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A study in healthy male volunteers was completed to evaluate the safety, tolerability, and pharmacokinetics of a single oral dose of the antiparasitic moxidectin (MOX). This drug is registered worldwide as a veterinary antiparasitic agent for use in companion and farm animals. This is the first study of MOX in humans. All subjects were between the ages of 18 and 45 years, with normal cardiac, hematologic, hepatic, and renal function. Doses of MOX studied were 3, 9, 18, and 36 mg in cohorts of 6 subjects each (5:1, MOX:placebo). At the 9-mg and 36-mg doses, two separate cohorts were completed, one in the fasted state and one after the consumption of a high-fat breakfast. For all other cohorts, administration was in the fasted state. Safety and tolerability were assessed by physical examinations, ongoing evaluation of adverse events (AEs), and measurement of laboratory values. Pharmacokinetic (PK) samples were collected just prior to dosing and at various time points until 80 days postdose. Safety assessments from all dose groups studied suggested that MOX was generally safe and well tolerated, with a slightly higher incidence of transient, mild, and moderate central nervous system AEs as the dose increased as compared to placebo. The PKs of MOX were dose proportional within the dose range studied, and the elimination half-life ($t_{1/2\ elim}$) was long (mean: 20.2-35.1 days). At the 9-mg and 36-mg doses, a high-fat breakfast was shown to delay and increase the overall absorption but did not increase maximal concentrations when compared to administration in the fasted state. In summary, the results from this study indicate that MOX is safe and well tolerated in humans between the doses of 3 mg and 36 mg.

Keywords: *Moxidectin; pharmacokinetics; onchocerciasis; parasites*

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Moxidectin (MOX) is a macrocyclic lactone structurally within the milbemycin family and derived from the actinomycete *Streptomyces cyanogriseus* spp. *noncyanogenus*. This compound is registered worldwide for several veterinary indications, including prevention of canine heartworm (ProHeart®) and for the treatment of internal and external parasites in cattle, sheep, deer, and horses (Cydectin®, Quest®, Equest®).

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In humans, MOX is currently under development for the treatment of onchocerciasis (river blindness). Onchocerciasis is a parasitic disease caused by the helminth *Onchocerca volvulus* and is transmitted to humans through the bite of a black fly of the genus *Simulium*. The flies breed in fast-flowing rivers. Onchocerciasis is endemic in sub-Saharan Africa, the Arabic peninsula, and Central and South America, leading to significant health and socioeconomic problems for affected areas.[1] Each adult (macrofilaria) female worm, which may live up to 14 years in the human body, produces millions of microfilariae that migrate throughout the host's body.[2] Microfilariae primarily affect the skin, eyes, and lymph nodes. Severe itching, generalized rash, and disfigurement are the most common skin manifestations, whereas irreversible visual impairment, including blindness, is the most debilitating result of the disease.[3-5] In addition, macrofilariae cause raised nodules under the skin, leading to further disfigurement. The current estimate

is that approximately some 80 million people remain at risk of the disease, and 18 million people are infected, of whom 6.5 million suffer from severe itching or dermatitis, 300,000 are blind, and an additional 500,000 have serious visual impairment.[6,7]

The exact mechanism of antiparasitic action of MOX is still under investigation; studies indicate that the primary mode of action results from MOX binding to glutamate-gated chloride channels in the parasites.[8] Binding to the ion channel results in hyperpolarization of nerves and muscle fibers, leading to paralysis and death of the organism.[9] These glutamate channels are specific for invertebrates and are not expressed in mammalian hosts,[9-13] allowing for the specificity of the action of MOX to be directed at the parasite. An additional action of MOX is its activity at the gamma-aminobutyric acid$_A$ (GABA$_A$) receptor complex.[14]

Studies in rats have shown that oral MOX is absorbed at a moderate rate, with a mean time to peak concentration of 4.8 hours. The bioavailability of MOX in rats was moderate at 19%, and the $t_{1/2\ elim}$ was long (22.9-44.6 h) (unpublished data). Studies in horses,[15] sheep,[16] and dogs[17] indicate that the $t_{1/2\ elim}$ of oral MOX is in the range of 20 days, with the time to maximal concentration (t_{max}) achieved in the various species approximately 2 to 9 hours after administration. With intravenous (IV) administration in swine, the clearance of MOX has been shown to be low and the steady-state volume of distribution high, indicating the compound is widely distributed to tissues.[18]

