Concentrations of Ivermectin in Bovine Serum as a 
Function of Treatments1,2

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ABSTRACT In a series of studies with ivermectin in cattle, we determined the drug concentrations in serum over time resulting from daily oral dosages at 50, 100, and 200 µg/kg and from daily subcutaneous injections at 5, 20, and 80 µg/kg. We also determined the profile of ivermectin in serum resulting from oral treatment at 75 µg/kg at 3-d intervals. For cattle treated orally at the same dosage, a significant difference in the level of drug in serum was found between animals held on pasture and those held in indoor stanchions. In contrast, no difference in serum ivermectin was found in cattle held on pasture and those held in stanchion if they were treated by injection. A subsequent trial showed that the quantity of foodstuff consumed by the animal can account for some of the differences observed in cattle treated orally. A simple spreadsheet model was developed for estimating the level of ivermectin in serum over time. The results of these trials provide a useful database for the development of a variety of delivery systems for ivermectin in cattle.

KEY WORDS Ivermectin, cattle, levels in serum, delivery systems

The discovery and development of ivermectin (Campbell 1989) introduced an important new class of endecticides for use in the animal health industry. The impact of this new drug on livestock pest management has been significant. In addition to its broad spectrum of activity (Drummond 1985, Lasota & Dybas 1991), its effectiveness at extremely low dosages is an important characteristic (Drummond et al. 1981). Because ivermectin is efficacious at treatment levels on the order of µg/kg body weight and serum levels in the ng/ml (ppb) range, the potential exists for the development of unique delivery systems heretofore not possible for drugs requiring larger dosages (Miller et al. 1983, Pope et al. 1985).

Drug/chemical delivery systems that are capable of improving the efficacy, increasing the efficiency, reducing the quantity, reducing the frequency of application, and improving the safety of treatments have been used in human medicine, veterinary medicine, agricultural systems, and consumer products for

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2 Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that also may be suitable.
many years. Only in recent years has attention been given to the potential of this technology in livestock arthropod pest control. The insecticidal ear tag for cattle and the sustained release bolus for delivery of insect growth regulators (IGRs) are two examples of such technology (Ahrens 1977, Miller et al. 1979, Miller et al. 1983).

Ritschel (1988) discusses the basic pharmacokinetics and biopharmaceutical aspects of development of drug delivery systems. Basic to the development of improved delivery systems is an understanding of the kinetics of the drug with respect to treatment regime, treatment level, and time in the animal. In the case of controlled-release delivery systems, it is not only necessary that they release the drug over the prescribed time but also that they provide and maintain an efficacious concentration in or on the animal. We have over several years conducted a series of studies using ivermectin to obtain basic information needed for developing improved delivery systems. The objectives of these studies were to determine the serum ivermectin concentrations resulting from various treatments and to develop a practical means of estimating the drug serum profile in cattle.

Materials and Methods

In the general procedure for this series of studies, we treated cattle with ivermectin either orally or by subcutaneous injection. The capsules used in the oral treatments were prepared by metering the appropriate amount of Ivomec Injectable from a syringe onto whole wheat flour in a 30 cc gelatin capsule. Each capsule was labeled by animal number, placed in a small paper bag, and held in a refrigerator until needed. The capsules were administered using a conventional balling gun. The injections were made in the prescapular area of the neck. Duplicate blood samples (13 ml Vacutainers) were collected from each animal prior to treatment and at selected intervals posttreatment for subsequent HPLC analysis of the drug concentration in the serum. The HPLC technique was capable of quantifying as little as 2 ppb ivermectin in a 5-ml serum sample (Oehler & Miller 1989).

Daily injection or oral treatments. Experiments were conducted in which Hereford steers were treated daily for 28 consecutive days with ivermectin either by subcutaneous injection or oral capsule. They were held outdoors in paddocks and maintained on a diet of ground grain mix and hygeria hay with water ad libitum. Each morning the steers were gathered and run through a chute where they were treated. In addition, at 3-4 d intervals, blood samples were taken from each animal. The collection of blood samples continued for 24 d after the treatments were terminated (total of 52 d).

In the trial with the subcutaneous injection, nine animals were treated with the Ivomec Injectable. The animals were randomly allotted to three groups of three animals each and were treated at 5, 20, and 80 µg/kg body weight, respectively. A tenth steer served as an untreated control. The 10 steers ranged in weight from 163-209 kg at the beginning of the trial.

Upon completion of the injection trial, the animals were given a 2-mo rest period on pasture before being used again in the oral treatment trial. As in the previous trial, three groups were randomly established, and the steers in
each group were treated at either 50, 100, or 200 μg/kg body weight. The tenth animal was the same untreated control as in the previous test. The animals weighed from 180-223 kg at the beginning of the trial.

