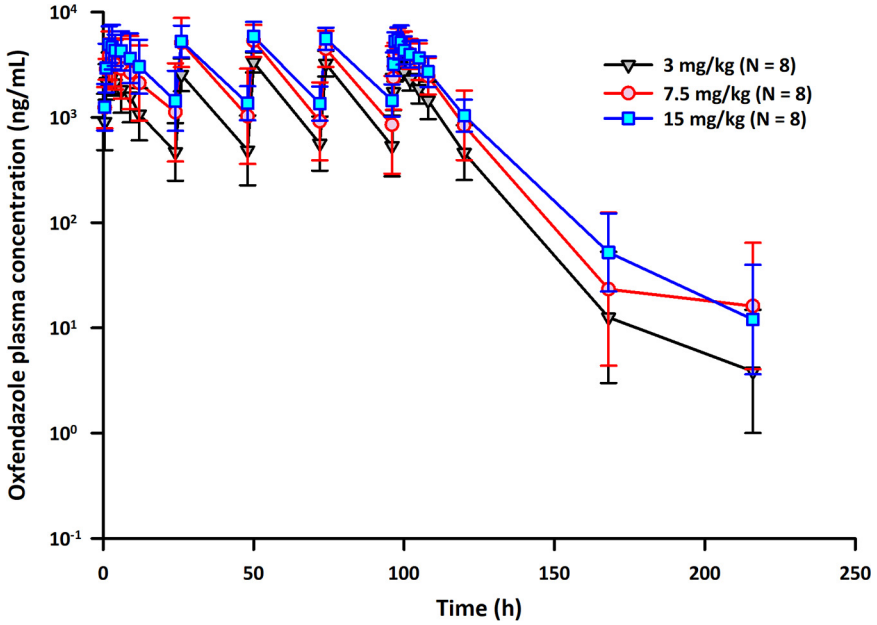

FIG 1 Concentration-time profiles of oxfendazole in healthy adults following multiple ascending doses at 3, 7.5, and 15 mg/kg once daily for 5 days. Each dose group consisted of 8 subjects. Data are presented as means ± SD.

174.1 cm, 82.4 kg, and 27.2 kg/m^2, respectively. Baseline characteristics were similar among groups.

Pharmacokinetics. (i) Multiple ascending dose evaluation. The mean pharmacokinetic profiles of oxfendazole following a once daily dosing regimen for 5 days are presented in Fig. 1. Table 2 provides oxfendazole pharmacokinetic parameters summarized by dose group. Following oral administration, oxfendazole underwent rapid

TABLE 2 Oxfendazole pharmacokinetic parameters following multiple ascending doses of 3, 7.5, and 15 mg/kg once daily for 5 days[a]

Day and parameter	Value following indicated dose		
	3 mg/kg (n = 8)	7.5 mg/kg (n = 8)	15 mg/kg (n = 8)
Day 1			
AUC_τ (ng · h/ml)	30,200 ± 22,900	52,500 ± 48,600	79,200 ± 40,200
AUC_τ/dose ([ng · h/ml]/[mg/kg])	9,970 ± 7,650	6,940 ± 6,480	4,380 ± 42,100
T_{max} (h)	1.96 (1.83–8.55)	2.02 (0.983–8.55)	2.56 (0.983–8.92)
C_{max} (ng/ml)	2,960 ± 1,360	4,160 ± 2,840	5,990 ± 3,510
C_{max}/dose ([ng/ml]/[mg/kg])	988 ± 454	555 ± 379	399 ± 234
C_{trough} (ng/ml)	470 ± 580	1,120 ± 1,650	1,600 ± 1,350
C_{trough}/dose ([ng/ml]/[mg/kg])	157 ± 193	149 ± 220	107 ± 90.3
Day 5			
AUC_τ (ng · h/ml)	38,200 ± 13,100	65,700 ± 23,800	69,600 ± 20,800
AUC_τ/dose ([ng · h/ml]/[mg/kg])	12,800 ± 4,420	8,800 ± 3,180	4,660 ± 1,380
AUC_{last} (ng · h/ml)	46,400 ± 21,900	82,100 ± 39,200	89,300 ± 29,000
AUC_{last}/dose ([ng · h/ml]/[mg/kg])	15,500 ± 7,340	11,000 ± 5,230	5,970 ± 1,940
T_{max} (h)	1.92 (1.02–3.00)	2.02 (1.78–3.08)	2.49 (0.917–3.02)
C_{max} (ng/ml)	3,500 ± 579	5,980 ± 1,080	6,000 ± 1,770
C_{max}/dose ([ng/ml]/[mg/kg])	1,170 ± 193	798 ± 144	400 ± 118
C_{trough} (ng/ml)	463 ± 506	843 ± 750	1,040 ± 388
C_{trough}/dose ([ng/ml]/[mg/kg])	154 ± 169	112 ± 99	69.3 ± 25.9
$t_{1/2}$ (h)	9.21 ± 2.34	10.5 ± 3.4	11.8 ± 2.7
CL_{ss}/F (liters/h/kg)	0.0785 ± 0.0194	0.114 ± 0.037	0.215 ± 0.065
V_z/F (liters/kg)	1.04 ± 0.44	1.72 ± 0.36	3.64 ± 1.00
Accumulation ratio	1.27 ± 0.33	1.25 ± 0.66	0.970 ± 0.568

[a]T_{max} values are presented as median (range); other parameters are presented as geometric mean ± SD.