In vitro and in vivo metabolism studies of MOX in cattle, deer, rabbit, and sheep have shown that there are two principal biotransformation products in these species, most likely the C_{14} and C_{29} monohydroxymethyl metabolites.[14,19] Additional studies have shown that in many of these species, cytochrome P450 3A (CYP3A) plays a major role in these biotransformations.[19,20] The route of human MOX metabolism has not been established. In mass balance studies of cattle,[14] horses,[21] rats (unpublished results), and sheep[22] dosed with ^{14}C-moxidectin, the principal route of excretion was found to be the feces, accounting for a high percentage of the administered dose.

This paper describes the first human experience with MOX. The goals of this present study were to determine the safety, tolerability, and pharmacokinetics of a single dose of MOX in humans. In addition, two doses (9 mg and 36 mg) were evaluated for the influence of food on the pharmacokinetics of MOX.

METHODS

Subjects

A total of 42 healthy male volunteers between the ages of 18 and 45 years were targeted for enrollment in this study. The study was conducted at a contract research organization (Chiltern House, Slough, UK). Prior to enrollment, all subjects gave written informed consent. The study protocol and informed consent were reviewed and approved by the East Berkshire Research Ethics Committee, John Lister Postgraduate Medical Centre, Wexham Park Hospital (Slough, UK). The assessment of health was based on preenrollment physical examination, medical history, vital sign measurements, electrocardiograms (ECGs), screening for common drugs of abuse (alcohol, barbiturates, amphetamines, benzodiazepines, cocaine, opiates, tetrahydro-cannabinol), and routine laboratory evaluations. Subjects were prohibited from taking prescription or over-the-counter medications within 72 hours prior to study start. Discontinuation of herbal or dietary supplements was required within 7 days prior to dosing.

Study Design

This study was a single ascending-dose, randomized, double-blind, placebo-controlled, safety, tolerability, and pharmacokinetic (PK) study. Subjects were to be enrolled into one of seven ascending dose cohorts at five different doses, each consisting of 6 subjects randomized 5:1/MOX:placebo. The five doses to be studied were 3, 9, 18, 36, and 54 mg. At the 9-mg and 36-mg doses, two cohorts were planned at each dose, with one dosing in the fasted state (at least 8 h) and the other dosing within 20 minutes of consuming a Food and Drug Administration (FDA)–recommended high-fat breakfast (approximately 30 g of fat). Safety and tolerability were assessed by physical examinations, vital sign measurements, ECGs, serum chemistry, hematology, prothrombin time, and reported adverse events (AEs) prior to and at various time points through 80 days postdosing. PK samples were collected just prior to dosing and at 1, 2, 4, 8, 12, 24, 36, and 48 hours and 4, 6, 8, 12, 24, 36, 48, 60, and 80 days after administration. In addition to refraining from smoking, subjects were prohibited from taking prescription or over-the-counter medications, herbal or dietary supplements, grape-

fruit-containing products, or consuming alcohol for up to 2 weeks after dosing.

Determination of MOX Plasma Concentrations

MOX plasma concentrations were determined using high-performance liquid chromatography (HPLC) with fluorescence detection, as previously described by Chen et al.[23] Briefly, the method used solid-phase extraction and fluorescent derivatization with trifluoroacetic anhydride and N-methylimidazole. Separation was achieved on a μBondaPak C_{18} column, 10 μm particle size, 300 mm × 3.9 mm (Waters, Milford, MA), with a mobile phase of tetrahydrafuran-acetonitrile-water (40:40:20, v/v/v). The method employed 200 μL of plasma, and the lowest level of quantitation was 0.2 ng/mL. Sample stability in the autoinjector was demonstrated over a 24-hour period. All samples were run within a 24-hour period or frozen at –20°C until analysis on the HPLC.

