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Article *in* The Journal of Clinical Pharmacology · November 2002

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J Clin Pharmacol 2002 42: 1122

Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects

Cynthia A. Guzzo, MD, Christine I. Furtek, BS, Arturo G. Porras, PhD, Cong Chen, PhD, Robert Tipping, MS, Coleen M. Clineschmidt, BA, David G. Sciberras, PhD, John Y-K. Hsieh, PhD, and Kenneth C. Lasseter, MD

*Safety and pharmacokinetics (PK) of the antiparasitic drug ivermectin, administered in higher and/or more frequent doses than currently approved for human use, were evaluated in a double-blind, placebo-controlled, dose escalation study. Subjects (*n = *68) were assigned to one of four panels (3:1, ivermectin/placebo): 30 or 60 mg (three times a week) or 90 or 120 mg (single dose). The 30 mg panel (range: 347-594* μg/kg*) also received a single dose with food after a 1-week washout. Safety assessments addressed both known ivermectin CNS effects and general toxicity. The primary safety endpoint was mydriasis, accurately quantitated by pupillometry. Ivermectin was generally well tolerated, with no indication of associated CNS toxicity for doses up to 10 times the highest FDA-approved dose of 200* μg/kg*. All dose regimens had a mydriatic effect similar to placebo. Adverse experiences were similar between ivermectin and placebo and did not increase with dose. Following single doses of 30 to 120 mg, AUC and C_{max} were generally dose proportional, with t_{max} ~4 hours and $t_{1/2}$ ~18 hours. The geometric mean AUC of 30 mg ivermectin was 2.6 times higher when administered with food. Geometric mean AUC ratios (day 7/day 1) were 1.24 and 1.40 for the 30 and 60 mg doses, respectively, indicating that the accumulation of ivermectin given every fourth day is minimal. This study demonstrated that ivermectin is generally well tolerated at these higher doses and more frequent regimens.*

Journal of Clinical Pharmacology, 2002;42:1122-1133

Ivermectin is a derivative of the avermectins, a family of macrocyclic lactones produced by the filamentous bacterium *Streptomyces avermitilis*. It is a highly effective antihelmintic agent used in animals and humans. Ivermectin was first approved for human use in 1987 and is donated by Merck & Co., Inc., as Mectizan® for the treatment of onchocerciasis and, more recently, lymphatic filariasis in Africa and Latin America. More than 200 million treatments have been distributed through the program. It is also approved as Stromectol® for the treatment of strongyloidiasis of the intestinal tract and onchocerciasis. Recently, approved human indications have been extended in France to include the treatment of scabies. The approved treatment regimens are as follows: 150 μg/kg once yearly for onchocerciasis, 200 μg/kg single dose for strongyloidiasis, and 150 to 200 μg/kg twice yearly or 300 to 400 μg/kg once yearly in endemic areas for lymphatic filariasis. The greatest experience with human use of ivermectin is in the dose ranges of 150 to 200 μg/kg.

Early pharmacokinetic studies conducted to support registration of the drug as a therapeutic agent against onchocerciasis demonstrated that plasma concentrations are approximately proportional to the dose, following oral administration of 6, 12, or 15 mg of ivermectin.[1] In two studies, after single 12 mg doses of ivermectin (2 × 6 mg) in fasting healthy volunteers (representing a mean dose of 165 μg/kg), the mean peak

From Merck Research Laboratories, Blue Bell and West Point, Pennsylvania, and Terlings Park, United Kingdom (Dr. Guzzo, Ms. Furtek, Dr. Porras, Dr. Chen, Mr. Tipping, Ms. Clineschmidt, Dr. Sciberras, Dr. Hsieh) and Clinical Pharmacology Associates, Miami, Florida (Dr. Lasseter). This study was sponsored by a grant from Merck Research Laboratories, a division of Merck & Co., Inc. Dr. Lasseter has no financial interest in Merck & Co. Dr. Sciberras was employed by Merck & Co., Inc., at the time of the study. All other authors are currently employed by Merck & Co., Inc. Submitted for publication March 5, 2002; revised version accepted June 30, 2002. Address for reprints: Ms. Christine Furtek, Merck & Co., Inc., BLX-29, P.O. Box 4, West Point, PA 19486.

DOI: 10.1177/009127002237994

plasma concentrations of the major component (H_2B_{1a}) were 46.6 ± 21.9 (range: 16.4-101.1) ng/ml and 30.6 ±15.6 (range: 13.9-68.4) ng/ml, respectively, at approximately 4 hours after dosing.[2] Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with < 1% of the administered dose excreted in the urine. Estimates of plasma half-life have varied from about 12 to 56 hours.[3-7]

Oral ivermectin has been considered as a possible treatment for head lice. In recent years, this condition has become a significant problem in developed countries, resulting in school absenteeism, social distress, and stigmatization. The economic loss to parents can also be substantial; informal estimates from the Centers for Disease Control and Prevention show that the cost of lost work time due to head lice infestations exceeds $1 billion annually.[8] Initial exploratory studies evaluated ivermectin doses of 100 to 200 μg/kg.[9-11] However, none of these early studies demonstrated eradication of head lice, suggesting that higher or more frequent doses may be necessary for this use.

Since the majority of safety and pharmacokinetic data on oral ivermectin are with single doses of 150 to 200 μg/kg, the primary objective of this study was to obtain additional information at higher and multiple doses. Doses up to 10 times the 200 μg/kg dose were evaluated to provide a substantial safety margin over the anticipated dosage range for head lice treatment. Specifically, for assessment of safety, signs observed in animal toxicity studies, as well as in documented human overdose cases, were chosen as safety endpoints. In particular, mydriasis was evaluated as the primary safety endpoint because it could be accurately measured with a previously validated method, pupillometry. The pharmacokinetic objectives were to evaluate the pharmacokinetics of ivermectin with higher doses, the extent of any ivermectin accumulated with multiple doses, and the effect of food and gender.

