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PHARMACO KINETICS OF IVERMECTIN (IVERMIC SUPER) FOLLOWING SINGLE DOSE SUBCUTANEOUS ADMINISTRATION IN SHEEP

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Abstract: The present study was undertaken to evaluate the pharmacokinetics of Ivermectin (Ivermic super®) 0.2 mg/kg b.wt in sheep. The plasma concentration of ivermectin was determined by HPLC. The decay in plasma concentration of drug was biexponential in sheep. The C_{max} value of 17.93, was obtained at T_{max} of 3.3 days in sheep, following SC administration of Ivermic super®. The elimination half life (β_HL), volume of distribution (V1_F) and AUC were calculated as 6.25 days, 4.11 $L.kg^{-1}$, 161.8 day.ng/mL in sheep , following SC administration of Ivermic super®. A dosage regimen of 0.2 mg/kg at 14 days interval is recommended in sheep.

Keywords: Ivermectin, Pharmacokinetics, Subcutaneous, Sheep.

INTRODUCTION

Ivermectin is being used to treat billions of livestock and pets around the world, helping to boost production of food and leather products, as well as keep billions of companion animals, particularly dogs and horses, healthy. Its use has revolutionized the treatment of nematode and arthropod parasites in animals and has provided hope for the control or even eradication of filariases in humans (Timothy, 2005). All important gastrointestinal and lung nematodes are susceptible to the drug, including sensitive mites (Campbell and Benz, 1984), ticks (Campbell, 1989), biting flies, and parasitic dipteran larvae (McKel-lar and Benchaoui, 1996). The pharmacokinetic parameters of Ivermectin vary extensively and in accordance with many factors that can all influence the drug's plasma concentration. The purpose of present study was undertaken to elucidate disposition kinetics and dose regimen of Ivermectin in cattle calves. The purpose of the present study was to determine the pharmacokinetics and dosage regimen of Ivermectin following single dose subcutaneous (SC) administration.

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MATERIALS AND METHODS

The present study was conducted in four adult, indigenous male Muzzaffarnagari sheep (1.5-2.5 yrs in age, weighing 23±2 kg). Indigenous male Muzzaffarnagari sheep for this study were procured from Department of Livestock Production and Management of the College of Veterinary and Animal Sciences, Pantnagar. All these animals were housed in animal house of department of Veterinary Pharmacology and Toxicology and kept on pre-experimental period for one month before the commencement of experiment to acclimatize them to new environment. Physical and clinical examination was done before the start of experiment. The animals were reared under uniform management and husbandry conditions, maintained on standard ration and water provided *ad libitum*. The animals were kept under constant observation before the commencement of the experiment.

Injectable formulation of Ivermic super® (M/s Montajat Vet. Pharmaceuticals Ltd.,) was used in the study. Pharmacokinetic study of Ivermectin was conducted following a single dose (0.2 mg kg^{-1}) Subcutaneous (SC) injection in neck region of sheep. The blood samples were collected from jugular vein of calves in heparinized microcentrifuge tubes by disposable plastic syringes at time interval of 0 min, 15 min, 30 min, 1h, 3 h, 6 h, 12 h, 1 day, 3 day, 6 day, 9 day and up to 42 days. The blood samples collected in heparinized tubes following administration of Ivermectin were centrifuged at 5000 rpm (15 min) for separation of plasma. The plasma thus obtained was collected in micro centrifuge tubes and stored at -20°C till further analysis. An intervening wash out period of one month was given to all the animals before commencement of new experiment.

EXTRACTION AND DERIVATIZATION OF IVERMECTIN FROM PLASMA SAMPLES

Extraction of plasma samples was carried out as per the method described by Perez *et al*. (2007) and Na-Bangchang *et al*. (2006) with slight modifications**.** 1 ml of acetonitrile and 0.25 ml of deionised water was added to 1 ml of plasma sample, vortex mixed for 20-30 seconds and centrifuged at 12,000g for 12 minutes (4°c). The supernatant was transferred to a clean tube and evaporated to dryness under a stream of nitrogen at 30-40°c. The residue was subjected to derivatization according to the method of De Montigny *et al*. (1990). The residue was dissolved in 100 µL of 1-methylimidazole solution in acetonitrile (1:2 v/v). To initiate the derivatization, 150 µL of Trifluoroacetic anhydride solution in acetonitrile (1:2 v/v) was added. After completion of the reaction (< 30 s), an aliquot (20 µL) of this solution was injected directly in to HPLC.