Data Analysis

Pharmacokinetics

PK analysis for MOX was completed using noncompartmental methods (WinNonlin, version 3.0, Pharsight, Mountain View, CA). The PK parameters determined were the maximum observed plasma concentration (C_{max}), the time of maximum concentration (t_{max}), the elimination half-life ($t_{1/2\ elim}$), the area under the plasma concentration versus time curve extrapolated to infinity ($AUC_{0-\infty}$), oral clearance (CL/F), and the oral apparent volume of distribution (Vd/F).

Statistical Analysis

The sample size for this study was aimed at detection of changes in safety and tolerability. The probability of detecting at least one adverse event of grade 2 (moderate) or higher (severe) with 5 healthy subjects was 0.049, 0.410, 0.672, and 0.832 when the true rates are 1%, 10%, 20%, and 30%, respectively. All statistical analysis was completed using SAS (SAS Institute, Inc., Cary, NC). Significance level was set at $p < 0.05$ for all analyses.

The baseline demographic parameters of race, weight, age, and body mass index (BMI) were compared among treatment groups using Fisher's exact tests (PROC FREQ) for discrete variables and Kruskal-Wallis (PROC NPAR1WAY) tests for continuous variables.

For assessment of adverse event and laboratory toxicity incidence rates among treatment groups, Fisher's exact tests were used to compare the overall differences and, if appropriate, followed by pairwise comparison between placebo and dose groups. Longitudinal differences in laboratory parameters were evaluated by computing a normalized area under the time-concentration curve (AUC) adjusted for baseline. To test overall differences of laboratory AUCs, analysis of variance (ANOVA) (PROC GLM) was conducted on ranks of the normalized AUCs. Pairwise comparisons were performed between the placebo and dose groups using *t*-tests (PROC GLM) on rank-transformed data.

Overall differences of log-transformed PK parameters between dose groups were compared by ANOVA on ranks. Pairwise comparisons were conducted using *t*-tests on the rank-transformed data. In addition, dose-response relationships were evaluated for C_{max} and $AUC_{0-\infty}$ by simple linear and quadratic regression analyses to examine monotone relationships between the parameters and dose level. Monotone relationships were determined by independently pooling the C_{max} and $AUC_{0-\infty}$ data from both the fed and fasted groups and also were completed by analysis of fasted groups alone.

RESULTS

Enrollment

Of 42 planned subjects, only 37 received test article (MOX or placebo) due to the closing of enrollment prior to the 54-mg cohort (described below). A total of 34 subjects completed treatment, and 3 discontinued after administration (unrelated to adverse event). One discontinued subject in the 9-mg fed cohort was replaced to have adequate information for the fed component of the study. Baseline mean demographics for the randomized subjects are listed for each cohort in Table I.

Tolerability and Safety

The planned doses to be studied were 3 mg fasted, 9 mg fasted, 9 mg fed, 18 mg fasted, 36 mg fasted, 36 mg fed, and 54 mg fasted. This was an ascending-dose study, and cohorts were enrolled sequentially starting with the lowest dose. Safety was assessed prior to enrollment of each cohort based on evaluation of a 4-week period of blinded data from the previous cohort. Assessment of the blinded data from the two 36-mg cohorts followed for 4 weeks suggested a greater fre-

Table I Baseline Demographics of 37 Subjects Who Received Test Article

	Placebo (*n* = 6)	3 mg Fast (*n* = 5)	9 mg Fast (*n* = 5)	9 mg Fed (*n* = 6)	18 mg Fast (*n* = 5)	36 mg Fast (*n* = 5)	36 mg Fed (*n* = 5)
Mean (*SD*) age, years	27.7 (5.2)	28.6 (5.6)	30.2 (9.6)	27.7 (4.4)	30.6 (10.4)	28.2 (6.1)	28.4 (6.4)
Mean body mass index	25.2 (3.1)	25 (2.8)	26.7 (1.8)	23.3 (1.9)	23.5 (3.1)	22.9 (1.6)	25.5 (1.8)
Ethnic origin (number of subjects)							
Caucasian	4	2	5	4	4	4	2
Black	1	2	0	2	1	1	2
Asian	1	0	0	0	0	0	0
Other	0	0	0	0	0	0	1
White Mediterranean	0	1	0	0	0	0	0

quency of CNS events (nausea, vomiting, and somnolence) in the high-dose cohorts (18 mg and 36 mg) compared to the low-dose cohorts (3 mg and 9 mg). Eight subjects (placebo = 1, 9 mg fasted = 1, 9 mg fed = 1, 18 mg fasted = 1, 36 mg fasted = 2, 36 mg fed = 2) experienced dizziness or somnolence/lethargy after taking the test article. In consideration of the slightly increasing frequencies of possibly drug-related AEs, seen during review of blinded data, a decision was made not to proceed to the 54-mg dose. When unblinded, the data confirmed a low frequency of CNS events in the MOX dose groups.