METHODS

Subjects

Both male and female subjects were considered eligible to participate if they were between 18 and 45 years of age and in good health on the basis of history, physical examination, and routine laboratory data. Female subjects of childbearing potential agreed to use an effective double-barrier birth control method from at least 1 month prior to the start of the study until 1 month after the completion of the study. Weight requirement for subjects varied with treatment panel: 50 to 90 kg for panels 1 and 2 and 60 to 90 kg for panels 3 and 4. All subjects must have been nonsmokers for ≥ 6 months.

Subjects were ineligible for enrollment if they had any ocular abnormality that might interfere with pupillometry assessment, including corrected visual acuity worse than 20/30 in both eyes (contact lenses acceptable), a current eye disorder requiring the attention of an ophthalmologist, or a history of intraocular surgery. Pregnant or breast-feeding women were excluded. Subjects with a history of neurologic or CNS disease; treated or untreated hypertension, asthma, or other pulmonary disease; major gastrointestinal abnormalities/peptic ulceration; cardiovascular, hepatic, or renal disease; drug allergy; drug or alcohol abuse; or any illness that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk in administering ivermectin to the subject could not participate. Other exclusion criteria included donation of a unit of blood or participation in another clinical trial with an investigational agent within 4 weeks prior to commencement of the study, regular use of any illicit drugs, intake of excessive amounts of caffeinated coffee or beverages (> 8 cups/day), or use of prescription or nonprescription medicine that could not be discontinued 2 weeks before the start of the study. Subjects with a known hypersensitivity to any component of the ivermectin product or who had any condition that the investigator felt might interfere with participation were not eligible.

This study was conducted at Clinical Pharmacology Associates (Miami, FL) in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. The study protocol and subject consent form were approved by a private, nonaffiliated institutional review committee (Southern Institutional Review Board, Inc., Miami, FL), which was properly constituted according to the applicable regulations. Written informed consent was obtained from each subject.

Study Design

This was a double-blind, placebo-controlled, multiple rising dose study in healthy adult men and women. Subjects were sequentially assigned to one of four treatment panels and were randomized to receive ivermectin or placebo within each panel (12 active, 4 placebo per panel) using a computer-generated allocation schedule. Subjects were also stratified by gender within each panel to ensure that equal numbers of sub-

jects of each gender were assigned to each treatment regimen.

Ivermectin was administered as a fixed dose extending from 30 mg in panel 1 to 120 mg in panel 4. Doses consisted of ten to forty 3 mg tablets of ivermectin as necessary to achieve the stipulated dose. When considering the weight limitations of the protocol, this corresponded to the potential delivery of 333 μg/kg to 2000 μg/kg. Actual dose range delivered (μg/kg) in enrolled subjects in each dose group is indicated in the following descriptions of the dosing regimens. Panel 1 subjects received treatment A: ivermectin 30 mg (347-594 μg/kg) or placebo, three times a week (days 1, 4, 7), in the fasted state during study week 1. After a washout period of at least 1 week, they then received treatment E: ivermectin 30 mg (347-541 μg/kg) or placebo, single dose, in the fed state during study week 3. Panel 2 received treatment B: ivermectin 60 mg (713-1091 μg/kg) or placebo, three times a week (days 1, 4, 7), in the fasted state during study week 5. Panel 3 received treatment C: ivermectin 90 mg (1031-1466 μg/kg) or placebo, single dose, in the fasted state during study week 9. Panel 4 received treatment D: ivermectin 120 mg (1404-2000 μg/kg) or placebo, single dose, in the fasted state during study week 11.

The treatment regimens were selected based on the possibility that doses higher than 200 μg/kg would be needed to eradicate head lice. The 30 and 60 mg doses were administered to evaluate safety in potential therapeutic dose ranges for head lice treatment, spanning 347 to 1091 μg/kg for the participants in this study. The regimen for these dose levels was the maximum frequency anticipated for head lice treatment (three doses in 7 days) and allowed for assessment of possible accumulation. The 90 and 120 mg doses were evaluated only to assess toxicity and provide an additional margin of safety; therefore, these treatments were administered as single doses.

Confirmation of quantifiable pupillometry was not initially an entrance criterion for the study. However, after completion of the original 16 subjects in panel 1, it was observed that pupillometry measurements for 5 subjects were difficult to quantify due to the unexpected extreme pigmentation of the iris in this particular study population. For one of these subjects, accurate pupil measurements could not be obtained. Therefore, the protocol was amended to add an entry criterion specifying that subjects must have a quantifiable pupil measurement at the prestudy visit (1-2 weeks prior to study start). Pupillometry was added to the prestudy visit procedures to accommodate this requirement. In addition, since testing of the primary hypothesis for this study was dependent on the pupillometry measurements from this subject panel, the protocol amendment also enrolled 4 additional subjects to panel 1 to compensate for the missing data. These 4 subjects received treatment A only (30 mg or placebo, days 1, 4, 7, fasted) and were dosed concurrently with panel 2. They were not administered treatment E (30 mg or placebo, single dose, fed) because the primary hypothesis related to treatment A only. A group of 4 subjects was considered appropriate because a blocking factor of 4 was used for the allocation schedule (3 active: 1 placebo). In addition, at the time of the amendment, it was unknown if more than 1 subject would have missing data.

All treatment doses were administered in the Clinical Research Unit (CRU) under medical supervision. Before each treatment period, subjects reported to the CRU at a predetermined time the evening prior to dosing on day 1. Subjects were required to fast from all food and liquid, except water, from midnight before all treatment days. Study drug was provided as ivermectin 3 mg tablets and matching placebo tablets and was administered with a total of 16 ounces of water to accommodate the large numbers of tablets administered at the higher doses. For consistency, the same amount of water was administered for all dose levels. For treatment E, subjects consumed a standard high-fat breakfast (31.3 g protein, 57.16 g carbohydrates, 48.6 g fat, 784 kcal) beginning 20 minutes before dosing. The dose was administered within 5 minutes after completion of the meal. For all other treatments, fasting (except for water) continued on all treatment days until the 4-hour plasma sample was collected, after which subjects consumed a meal of approximately 500 calories. Subjects resumed regular meals after the 8-hour plasma sample had been collected. Standardized meals were provided in the CRU at scheduled times.