The isocratic mobile phase consists of acetic acid (0.2% in water), methanol, and acetonitrile (4:32:64, v/v/v). The flow rate was kept at 0.7 $ml.min^{-1}$ at a temperature of 30°C with fluorescence detection at an excitation wavelength of 365 nm and an emission wavelength of 475 nm. Ivermectin was quantified from its respective retention time.

The standards for Ivermectin were made by dissolving 1 mg of pure Ivermectin in 1 ml of methanol from which concentrations of 100, 50, 25, 10, 5, 1 $ng.ml^{-1}$ were made in methanol. 20 µl of these concentrations was injected into HPLC system and quantified under the HPLC conditions mentioned above. The standard calibration curve for Ivermectin was obtained by plotting concentrations *versus* mean of the peak areas obtained for their respective standards. The limit of quantification (LOQ) for Ivermectin was $1ng.ml^{-1}$. The method for Ivermectin was found to be linear and reproducible in the concentrations ranging 100 to 1 $ng.ml^{-1}$. A retention time of 24 .1 min for Ivermectin was observed**.**

The concentrations of the Ivermectin standard were made in drug free plasma as 100, 50, 25, 10, 5, 1 $ng.ml^{-1}$ applying serial ten times dilution (100 µl standard + 900 µl drug free plasma) of 1000, 500, 250, 100, 50, 10 $ng.ml^{-1}$ of standard in methanol, in equal volumes of drug free plasma, each time. The extraction from plasma was done by the same procedure as mentioned earlier. The areas obtained by chromatography were plotted against concentration in order to get a standard calibration curve. Recovery of the drug was done by deproteinizing the plasma having above mentioned drug concentration. Recovery percent of Ivermectin from plasma was 83.2.

The plasma concentrations and pharmacokinetic variables of Ivermectin were expressed as mean ± S.E. The pharmacokinetic analysis of the plasma concentration obtained following SC administration of Ivermectin in this study was done by pharmacokinetic software "Phasight WinNonlin" version 5.3.

RESULTS & DISCUSSION

A two-compartment model adequately described the plasma concentration-time profile of Ivermic super® in sheep following single dose (0.2 $mg.kg^{-1}$) SC administration in the present study.

The values of C_{max} were 17.93 $ng.ml^{-1}$ in sheep following SC administration of Ivermic super®. These findings could be well corroborated with C_{max} in sheep (16.3 ng/mL; Atta and Abo-Shihada, 2000).

The higher peak plasma C_{max} level compared to present study has been reported in cattle (42.8, 46.4 and 40 ng/mL; Lanusse *et al*., 1997, Lifschitz *et al*., 1999a and Lifschitz *et al*.,

2000, respectively), sheep (41.2 and 30 ng/mL; Echeverria *et al*., 2002 and Mckellar *et al*., 1991, respectively), pigs (39.6; Lifschitz *et al*., 1999a), horses (51.3 ng/mL; Perez *et al*., 2002) and dogs (44.3 ng/mL; Daurio *et al*., 1992).

However, lower peak plasma C_{max} level compared to present study has been reported in sheep as (12.2, 16 and 11.9 ng/mL; Gayrard *et al*., 1999, Laffont *et al*., 2001 and Cerkvenik *et al*., 2002, respectively), goats (9.3 and 6.1 ng/mL; Escudero *et al*., 1997 and Alvinerie *et al*., 1993, respectively).

The lower plasma levels in sheep in the present study may be due to a wider distribution rather than to faster elimination. The considerable peak plasma concentration (C_{max}) in the present study is due to the formulations of propylene glycol: glycerol-formal (60:40 v/v) as vehicle in the injectable product (Ivermic super®). Injectable product has the advantage that higher maximum plasma concentration are achieved and, thus presumably (by gradient diffusion) greater skin penetration and ectoparasiticidal activity, whereas the oral product is more easily administered and may have greater activity against some intestinal nematodes.