All adverse events were grade 1 (mild) or 2 (moderate), with the exception of one grade 3 (severe) enteritis at 57 days postadministration. This event was determined to be due to food poisoning and was considered unrelated to test article. There were no serious adverse events (SAEs), and no subjects discontinued due to AEs. In addition, there was no statistical difference among dose groups in the total incidence of AEs. The most frequently reported AEs in subjects dosed with MOX were headache (35%), infection (29%), pharyngitis (16%), leukopenia (13%), and dizziness (13%). Information on the reported infections, including dose group, infection type, and days on study drug, is as follows:

3 mg fasted—upper respiratory tract infection (URTI) on day 19 and day 63 (same subject), viral URTI on day 14;
9 mg fasted—toe infection on day 52;
9 mg fed—URTI on day 30 and day 78 (different subjects);
36 mg fasted—tooth abscess on day 47, head cold on day 50 and day 66 (different subjects);
36 mg fed—cold on day 42 and cold-like symptoms on day 59 (same subject).

Placebo-treated subjects most frequently experienced headache (33%), rhinitis (33%), and infection, accidental injury, back pain, chills, edema, hematoma, SGOT increase, twitching, somnolence, pharyngitis, pruritus, and ear pain (17%).

Subjects in the 36-mg fed group had higher incidences of hematologic AEs (leukopenia, leukocytosis, eosinophilia, monocytosis) when compared to placebo subjects (p = 0.015). All were a toxicity of grade 1 (mild). These results, although statistically significant, were clinically inapparent.

Longitudinal analysis of the laboratory values revealed various statistically significant pairwise results when means from MOX-dosed subjects were compared to those of placebo subjects. Compared to placebo, the 3-mg fasted group had significantly lower sodium (p = 0.028) and creatinine (p = 0.049) and significantly higher chloride (p = 0.027), phosphorus (p = 0.008), and gamma-glutamyltranspeptidase (GGT) (p = 0.015); the 9-mg fed and fasted groups had significantly lower alkaline phosphatase (p = 0.038 and 0.047, respectively); the 18-mg fasted group had significantly higher phosphorus (p = 0.031) and alkaline phosphatase (p = 0.016); the 36-mg fasted group had significantly higher creatinine (p = 0.031); and the 36-mg fed group had significantly increased GGT levels (p = 0.002). None of these changes was determined to be clinically meaningful by either the investigator or the medical monitor.

Pharmacokinetics

The PK parameters for all doses are displayed in Table II. A mean concentration versus time profile for all dose groups is shown in Figure 1.

For all dose groups studied, the mean t_{max} ranged from 0.075 to 0.167 days (1.8-4 h). The mean t_{max} for the 36-mg fed group was significantly higher than the mean t_{max} for all other dose groups, with the exception

Table II Mean (*SEM*) Pharmacokinetic Parameters for Each Dose of Moxidectin

Dose Group	C_{max} (ng/mL)	t_{max} (Days)	$AUC_{0-\infty}$ (ng • Days/mL)	CL/F (L/Day)	Vd/F (L)	$t_{1/2}$ (Days)
3 mg fast (n = 5)	22.4 (2.4)	0.108 (0.025)	60.1 (17.7)	82.9 (33.1)	2080 (561)	33.8 (11.8)
9 mg fast (n = 5)	57.9 (3.7)	0.075 (0.008)[a]	126 (9.2)[b]	72.9 (5.1)	3549 (180)**	34.6 (3.6)
9 mg fed (n = 6)	53.6 (3.9)	0.139 (0.018)[a]	168 (16.6)[b]	56.8 (6.7)	2643 (207)	35.1 (5.2)
18 mg fast (n = 5)	141 (12.0)	0.083	244 (20.6)	75.9 (6.8)	2439 (379)	22 (2.1)
36 mg fast (n = 5)	289 (23.3)	0.084	451 (48.2)[c]	84.1 (10.5)	2438 (282)	20.2 (0.6)
36 mg fed (n = 5)	296 (21.0)	0.167*	624 (41.6)[c]	58.7 (3.7)	2152 (364)	25.7 (4.2)

Values with the same letter superscript are significantly different from one another ($p < 0.05$).
*Statistically significant ($p < 0.05$) versus other groups, except 9-mg fed group, based on rank-transformed data. **Statistically significant ($p < 0.05$) versus other groups based on rank-transformed data.