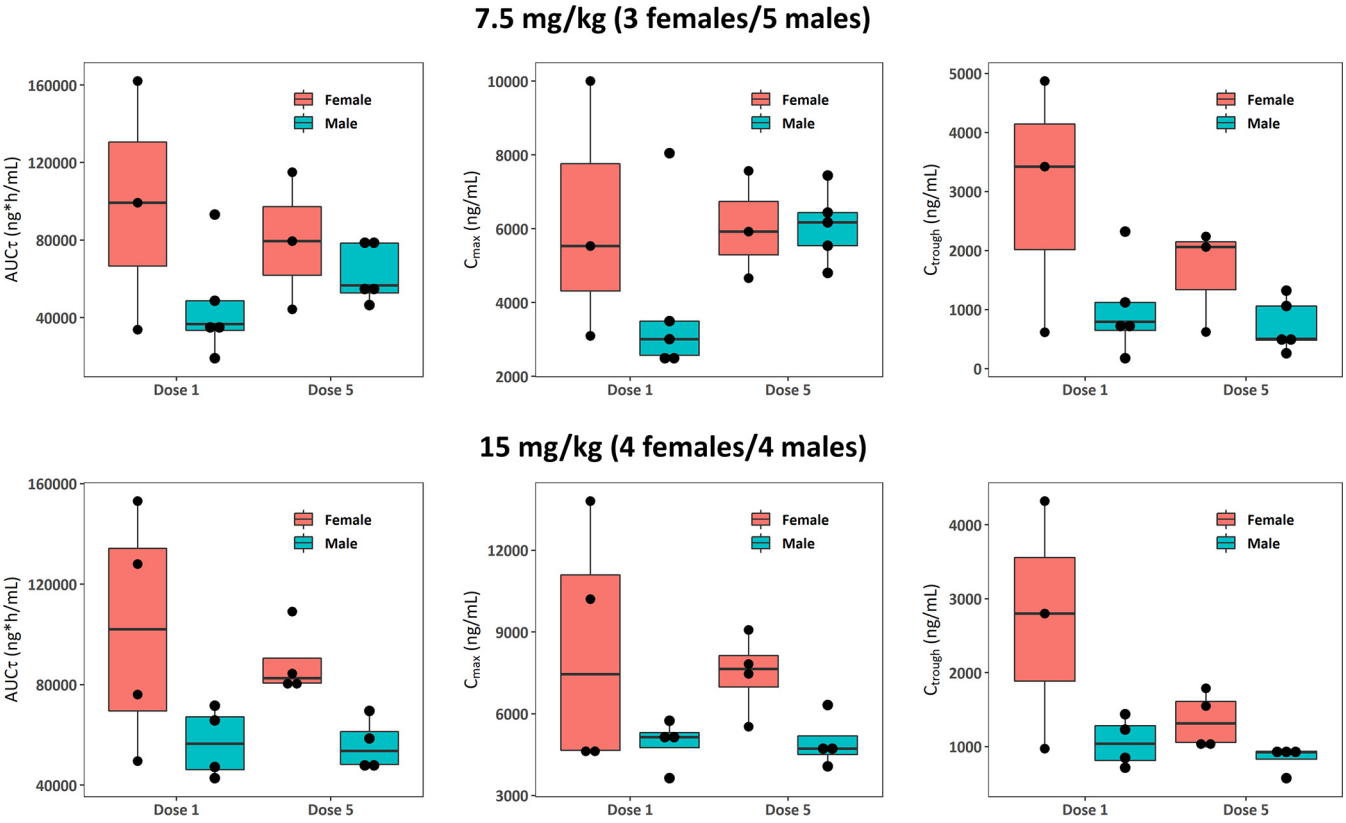

FIG 2 Effect of sex on oxfendazole exposure (AUC_{τ}), peak concentration (C_{max}), and trough concentration (C_{trough}) following the first and fifth doses in 7.5-mg/kg and 15-mg/kg dose groups. The dots represent individual observed data. The middle lines represent the medians. The lower and upper hinges correspond to 25th and 75th percentiles. The upper and lower notches extend to the largest and smallest values, respectively, that are no more than 1.58 times the interquartile range (i.e., the distance between 25th and 75th percentiles).

absorption, reaching the peak plasma concentration around 2 h postdose. Oxfendazole plasma levels attained steady state after 3 doses at the dosing interval of 24 h, as evidenced by the geometric mean of the ratio of C_{max} on day 4 versus day 3 and of day 5 versus day 3 being close to 1 (P value > 0.05). On day 5, the average C_{max} increased from 3,500 to 6,000 ng/ml, the average trough concentration (C_{trough}) increased from 463 to 1,040 ng/ml, and the average area under the concentration-time curve during one dosing interval (AUC_{τ}) increased from 38,200 to 69,600 ng · h/ml with ascending doses from 3 mg/kg to 15 mg/kg. As shown in Table 2, there was a dose-dependent increase in C_{max}, C_{trough}, and AUC, although these increases were less than dose proportional. According to statistical analysis of dose proportionality, β was 0.371 (90% confidence interval [CI], 0.117 to 0.625) and 0.440 (90% CI, 0.143 to 0.738) for C_{max} and AUC_{τ}, respectively, following the first dose. After the last dose, β for C_{max} was 0.310 (90% CI, 0.177 to 0.442) and β for AUC_{τ} was 0.331 (90% CI, 0.163 to 0.500). Because the calculation of apparent clearance at steady state (CL_{ss}/F) depends on AUC_{τ}, there was an increase in apparent clearance from 0.0785 to 0.215 liters/h/kg with increasing dose, even though there was no prominent change in elimination half-life across dose groups. Similarly, the apparent volume of distribution (V_z/F) increased from 1.04 to 3.64 liters/kg with increasing doses. CL_{ss}/F and V_z/F increased at relatively the same rate with ascending doses. The mean elimination half-life ranged from 9.21 h (at 3 mg/kg dose) to 11.8 h (at 15 mg/kg dose), and the average accumulation ratio was minimal, ranging from 0.970 to 1.27.

Figure 2 compares AUC_{τ}, C_{max}, and C_{trough} values on days 1 and 5 in male and female subjects receiving 7.5 mg/kg and 15 mg/kg of oxfendazole (since there was only one female receiving 3 mg/kg of oxfendazole, the influence of sex on oxfendazole pharmacokinetics was not evaluated at this dose level). In general, oxfendazole expo-

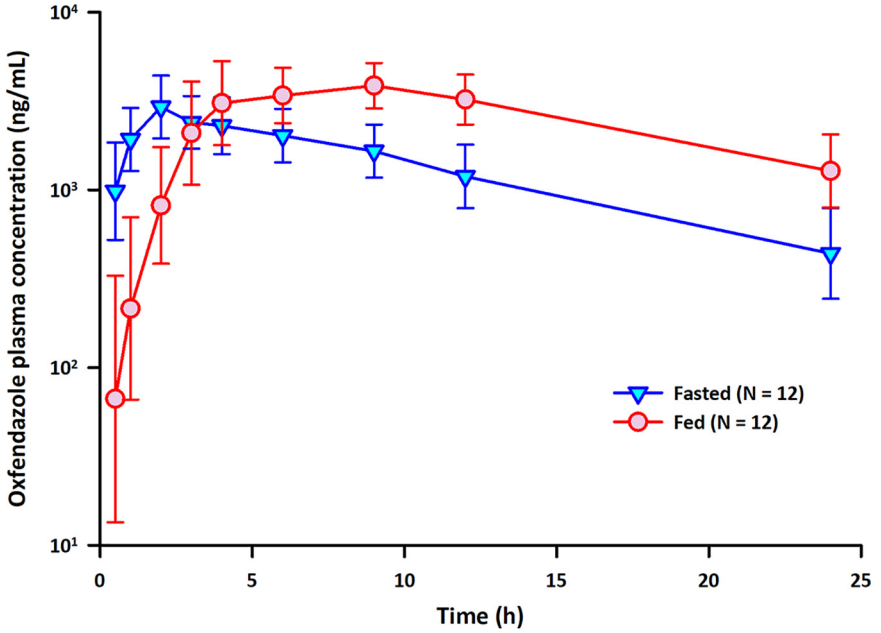

FIG 3 Concentration-time profiles of a single dose of oxfendazole at 3 mg/kg under the fasted state and the fed state. Food effect on the pharmacokinetics of oxfendazole was evaluated using a randomized two-period crossover study design with 12 subjects in which each subject received a single dose of oxfendazole under the fasted state and fed state, but with different sequences. Data are presented as means ± SD.