The average value of T_{max} in sheep in the present study was 3.3 days following SC administration of Ivermic super®. These findings could be well corroborated with T_{max} (3.4 days) in cattle (Gayrard *et al*., 1999) and goats (3 days; Gonzalez *et al*., 2006).

A lower level of T_{max} (2.25 days) compared to present study has been reported in cattle (Lifschitz *et al*., 1999b), sheep (1.7 and1.24 days; Cerkvenik *et al*., 2002 and Barber *et al*., 2003, respectively). However, higher level of T_{max} (15 days) has been reported in cattle (Alvinerie *et al*., 1998). The difference in the value of T_{max} in the present study could be due to the species variation.

The mean elimination half -lives were 6.25 days in sheep following SC route of administration of Ivermic super®. These findings of mean elimination half -lives could be corroborated with (7.4 days) in goats (Gonzalez *et al*., 2006).

The higher mean elimination half-lives compared to present study has been reported (17.2 days) in cattle (Lanusse *et al*., 1997), in sheep (9.6 days; Gonzalez *et al*., 2007). However, lower mean elimination half-lives compared to present study has been reported (1.18 days) in pigs (Craven *et al*., 2001).

In the present study, the volume of distribution (V1_F) was 4.11 $L.kg^{-1}$ in sheep following SC of Ivermic super®. These findings could be well corroborated with volume of distribution (4.6 $L.kg^{-1}$) in sheep (Lo *et al*., 1985). Distribution in the sheep is faster and wider than in cattle or dogs (Lo *et al*., 1985) due to substantial deposition into adipose tissue, which may act as a

drug depot (Prichard *et al*., 1985). The larger fat reservoir in sheep compared to cattle could contribute not only to the more extensive distribution but also the greater persistence in plasma at lower concentrations, probably because less blood is supplied to fatty tissues (Atta and Abo-Shihada, 2000).

A lower volume of distribution (1.2 $L.kg^{-1}$) compared to present study has been reported in cattle (Echeverria *et al*., 1997), goats (2.8 $L.kg^{-1}$; Gonzalez *et al*., 2006), pigs (2.7 $L.kg^{-1}$; Craven *et al*., 2001) and sheep (3 $L.kg^{-1}$; Gonzalez *et al*., 2007). However, higher volume of distribution compared to present study has been reported (8.8 $L.kg^{-1}$) in sheep (Echeverria *et al*., 2002), and goats (12.8 $L.kg^{-1}$, Gonzalez *et al*., 2006).

The area under curves (AUC) were 161.81 $ng.ml^{-1}$ day in sheep following SC administration of Ivermic super® respectively. The findings of the present study could be compared with that reported (153 $ng.ml^{-1}$day) in goats (Gonzalez *et al*., 2006), pigs (165 $ng.ml^{-1}$day; Lifschitz *et al*., 1999a), and cattle (149 $ng.ml^{-1}$day; Lo *et al*., 1985).

However, higher area under curve (AUC) compared to present study has been reported in cattle (459, 595.1 and 328.8 $ng.ml^{-1}$ day; Lanusse *et al*., 1997, Laffont *et al*., 2001 and Echeverria *et al*., 1997, respectively)**,** horses (550.4 $ng.ml^{-1}$ day; Marriner *et al*., 1987), sheep (197,175 and 207.5 $ng.ml^{-1}$day; Gonzalez *et al*., 2007, Mckellar *et al*., 1991 and Echeverria *et al*., 2002, respectively). The lower area under curve (AUC) compared to present study has been reported (121.5 $ng.ml^{-1}$day) in cattle (Gayrard *et al*., 1999), sheep (64, 82.1 and 74.6 $ng.ml^{-1}$day; Cerkvenik *et al*., 2002, Barber *et al*., 2003 and Mckellar *et al*., 1991, respectively), goats (60 and 34.4 $ng.ml^{-1}$day; Alvinerie *et al*., 1993 and Escudero *et al*., 1997, respectively), pigs (71.41 and 85.7 $ng.ml^{-1}$day; Scott and Mckellar, 1992 and Craven *et al*., 2002a, respectively) horses (137.1 $ng.ml^{-1}$day, Perez *et al*., 2002), donkeys (119.3 $ng.ml^{-1}$day; Gokbulut *et al*., 2005) and dogs (4.5 $ng.ml^{-1}$day; Daurio *et al*., 1992).