Safety monitoring included careful clinical observation for adverse experiences as well as physical examinations (1-2 weeks prestudy [PS] and 5-7 days posttreatment [PT]), neurological examinations (PS; –1, 4, and 12 h; and PT), pupillometry (PS; –1, 4, 6, and 24 h; and PT), vital signs (PS; –1, 0, 1, 2, 4, 8, and 24 h; and PT), electrocardiograms (PS, –1 and 4 h, and PT), and clinical laboratory tests consisting of a CBC, blood chemistry, and urinalysis (PS, –1 h, and PT). In the neurological exam, tests to detect signs of ivermectin toxicity were emphasized and accurately quantitated when possible (e.g., heel-toe to evaluate ataxia). Details of pupillometry are described in the next section. All adverse events were recorded. The investigator paid par-

ticular attention to any evidence of CNS toxicity, such as vomiting, mydriasis, or gait disturbance.

Treatment panels were dosed sequentially so that safety was established at a lower dose level (given in the fasted state) before proceeding to the next higher dose level. Safety parameters were chosen based on experience with human overdose and animal toxicity. For an individual subject, the investigator was instructed to discontinue a subject's test drug if any of the following signs or symptoms were observed postdose: one or more episodes of drug-related vomiting (excluding episodes occurring within 1 h of dosing), mydriasis (defined as absence of change in pupil size upon transition from low-light to high-light conditions during pupillometry), or gait disturbance (defined as a confirmed abnormal result from heel-toe test as compared with baseline prestudy assessment). For a dosage panel, the investigator was instructed to discontinue advancement to the next dose level if any of the following situations occurred: mydriasis or gait disturbance (as defined above for an individual subject) was observed in 1 or more subjects, a ≥ 2 mm increase in pupil diameter over baseline (predose) was observed in 2 or more subjects, or drug-related vomiting (excluding episodes occurring within 1 h of dosing) was observed in 3 or more subjects in a panel. In addition, the incidence of one or more drug-related serious adverse experiences or two or more drug-related severe adverse experiences in a panel would have warranted consideration of discontinuing dose-level advancement.

For pharmacokinetic analysis, plasma samples were collected at predefined intervals on days 1, 4, and 7 for treatments A and B and on day 1 only for treatments C, D, and E and analyzed for ivermectin concentration. The predefined intervals were predose (0 h) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 60 hours postdose on days 1 and 7 and predose only on day 4.

For treatments A and B, subjects remained in the CRU until the final day 7 blood sample was obtained (60 h after the day 7 dose). For treatments C, D, and E, subjects remained in the CRU until the final day 1 blood sample was obtained (60 h after the day 1 dose). Subjects returned for a posttreatment assessment 5 to 7 days following the last dose of study drug in a treatment period.

Pupillometry

To monitor for any evidence of mydriasis, this study used a method of pupillometry that had been validated internally and successfully used in a previous study of a mydriatic agent. The method accurately and reproducibly measures pupil diameter by photograph under standard lighting conditions. Photographic equipment consisted of a single-lens reflex camera (Nikon F70 camera body and Nikon 105 micro lens) with flash unit (Nikon SB23 with remote link), mounted on a support device in front of and facing the subject with the camera lens projecting through a reflective lighting screen. The subject's head was positioned on a head rest (similar to those found in a slit lamp unit). To reduce the influence of accommodation movement on the pupil, subjects focused through a hole in the reflective screen on an object 3 m beyond the camera.

All pupil measurements were made in a room equipped with black-out shades. Standard lighting conditions were created using two banks of four low-voltage tungsten lamps, projected from behind the subject onto a white screen located approximately 0.5 m in front of the subject. Dimmer switches attached to each bank of lights enabled the lamp units to be adjusted to either low-light (10-foot candles) or high-light (200-foot candles) conditions. A calibrated light meter (Gossen) placed at the temple of the subject's head, adjacent to the eye, was used to confirm that the proper light levels reached the subject's corneal plane. The left eye was photographed under both standard lighting conditions, in duplicate, at each time point prescribed by the protocol. In cases where a subject's corrected visual acuity was worse than 20/30 in the left eye, the right eye was photographed. Measurements of the maximal horizontal diameter of the pupillary area were obtained via image analysis of the developed transparencies (MCID M1 image analysis system, Imaging Research Inc., Ontario) and recorded in millimeters for statistical analysis. Photographs taken of a measuring scale (graph paper), placed at the same eye-to-camera distance used for pupil measurement, were used for calibration.

Prior to enrolling subjects into this study, pupil measurement standards and reproducibility were established at the study site. The method was tested under the same lighting conditions and in the same examination room subsequently used in performing the pupil measurements for the clinical study. Prestudy testing of the photographic measurement methodology was conducted by the same study personnel who performed pupil measurements during the study.

In addition, visual accommodation was measured predose for all subjects to obtain a baseline value (before the first dose of study drug only). Subsequently, if mydriasis was observed in a subject at any time during the study, accommodation was to be measured (as soon as possible after observation of mydriasis) to determine if there was accompanying cycloplegia.