**Cyclic oral treatment.** Four previously untreated Hereford heifers weighing from 200-232 kg were placed in stanchions and maintained on a ground grain and hay ration. Three of the animals were treated by oral capsule at a dose of 75 μg/kg at 3-d intervals over a period of 21 d. The fourth animal was an untreated control. Blood samples were collected as previously described from each animal on day 0, 3, 6, 9, 12, and daily thereafter through day 24.

**Stanchioned vs. outdoor treatments.** Because of concern that the levels of ivermectin in the serum of treated cattle could be influenced by whether the cattle were held in stanchions or allowed to graze on pasture, we conducted two additional trials. In the first trial, the animals were treated orally by capsule, and in the second trial they were treated by subcutaneous injection. In both trials, two groups of three Hereford steers (236-281 kg) were randomly established. One group was held on pasture and the other was placed in stanchions in a barn. Those in stanchions were fed ground grain and hay twice daily, while those on pasture were provided the same feed as a supplement to the available grass. The cattle were treated and bled twice weekly at 3-4 d intervals. At the end of 14 d of treatment, the three animals that were on pasture were moved into the stanchions, and those in stanchions were moved onto pasture. In the trial using the oral treatment, the cattle were treated at 200 μg/kg for 30 d; whereas, the cattle were treated at 40 μg/kg for 28 d in the trial using the injection.

**Feed intake vs. drug serum levels.** A trial was conducted to test the hypothesis that, for cattle treated orally, differences observed in drug serum levels for cattle held on pasture and those held in stanchions might, in part, be due to the quantity of feed intake and, therefore, to the flow of foodstuff through the digestive tract. Six Hereford steers (236-318 kg) were randomly assigned to two equal groups and placed in stanchions. Both groups were fed alfalfa cubes in two portions, morning and afternoon, and provided with water ad libitum. One group was fed at a rate of 1.5% of body weight per day and the other group was fed at 3% body weight. All animals were treated by oral capsule at 200 μg/kg twice a week at 3-4 d intervals for 17 d. Blood samples were collected just prior to each treatment.

**Results and Discussion**

**Daily injection or oral treatments.** The mean levels of ivermectin found in the serum of cattle given daily subcutaneous injections of 5, 20, and 80 μg/kg for 28 consecutive days are shown in Fig. 1A, 1B, and 1C, respectively. When considering daily treatments, the plateau or equilibrium level, the level at which the amounts of drug being absorbed into and eliminated from the bloodstream are equal, is of great interest. We used the mean serum ivermectin levels for the last three samples, days 21, 24, and 28 of the treatment period, as an indicator of the plateau. Those cattle treated at 5 μg/kg daily appeared to reach a plateau of 5 ppb. The plateaus for those...
Fig. 1. Observed and modeled concentrations of ivermectin in serum of cattle injected daily for 28 d with (A) 5 µg/kg, (B) 20 µg/kg, and (C) 80 µg/kg.
injected at 20 μg/kg and 80 μg/kg were 25 ppb and 122 ppb, respectively. These equilibrium levels are not accurately estimated as a constant multiple of the dose. With increasing dose, larger proportions are seen in the serum.

The mean serum ivermectin levels for the cattle given daily oral capsules of 50, 100, and 200 μg/kg for 28 consecutive days are shown in Fig. 2A, 2B, and 2C, respectively. The equilibrium levels for the 50, 100, and 200 μg/kg oral treatments were 18, 39, and 72 ppb, respectively. These plateaus can be reasonably estimated as 0.37 × dose in μg/kg body weight.

With the exception of the 80 μg/kg daily injections, the level of ivermectin in serum declined to undetectable levels within 21 d of terminating the treatments.

The mathematics of the pharmacokinetics of a drug are complex but fairly well developed (Ritschel 1988). The compartment model (usually 1-3 compartments) is used to express the concentration-time relationship and is expressed as the sum of exponentials (Lo et al. 1985, Wilkinson et al. 1985). These experiments established a biological half-life of ivermectin of 2.7–2.8 d. Schnitzerling & Nolan (1985) found the biological half-life in cattle to be 3 d.

To determine if a reasonable estimate of the concentration-time profile of ivermectin in serum of these treated cattle could be described, we developed a simple spreadsheet model. The assumption was made that a fixed portion of the daily dose was absorbed into the bloodstream of cattle and, thereafter, this quantity of drug decreased according to the biological half-life of the drug. For example, for cattle treated orally beginning on Day 0 with 100 μg/kg, for each treatment, some quantity, say 100 × .072 or 7.2 ppb, would be detected in the bloodstream the following day (Day 1). The quantity in the bloodstream for Day 2 would be 7.2 ppb plus the residual from Day 1. Using a biological half-life of 3 d, 79.37% of the Day 1 level would remain or 0.7937 × 7.2 ppb. Thus, the expected drug concentration in the blood for Day 2 would be 7.2 ppb plus 7.2 ppb × 0.7937 or 12.9 ppb. Therefore, the expected concentration in the blood for any day would be the contribution of previous day's treatment plus the sum of the residuals from each of the preceding days of treatment.

