Oral Controlled-Release Delivery of Ivermectin in Cattle via an Osmotic Pump

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Abstract □ Ivermectin, a potent antiparasitic agent with activity against internal and external parasites, was delivered to cattle at a controlled zero-order rate for 35 d via orally administered, specially weighted, ALZET 2ML4 osmotic pumps. The osmotic pumps delivered the drug consistently over the trial period. Steady-state levels in plasma were achieved in 7–14 d, and plasma concentration depletion curves were observed to start at approximately day 35, the theoretical delivery lifetime of the osmotic pumps. Bioavailability was estimated to be 40%, and dose rate–plasma steady-state interrelationships were shown to be linear.

A major problem associated with the development of controlled sustained-release delivery systems for oral use is that the period over which the system delivers the drug is limited by the target animal's gastrointestinal transit time. When sustained drug delivery by oral administration is required for ruminant animals (cattle, sheep, goats), however, the transit time of the formulation or device can be controlled.

The alimentary tract of ruminants is expanded anteriad to their true stomach (abomasum) into a series of chambers (rumen, reticulum, and omasum) (Fig. 1). Prolonged retention within the ruminoreticulum can be achieved by controlling either the density of the formulation[1] or the size of the delivery device.[2,3] The delivery device or formulation can be maintained in the ruminoreticulum for days, weeks, months, or years, depending upon the drug delivery time required. The various formulation methodologies and delivery device configurations have been reviewed by Pope,[4–6] using the principles of density and size.

Because of its potency, ivermectin, a macrocyclic lactone disaccharide with antiparasitic activity against internal and external parasites,[7,8] lends itself to the development of a controlled sustained-delivery formulation. In order to design a sustained-release, zero-order oral delivery system for administration of ivermectin to ruminants, a knowledge of the bioavailability and pharmacokinetic profile after sustained delivery to the ruminoreticulum is necessary.

The sustained delivery was achieved in the bovine by the oral administration of an ALZET 2ML4 mini-osmotic pump[9] containing a micellar solution of ivermectin. The ALZET pump was suitably weighted to 2.7 g/mL to ensure retention within the ruminoreticulum. This density was selected on the basis of studies performed by Marston,[10] Siegrist and Katz,[11] Roebuck and Whitehead,[12] and Riner et al.[13] These studies indicate that, within wide limits, a density of 1.5–1.9 g/mL results in ruminal residence; a density of 2.2 g/mL results in translocation between the rumen and the reticulum; and a density of greater than 2.4 g/mL with a weight of greater than 10 g most likely results in reticular retention.

Although a number of devices which rely upon size for retention have been patented,[2,3] density was selected for use as the primary mechanism for ALZET pump retention.

Experimental Section

Drug Delivery Device—Ivermectin was administered as a micellar solution contained within an ALZET 2ML4 mini-osmotic pump (ALZA Corp., Palo Alto, CA 94304) which was placed within a two-piece cylindrical stainless-steel cage (18 × 105 mm) equipped with a radio transmitter[14] (Fig. 2). The total combined delivery system had a density of 2.7 g/mL.

The amount of ivermectin to be delivered per day was calculated on the basis of determinations of body weight made 5 days prior to dosing. The osmotic pumps were filled with the appropriate concentration of ivermectin solution to ensure that the defined dose rate (μg/kg/d) was achieved. On d 0, individually numbered osmotic

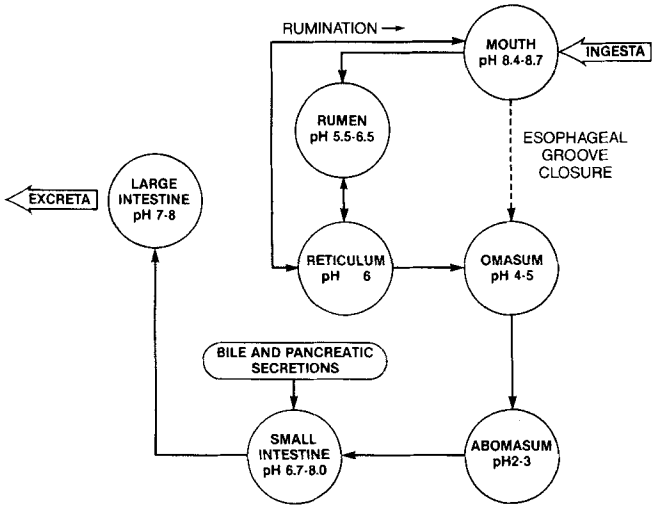

Figure 1—*Diagrammatic delineation of the ruminoreticular gastrointestinal tract of ruminant animals.*