The values of clearance in this study were 1.23 $L.kg^{-1}.day^{-1}$ in sheep following SC administration of Ivermic super®. The findings of the present study could be compared with that plasma clearance observed (1.11 $L.kg^{-1}.day^{-1}$) in sheep (Gonzalez *et al*., 2007) and goats (1.56 $L.kg^{-1}.day^{-1}$; Gonzalez *et al*., 2006).

The higher plasma clearance compared to present study has been reported (3.24 $L.kg^{-1}.day^{-1}$) in sheep (Cerkvenik *et al*., 2002), and pigs (4.15 $L.kg^{-1}.day^{-1}$, Craven *et al*., 2001).

However, lower plasma clearance compared to present study has been reported in cattle (0.27, 0.35 and 0.48 $L.kg^{-1}.day^{-1}$; Laffont *et al*., 2001, Bousquet-Melou *et al*., 2004 and Lanusse *et al*., 1997, respectively) and sheep (0.56 $L.kg^{-1}.day^{-1}$; Prichard *et al*., 1985).

A dosage regimen based on the pharmacokinetic data obtained following SC administration Ivermectin (Ivermic super®) in adult male sheep was calculated with therapeutic concentration of 1 $ng.ml^{-1}$ at dosing intervals of 7, 14 and 21 days. Priming doses of 0.24041, 0.53773 and 1.20274 $mg.kg^{-1}$ and maintenance doses of 0.13292, 0.43024 and 1.09526 $mg.kg^{-1}$ was calculated (C^{ss}_{min} =15.04, 4.64 and 1.82 $ng.ml^{-1}$ respectively, C^{ss}_{max} =33.65, 23.25 and 20.43 $ng.ml^{-1}$, respectively) at 7, 14 and 21 days interval, respectively

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Figure 1: Plasma concentration-time plot of observed concentration (mean) Vs predicted profile of Ivermectin (Ivermic super®) following single dose (0.2 mg.kg^{-1}) subcutaneous administration in sheep (n=4)

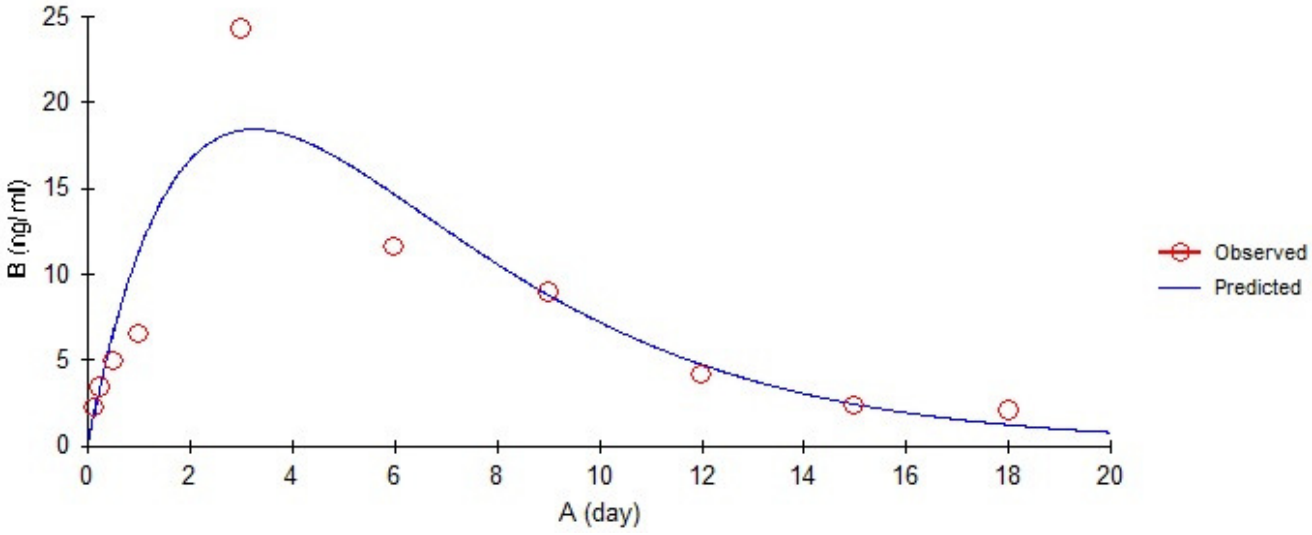

Table1: Pharmacokinetic parameters of Ivermectin (Ivermic super®) in plasma following its single dose (0.2 mg.kg^{-1}) subcutaneous administration in sheep (n=4)