Ivermectin Assay

Plasma was separated by centrifugation from blood samples collected from the original 48 subjects on active treatment, at the time points specified above, and analyzed for ivermectin H_2B_{1a}. The additional 4 subjects added per protocol amendment were for safety assessment only, and samples from these subjects were to be assayed only in the event of a drug-related or serious adverse experience. Assay of plasma samples for ivermectin H_2B_{1a} concentration was performed by the Drug Metabolism Department, Merck Research Laboratories (West Point, PA), using a high-performance liquid chromatography (HPLC) method with fluorescence detection. The protein was removed from plasma samples by precipitation with acetonitrile. Ivermectin and the internal standard were then recovered from the matrix by liquid/solid-phase extraction on ChemElut cartridges. Reconstituted extracts were online derivatized and separated by reverse-phase HPLC and quantitated by fluorescence detection.

A standard curve of 0.5, 1, 2.5, 5, 10, 20, and 40 ng/ml ivermectin spiked into human control plasma was analyzed daily along with clinical samples. Accuracy ranged from 98.6% to 102% of nominal concentrations; precision ranged from 2.2% to 5.9% through the entire curve. Plasma quality control samples at low (1.25 ng/ml), medium (7.5 ng/ml), and high (25 ng/ml) concentrations were prepared prior to the start of the study and subjected to replicate within-day analyses (n = 5). Two high, two medium, and two low quality control samples were analyzed daily along with clinical samples to assess interday variability. Accuracy averaged 99.9%, 104.7%, and 102.6% for the low, medium, and high quality control samples, respectively. The corresponding values for precision were 7.9%, 6.1%, and 4.7%, respectively. The limit of reliable quantification for ivermectin H_2B_{1a} was 0.5 ng/ml.

Pharmacokinetic Calculations

The following pharmacokinetic parameters were evaluated: area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time of occurrence for maximum (peak) plasma concentration (t_{max}), and half-life ($t_{½}$). $AUC_{0-\infty}$ was estimated by the trapezoidal method to the 60-hour point and extrapolated to infinity by the half-life estimated for that curve. C_{max} and t_{max} values were estimated by inspection of the plasma concentration-time curve. Half-life was estimated by the method of Kwan et al.[12] Accumulation ratios were approximated from ratios of $AUC_{0\text{-}60\ h}$ since these were the closest values available to the ratio of AUC_{τ} (τ = 72 h) for this study. Computed values of AUC and half-life were calculated in EXCEL (Microsoft Corporation, Redmond, WA).

Statistical Analysis

Safety

The primary parameter for the safety assessment of ivermectin was change in pupil size under high-light conditions between baseline (day 1 predose) and the approximate time of maximum drug concentration (C_{max}) on day 7 (maximum of the 4- and 6-h time points). The primary hypothesis was that oral administration of ivermectin in the fasted state, at a regimen of 30 mg for three doses over 1 week (days 1, 4, 7), does not affect the maximum pupil diameter change from baseline at high-light conditions on day 7 as compared to placebo; a mean difference of 1 mm between the 30 mg ivermectin and placebo groups was considered significant. The difference in maximum (of the 4- and 6-h time points) pupil diameter change from baseline (day 1 predose) at high-light conditions on day 7 between the groups receiving 30 mg ivermectin (in the fasted state) and placebo (pooled from treatments A and B) was assessed using an analysis of variance (ANOVA) model with gender, treatment, and gender-by-treatment interaction as factors. A 90% confidence interval for the mean difference (30 mg ivermectin [in the fasted state] vs. placebo) in maximum (of the 4- and 6-h postdose time points) pupil diameter change from baseline (day 1 predose) at high-light conditions on day 7 was calculated using the MSE from the ANOVA referencing a t-distribution. Whether or not to combine the results from males and females within each treatment was determined by assessing the gender-by-treatment interaction. The assumption of normality was tested using the Shapiro-Wilk statistic.

Given a parallel study with 12 subjects in one group (30 mg fasted) and 8 in the other (placebo) and similar between-subject variation (mean square error = 0.0361) as estimated from historical data, there is a > 99% probability that the observed 90% confidence interval for the mean difference in maximum pupil diameter change from baseline (day 1 predose) between the 30 mg ivermectin (in the fasted state) group and the placebo group would fall within the equivalence interval of (–1.0, 1.0), if the true difference was 0. Probabilities were calculated using SAS 6.12 (SAS Institute, Cary, NC).

Although not specified in the primary hypothesis, an analysis of the pupil diameter changes for the other 30 mg time points (days 1 and 4, high light; days 1, 4, and 7, low light) and for the other dose groups was done using the same criteria as for the primary analysis.

General safety and tolerability were assessed by examining adverse experiences and laboratory data. Adverse experiences were tabulated and summarized.

Pharmacokinetics

Estimation of the pharmacokinetic parameters of ivermectin in this four-panel, escalating dose study was accomplished by using an ANOVA model with gender, dose, and gender-by-dose interaction as factors. The analysis of the day 1 data included data from treatments A, B, C, and D. The day 7 analysis included data from only treatments A and B. Whether or not to combine the results from males and females within each treatment was determined by assessing the gender-by-dose interaction. The assumption of normality was tested using the Shapiro-Wilk statistic.

The effect of food on the pharmacokinetics of ivermectin on day 1 was estimated by comparing the natural log-transformed $AUC_{0-\infty}$ values for the 30 mg dose of ivermectin in the fed and fasted states (treatment E vs. treatment A). An ANOVA model, including treatments A and E with subject and treatment as factors, was used. A 95% confidence interval for the AUC geometric mean ratio (30 mg ivermectin fed [treatment E]/30 mg ivermectin fasted [treatment A]) was calculated using the MSE from the ANOVA referencing a *t*-distribution.

Ivermectin accumulation was assessed in the following manner: an ANOVA model including treatments A and B with dose, day, and dose-by-day interaction as factors was used to analyze the natural log-transformed $AUC_{0\text{-}60\ h}$ values. Ninety-five percent confidence intervals for the AUC geometric mean ratio (day 7, last dose/day 1, first dose) were calculated using the MSE from the ANOVA referencing a *t*-distribution for the 30 mg ivermectin fasted (treatment A) and 60 mg ivermectin (treatment B) treatment groups.