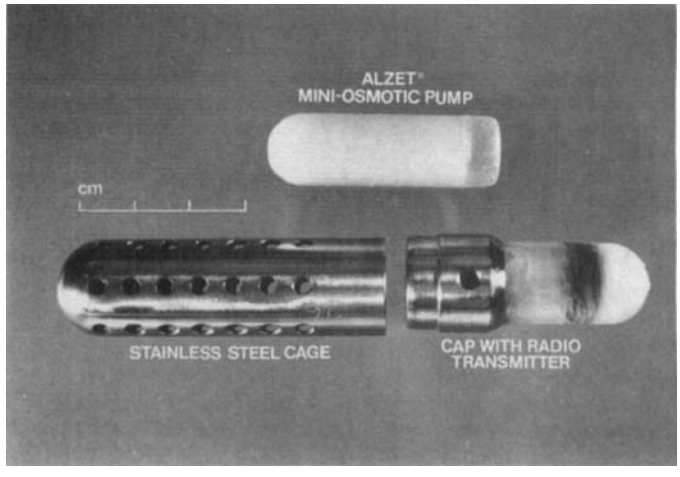

Figure 2—*Photograph of the drug delivery system used for administering ivermectin to the ruminoreticulum of cattle via zero-order delivery over a 4-week period.*[14]

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pumps were inserted into the appropriately coded stainless-steel cages. The boluses were administered to the cattle by means of a standard balling gun. Retention within the rumino-reticulum was monitored by radio transmission.

Animals—Two trials were performed. The mean drug delivery rates for ivermectin were 0, 2.5, 4.3, 9.2, 21.5, and 40.3 μg/kg/d for the first trial and 0, 16.6, 24.4, and 33.7 μg/kg/d, for the second trial. Individual dose rates are depicted in Fig. 3.

In the first trial, 24 young cattle were allocated to six treatment groups of four cattle each by restricted randomization based on breed, sex, and body weight. Six treatments were assigned to the groups by randomly matching numbers 1–6. In the second trial, 20 young cattle were allocated to four treatment groups of five calves each in a manner similar to the first trial. At the completion of the blood sampling period, necropsies were performed on the calves for recovery of the boluses, and the ruminoreticulum was examined for tissue damage.

Biological Samples—Whole blood samples were drawn at preselected times in heparinized tubes and immediately centrifuged. The plasma was separated and frozen until assayed for ivermectin.

Plasma Assay—Ivermectin was determined in plasma by suitable sample preparation and assay by reversed-phase HPLC with UV photometric detection. An accuracy of 2 ng/mL (mean deviation) and a precision in the range of 1–3 ng/mL (standard deviation) are typically observed for the method.[15]

Results and Discussion

Mean drug levels in plasma in each treatment group at each time interval are illustrated in Figs. 4 and 5 for trials 1 and 2, respectively. Data for the groups that received doses of 2.5 and 4.3 μg/kg/d are not included, as these were at or below assay sensitivity. Steady-state concentrations in plasma were achieved in 7–14 days, and plasma concentration depletion curves were observed to start at approximately day 35. The day 35 plasma concentration depletion was in direct accord with the theoretical shutdown of the pumps used in the study. The ALZET 2ML4 pumps (lot 52151) had a mean ± SD pump rate of 2.33 ± 0.18 μL/h at 39°C, the temperature of the rumen. Each pump had a mean ± SD pump volume of 2.092 ± 0.065 mL. The theoretical "zero-order" lifetime of the ALZET pump is 85% of its volume lifetime,[16] i.e., 0.85 (34–42 d) = 29 to 36 d.

At steady state, the mean output of the ALZET 2ML4 pump was related to the steady-state concentration in plasma by the relationship:

$$F \cdot \frac{\Delta m}{\Delta t} \cdot \frac{1}{w} = CL \cdot C_{ss}$$

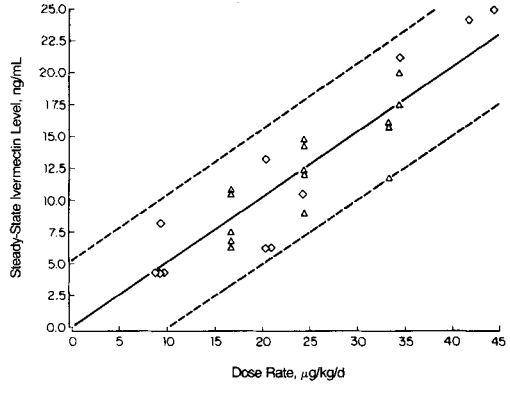

Figure 3—*The mean 14–35-day ivermectin steady-state plasma concentration–dose rate interrelationships are depicted for each animal dosed in the study together with the individual predicted 95% confidence limits for the best-fit line forced through the origin. Key: ◇, trial 1; Δ, trial 2.*

