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Investigation of Plasma Concentrations After Topical Administration Selamectin in Sheep and Goats*

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The objective of this study was to investigate of plasma concentration and pharmacokinetic parameters after off-label use of selamectin. One years of ago, 12 ewes and 12 female goats were used in this study. In both groups, a single dose of 12 mg/kg selamectin (Stronghold® 12% 240 mg) was administered topically. During the 35 days following administration, blood samples were taken with different intervals and required analyzes were conducted. Plasma concentrations of selamectin were analysed by high performance liquid chromatography (HPLC). As a result of analyzes, for sheep mean plasma concentration, maximum plasma concentration (C_{max}), the area under the concentration-time curve (AUC), the mean residence time (MRT) and time to reach peak concentration (T_{max}) values determined as 1427.27±90.52 pg/mL, 4.78±0.61 ng/mL, 810.35±115.95 ng.h/mL, 10.86±0.89 days and 72 hours, respectively and for goats these values were determined as 1195.03±70.81 pg/mL, 3.27±0.52 ng/mL, 664.42±72.62 ng.h/mL, 10.46±0.74 days and 72 hours, respectively. As a result, plasma concentration, C_{max} and AUC values were found higher in sheep compared to goats ($P<0.05$) and there was no significant difference between MRT and T_{max} values ($P>0.05$) using selamectin topically in sheep and goats.

Key Words: *Selamectin, sheep, goat, HPLC.*

Topikal Selamektin Uygulaması Sonrası Koyun ve Keçilerde Plazma Konsantrasyonlarının Araştırılması

Selamektinin koyun ve keçilerde etiket dışı kullanılmasını takiben plazma konsantrasyonu ve farmakokinetik parametrelerinin belirlenmesi amacıyla yapılan bu çalışmada 1 yaşında dişi 12 adet koyun ile 12 adet keçi kullanılmıştır. Her iki gruba tek doz 12 mg/kg selamektin (Stronghold® %12 240 mg) topikal olarak uygulanmıştır. 35 günlük süre boyunca farklı aralıklarla kan örnekleri alınmış ve gerekli analizler yapılmıştır. Selamektinin plazma konsantrasyonu yüksek basınçlı sıvı kromotografisiyle ölçülmüştür (HPLC). Analizler sonucunda ortalama plazma konsantrasyonu, plazma maksimum konsantrasyon (C_{max}), eğri altında kalan alan (AUC), ortalama kalış süresi (MRT) ve plazma maksimum konsantrasyona ulaşma süresi (T_{max}) koyunlarda sırasıyla 1427.27±90.52 pg/mL, 4.78±0.61 ng/mL, 810.35±115.95 ng.saat/mL, 10.86±0.89 gün ve 72 saat; keçilerde ise 1195.03±70.81 pg/mL; 3.27±0.52 ng/mL, 664.42±72.62 ng.saat/mL, 10.46±0.74 gün ve 72 saat olarak belirlenmiştir. Sonuç olarak, selamektinin koyun ve keçilere topikal olarak uygulanması halinde plazma konsantrasyon düzeyi, C_{max} ve AUC değerlerinin koyunlarda keçilere göre daha yüksek bulunduğu ($P<0.05$), MRT ve T_{max} değerleri arasında ise önemli bir fark olmadığı ($P>0.05$) tespit edilmiştir.

Anahtar Kelimeler: *Selamektin, koyun, keçi, HPLC.*

Introduction

Because macrocyclic lactones (ML) has a wide spectrum and are reliable drugs, they are used widely at animals to treat parasitic diseases (1-3). Selamectin is created using by chemical modification of doramectin, a new semi-synthetic product (4). It has mininum dosage of 6 mg/ kg with very wide spectrum including most of ecto and endoparasites and marketed worldwide with the name of Stronghold® (Europe) and Revolution® (USA) as a topical product (5-7).