The mathematical expression for the concentration (ppb) on any day \( t \) is:

\[
C_t = \sum_{0}^{t-1} D \times F \times \exp(-0.23105t)
\]

where:
- \( C_t \) = ppb in the bloodstream on day \( t \)
- \( D \) = dose in μg/kg
- \( F \) = portion of dose contributing to blood level
- \( t \) = day of treatment

The described relationships were easily established in a spreadsheet model for both the oral and the subcutaneous injections. The value for the biological half-life for ivermectin was fixed at 3 d on the basis of the literature reported above. The model results for each treatment level were
Fig. 2. Observed and modeled concentrations of ivermectin in serum of cattle treated by oral capsule daily for 28 d with (A) 50 μg/kg, (B) 100 μg/kg, and (C) 200 μg/kg.
then compared to the mean serum ivermectin levels observed in our study. The value for the factor $F$ giving the best fit of the model to the observed data was obtained by minimizing the sum of squares of deviations (model value - observed value) divided by the observed value. This procedure is similar to the use of the Chi-square goodness of fit test.

Using the described procedure, we showed that the values of $F$ that gave the best fit for the oral treatments and for the injections were 0.072 and 0.26, respectively. Figure 1 shows the comparison of the model to the observed data for the injection treatments. Figure 2 shows the same comparison for the oral treatments. It appears that the simple spreadsheet model can provide reasonable estimates of serum ivermectin levels resulting from either oral or injection treatments within the ranges tested in our study. The model was least effective in predicting the serum levels resulting from 80 $\mu g/kg$ per day injections, and for this treatment it was least effective in predicting the decay phase of the curve. One possibility may be that rates of absorption and elimination in an animal are somewhat different at the 80 $\mu g/kg$ dose.

**Cyclic oral treatment.** The serum ivermectin concentrations resulting from the treatment of cattle orally at 75 $\mu g/kg$ at 3-d intervals are shown in Fig. 3. Prior to conducting the study, the spreadsheet model was used to predict the concentration profile that would be expected from such a treatment. As shown in Fig. 3, there is good concurrence between the cyclic sawtooth pattern predicted by the model and that actually observed in treated animals. The lack of the sawtooth pattern from day 0 to day 12 suggest that sampling during this period (at 3-d intervals) was unable to detect the peaks and valleys.

**Stanchioned vs. outdoor treatments.** Fig. 4A shows the levels of ivermectin in the serum in cattle that were treated orally at 200 $\mu g/kg$ twice weekly and allowed to graze on pasture as compared to animals held in stanchions in a barn. When the animals were in stanchions, the level of ivermectin in serum reached ca. 15-16 ppb; however, when they were moved to pasture, the concentration declined to 5-8 ppb. Animals moved from pasture to the indoor stanchions showed an increase in serum ivermectin levels. A paired $t$-test of the means for indoor vs outdoor conditions showed significant differences at the 5% level.

In contrast, when the animals were treated with the subcutaneous injections at a rate of 40 $\mu g/kg$ twice weekly, the effect of moving the animals from indoor stanchions to outdoor pasture and vice versa was not obvious (Fig. 4B). The paired $t$-test of means indicated no significant difference ($P > 0.05$) for indoor and outdoor holding.

**Feed intake vs. drug serum levels.** Figure 5 shows a comparison of the levels of ivermectin in the serum of stanchioned cattle treated at 200 $\mu g/kg$ twice weekly and fed either 1.5% or 3% of body weight. Those animals fed the alfalfa cubes at 3% of body weight had lower levels of ivermectin in their serum. A paired $t$-test of means indicated a significant difference ($P \leq 0.05$) due to the level of feeding. Therefore, it appears that the quantity of feed can significantly influence the uptake of ivermectin in oral treatments and impact serum ivermectin levels. The results of this trial provide an
The results of these trials provide a useful database for the development of improved delivery systems for ivermectin in cattle. Serum levels resulting from daily injections can provide an indication of expectations for sustained-release implants (Miller et al. 1983). Daily oral treatments should mimic the results from sustained-release boluses (Miller et al. 1979) and osmotic pumps (Pope et al. 1985). The results also provide an indication of possible serum levels resulting from daily or cyclic consumption of medicated feeds or mineral mixes (Miller et al. 1989). Moreover, the use of the spreadsheet model can enable estimates of serum levels resulting from various treatment levels and strategies.
Fig. 4. Concentrations of ivermectin in the serum of cattle treated twice weekly either by (A) oral capsules at 200 µg/kg or (B) subcutaneous injections at 40 µg/kg. One group was held on pasture and the other in indoor stanchions, and on day 14 the groups were switched.
Fig. 5. Concentrations of ivermectin in the serum of cattle treated by oral capsules at 200 μg/kg twice weekly. One group was fed alfalfa cubes at 1.5% body weight daily, and the other group was fed the cubes at 3.0% body weight daily.

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