Parameters	Units	I	II	III	IV	Mean±SE
V1_F	ml/kg	4037.039	4071.039	4096.186	4272.516	4119.1±52.52
K01	1/day	0.309	0.301	0.305	0.300	0.303±52.52
K10	1/day	0.300	0.298	0.300	0.301	0.299±0.0006
K12	1/day	0.003	0.0004	0.0018	0.0015	0.001±0.0005
K21	1/day	0.097	0.138	0.144	0.088	0.116±0.01
AUC	day.ng/ml	164.638	164.386	162.742	155.500	161.81±2.14
K01_HL	Day	2.238	2.295	2.272	2.309	2.278±0.01
K10_HL	Day	2.303	2.319	2.310	2.302	2.308±0.003

Alpha	1/day	0.306	0.299	0.303	0.303	0.302±0.001
Beta	1/day	0.095	0.138	0.142	0.087	0.115±0.01
Alpha_HL	Day	2.259	2.313	2.283	2.285	2.285±0.01
Beta_HL	Day	7.256	5.014	4.852	7.91	6.258±0.77
A	ng/ml	5138.047	6492.150	9341.190	4500.009	6367.8±107
B	ng/ml	0.623	0.201	0.947	0.199	0.492±0.18
CL_F	ml/day/kg	1214.783	1216.641	1228.901	1286.165	1236.6±16.8
V2_F	ml/kg	164.030	12.24	51.737	76.903	76.227±32.15
CLD2_F	ml/day/kg	15.969	1.697	7.475	6.783	7.981±2.95
Tmax	Day	3.260	3.327	3.299	3.320	3.301±0.015
Cmax	ng/ml	18.382	18.154	18.067	17.155	17.939±0.26

Pharmacokinetic Parameters: Symbols & Units

A	$ng.ml^{-1}$	Coefficient of biexponential equation describing disposition curve; zero time intercept of plasma concentration in the distribution phase
B	$ng.ml^{-1}$	Zero-time plasma drug conc. intercept of regression line of absorption phase
α	day^{-1}	First order rate constant; Regression coefficient for the distribution phase of the disposition curve
AUC	$ng.day.ml^{-1}$	Total area under the curve (from time zero to infinity); characterizes the relation between drug concentration and the time for which these concentrations persist in the blood; calculated by trapezoidal rule
B	$ng.ml^{-1}$	Zero time intercept of plasma concentration in the elimination phase
β	day^{-1}	Regression coefficient for the elimination phase, it is the terminal slope of the least-squares linear regression line through a plot of the natural logarithm of plasma-serum conc. (lnC) versus time (t)
CL_F	$L.kg^{-1}.day^{-1}$	Total body clearance; it is the portion of the volume of blood cleared off the drug per unit time. It equals the sum of renal clearance and metabolite or hepatic clearance
K_{12}	day^{-1}	The first order rate constant of transfer of unbound drug from central to peripheral compartment
K_{21}	day^{-1}	The rate constant of drug transfer from peripheral to central

		compartment
K01	day^{-1}	First order absorption rate constant in one compartment model
K10	day^{-1}	First order rate constant for elimination of drug from central compartment in one compartment model or elimination half life first phase in two compartment
Alpha_HL	Day	Distribution half-life in two compartment model
Beta_HL	Day	Elimination half-life in two compartment model
K01_HL	Day	Absorption half life in one compartment model
K10_HL	Day	Elimination half life in one compartment
V1_F	$L.Kg^{-1}$	Volume of distribution in central compartment when fraction of drug absorption is not known
V2_F	$L.Kg^{-1}$	Volume of distribution in peripheral compartment when fraction of drug absorption is not known
Tmax	Day	Time to reach peak plasma concentration
Cmax	$ng.ml^{-1}$	Peak plasma concentration