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A PRELIMINARY KINETIC STUDY OF EPRINOMECTIN IN THE DROMEDARY CAMEL

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ABSTRACT

The present study was conducted to investigate the effect of the administration site on the plasma kinetics of eprinomectin in five dromedary camels following a single pour-on administration (0.500 mg/kg bw). Three camels received uniformly the drug along the dorsal line, from the base of the tail to the withers, including hump whereas the others received the drug dose half administered in the withers region while the other half was given in the croup zone.

The obtained results showed that the peak plasma concentration (C_{max}) was about two-fold higher and the area under plasma concentration curve (AUC) increased by 64% when the hump was excluded from the site of administration.

Key words: Camel, dromedary, eprinomectin, pharmacokinetics

Eprinomectin is a new member of the endectocide avermectin family which is marked for use in cattle including dairy cows without withdrawal time for milk (Shoop *et al,* 1996a). Eprinomectin exhibits potent acaricidal, insecticidal and_nematodicidal activities in several ruminant species (Shoop *et al,* 1996b; Barth *et al,* 1997; Holste *et al,* 1997; Pitt *et al,* 1997; Chartier *et al,* 1999). The pharmacokinetics of eprinomectin has been investigated in cattle (Shoop *et al,* 1996b ; Alvinerie *et al,* 1999) and goats (Alvinerie *et al,* 1999). In cattle, eprinomectin was developed only for topical use. This route of administration could be more adequate in animal species that are difficult to handle for drug administration such as the camel. However, the drug absorption following topical administration was reported to be affected by environmental conditions, particularly ambient temperature (Taylor *et al,* 1983). Moreover, in the camel, the presence of the hump, which content is mainly fate, is likely to interfere with the topically administered drug absorption, especially when using highly lipophilic molecules such as endectocide agents.

Present study was, therefore, undertaken to investigate the effect of the administration site on the plasma kinetics of eprinomectin in the dromedary camel following a single pour-on administration using the recommended dose for cattle.

Materials and Methods

Five adult non-lactating, non-pregnant female camels (*Camelus dromedarius*) weighing between 380 and 412 kg were used in this study. The animals were in good health based on physical examination. The animals were kept in half-shaded paddock and received barely (2 kg/animal) and wheat straw and water *ad-libitum*.

The ambient temperature varied between 18°C and 23°C and no rainfall was recorded in the area during the experiment period.

The animals were allocated into two groups H and NH of 3 and 2 animals each, respectively. They were administered eprinomectin (Eprinex^{R}; Merial) at two different sites using the recommended dose rate for cattle (0.500 mg/kg bodyweight corresponding to 1 ml/10 kg bodyweight). Group H received uniformly the drug along the dorsal line, as recommended for cattle, from the base of the tail to the withers, including hump. The dense hair on the hump line was manually moved apart to make sure drug touching closely the skin. Whereas, in the group NH, the drug dose half administered in the withers region while the other half was given in the croup zone.

Blood samples (6-8 ml) were taken by direct venipuncture from the external jugular vein into heparinised tubes at times 0 (immediately before treatment), and at 1, 4 and 8 h and 1, 2, 4, 6, 8, 12, 16,

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20, 25, 30, 35 et 40 days after treatment. The blood sample were immediately centrifuged at 3000 g for 15 minutes and plasma stored at -20° C for subsequent analysis.

The plasma concentrations of eprinomectin were determined using a validated high-performance liquid chromatography (HPLC) method as described by Sutra *et al* (1998). The mean extraction recovery rate was about 99.7% with an inter-assay coefficient of variation of 2.8% and a limit of quantification of 0.1 ng ml^{-1} of plasma.

The plasma concentrations *vs.* time data were best fitted to a mono-compartmental model with an absorption phase. Pharmacokinetic analysis was performed using a program for non-linear regression analysis adapted from MULTI (Yamaoka *et al,* 1981). The area under the concentration (AUC) *vs.* time curve and the mean residence time (MRT) were calculated from t=0 to the last measurable concentration (t_{last}) using the arithmetic trapezoidal rule. The AUC, MRT, the absorption and elimination half-lives ($t_{1/2ka}$, $t_{1/2k10}$), the peak plasma concentration (C_{max}) and its occurring time (T_{max}) were calculated using standard equations (Gibaldi and Perrier, 1982).

Due to the small number of animals used in each group, data were not subjected to statistical analysis. Data are expressed as means ± SD.

