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BIOAVAILABILITY OF IVERMECTIN ADMINISTERED ORALLY TO DOGS

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ABSTRACT

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The bioavailability of three formulations of ivermectin was determined following oral administration to dogs. The average peak plasma level (C_{max}) of ivermectin administered in the standard tablet formulation at 6 and 100 μg/kg of body weight was 2.97 and 44.31 ng/g, respectively. This suggest dose-dependent pharmacokinetics. C_{max} and total ivermectin bioavailability, as assessed from the area under the plasma curve (AUC), were similar between two tablet formulations of ivermectin administered at 100 μg/kg. Furthermore, C_{max} was similar following administration of radiolabelled ivermectin at 6 μg/kg in either a beef-based chewable formulation or in the standard tablet formulation.

Keywords: bioavailability, dogs, ivermectin, oral formulations, pharmacokinetics

INTRODUCTION

Ivermectin has been used for prevention of canine heartworm disease (Heartgard-30, Merck) and was first made available commercially in a standard oral tablet formulation. Subsequently, a beef-based chewable formulation was developed and also a modified tablet was manufactured that incorporated ivermectin in a solid-state, crystalline form. Two independent bioavailability trials are described here. One compared the pharmacokinetics of ivermectin in the standard tablet and chewable formulations and the other compared the pharmacokinetics of the compound in the standard and the modified tablet formulations.

MATERIALS AND METHODS

Test animals and study designs

Each of the trials used a crossover design that included 16 dogs. In Trial 1, non-pregnant female Beagles, 1.2–2.2 years old, from White Eagle Laboratories in Doylestown, Pennsylvania, were used. In Trial 2, non-pregnant female Beagles, approximately 1 year old, from Hazelton-LRE, Inc. in Kalamazoo, Michigan, were used. The animals were acclimatized to the trial facility for at least 4 weeks before each trial and were fed maintenance rations once daily. The dogs were paired by pre-trial body weight and allocated to individual cages and treatment sequence groups.

The dogs in Sequence 1 of Trial 1 received standard tablets on Day 0 (Period 1) and chewables on Day 42 (Period 2), while the dogs in Sequence 2 received these treatments in the reverse order. In Trial 2, conducted 6 months after Trial 1, the dogs in Sequence 1 received standard tablets on Day 0 (Period 1) and modified tablets on Day 35 (Period 2), with the treatment sequence reversed for the dogs in Sequence 2. In both trials, the dogs were carefully observed for emesis for 4 hours following dosing in each period.

Formulation preparation

In Trial 1, ivermectin (Fisher and Mrozik, 1989) was labelled with tritium in the C-22,23 positions before preparation of the standard tablet and chewable formulations, each of which was administered orally to provide ivermectin at a dose of 6 μg/kg of body weight. The radiochemical purity of the radiolabelled ivermectin was at least 99.3% before formulation and averaged at least 96.2% after formulation. The specific activity, as determined by use of a scintillation spectrometer (Packard Model 3255) with external quench correction, was 9.805 and 10.14 μCi/μg in Periods 1 and 2, respectively. The stability of the drug concentration was satisfactory (<8% change) under conditions used for this study when dosing was within 6 days of manufacture. The chewable formulation consisted of ivermectin in a beef and soy protein base.

In Trial 2, the solid-state crystalline ivermectin in the modified tablet formulation could not be radiolabelled. To ensure that the blood concentrations would be sufficient for a reliable plasma ivermectin assay, the ivermectin dose was increased to 100 μg/kg. The dogs were weighed 1 week before dosing in each period to allow time to prepare the test drug tailored to the dog's weight.

Blood collection

In Trial 1, blood was collected from each dog approximately 24 hours before dosing, on the day of dosing (Day 0) at 1, 2, 3, 4, 6 and 10 hours, and on Days 1 (24 hours), 2, 3, 5, 7, 10 and 14. In Period 2, additional blood samples were collected at 8, 12 and 15 hours on the dosing day (Day 42) and this augmented schedule was employed in both periods of Trial 2. In Trial 1, approximately 5 ml of whole blood was taken at each bleeding from the jugular, cephalic or recurrent tarsal veins using heparinized, evacuated bleeding-tubes or disposable glass syringes. In Trial 2, catheters were implanted in the jugular or cephalic vein of the dogs and approximately 10 ml was collected at each bleeding. If problems arose with the implanted catheters, procedures similar to those in Trial 1 were used for blood collection. In both trials, to prevent haemolysis, blood samples were stored in ice. Plasma was frozen immediately for later assay.