RESULTS

Subjects

Sixty-eight subjects (51 ivermectin, 17 placebo) entered the study and were sequentially assigned to one of four treatment panels. The subjects' ages ranged from 21 to 45 years, with a median of 34.5 years. Thirty-five subjects (51.5%) were male and 33 subjects (48.5%) were female. Subjects were 89.7% Hispanic, 4.4% Caucasian, 4.4% Black, and 1.5% Asian. The distribution of age, gender, and racial origin appeared to be similar across the treatment groups. Overall, the study population was generally healthy with few medical problems. Secondary diagnoses were similar across the treatment groups, consisting primarily of a history of cesarean section or tubal ligation.

Safety

Pupillometry

Table I summarizes pupil diameter changes from baseline (day 1 predose) in all study groups postdose (days 1, 4, and 7, when measured) at both low-light and high-light conditions. The mean pupil diameter in the ivermectin 30 mg (fasted) treatment regimen decreased slightly from baseline for both males (–0.119 mm) and females (–0.107 mm). The mean pupil diameter in the placebo regimen remained virtually unchanged from baseline for both males (–0.002 mm) and females (0.035 mm). Gender effect was not significant at the 95% confidence level from an analysis of variance (ANOVA) model with gender, treatment, and gender-by-treatment interaction as factors.

The difference in pupil diameter change from baseline (day 1 predose) at high-light conditions on day 7 between the groups receiving 30 mg ivermectin in the fasted state and placebo (pooled from treatments A and B) was –0.013. The 90% confidence interval (–0.239, –0.021) for the difference falls within the equivalence interval (–1.0, 1.0), indicating that the ivermectin 30 mg regimen in the fasted state had an equivalent mydriatic effect as compared with placebo, according to prespecified criteria. Exploratory examination of pupil size of all other groups on days 1, 4, and 7 at both high-light and low-light conditions confirmed that there was no evidence of a mydriatic effect.

Adverse Events

Clinical adverse experiences reported during the study are presented in Table II. Of the 51 subjects who received ivermectin, 12 subjects (24%) reported at least one clinical adverse experience. This rate was similar to that observed in the placebo group (6 subjects, 35%). In addition, there was no consistent trend in the incidence of adverse experiences indicative of a dose response. All clinical adverse experiences were transient and mild, and no adverse experience recurred with repeated dosing. The most commonly reported adverse experiences were headache, nausea, dizziness, and rash, occurring in both ivermectin- and placebo-treated

Table I Mean (*SD*) of Pupil Diameter Changes (mm) from Baseline by Treatment Regimen and Light Conditions

	Placebo[a]	Ivermectin 30 mg (fasted) (*n* = 15)	Ivermectin 60 mg (fasted) (*n* = 12)	Ivermectin 90 mg (fasted) (*n* = 12)	Ivermectin 120 mg (fasted) (*n* = 12)	Ivermectin 30 mg (fed) (*n* = 11[b])
At high-light conditions						
Day 1	0.064	–0.103	0.050	0.088	0.020	0.013
	(0.167)	(0.165)	(0.132)	(0.104)	(0.129)	(0.089)
Day 4	0.001	–0.021	–0.097	NA	NA	NA
	(0.146)	(0.263)	(0.136)			
Day 7	0.016	–0.114	–0.036	NA	NA	NA
	(0.155)	(0.140)	(0.294)			
		(–0.239, –0.021)[c]				
At low-light conditions						
Day 1	0.139	0.050	0.151	0.273	0.237	–0.009
	(0.471)	(0.382)	(0.363)	(0.417)	(0.207)	(0.283)
Day 4	0.113	–0.016	–0.028	NA	NA	NA
	(0.469)	(0.486)	(0.339)			
Day 7	0.199	–0.081	0.095	NA	NA	NA
	(0.903)	(0.458)	(0.570)			

a. Excluding 1 subject from panel 1 whose pupillometry measurements were not quantifiable. For day 1, pooled from treatments A, B, C, and D, $n = 16$; for days 4 and 7, pooled from treatments A and B, $n = 8$.

b. One subject discontinued prior to receiving fed treatment and did not contribute to the corresponding analysis.

c. The 90% confidence interval (CI) for the primary endpoint (difference in mean change between ivermectin 30 mg, fasted and placebo at high-light conditions on day 7). The 90% CI falls within the predetermined equivalence interval of (–1.0, 1.0) mm.

subjects. Seven ivermectin-treated subjects (14%) and 3 placebo-treated subjects (18%) had drug-related clinical adverse experiences. None of the subjects discontinued due to clinical adverse experiences. None of the clinical adverse experiences was serious.

Two subjects experienced laboratory adverse experiences, both in the 30 mg ivermectin group. A 37-year-old female developed increased alanine transaminase (ALT) to approximately 2.5 times normal on day 14 and elevated gamma-glutamyl transferase (GGT) to approximately 4 times normal on day 18. ALT returned to normal on day 23, but GGT remained mildly elevated (no baseline values obtained). Further hepatic evaluation revealed cholelithiasis (a gallbladder filled with stones). The investigator rated both laboratory adverse experiences as possibly related to study drug. The second subject, a 25-year-old male, developed hematuria that resolved after passing a kidney stone, and the event was evaluated as definitely not related to study drug.

Two subjects developed elevated liver function tests (LFTs) at least two times the upper limit of normal. The first subject was in the 30 mg ivermectin group and developed increased ALT and GGT levels, which were reported as laboratory adverse experiences (described above). The second subject, a 38-year-old male on placebo treatment, developed increased aspartate transaminase (AST) and ALT levels to approximately two times normal on day 7. The investigator considered these elevations to be not clinically significant.

Two subjects discontinued the study. One subject in the 30 mg ivermectin group discontinued due to a laboratory adverse experience (37-year-old female described above). One subject in the placebo group was lost to follow-up.