sure (AUC_{τ}, C_{max}, and C_{trough}) was higher in females than in males, except for the C_{max} on day 5, at 7.5 mg/kg. However, these sex differences in pharmacokinetics were not statistically significant, probably because of the great variability in exposure parameters and small number of subjects included in the present study. There was no noticeable difference between sexes in the elimination half-life.

(ii) Food effect evaluation. The time courses of the oxfendazole concentration in plasma after the administration of a single 3-mg/kg dose under fasted and fed conditions are presented in Fig. 3, and pharmacokinetic parameters under each condition are summarized in Table 3. The time course of oxfendazole disposition under the fed condition differed from that under the fasted condition. Under the fed condition, the increase in the oxfendazole plasma concentration was slower than that observed following an overnight fast, and oxfendazole reached its peak plasma concentration much later than under the fasted condition. The median time to C_{max} (T_{max}) values were 1.99 h and 8.90 h under the fasted and fed conditions, respectively. Due to the increase in T_{max}, for some subjects, there were insufficient data to estimate the oxfendazole elimination half-life under the fed condition. However, for subjects for which the half-life was estimable, oxfendazole elimination half-lives were very similar under the two feeding conditions. In addition, under the fed condition, oxfendazole reached a

TABLE 3 Pharmacokinetics of a single dose of oxfendazole given in fed state or fasted state[a]

Parameter	Fasted state (n = 12)	Fed state (n = 12)
AUC_{last} (ng · h/ml)	31,600 ± 12,800	58,900 ± 15,500
AUC_{∞} (ng · h/ml)	34,800 ± 16,000	65,400 ± 12,300
T_{max} (h)	1.99 (1.00–2.98)	8.90 (3.90–11.5)
C_{max} (ng/ml)	3,010 ± 1,330	4,500 ± 892
$t_{1/2}$ (h)	7.65 ± 1.26	8.05 ± 0.78
CL/F	0.0863 ± 0.0352	0.0459 ± 0.0096
V_z/F	0.940 ± 0.339	0.531 ± 0.155

[a]T_{max} values are presented as median (range); other parameters are presented as geometric mean ± SD.

TABLE 4 Changes in oxfendazole pharmacokinetic parameters under fed state versus fasted state[a]

Parameter	GM in fasted state	GM in fed state	Ratio of fed/fasted GM	90% CI of ratio
AUC_{last} (ng · h/ml)	31,600	58,900	1.86	1.64–2.12
AUC_{∞} (ng · h/ml)	36,600	64,500	1.76	1.34–2.31
C_{max} (ng/ml)	3,010	4,500	1.49	1.27–1.75
T_{max} (h)[b]	1.99	8.90	6.88	3.15–7.12

[a]GM, geometric mean.

[b]The values for Tmax are, from left to right, median in fasted state, median in fed state, median difference (h), and 90% CI of median difference (h). The Wilcoxon signed rank test P value was 0.0005.

higher C_{max} (4,500 ng/ml versus 3,010 ng/ml) and a higher AUC from time of dosing to the time of the last observed concentration (AUC_{last}) (58,900 ng · h/ml versus 31,600 ng · h/ml) than under the fasted condition. Statistical analysis showed that when oxfendazole was administered immediately after a high-fat meal, AUC_{last} increased 1.86 times (90% CI, 1.64 to 2.12), the C_{max} increased 1.49 times (90% CI, 1.27 to 1.75), and the T_{max} increased 6.88 h (P value = 0.0005) compared to when oxfendazole was administered on an empty stomach (Table 4), indicating that consumption of a high-fat meal increases oxfendazole exposure.

Safety. A summary of adverse events (AEs) is presented in Table 5. Of the 36 subjects enrolled in the study, 11 subjects (31%) experienced at least one unsolicited AE. Nine out of 36 (25%) subjects reported AEs that were considered treatment related. In group 1 (3 mg/kg), two subjects experienced headache and one subject reported mild decrease in appetite, all of which were considered treatment related. In group 2 (7.5 mg/kg), dizziness, headache, diarrhea, and nausea, each reported in 1 out of 8 subjects, were considered to be related to the study product. In group 3 (15 mg/kg), one subject experienced mild treatment-related dyspepsia and nausea, and one subject reported a treatment-unrelated headache. In group 4 (fed versus fasted), diarrhea, mild QTc prolongation, and oropharyngeal pain were each reported in 1 out of 12 subjects; only diarrhea and QTc prolongation were considered treatment related. Overall, headache was the most common treatment-related AE and most AEs were mild in severity. Only one subject in group 2 experienced diarrhea of moderate severity level. There were no deaths, serious AEs (SAEs), or discontinuations due to AEs.

Twelve subjects in the study (33%) demonstrated abnormalities in biochemistry, and 5 subjects (14%) showed changes in hematology. Of the reported laboratory abnormalities, only a single event was of grade 3 severity, a subject from group 1 that had an elevated blood urea nitrogen (BUN) on the final day of the study (day 10) following significant exercise. This abnormal BUN was considered unrelated to the study drug but

TABLE 5 Summary of AEs under different dosing regimens and dosing conditions[a]

	Value for:				
	Multiple ascending dose study				
Parameter	3 mg/kg	7.5 mg/kg	15 mg/kg	Food effect study	All subjects
Total no. of subjects	8	8	8	12	36
≥1 AE	3 (38)	3 (38)	2 (25)	3 (25)	11 (31)
≥1 AE related to study drug	3 (38)	3 (38)	1 (13)	2 (17)	9 (25)
Mild (grade 1)	3 (38)	3 (38)	1 (13)	2 (17)	9 (25)
Moderate (grade 2)	0 (0)	1 (13)	0 (0)	0 (0)	1 (3)
Severe (grade 3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study drug-related AEs by MedDRA system organ class	3 (38)	3 (38)	2 (25)	3 (25)	11 (31)
Nervous system disorders	2 (25)	2 (25)	1 (13)	0 (0)	5 (14)
Gastrointestinal disorders	0 (0)	2 (25)	1 (13)	1 (8)	4 (11)
Investigations	0 (0)	0 (0)	0 (0)	1 (8)	1 (3)
Metabolism and nutrition disorders	1 (13)	0 (0)	0 (0)	0 (0)	1 (3)