Plasma assays

In Trial 1, weighed duplicate (or triplicate) plasma aliquots of approximately 0.5 g each were combusted in a Packard Model 306 Sample Oxidizer. The tritiated water

derived from this procedure was mixed with 15 ml of Monophase 40 Plus scintillation cocktail (Packard Instruments, Sterling, VA) and analysed for total radioactivity in a TriCarb Spectrometer Model 3255 (Packard). Quench correction was performed by the external standard method. The recovery of tritium from labelled ivermectin was >97%. In Trial 2, plasma sample analyses were performed by and at Merck & Co., Inc. The ivermectin content in the plasma samples was determined as the H_2B_{1a} component using fluorescence detection as described by Kojima *et al.* (1987) and by Stong (1987).

Statistical methods

For each dog, following each treatment, the area under the plasma concentration curve (AUC) from 0 to 336 hours was calculated using the trapezoidal method; the peak plasma concentration (C_{max}) was the highest ivermectin concentration recorded; the time to peak concentration (T_{max}) was the hour associated with C_{max}.

In each trial, the comparison of the formulations was based on AUC and C_{max}, using an analysis of variance for a two-period crossover design. In addition, following a procedure described by Schuirmann (1987), 90% confidence intervals for the difference between the formulations were constructed. T_{max} was analysed similarly in Trial 2 but no analysis of T_{max} was done in Trial 1.

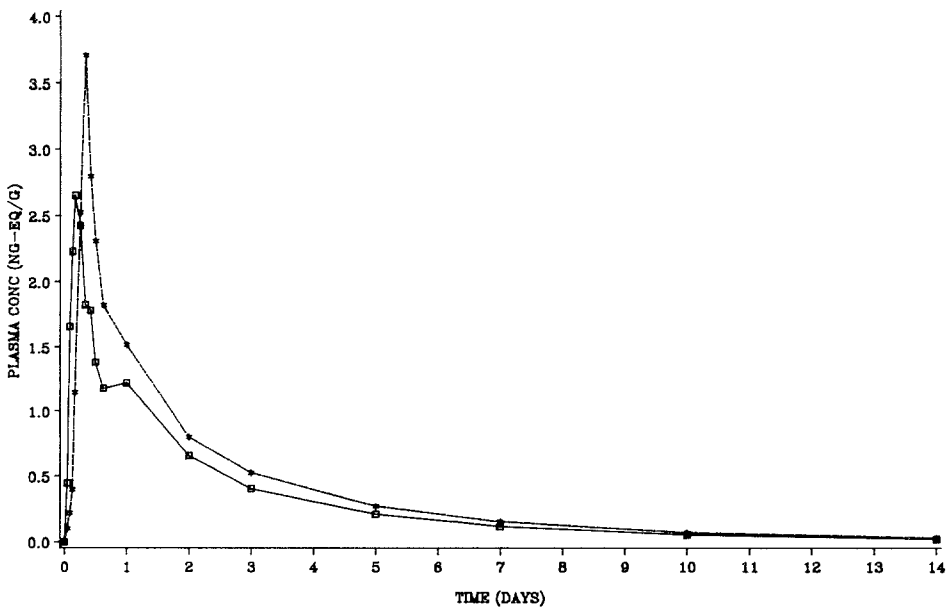

Figure 1. Mean ivermectin plasma concentration curves following an orally administered radiolabelled dose of 6 μg/kg. *, chewable formulation; □, standard tablet formulation