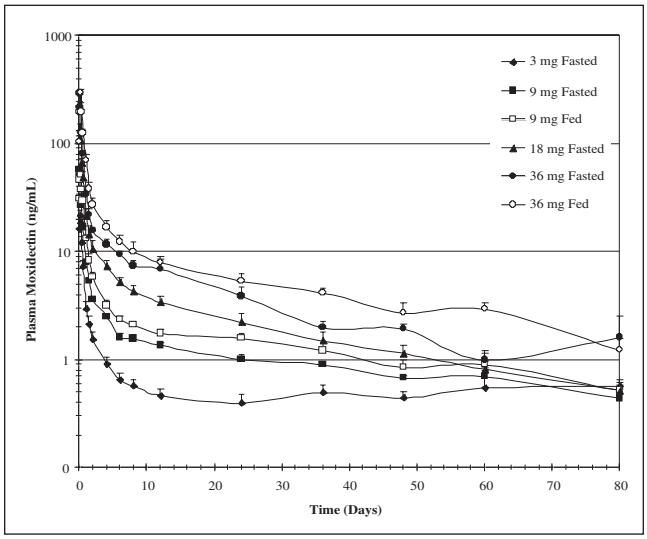

Figure 1. Mean plasma moxidectin verses time profile for each dose cohort. Error bars represent the SEM *for each time point.*

of the 9-mg fed group. Both the 9-mg and 36-mg fed groups had significantly longer t_{max} values compared to the fasted group of the same dose.

Linear pharmacokinetics were displayed within the dose range studied as C_{max} and $AUC_{0-\infty}$ increased in proportion to dose. Statistically significant positive slopes were estimated from the simple linear regression models. Quadratic regression models in which no statistical significance was shown confirmed these results. This was true regardless of whether the data from the fasted and fed groups were pooled or if only the fasted groups were used in the analysis. The $AUC_{0-\infty}$ was significantly higher in both fed groups when compared to the fasted group of the same dose, whereas no difference was seen for C_{max}.

The distribution of MOX in the body was extensive, as indicated by large mean V_d/F values for all groups (2080-3549 L). The mean V_d/F of the 9-mg fasted group was significantly higher than the mean V_d/F for any of the other groups. Since F is an unknown, the significance of this difference cannot be assessed. The $t_{1/2\ elim}$ of MOX was long, with means ranging from 20.2 to 35.1 days. There were no statistically significant differences in mean $t_{1/2\ elim}$ or CL/F among dose groups.

DISCUSSION

MOX is currently approved and marketed worldwide as a treatment for internal and external parasites in a wide variety of companion and farm animals. Currently, MOX is under investigation for the treatment of human onchocerciasis, a parasitic disease caused by *O. volvulus* and transmitted by the black fly of the genus *Simulium*. Onchocerciasis is also referred to as river blindness due to its high prevalence in river areas that provide fertile soil for agriculture and rich breeding grounds for the vector, as well as for the eye manifestations that lead to progressive degeneration of eyesight. This disease is endemic in sub-Saharan Africa, the Arabic peninsula (Yemen), and Central and South America, with approximately 18 million people infected worldwide.[1] These endemic areas face major health and socioeconomic hardship as a result of this disease.