[a]Different dosing regiments consisted of 3 mg/kg, 7.5 mg/kg, and 15 mg/kg once daily for 5 days (multiple ascending dose study); different dosing conditions consisted of a single dose of 3 mg/kg under the fasted state and the fed state (food effect study). Data are presented as the number (%) of subjects with adverse events (AEs).

rather related to volume depletion from exercise. Two women experienced a moderate change in hemoglobin concentration, and both were in group 3. Both started the study with low normal hemoglobin values. Assessment of the trends in hemoglobin level after multiple doses showed that there were other women who showed a decline in hemoglobin over the course of drug administration (Fig. 4), though most of the values continued to remain within the normal range. A similar trend was seen in a few men, but the trend was less pronounced. No trend was observed in white blood cell, neutrophil, or platelet count. No abnormal results were reported for urinalysis or coagulation.

DISCUSSION

The current study evaluated the pharmacokinetics and safety of oxfendazole following multiple oral doses (3, 7.5, and 15 mg/kg once daily for 5 days) as well as food effect on oxfendazole exposure following a single oral dose (3 mg/kg). Prior to this study, the pharmacokinetics and safety of oxfendazole following the administration of seven different single doses (0.5, 1, 3, 7.5, 15, 30, and 60 mg/kg) had been evaluated (24). A comparison of the oxfendazole pharmacokinetic parameters obtained in that study with those observed in the present study showed the following. (i) Similar T_{max} values were obtained: under the fasted condition, oxfendazole had fast absorption, with similar T_{max} values (~1 to 2 h) in all dose groups evaluated in both studies. (ii) Similar $t_{1/2}$ values were observed: the mean terminal-phase elimination $t_{1/2}$ of oxfendazole ranged from 8.50 to 11.0 h in the doses evaluated in the FIH single ascending dose study and from 9.21 to 11.8 h in the doses evaluated in the current multiple ascending dose study. (iii) The same trend of non-dose-proportional pharmacokinetics was observed: both studies showed that oxfendazole exhibited less than a dose-proportional increase in exposure.

Regarding the nonlinear pharmacokinetics of oxfendazole, the source of the nonlinearity is likely to be related to the oxfendazole absorption process, rather than its elimination phase, because the terminal $t_{1/2}$ of oxfendazole remained similar across all doses evaluated in both studies. Accordingly, the substantial difference in CL/*F* observed in different dose groups was most likely to be the result of decreased bioavailability with increase in dose rather than changes in clearance of the drug. Since oxfendazole is a Biopharmaceutics Classification System (BCS) class II drug (i.e., drug with low solubility and high permeability), as the oxfendazole dose increases, the fraction of the dose that is solubilized in the gastrointestinal fluid and available for absorption decreases, leading to a decrease in bioavailability with escalating dose.

In the current multiple ascending dose study, in addition to the evaluation of dose proportionality and pharmacokinetic linearity, the attainment of steady state and the accumulation of oxfendazole following repeated doses were also evaluated. Following the once daily administration of oxfendazole, a steady-state drug plasma level was achieved by study day 3 (approximately 72 h). This is expected, since it usually takes five half-lives for a compound to reach its steady state, and the $t_{1/2}$ of oxfendazole ranged from 9.21 to 11.8 h. The accumulation of oxfendazole was minimal when it was given in a once daily regimen under a fasting condition, with the accumulation ratios at steady state ranging from 0.970 to 1.27 over the 3- to 15-mg/kg once daily dose range.

In addition to the multiple-dose pharmacokinetics of oxfendazole, the effect of food on oxfendazole pharmacokinetics was also evaluated in the current study. Following consumption of a high-fat meal, the oxfendazole plasma concentrations reached a peak level at 8.90 h, a time significantly longer than the 1.99 h observed when oxfendazole was given following an overnight fast (*P* value = 0.0005). This result indicated that food significantly delayed the rate of oxfendazole absorption. Food is known to delay gastric emptying (27), a potential reason underlying the delayed oxfendazole absorption. In addition to the delay in absorption rate (as reflected by the delay in T_{max}), the extent of oxfendazole absorption (i.e., bioavailability, reflected by C_{max} and AUC) was also altered by the food consumption of subjects, as consumption of a fatty breakfast prior to drug administration increased the oxfendazole C_{max} and AUC by 49.2% and 86.4%,