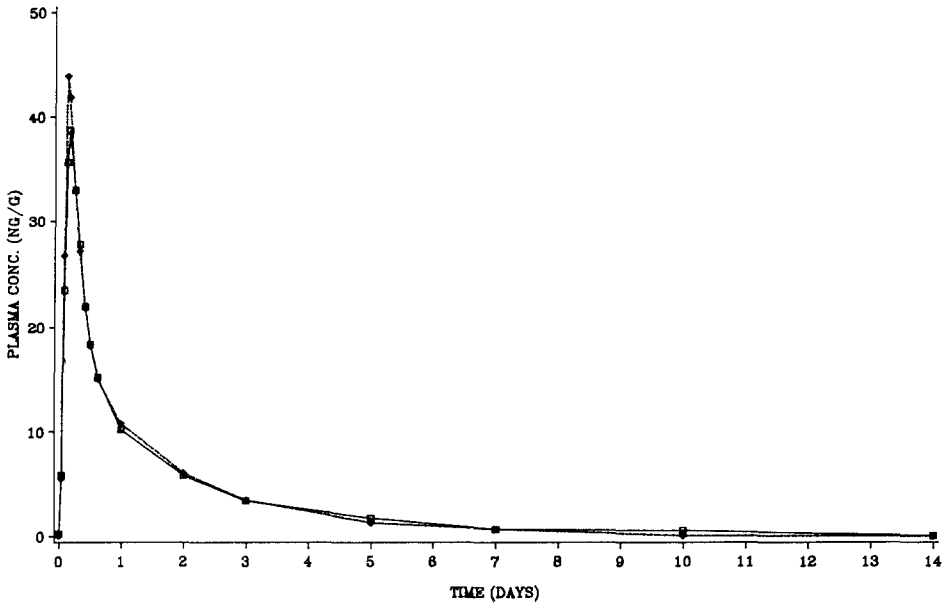

Figure 2. Mean ivermectin plasma concentration curves following an oral dose of 100 μg/kg. □, standard tablet formulation; ◊, new tablet formulation

TABLE I
Summary of pharmacokinetic data after radiolabelled ivermectin was given orally at 6 μg/kg in standard tablet and chewable formulations to 16 dogs in a crossover study

Variable	AUC_{0-336}(ng h g^{-1})	C_{max}(ng/g)
Standard tablet mean	107.318	2.968
Chewable formulation mean	130.885	3.370
Standard deviation[a]	27.897	0.885
Formulation effect[b]	0.032	0.220
Lower 90% confidence limit[c]	5.78%	−5.02%
Upper 90% confidence limit	38.14%	32.12%

[a]Square root of MSE in the ANOVA
[b]p-value from ANOVA
[c]Confidence limit of the difference between the means, expressed as a percentage relative to the standard tablet mean

TABLE II
Summary of pharmacokinetic data after ivermectin was given orally at 100 μg/kg in two tablet formulations to 16 dogs in a crossover study

Variable	AUC_{0-336}(ng h g^{-1})	C_{max}(ng/g)
Standard tablet mean	1035.094	44.313
New tablet mean	1000.500	48.375
Standard deviation[a]	156.006	9.121
Formulation effect[b]	0.541	0.228
Lower 90% confidence limit[c]	−12.73%	−3.65%
Upper 90% confidence limit	6.04%	21.98%

[a]Square root of MSE in the ANOVA
[b]p-value from ANOVA
[c]Confidence limit of the difference between the means, expressed as a percentage relative to the standard tablet mean

RESULTS

Means, standard deviations, statistical significance and confidence intervals are given for AUC and C_{max} in Tables I and II for Trials 1 and 2, respectively. Mean plasma concentrations for the formulations in each trial are given in Figures 1 and 2.

In Trial 1, a distinct difference was observed between formulations for T_{max}: the average T_{max} was 5.33 hours (median = 3 hours) for the standard tablet formulation, and 8.51 hours (median = 8 hours) for the chewable. In the first period, 7 of 8 dogs given the chewable formulation had reached T_{max} at 10 hours. When a blood collection was added to the second period at 8 hours, 6 of 8 dogs given the chewable formulation had reached T_{max} at this time. In Trial 2, the average T_{max} was 4.22 hours for the standard tablet formulation and 3.75 hours for the modified tablet ($p > 0.20$).

DISCUSSION

The linearity of dose with mean C_{max} for the standard ivermectin tablet supports the dose-independent pharmacokinetics noted by Fink and Porras (1989), as does the observation that T_{max} was consistently around 4 hours following administration of the standard or new tablet formulations at either dose level.

Based on the results of Trial 2, the two tablet formulations were considered to be bioequivalent. In Trial 1, the total bioavailability of ivermectin (as measured by AUC) for the chewable formulation was somewhat more complete and absorption was slower than with the standard tablet, although the peak ivermectin concentrations were similar.

Bioequivalency has also been established by clinical efficacy trials. Field safety and efficacy trials with ivermectin in the chewable formulation and in the modified tablet formulation demonstrated safety in field use and 100% efficacy of ivermectin given at 6 μg/kg in either formulation in preventing the development of *Dirofilaria immitis* larvae in dogs. These trials have been reported by Paul *et al.* (1991) and by Plue *et al.* (1989).

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