Results and Discussion

The semi-logarithmic plot of the mean plasma concentration of eprinomectin *vs.* time is shown in figure 1 and the corresponding parameters are presented in table 1. Eprinomectin was first detected in plasma at 4 h after dosing and the plasma concentration increased thereafter slowly to reach maximal value toward 2 days in both groups. However, the absorption rate of eprinomectin ($t_{1/2ka}$, T_{max}) was somewhat faster when the drug was partly administered on the hump. In contrast, for the extent of eprinomectin absorption, the peak plasma concentration (C_{max}) was about two-fold higher and the area under plasma concentration curve (AUC) increased by 64% in group NH. The mean residence time (MRT) and the plasma half-life of elimination were comparable for both site of administration

The most striking result in the present study was the lower systemic availability of eprinomectin when the hump line was included within the administration site. This result could be explained by the sequestration of this lipophilic drug in the hump fate content. The poor vascular bed encountered in the camel hump also corroborate this finding.

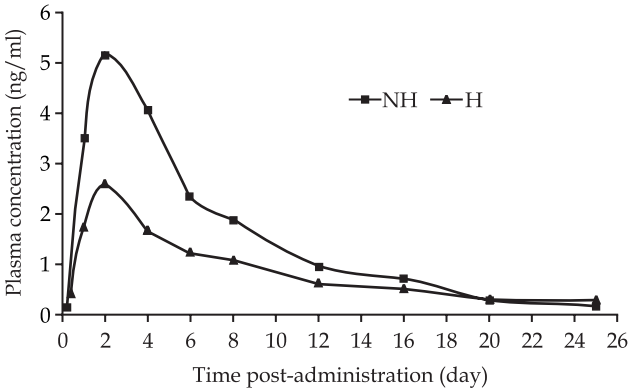

Fig 1. Mean plasma concentrations of eprinomectin after topical administration (0.500 mg/kg BW) to camels at two sites of administration H (including the hump) and NH (excluding the hump).

Table 1. Pharmacokinetic parameters describing the plasma disposition of eprinomectin after pour on administration (0.500 mg/kg) at two sites of administration in camels.

Parameters (units)	Group	
	H*	NH**
$t_{1/2ka}$ (day)	0.23^a ± 0.24	0.61^a ± 0.46
$t_{1/2k10}$ (day)	6.12^a ± 3.87	3.37^a ± 1.11
T_{max} (day)	1.67^a ± 0.57	2.29^a ± 1.07
C_{max} (ng/ml)	2.57^a ± 0.84	5.50^a ± 1.89
MRT (day)	10.56^a ± 4.07	7.17^a ± 0.99
AUC (ng.day/ml)	23.54^a ± 3.19	38.79^b ± 1.92
AUC_{NH}/AUC_H (%)+	164.78	

*H: including the hump; **NH: excluding the hump.
+AUC_{NH}/AUC_H : relative bioavailability.
For each parameter, means bearing different superscripts are significantly different at P<0.05 between site H and site NH.

The plasma kinetics of eprinomectin has been reported in cattle (Alvinerie *et al*, 1999) and goats (Alvinerie *et al,* 1999). Overall finding of these studies were markedly different with those obtained in the present study particularly when camel is compared to cattle. The AUC obtained in our study (23.54 to 38.79 ng/day/ml) was considerably lower than values reported in cattle (239. 07 ng/day/ml) (Alvinerie et *al*, 1999).

Considering the efficacy, the plasma concentration profile is often used to predict antiparasitic activity of anthelmintic agents. This prediction relies on the assumption that drug plasma concentration reflects concentration at the parasite location. The correlation between plasma and target tissues concentrations was reported for moxidectin (Lifshitz *et al*, 1999), ivermectin and doramectin (Lifshitz et *al*, 2000) in cattle. These studies have shown that plasma concentrations of

both endectocides were significantly correlated to concentrations in various target tissues such abomasal and intestinal mucosa, skin and lung. Regarding these data, it could be expected that the higher systemic availability of eprinomectin in the present study when the hump was not included in the site of administration would enhance the efficiency of this agent in camels. However, as reported for ivermectin and moxidectin (Oukessou et *al*, 1999), the lower plasma concentration of eprinomectin in camels, when compared to cattle, might suggest that the recommended dose for cattle (0.500 mg/kg BW) would be less effective in camels and therefore support the necessity to establish specific drug dosage regimens for camels.

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