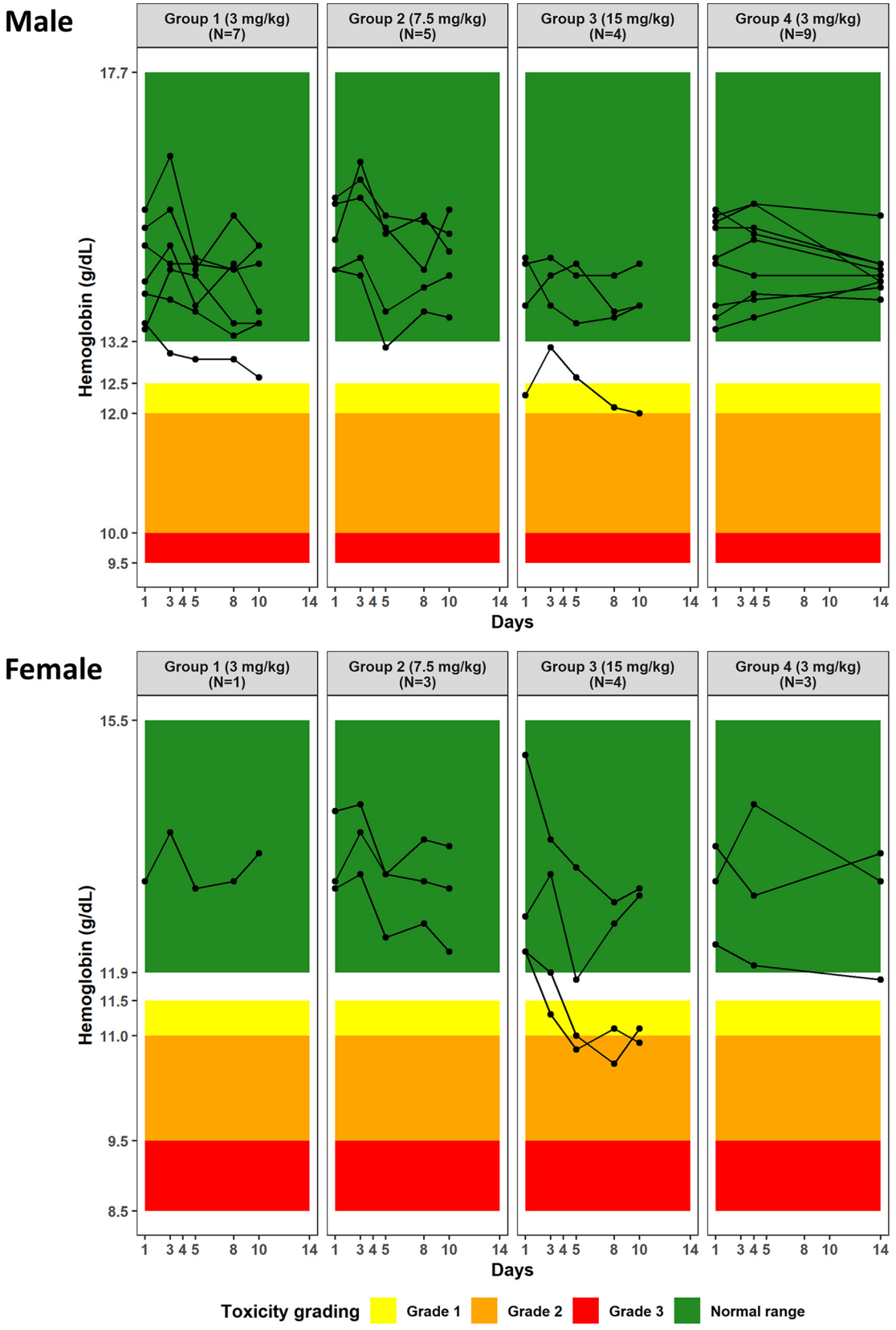

FIG 4 Time courses of hemoglobin concentrations in male subjects (top panels) and female subjects (bottom panels) in the multiple ascending dose study (group 1, 7 males/1 female; group 2, 5 males/3 females; group 3, 4 males/4 females) and the food effect study (group 4, 9 males/3 females). The green rectangles represent the normal range of hemoglobin concentrations for each gender. The yellow, orange, and red rectangles represent grade 1 (mild), grade 2 (moderate), and grade 3 (severe) toxicity levels, respectively.

TABLE 6 Comparison of oxfendazole, albendazole, and mebendazole pharmacokinetic parameters when drug is administered after an overnight fast or consumption of a fatty meal

	Value for indicated drug and condition					
	Oxfendazole (present study)		Albendazole sulfoxide[a] (25)		Mebendazole (26)	
PK parameter	Fasted	Fed	Fasted	Fed	Fasted	Fed
Dose	3 mg/kg (~200 mg)	3 mg/kg (~200 mg)	400 mg	400 mg	500 mg	500 mg
C_{max} (ng/ml)	3,010	4,500	220	1,310	14.0	56.2
T_{max} (h)	1.99	8.90	2.25	3.75	1.5	4.0
AUC (ng · h/ml)	31,600	58,900	1,090	5,460	175	456

[a]Albendazole is rapidly metabolized to its active metabolite albendazole sulfoxide; plasma levels of parent drug are virtually undetectable.

respectively, compared to those parameters measured following drug administration after an overnight fast. The statistical significance of these findings is shown by the 90% CI for both AUC and C_{max} fed/fasted ratios exceeding the 0.8 to 1.25 bioequivalence range. Oxfendazole is a lipophilic compound with poor aqueous solubility. The significant increase in the exposure of oxfendazole following food consumption is not surprising, since it is well known that the bioavailability of lipophilic drugs is often increased by consumption of food with a high fat content, either because of increased drug solubility and/or stimulation of bile secretion (27, 28). The oxfendazole absolute bioavailability in humans remains unknown, as oxfendazole pharmacokinetics following intravenous administration has never been investigated in humans. However, given that the administration of oxfendazole after a high-fat meal almost doubled oxfendazole exposure, it is speculated that oxfendazole absolute bioavailability at 3 mg/kg is at most 50% and that bioavailability decreases with increasing doses.

The food effects on drug exposure when a fatty meal was consumed prior to the administration of other benzimidazole anthelmintics used in deworming campaigns have also been studied. Table 6 compares plasma levels (expressed via some standard pharmacokinetic parameters) following the oral administration of the anthelmintics albendazole, mebendazole, and oxfendazole to humans. For the FDA-approved drugs albendazole and mebendazole, the data were taken from their FDA-approved labels as well as from a publication; for oxfendazole, the data are from the present clinical study. For each of the three drugs, eating a fatty meal prior to drug administration increases the plasma levels of the drug: for oxfendazole, this increase is approximately a doubling, for albendazole, the increase is about 5-fold, and for mebendazole, the increase is 3- to 4-fold. Whether administered following an overnight fast or after consumption of a fatty meal, however, exposure to oxfendazole is higher than exposure to either albendazole (albendazole sulfoxide) or mebendazole. In the fasted state, the dose-normalized exposure (i.e., dose-normalized C_{max}) of oxfendazole was 27 times and 538 times higher than that of albendazole sulfoxide and mebendazole, respectively. In the fed state, oxfendazole showed a dose-normalized exposure 7 times and 200 times higher than albendazole and mebendazole, respectively.

The three major soil-transmitted helminths reside in various portions of the gastrointestinal tract, enabling an orally administered drug to reach them directly via the digestive system. However, the recent work of Hansen et al. (29–31) showed the importance of drug plasma levels for the levels of the drug found in *Trichuris* worms, which are partially embedded in the walls of the intestine. Indeed, oxfendazole has a higher plasma exposure than albendazole sulfoxide in pigs (22, 23), and greater efficacy of oxfendazole in eliminating *Trichuris* infections was observed in this animal species. Thus, as shown in Table 6, the higher plasma levels of oxfendazole (compared to those of mebendazole and albendazole sulfoxide) give it an obvious advantage in reaching the parasite, a key need in effecting elimination of the *Trichuris* infection.