Pharmacokinetics

General

Pharmacokinetic results ($AUC_{0-\infty}$, C_{max}, t_{max}, and half-life) are shown in Table III. In addition, box plots of $AUC_{0-\infty}$ by ivermectin dose (day 1, fasted only) are displayed in Figure 1. For single doses of 30 to 120 mg administered in the fasted state, the AUC and C_{max} of ivermectin increase with increasing dose and appear generally dose proportional in this range. A high variability in absorption is apparent from examination of

Table II Clinical Adverse Experiences by Body System

	Placebo (n = 17)		Ivermectin 30 mg (n = 15)		Ivermectin 60 mg (n = 12)		Ivermectin 90 mg (n = 12)		Ivermectin 120 mg (n = 12)	
	Number	%	Number	%	Number	%	Number	%	Number	%
Subjects with one or more adverse experiences	6	35.3	5	33.3	5	41.7	2	16.7	0	0.0
Subjects with no adverse experience	11	64.7	10	66.7	7	58.3	10	83.3	12	100
Body as a whole/site unspecified	0	0.0	2	13.3	1	8.3	0	0.0	0	0.0
Fever	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Flu-like illness	0	0.0	0	0.0	1	8.3	0	0.0	0	0.0
Pain, abdominal	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Digestive system	1	5.9	1	6.7	1	8.3	1	8.3	0	0.0
Dry mouth	0	0.0	0	0.0	0	0.0	1	8.3	0	0.0
Fecal abnormality	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Nausea	1	5.9	0	0.0	1	8.3	0	0.0	0	0.0
Vomiting	0	0.0	0	0.0	1	8.3	0	0.0	0	0.0
Musculoskeletal system	1	5.9	2	13.3	0	0.0	0	0.0	0	0.0
Pain, back	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Pain, leg	1	5.9	0	0.0	0	0.0	0	0.0	0	0.0
Stiffness	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Nervous system and psychiatric disorder	3	17.6	1	6.7	4	33.3	1	8.3	0	0.0
Anxiety	0	0.0	0	0.0	1	8.3	0	0.0	0	0.0
Dizziness	1	5.9	0	0.0	1	8.3	0	0.0	0	0.0
Headache	2	11.8	1	6.7	3	25.0	1	8.3	0	0.0
Skin and skin appendage	1	5.9	0	0.0	1	8.3	0	0.0	0	0.0
Rash	1	5.9	0	0.0	1	8.3	0	0.0	0	0.0
Urogenital system	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Urolithiasis	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0

Although a subject may have had two or more adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories. All body systems are listed in which at least 1 subject had an adverse experience.

standard deviations and from the overall trends in AUC and C_{max} with increasing dose. Specifically, AUC and C_{max} do not appear to increase between the doses of 60 and 90 mg. However, a nearly proportional increase is seen with the 120 mg dose, indicating that absorption is not saturated in this range. t_{max} and half-life were generally invariant across the dose range, as would be expected from linear kinetics. There was no significant trend indicative of a gender effect.

Accumulation

The mean plasma concentration profiles on days 1 and 7 following multiple doses of 30 and 60 mg ivermectin given in the fasted state are shown in Figure 2. The geometric mean ratio (GMR) of the $AUC_{0\text{-}60\ h}$ of ivermectin on day 7 to the $AUC_{0\text{-}60\ h}$ on day 1 was calculated for assessing accumulation. GMRs (day 7/day 1) were 1.24 and 1.40 for the ivermectin 30 and 60 mg doses, respectively. This result suggests minimal accumulation of drug with day 1, 4, and 7 dosing, consistent with a short half-life relative to the dosing interval (72 h). The 95% confidence interval was (0.80, 1.92) and (0.91, 2.18) for the 30 mg (in the fasted state) level and the 60 mg level, respectively.

Food Effect

The effect of food on the pharmacokinetics of ivermectin was estimated by comparing the mean natural log-transformed $AUC_{0\text{-}\infty}$ values for the 30 mg dose of ivermectin in the fed and fasted states (treatment E vs. A). The mean plasma concentration profiles in the fed and fasted states are presented in Figure 3. The geo-

Table III Mean (*SD*) of Pharmacokinetic Parameters by Treatment Regimen

Parameter	Ivermectin 30 mg (fed) (n = 11[b])	Ivermectin 30 mg (fasted) (n = 12)[a]		Ivermectin 60 mg (n = 12)		Ivermectin 90 mg (n = 12)	Ivermectin 120 mg (n = 12)
		Day 1	Day 7	Day 1	Day 7		
$AUC_{0-\infty}$ (ng•h/ml)[c]	4564.6	1724.3	2819.4	2984.0	6061.7	2910.2	4547.7
	(1892.5)	(830.5)	(1691.2)	(1530.1)	(4243.7)	(1801.9)	(2402.9)
AUC_{0-60} (ng•h/ml)[d]	NA	1166.3	1444.3	2099.3	2947.2	NA	NA
$AUC_{0-\infty}$ (ng•h/ml)[d]	3951.9	1538.4	NA	NA	NA	NA	NA
C_{max} (ng/ml)[c]	260.5	84.8	87.0	165.2	186.2	158.1	247.8
	(172.1)	(42.7)	(43.2)	(98.6)	(130.8)	(87.6)	(158.9)
$t_{1/2}$ (h)[e]	15.0	20.1	17.7	19.6	17.5	18.8	19.1
t_{max} (h)[c]	4.6	4.3	4.2	3.6	4.0	4.9	4.2
	(0.9)	(1.0)	(0.9)	(0.9)	(1.1)	(1.8)	(0.9)

a. As prespecified in the protocol amendment, the plasma samples from the 3 additional subjects receiving 30 mg ivermectin treatment were not analyzed and did not contribute to the pharmacokinetic analyses.
b. One subject discontinued prior to receiving fed treatment and did not contribute to the corresponding analysis.
c. Arithmetic mean (standard deviation).
d. Geometric mean.
e. Harmonic mean.