This study was the first to evaluate the administration of MOX to humans. Safety assessments from a single dose between 3 and 36 mg suggested that MOX was safe in this dose range. As the dose was increased, a slightly higher incidence of CNS AEs was observed. These events were transient and of mild or moderate severity. CNS effects may be related to the potential of MOX to interact with the mammalian $GABA_A$ receptor

system.[14] However, macrocyclic lactones are generally excluded from the cerebrospinal fluid when the blood-brain barrier is intact due to the presence of the ABC transporter, P-glycoprotein (P-gp). Nevertheless, in the interest of maintaining a conservative approach with respect to safety, and because 36 mg is well above the predicted therapeutic dose, it was decided to end the study prior to enrollment of the 54-mg cohort. Veterinary data from a variety of companion and farm animals suggest that, at therapeutic doses, MOX is safe and well tolerated. Based on preclinical models, clinically active doses of MOX in humans are expected to be in the lower range of those tested in this study.

The pharmacokinetics of MOX were dose proportional within the dose range studied. As predicted from the extensive animal data, the $t_{1/2\ elim}$ was very long and the V_d/F was quite high, reflecting the lipophilic properties of MOX. These pharmacokinetic characteristics make MOX an attractive compound for the treatment of human onchocerciasis. Since the life span of the macrofilariae is approximately 14 years, the microfilaricidal effects do not protect patients from reinfection.[2] The thought is that longer exposure could facilitate a lethal effect on the macrofilariae as well as on the microfilariae, potentially resulting in a major advance in the treatment of onchocerciasis.[5,24] The ultimate goal of the World Health Organization's onchocerciasis control program is to eliminate the disease as a public health problem due to its impact on both the health and socioeconomics of endemic countries. A macrofilaricide has the greatest chance of having an impact on this goal. This need is not met by the current treatment of choice of the control program, ivermectin (IVM) (Mectizan®), another macrocyclic lactone.[25] IVM is quite efficacious as a microfilaricide and thus is an effective control agent that has been shown to have some activity against other stages of *O. volvulus*.[25-28] However, the pharmacokinetics of IVM in humans do not allow for macrofilaricidal activity with dosing once a year. Compared to MOX, the $t_{1/2\ elim}$ of IVM is much shorter and the V_d/F smaller,[15,29,30] leading to a shorter exposure time of the macrofilariae to IVM. The hope is that the pharmacokinetic profile of MOX could greatly increase its potential for macrofilaricide activity, leading to a permanent interruption of the parasite's life cycle and, ultimately, transmission and elimination of the disease.

The effect of high-fat food on the pharmacokinetics of MOX was shown to delay and increase the overall absorption for both of the dose groups in which it was studied (9 mg and 36 mg). The limitation of these results was that there was no crossover design to allow for control of intrasubject variation. However, the mean data are suggestive that high-fat food may have an impact on the overall exposure of MOX. This result would need to be followed up in a properly designed food-effect study to validate these findings. Guzzo et al[29] showed that the mean AUC of a 30-mg dose of oral IVM increased 2.6-fold when administered after the consumption of a high-fat meal compared with fasted administration.

In terms of MOX disposition, an additional consideration is its transport by P-gp, the gene product of the multidrug resistance gene 1 (MDR1) in humans. IVM is a well-known substrate of P-gp.[31,32] This transporter system is also expressed in nematodes and believed to contribute to resistance in certain strains of this organism.[33,34] In vitro data support that MOX is also a substrate for this transporter.[20,34] Coadministration with other P-gp substrates could cause interaction at the level of the transporter, whereas additional effects could be caused by polymorphisms in the MDR1 gene. Known susceptibilities to the macrocyclic lactones are seen in collie dogs due to a deletion in their MDR1 gene.[35,36] It appears that avermectin-sensitive collie dogs have less CNS toxicity with MOX compared to other macrocyclic lactones,[37] but there have been isolated reports of drug sensitivity.[38] In humans, mutations that confer functional changes in P-gp have been found in the MDR1 gene. The frequency of certain MDR1 polymorphisms has been found at different rates in African populations compared to Caucasians and Japanese populations.[39] These findings suggest that the MDR1 genotype may have an influence on MOX pharmacokinetics and that understanding of functional variations of MDR1 genotypes represented in the target population is of importance. Further study, especially in target populations, is suggested to gain a better understanding of these issues and how they may affect overall MOX disposition.

In summary, this study suggests that MOX is safe and well tolerated in humans between the doses of 3 mg and 36 mg. Further study in humans is ongoing and will determine whether this agent is active against *O. volvulus* macrofilariae and microfilariae in humans.

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