To evaluate potential sex differences in oxfendazole pharmacokinetics, oxfendazole exposures (AUC, C_{max}, and C_{trough}) in male and female subjects in each dose group on both study day 1 and study day 5 were evaluated. Group 1 (3 mg/kg; 1 female/7 male) contained only one female subject; no gender difference in oxfendazole exposure was

apparent. In both group 2 (7.5 mg/kg; 3 female/5 male) and group 3 (15 mg/kg; 4 female/4 male), the oxfendazole AUC was higher in female subjects than in male subjects (on average 79.6 to 113% higher on day 1 and 27.3 to 58.3% higher on day 5). Similarly, in groups 2 and 3, median oxfendazole C_{max} and C_{trough} values were also higher in female subjects than in male subjects, except for the C_{max} on day 5 in group 2. In addition to the sex difference in the median exposure of oxfendazole, as shown in Fig. 2, there were also differences in variability of exposure with respect to sex and time. Specifically, there was greater variability in exposure in female subjects on day 1 than in female subjects on day 5 and in male subjects on both day 1 and day 5. The greater variability in exposure in female subjects on day 1 may be attributed to the variability in absorption as reflected by T_{max}. Oxfendazole T_{max} for female subjects on day 1 ranged from 1.00 to 8.92 h, which is more variable than the range of 0.983 to 3.95 h observed in female subjects on day 5 or in male subjects on both day 1 and day 5. Among the 7 female subjects enrolled in group 2 and group 3, 3 of them had an oxfendazole T_{max} value of approximately 8.5 h on day 1; this prolonged absorption resulted in an increase in the extent of absorption and subsequent increase in oxfendazole exposure. The large intersubject variability in oxfendazole absorption (i.e., wide T_{max} range) as well as the prolonged absorption (i.e., large T_{max} values) observed in several female subjects on day 1 resulted in greater variability and higher exposure on day 1 than on day 5, as observed with the female subjects in groups 2 and 3 (Fig. 2).

Regarding the sex effect on oxfendazole pharmacokinetics, since the elimination of oxfendazole (as reflected by terminal $t_{1/2}$) was similar in male and female subjects in both the 7.5- and 15-mg/kg dose groups, the difference in oxfendazole pharmacokinetics between sexes is more likely a consequence of a difference in oxfendazole bioavailability. Gastric emptying, small-bowel transit, and colonic transit are reported to be significantly slower in healthy females than males (gastric emptying time, 2.9 h versus 2.4 h; small-bowel transit time, 4.4 h versus 3.2 h; colonic transit time, 1.5 days versus 1.3 days) (32). Sex-related differences in gastric residence time is suggested as the major cause for the prolonged T_{max} of sodium salicylate solution in females than in males in the fasted state (33). Given that oxfendazole absorption is solubility limited, the extended residence in the upper gastrointestinal tract of females might enhance oxfendazole bioavailability by allowing more time for its absorption. Indeed, as mentioned earlier, a prolonged absorption phase of oxfendazole was observed with three female subjects in groups 2 and 3 on study day 1, and the exposure of oxfendazole (AUC_{τ}, C_{max}, and C_{trough}) in these females was higher than the exposure of oxfendazole in other subjects on study day 1. In addition to gut transit time, gastrointestinal luminal pH is also a determining factor for the absorption of drugs that are a weak base or weak acid (34). A study conducted on 113 females and 252 males reported that gastric pH is lower in males than in females (2.16 ± 0.09 versus 2.79 ± 0.18, respectively) (35). Oxfendazole is predicted to have a basic group with a pKa of 3.03 (ADMET Predictor, SimulationPlus); thus, the lower the pH, the larger the fraction of ionized molecule and the lower the permeability. This may contribute to the lower bioavailability of oxfendazole observed in male subjects.

Overall, oxfendazole was well tolerated in all study groups, and there were no major safety signals identified in this study. Importantly, comparison of various safety parameters in male and female subjects following oxfendazole administration revealed no sex-associated differences in safety parameters, except for hemoglobin. This finding contrasts with those of a 2-week toxicology study in rats in which greater toxicity was observed in female than in male rats (36). Key to the safety findings in rat may be differing biotransformation profiles of oxfendazole in rat than in human: whereas oxfendazole is the primary analyte in human plasma (89% of the oxfendazole-related analytes), oxfendazole sulfone is the primary analyte in the rat (71% of the oxfendazole-related analytes) (37, 38). Thus, oxfendazole sulfone may underlie the toxicity observed at high doses in rat.

As shown in Fig. 4, there was a mild trend of hemoglobin decline with repeated oxfendazole administration in women, most pronounced in the highest dose level

group. This finding was not paralleled by similar declines in other hematology parameters. The incidence of decreased hemoglobin values in females may be due to the higher exposure of oxfendazole in female subjects, but it is important to note that the number of anemia events that showed graded severity was low and that the two women with moderate anemia at the end of the study had low (but within) normal hemoglobin values at study initiation. Further, in the present study, the number of women was small, as only 11 of the 36 subjects (31%) were women.

Going forward, especially with a drug like oxfendazole whose exposure is less than dose proportional, it is valuable to utilize a pharmacometric modeling approach to elucidate the quantitative relationship between drug exposure and response. The development of population pharmacokinetic and pharmacokinetic/pharmacodynamic models of oxfendazole using a nonlinear mixed-effects modeling approach to characterize the observed pharmacokinetics and safety data is under way.

The findings of significant oxfendazole exposure in healthy subjects with oral administration of the drug and the good tolerability of those subjects to oxfendazole open the door to investigation of oxfendazole efficacy in proof-of-concept (PoC) studies in patients. In light of the preclinical data showing excellent oxfendazole efficacy against *Trichuris* species that infect animals, a clinical study of oxfendazole efficacy against *Trichuris trichiura* in human patients is being planned, and given the good tolerability of oxfendazole in the present study, the design of the PoC study includes the administration of oxfendazole both for one and for multiple days (ClinicalTrials.gov registration no. NCT03435718).

MATERIALS AND METHODS

The study, conducted at the University of Iowa, followed the Declaration of Helsinki and good clinical practices, was approved by the University of Iowa Institutional Review Board, and was registered at ClinicalTrials.gov (ClinicalTrials.gov registration no. NCT03035760). All subjects provided informed consent prior to the initiation of any study-related activity.

Subjects. Thirty-six subjects participated in this study (24 in the multiple ascending dose evaluation and 12 in the food effects portion of the study). Men and women between 18 and 45 years of age who were in good health based on medical history, physical examination, screening hematology, blood chemistry, and urinalysis were included. The following serology tests were required to be negative: HIV-1/2 antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody. Women of childbearing potential and all men agreed to practice adequate contraception starting 28 days before and until 4 months after study drug administration. All subjects were required to abstain from drug and alcohol use from 48 h prior to enrollment until the end of the study. Subjects were excluded if they had any of the following: were pregnant or breastfeeding women, were women who were planning to become pregnant in the next 4 months; body temperature of ≥38°C or acute illness within 3 days prior to the administration of study drug; chronic or acute medical disorder; use of systemic chronic medications; history of sensitivity to benzimidazole compounds; having received an experimental agent within 1 month before study drug administration; history of heavy alcohol or illicit drug use; and any other condition that would have interfered with the study result evaluation.