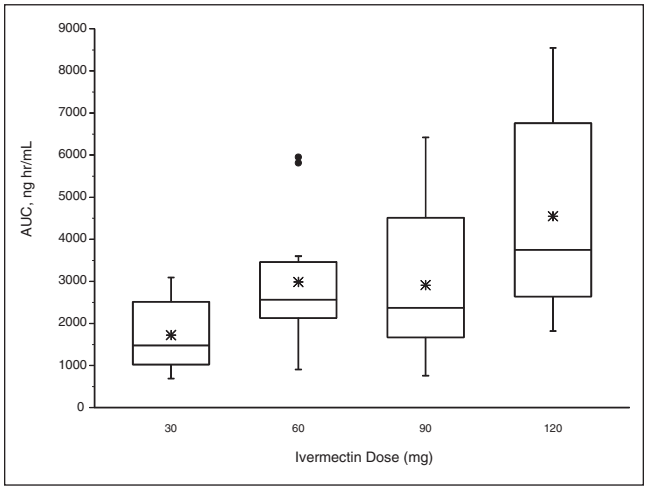

Figure 1. Box plots of AUC by ivermectin dose (day 1, fasted only). The box represents the middle half of the data with the bottom and top of the box representing the 25th and 75th percentiles. The median is portrayed by a horizontal line segment within the box, and the mean is represented by an asterisk. The height of the box is multiplied by 1.5 to determine the height of the "step." The upper vertical line extends up to the highest data value within the step, and the lower vertical line extends down to the lowest data value within the step. Circles represent data values that exceed the 25th and 75th percentiles by more than the height of the step. Mean AUC does not appear to increase between the doses of 60 and 90 mg, largely due to the influence of the two outliers in the 60 mg dose group. A nearly proportional increase is seen with the 120 mg dose, indicating that absorption is not saturated in this range.

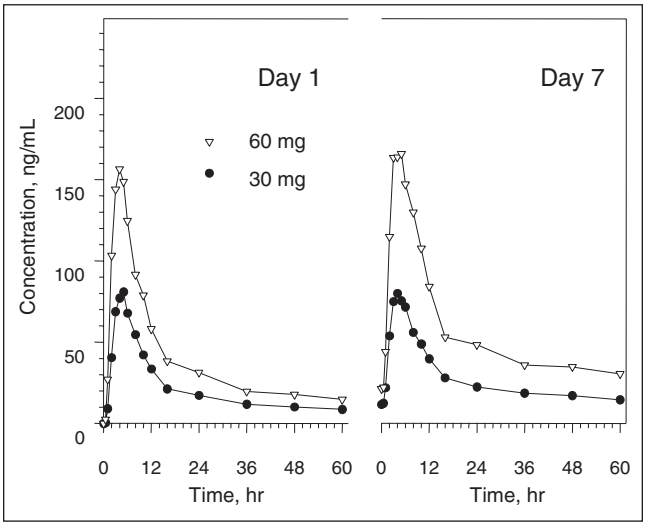

Figure 2. Mean plasma concentration (ng/ml) profiles of ivermectin on days 1 and 7 following multiple oral doses of 30 and 60 mg given fasted on days 1, 4, and 7.

metric mean ratio of $AUC_{0-\infty}$ values (fed/fasted) was 2.57. The 95% confidence interval was (2.16, 3.05).

DISCUSSION

This study was designed primarily to evaluate the safety and tolerability of oral ivermectin to support its

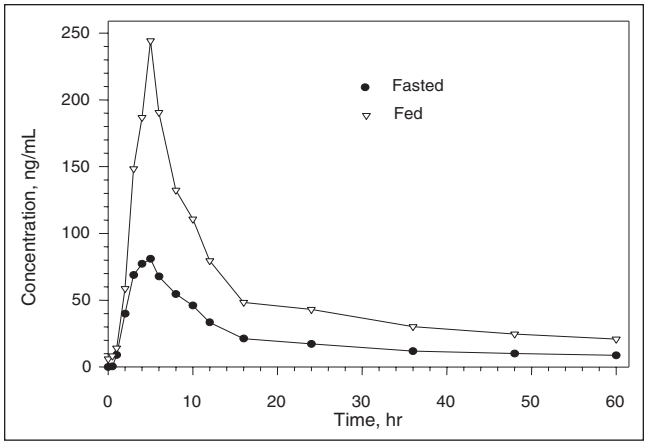

Figure 3. Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30 mg (fed and fasted administration).

use for the treatment of head lice infestation. Head lice predominantly affect school-age children. However, for both ethical and practical reasons, it was felt appropriate to conduct this study in healthy adult subjects. Extensive safety data are available for ivermectin, primarily at dose levels of 150 to 200 μg/kg. There also are published studies conducted at doses higher than 200 μg/kg for the treatment of internal parasites.[13-21] The present study expanded the safety data available for ivermectin at higher doses in subjects without internal parasitic infestations. The safety and tolerability of ivermectin were evaluated from two perspectives in this study: (1) assessment of CNS effect, the sole target of previously documented ivermectin toxicity, and (2) assessment of the general toxicity of ivermectin. No CNS toxicity was detected in the study, and ivermectin was generally well tolerated. Therefore, this study demonstrates that ivermectin is well tolerated in healthy subjects and provides additional evidence that the more severe reactions observed in the treatment of onchocerciasis and lymphatic filariasis are most likely due to the death of the organisms.[22]

A second purpose of the study was to collect additional pharmacokinetic data on ivermectin. Specifically, the study was designed to extend the kinetic understanding of this drug beyond the doses (up to 15 mg) examined previously, to document its behavior when administered in repeated doses in the manner contemplated for use against head lice, and to examine the effect of a high-fat meal on absorption.