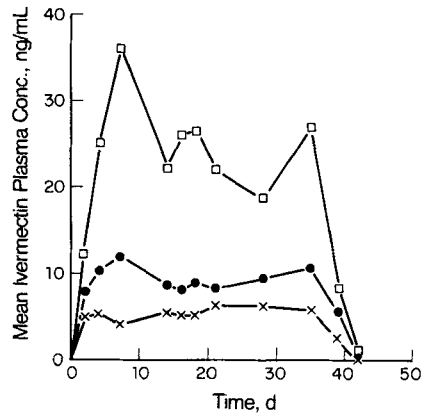

Figure 4—*The mean plasma levels obtained from a zero-order delivery of ivermectin to the ruminoreticulum of cattle in trial 1. Key: □, 40.3 μg/kg/d (n = 3) (one animal died due to non-study-related causes); ●, 21.5 μg/kg/d (n = 4); ×, 9.2 μg/kg/d (n = 4).*

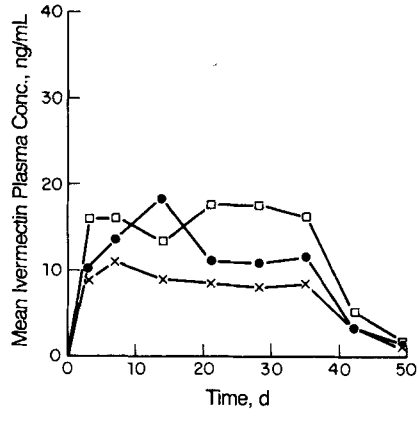

Figure 5—*The mean plasma levels obtained from a zero-order delivery of ivermectin to the ruminoreticulum of cattle in trial 2. Key: □, 33.7 μg/kg/d (n = 5); ●, 24.4 μg/kg/d (n = 5); ×, 16.6 μg/kg/d (n = 5).*

where F is the extent of absorption, $\Delta m/\Delta t$ is the ALZET 2ML4 delivery rate of ivermectin at steady state (μg/d), w is the animal body weight (kg), $(\Delta m/\Delta t) \cdot (1/w)$ is the ivermectin dose rate (μg/kg/d), CL is the total body clearance (L/kg/d), and C_{ss} is the concentration in plasma at steady state (ng/mL), calculated by using all the data points for each animal between days 14 and 35.

Therefore, plotting the mean steady-state ivermectin level in plasma (C_{ss}) versus the dose rate for each animal used in the two trials $(\Delta m/\Delta t) \cdot (1/w)$ resulted in the linear relationship shown in Fig. 3. Regression analysis forcing the best fit line through zero (best-fit line intercept not significantly different from zero [$p > 0.5$]) resulted in a slope of 0.512 ± 0.11 g/d/mL, with a correlation coefficient of 0.983.

Ivermectin clearance in cattle has been evaluated to be 0.79 L/kg/d;[17] hence, the bioavailability of ivermectin from this sustained oral delivery system in cattle is of the order of:

$$\begin{aligned} F &= CL \times \text{slope} \\ &= 0.79 \times 0.512 \\ &= 0.40 \text{ or } 40\% \end{aligned}$$

This low bioavailability is of the same order of magnitude as that found by Prichard and co-workers.[18] They found that in sheep, intraruminal administration gave 29% bioavailability, whereas intraabomasal administration resulted in 95%

bioavailability. The low oral bioavailability from the ruminoreticulum was attributed to rapid metabolism of ivermectin in the environment of the ruminoreticulum.

Using the pharmacokinetic micro-constants developed for ivermectin given intravenously,[17] we evaluated the estimated steady-state plasma level–dose rate interrelationship on the basis of a computer simulation of a three-compartment open model with a constant rate input and elimination from the central compartment. The integrated rate expression[19] (i.e., bioavailability × input rate) was adjusted to reflect the 40% relative bioavailability reported above. This resulted in a steady-state plasma level–dose rate interrelationship with a slope of 0.495 g/d/mL. This slope is not significantly different ($p > 0.25$) from the regression slope calculated from the actual data.

At necropsy, the ruminoreticulum of each calf from each treatment group was examined. No adverse effects were noted. Examination of the boluses revealed some degree of scaling on the stainless-steel cage, with little scale evident on the ALZET pumps. All pumps during the trial periods were estimated to be lodged in the ruminoreticulum within the vicinity of the reticulum, as determined by radio detection. At necropsy, all pumps were recovered from either the reticulum or the anterior cranial sac of the rumen close to the ruminoreticular fold.

Conclusions

This study showed that an orally administered densified drug delivery system can render ivermectin at a controlled rate to cattle and achieve predictable levels in plasma. For a drug delivery rate of R (μg/kg/d), mean steady-state levels of R (0.512) ng/mL are obtained in plasma. This predictability holds over the dosage range of 0–40 μg/kg/d. This predictability may also extend to higher dose ranges, as shown by the fact that a similar interrelationship was obtained when the microconstants from an intravenous three-compartment pharmacokinetic study were used in the determination of the dose–rate steady-state predictions.

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