Study design. The trial consisted of two parts: (i) a randomized study to evaluate the pharmacokinetics and safety of oxfendazole in healthy adults following multiple ascending doses at 3, 7.5, and 15 mg/kg once daily for 5 days (groups 1, 2 and 3, respectively) and (ii) a randomized two-period crossover study assessing the effect of food on oxfendazole pharmacokinetics and safety after a single 3-mg/kg dose (group 4). A schematic diagram of the study design is presented in Fig. 5.

In the multiple ascending dose study, 24 subjects were randomized into three groups with 8 subjects in each group. The study sequentially evaluated the group of 8 subjects in the lowest-dose group before proceeding to the next higher dose group. For safety purposes, 2 sentinel subjects were dosed with oxfendazole for 5 days and monitored for 7 days for any adverse events (AEs). If there were no AEs in either of these 2 subjects, the remaining subjects in the dose group were enrolled. Subjects in the next higher dose groups were enrolled after safety assessment of the preceding group was completed.

In the food effect study, 12 subjects were randomized in a 1:1 ratio to group 4A and group 4B. The study consisted of two periods. In the first period, subjects in group 4A received a single 3-mg/kg dose of oxfendazole after an 8-h fast while subjects in group 4B received oxfendazole subsequent to the consumption of a high-fat meal. In the second period, subjects were crossed over to receive a single oxfendazole dose following a high-fat meal or 8-h fast. The two periods were separated by a 7-day washout.

(i) Pharmacokinetics assessment. To evaluate the pharmacokinetics of oxfendazole following the administration of multiple ascending oxfendazole doses, blood sampling was performed on days 1 and 5 at predose and at 30 min and 1, 2, 3, 4, 6, 9, and 12 h after dosing. On days 2, 3, and 4, samples were collected prior to dosing and 2 h postdose. Samples were collected on day 6 approximately 24 h after the dose on day 5. Samples were collected once on days 8 and 10. In the food effect study, blood sampling was performed predose and at 30 min and 1, 2, 3, 4, 6, 9, 12, and 24 h postdose on days 1 and

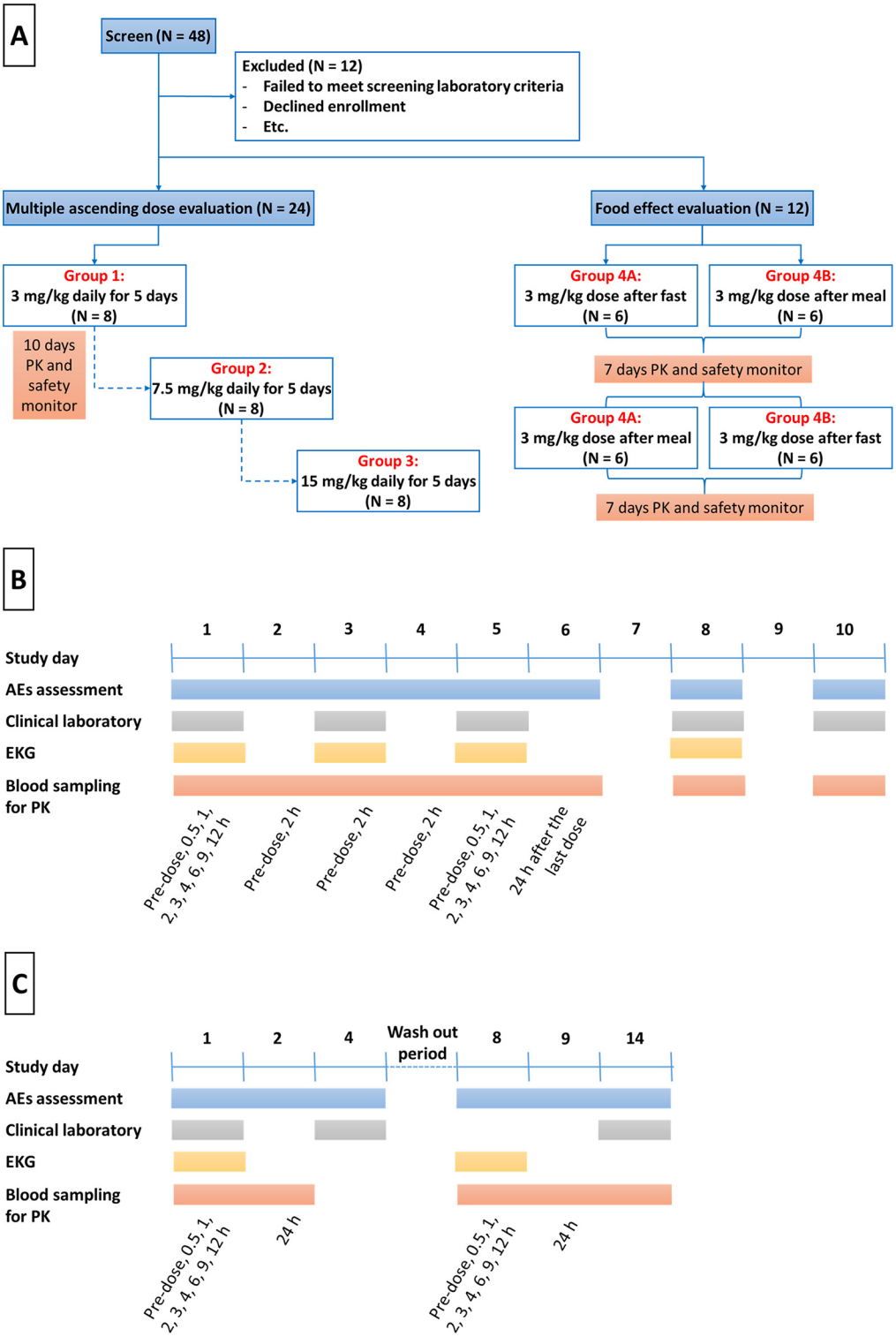

FIG 5 (A) Schematic diagram of the multiple ascending dose study and the food effect study. (B and C) Schedules of blood sample collection for pharmacokinetics assessment and adverse event assessment for subjects participating in the multiple ascending dose evaluation (B) and the food effect evaluation (C).

8 and once on day 14. Blood samples were stored on ice and centrifuged within 1 h at 4 to 8°C at 3,000 rpm for 15 min. The plasma was collected and stored at −80°C until analysis.