Safety and Tolerability

Specific signs or symptoms of CNS toxicity were based on those determined in previous high-dose animal studies and observations of human overdose and included emesis, mydriasis, and ataxia. Mydriasis was chosen as the endpoint for the primary hypothesis since it can be accurately quantitated through pupillometry. Pupillometry is a simple, accurate, and reproducible method to measure pupil diameter quantitatively, which was validated internally prior to use in this study. It was observed in the first treatment panel that measurement of pupil diameter was difficult in persons with extremely dark iris color. However, with the addition of a screening evaluation at the prestudy visit, this difficulty was resolved.

No indication of CNS toxicity associated with oral ivermectin was observed for any of the doses administered in this study. This was most strongly supported by the absence of a mydriatic effect using quantitative pupillometry. The primary analysis of the pupillometry data was in the 30 mg ivermectin treatment group since this fixed dose spanned the range (in μg/kg) most likely to be employed in head lice therapy. Comparison of pupil size to baseline was made after the third dose, when maximum drug concentration was likely to be present if any accumulation occurred. Considering this criterion, the change in pupil size following 30 mg ivermectin administration was not different from that observed with placebo. Escalation to a single dose of up to 2 mg/kg, 10 times the approved dose, was also unassociated with any mydriatic effect. This supports the safety of ivermectin in the anticipated dosage range for head lice and provides a significant margin of safety.

Ivermectin was generally well tolerated. There were no serious clinical or laboratory adverse experiences. Clinical adverse experiences were similar between the ivermectin and placebo groups.

Specific adverse experiences to consider are those within the gastrointestinal and nervous systems since emesis, ataxia, and mydriasis are cardinal signs of ivermectin toxicity. Three of 51 subjects in the ivermectin-treated groups (1 fecal abnormality, 1 nausea, 1 vomiting) and 1 of 17 subjects in the placebo groups (1 nausea) experienced gastrointestinal adverse experiences. The adverse experience of vomiting occurred in a subject administered 60 mg of ivermectin on day 4. The event was evaluated as not related to ivermectin and did not occur after the day 1 dose, nor

did it recur with the day 7 dose. Six of the 51 subjects in the ivermectin-treated groups (4 headache, 1 anxiety, 1 dizziness) and 3 of the 17 subjects in the placebo groups (2 headache, 1 dizziness and headache) experienced nervous system adverse experiences. No increase in any adverse experiences was noted with dose escalation, and no adverse experience recurred with repeated dosing. Of note, no adverse experiences were reported in the subjects who received 120 mg of ivermectin.

Two subjects developed increases in LFTs during the study, 1 on ivermectin 30 mg and 1 on placebo. The subject on active drug was subsequently identified as having cholelithiasis, which was unlikely to be related to acute treatment with ivermectin. No other clinically significant LFT abnormalities occurred despite dose escalation to 120 mg. These data, together with extensive animal and human exposure, suggest that routine monitoring of laboratory values is unnecessary at the dose levels anticipated for head lice treatment.

Pharmacokinetics

Pharmacokinetic parameters of ivermectin following single doses were consistent with previous observations[1] and with linear behavior up to single doses of 120 mg. Substantial variability in absorption was apparent across doses, but this phenomenon was attributable to absorption rates of < 50% in the fasted state and to the parallel panel design of the study.

Absorption of ivermectin was significantly higher when administered following a high-fat meal, approximately 2.5 times that in the fasted state. Although the effect of food on absorption of ivermectin had not been previously studied, this result was not unexpected. When the drug was administered in a hydroalcoholic solution,[1] a similar increase in bioavailability was observed (compared to administration as a tablet). The extent of agreement between these results suggests that the poor solubility in water of the lipophilic ivermectin molecule limits absorption, but agents that help to solubilize the molecule (such as alcohol or bile) increase absorption of the drug. However, the standard high-fat meal is not representative of typical food ingestion. Furthermore, it is reassuring that despite a substantial increase in the AUC of ivermectin with administration of a high-fat meal, no toxicity was noted.

The apparent half-life for ivermectin identified in the product label is 16 hours or longer. The overall estimate from this study (approximately 18 h) is slightly longer. Half-life estimates varied somewhat with dose and means of administration from approximately 15 hours in fed subjects given 30 mg ivermectin doses to approximately 20 hours in the same group following administration of 30 mg ivermectin in the fasted state. Since the bioavailability is substantially higher when the drug is administered in the fed state, and a shorter half-life was observed in this state, it is possible that the half-life observed following oral administration is influenced by slow absorption of the drug, rather than being a true estimate of elimination half-life.

The accumulation observed following administration of drug every fourth day was rather modest and consistent with a moderate elimination half-life. The apparent change observed between the 30 and 60 mg dose regimens is likely attributable to the significant variability in absorption and the small number of subjects studied. In fact, accumulation ratios for both doses were statistically indistinguishable from 1. No significant pharmacokinetic differences were observed between men and women. No information has been gathered on the pharmacokinetics of ivermectin in children, but given the generally consistent kinetic behavior among many different species of widely distributed body sizes, it is expected that the pharmacokinetics in children will be consistent with those in adults.

In summary, the safety profile generated in this study supports the use of oral ivermectin at the approved dose levels and at dose levels being considered for the treatment of head lice. Furthermore, a significant safety margin is demonstrated. However, studies in the pediatric population are necessary to confirm safety in children at higher dose levels. The pharmacokinetic parameters are consistent with those previously established, with the exception of a slightly longer half-life. A significant food interaction was demonstrated.

We would like to acknowledge the following individuals for their considerable contributions to this study: Mr. Manuel Pinto and the staff of Clinical Pharmacology Associates for their invaluable help with study conduct and patient recruitment, Ms. Geraldine Bolden of Merck Research Laboratories for her excellent work in conducting the image analysis of the pupillometry transparencies, Ms. Mitra Asgary of Merck Research Laboratories for her contribution in analyzing the pharmacokinetic samples, and Dr. Stephanie Larouche, formerly of Merck Research Laboratories, for her encouragement and scientific guidance.

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