Avermectin's pharmacokinetic profiles significantly affected by important factors, such as species, age, sex and physiological condition of the animal, aplication route and formulation of drug, nutrition, intra-species and interspecies variatons, differences at metabolism or elimination process (8-10). Avermectins has less soluble ratings in water and highly soluble in oil (11). Due to high soluble rating in oil, adipose tissue has been served as drug storage. High proportion fat soluble of this group of drugs; has a large volume of distribution and accumulated at liver and adipose tissue to be eliminated slowly (2).

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There is no data on the kinetic disposition of selamectin following topical administration in sheep and goats. Thus, the aim of study was to determine plasma concentrations and some pharmacokinetic profiles during 35 days after administration topically selamectin used widely at animals to treat ecto and endoparasitic diseases and a new product avermectin derivation with doses of 12 mg/kg at sheep and goats

Materials and Methods

Experimental animals and sampling: Twelve healty and 1 year old, weighing 40 kg on average sheep and 30 kg goats were used in this study. The animals were allocated into two groups of twelve animals each. They were all female provided by Agriculture and Livestock Research Centre of Fırat University. The animals were housed and fed (barley and concentrated feed) for at least 30 days. Water was supplied ad libitum. Both group was applied topically skin on the back at a dose of 12 mg/kg bodyweight selamectin (Stronghold®, Pfizer, ABD). Heparinized blood samples (5 mL) were collected by jugular vein puncture prior to drug administration then at 0, 1, 2, 3, 4, 6, 7, 8, 9, 10, 14, 16, 18, 21, 28 and 35 days. Blood samples were centrifuged at 3500 g for 15 min.

Analytical procedures: The plasma concentration of selamectin was analysed by high performance liquid chromatography (HPLC) according to the method of Sutra et al. (12) and Walker and Fenner (13) using HPLC system (Schimadzu LC-20 AT, Japan). The mobile phase (13) consisted of acetonitrile- water-tetrahidrofuran (68:17:15, v/v/v) and at a flow rate of 1 mL/minute. A C_{18} analytical column (5 µ; 250x4.6 mm, Phenomenex, UK) was used for analysis. Fluorescence detection was at an excitation wavelength of 360 nm and emission wavelength of 450 nm. Each sample run was 15 min.

Pharmacokinetic and statistical analysis of data: The plasma concentration-time data after administration of drug for each animal were created by using WinNonlin® 4.1 software programme (Scientific Consulting Inc., USA). Pharmacokinetic parameters for each animal were analyzed using topical route of administration and non-compartmental model. SPSS software (for Windows 11.5) was used for the statistical analysis. Mann Whitney U-test was used to test for between species differences in plasma concentration and some pharmacokinetic parametres. Results mean ± standart deviation (SD) were expressed and mean values were considered statistically was different at $P<0.05$.

Results

The mean pharmacokinetic parameters of selamectin after topical administration in sheep and goats are shown in Table 1 with mean plasma concentrations time curve goats and sheep (Figure 1 and 2). Plasma concentration of sheeps (1427.27±90.52 pg/mL) was found to significantly higher compared to goats (1195.03±70.81 pg/mL) ($P<0.05$). Accordingly, C_{max} and AUC in sheep were found to be higher compared goats ($P<0.05$). However, there was no statistically significant differences in terms of the values of MRT and T_{max} ($P>0.05$).

Table 1. Mean (±SD) pharmacokinetic parameters of selamectin in sheep and goats following topical administration at a dose rate of 12 mg/kg (n: 20)

Parameters	Sheep	Goat
C_{max} (ng/mL)	4.78±0.61*	3.27±0.52
AUC (ng.h/mL)	810.35±115.95*	664.42±72.62
MRT (day)	10.86±0.89	10.46±0.74
T_{max} (h)	72	72

T_{max}: Time to reach peak concentration; C_{max}: Maximum plasma concentration; AUC: Area under the concentration-time curve; MRT: Mean residence time. Mean kinetic parameters of selamectin in sheep significantly different (*$P<0.05$) from goats.