(ii) Safety assessment. Safety was evaluated through performance of an electrocardiogram (EKG) and laboratory tests, including hematology (hemoglobin, white blood cell count, neutrophil count,

platelet count), biochemistry (alanine transaminase [ALT], aspartate transaminase [AST], total bilirubin, creatinine, Na, K, Cl, CO_2, BUN), coagulation studies (international normalized ratio [INR], prothrombin time test [PTT]), and urinalysis (urine dipstick for protein and glucose). On study day 1, before study drug administration, blood sampling for laboratory tests and the urine dipstick test were performed for baseline characteristics. To assess safety in the multiple ascending dose study, laboratory tests were performed after dosing on days 1, 3, 5, 8, and 10. The EKG was evaluated at screening and 2 h postdose on days 1, 3, 5, and 8. In the food effect study, subjects were followed with clinical laboratory tests postdose on days 1, 4, and 14. The EKG was recorded at screening and 2 h postdose on days 1 and 8. All subjects were interviewed throughout the study for any AEs and serious adverse events (SAEs). AEs were graded as mild (grade 1) for events requiring minimal or no treatment and that did not interfere with the subject's daily activities, moderate (grade 2) for events that resulted in a low level of inconvenience or concern with the therapeutic measures and that could cause some interference with functioning, or severe (grade 3) for events that interrupted a subject's usual daily activity and may have required systemic drug therapy or other treatment. Severe events are usually incapacitating.

Study drug. Oxfendazole was supplied as the commercial veterinary product Synanthic suspension 22.5%. After administration of the study product by oral syringe, subjects drank 100 ml of water to ensure complete drug ingestion. All subjects were required to fast overnight (water was allowed), except for the subjects in the food effect portion of the study who required prior consumption of a fatty breakfast, and for 2 h after dosing.

Bioanalytical methods. Oxfendazole levels in plasma were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method reported recently by our group (39). Briefly, 100 μl of each sample was spiked with 10 μl of an internal standard (i.e., albendazole) working solution at 2,500 ng/ml and then extracted using protein precipitation with 400 μl of acetonitrile. Quantification was performed using an API4000 triple-quadrupole mass spectrometer (AB Sciex LLC, Redwood City, CA, USA) with a TurbolonSpray probe in positive mode. The *m/z* transitions used to monitor oxfendazole and albendazole were 316.1 $\rightarrow$ 191.3 and 266.3 $\rightarrow$ 234.1, respectively. Chromatographic separation was performed on a Shimadzu UFLC LC-AD20 system (Shimadzu, Japan) equipped with a Phenomenex Synergi C_{18} column (150 by 2 mm, 4 μm) coupled with a Phenomenex 4- by 2-mm SecurityGuard cartridge (Phenomenex, Torrance, CA, USA). Samples were eluted under isocratic conditions with 50:50 (vol/vol) water and acetonitrile, with a total flow rate of 0.2 ml/min. The assay was linear from 0.5 to 1,000 ng/ml, with intraday and interday accuracies in the range of 102.6 to 109.5% and a coefficient of variation of $\leq$13.6% at three quality control levels (1.5, 75, and 750 ng/ml). The lower limit of quantification (LLOQ) was 0.5 ng/ml. Samples with concentrations higher than the upper limit of quantification were diluted with blank plasma for reanalysis. All clinical samples were analyzed within the validated stability time period.

(i) Pharmacokinetics analysis. Noncompartmental analysis of oxfendazole pharmacokinetics in plasma was performed using Phoenix WinNonlin 8.0 (Certara, Princeton, NJ, USA). The maximum observed plasma oxfendazole concentration (C_{max}) and time to C_{max} (T_{max}) were determined directly based on the time course of the plasma oxfendazole concentration. The terminal elimination rate constant (λ_z) was computed as the slope of the terminal region of the log-transformed concentration versus time curve. The elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. The estimated elimination rate constant was accepted if the terminal slope contained at least 3 points after T_{max}, the adjusted R^2 was $\geq$0.85, and the concentration time profile spanned at least 1.5 half-lives. The area under the concentration time curve during one dosing interval (AUC_τ) and the AUC from the time of dosing to the time of the last observed concentration (AUC_{last}) was estimated using a linear-up log-down trapezoidal method. The AUC from time of dosing to infinity (AUC_∞) was calculated using the equation $\mathrm{AUC}_\infty = (\mathrm{AUC}_{last} + C_{last})/\lambda_z$, where C_{last} is the last observed concentration. For the multiple-dose study, apparent clearance at steady state (CL_{ss}/F) and apparent volume of distribution (V_z/F) were calculated as $\mathrm{CL}_{ss}/F = \mathrm{dose}/\mathrm{AUC}_\tau$ and $V_z/F = \mathrm{dose}/(\lambda_z \times \mathrm{AUC}_\tau)$. The accumulation ratio (R_{ss}) was calculated as the ratio of exposure (AUC_τ and C_{max}) following the last dose to that after the first dose. For the food effect study, apparent clearance (CL/*F*) and apparent volume of distribution (V_z/F) were calculated using the equations $\mathrm{CL}/F = \mathrm{dose}/\mathrm{AUC}_\infty$ and $V_z/F = \mathrm{dose}/(\mathrm{AUC}_\infty \cdot \lambda_z)$.

Statistical analysis. Descriptive statistics were performed on demographics and baseline characteristics for all enrolled subjects as a whole and per group. Oxfendazole plasma concentration and pharmacokinetic parameters were summarized and compared among dose groups, dosing conditions, and sex, when applicable. In the multiple ascending dose study, the attainment of steady state was evaluated using statistical comparisons of oxfendazole plasma concentrations at 2 h after dose (C_{max}) on days 3, 4, and 5. The geometric mean and 95% confidence interval (CI) of exposure ratios (i.e., $C_{max,5}/C_{max,4}$ and $C_{max,5}/C_{max,3}$) were calculated using a mixed-effects model of the log-transformed exposure parameters, with sex, day, dose group, and the interaction between day and dose group as fixed effects. To assess dose proportionality, power models were applied to the exposure parameters AUC_τ, C_{max}, and C_{trough} (oxfendazole plasma concentration 24 h postdose) recorded on days 1 and 5. The general form of the power model was $\ln(Y) = \alpha + \beta \cdot \ln(\mathrm{dose}) + \gamma \cdot \mathrm{sex} + \epsilon$, where *Y* is an exposure parameter and ϵ is residual error. A β value of approximately 1 indicates dose proportionality. For the food effect study, the exposure parameters AUC_∞, AUC_{last}, and C_{max} were compared between the fed and fasted state. Specifically, the geometric mean and 90% CI of the exposure ratio (fed/fasted) were derived using a mixed-effects model of the log-transformed exposure parameters (AUC_{last}, AUC_∞, C_{max}); fixed effects included sex, period, condition (fasted or fed), and the interaction between period and condition; subject was included as a random effect. Bioequivalence was concluded if the 90% CI of the geometric mean of the ratio of AUC_{last}, AUC_∞, and C_{max} was contained inclusively within 0.8 to 1.25.

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