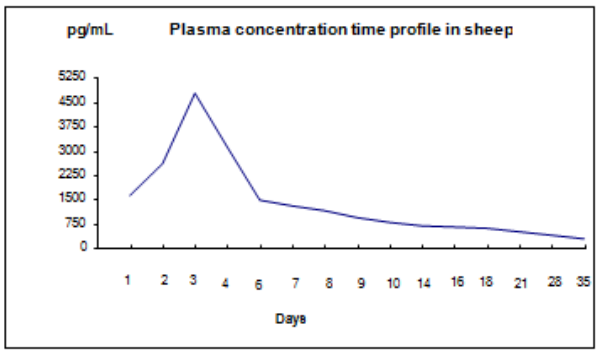

Figure 1. Mean (±S.D.) plasma concentration time profile after topical administration selamectin at a dose of 12 mg/kg in sheep

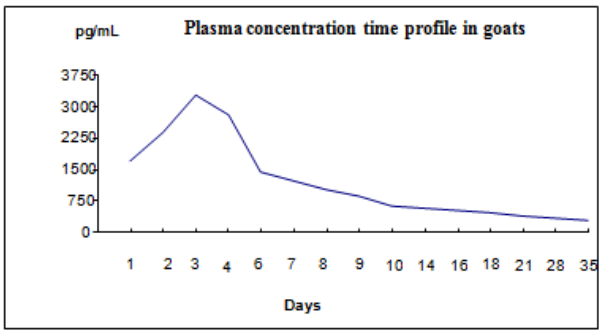

Figure 2. Mean (±S.D.) plasma concentration time profile after topical administration selamectin at a dose of 12 mg/kg in goats

Discussion

Pharmacokinetic studies on selamectin (1, 14, 15) usually carried out in cats and dogs. In sheep, goats and cattle, there was no study conducted. In this study, there were evaluated mean plasma concentration levels, C_{max}, AUC, MRT and T_{max} values during following 35 days after topically administration of selamectin with a single

dose 12 mg/kg in sheep and goats. Animal species, sex, route of administration, and feeding, body-fat ratio, physico-chemical structure and formulation of drug were known on pharmacokinetic of selamectin (1, 8, 14-22).

As a result of the analysis, for sheep mean plasma concentration, C_{max}, AUC, MRT and T_{max} values determined as 1427.27±90.52 pg/mL, 4.78±0.61ng/mL, 810.35±115.95 ng.h/mL, 10.86±0.89 days and 72 hours, respectively and for goats plasma concentration, C_{max}, AUC, MRT and T_{max} values determined as 1195.03±70.81 pg/mL, 3.27±0.52 ng/mL, 664.42±72.62 ng.h/ml, 10.46±0.74 days and 72 hours, respectively.

In a study conducted by Sarasola et al. (15), after topically administration of selamectin C_{max} and T_{max} values were determined as 86.5±34.0 ng/mL and 3 days in dogs, respectively and for cats 5513±2173 ng/mL and 15 hours, respectively.

In a study conducted by Dupuy et al. (1), after topically administration of selamectin with 6 mg/kg dose C_{max}, AUC, MRT, T_{max} values determined as 12.72±5.13 ng/mL, 192.08±63.85 ng.d/mL, 12.55 days, 4.86±3.56 days at male dogs, respectively and 22.65±11.95 ng/mL, 370.97±146.87 ng.d/mL, 12.55 days, 5.2±1.87 days for female dogs, respectively.

As a result, selamectin was topically administered for treatment and control of parasitic diseases of sheep and goats, mean plasma concentration, C_{max} and AUC values were found higher in sheeps compared to goats and no significant difference were identified between goats and sheep for MRT and T_{max} values.

This study has contributed to pharmacokinetic values of selamectin at sheep and goats. We believe that new studies must be conducted for dose and dose limits, planned a variety of pharmacokinetic studies, revealing drug interactions and determination of residual period of selamectin at sheep, goat and cattle.

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