Int.J.Curr.Microbiol.App.Sci (2020) *9*(6): 4222-4231

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 9 Number 6 (2020)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2020.906.495

Disposition Kinetics of Ivermectin (Ivomec Super®) Following Single Dose Subcutaneous Administration in Cattle Calves

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Keywords

Cattle calf, Ivermectin, Pharmacokinetics, Subcutaneous

Article Info

Accepted:
12 May 2020
Available Online:
10 June 2020

A B S T R A C T

The present study was undertaken to evaluate the pharmacokinetics of Ivermectin (Ivomec super®) 0.2 mg/kg b.wt in cattle calves. The study was conducted in four cross-bred male cattle calves (1.0-1.5 yrs in age, weighing 110±5 kg). The plasma concentration of ivermectin was determined by HPLC. The decay in plasma concentration of drug was biexponential in cattle calves. The C_{max} value of 33.38 ng/mL was obtained at T_{max} of 4.49 days in cattle calves, following SC administration of Ivomec super ®. The elimination half life (β_HL), volume of distribution (V1_F) and AUC were calculated as 24.59 days, 2.28 $L.kg^{-1}$, 393.9 day.ng/mL in cattle calves , following SC administration of Ivomec super ®. A dosage regimen of 0.2 mg/kg at 14 days interval is recommended in cattle.

Introduction

Ivermectin used to treat billions of livestock and pets around the world. Ivermectin was the world's first endectocide, forerunner of a completely new class of antiparasitic agents, potently active against a wide range of internal and external nematodes and arthropods. It is a semisynthetic derivative of avermectin B1and consists of an 80:20 mixture of the equipotent homologous 22, 23 dehydro B1a and B1b. This antiparasitic agent, developed by Merck & Co., is frequently used in veterinary medicine, due to its broad spectrum of activity, high efficacy and wide margin of safety (Fisher *et al.*, 1989). It is a highly lipophilic substance that dissolves in most Organic solvents, but is practically insoluble in water (0.0004% m/v). Ivermectin was first marketed in 1981 by Merck Sharp and Dohme as an antiparasitic agent (Steel, 1993), and it remains the leading worldwide antiparasitic agent for livestock.

It has exceptional potency against endo- and ectoparasites at extremely low doses (doses recommended are expressed as µg/kg); this accounts for its large margin of safety. Toxicity to ivermectin is rare across animal species. The signs of toxicosis are mydriasis

and depression, followed by ataxia, recumbency, and death. It has no adverse effects on breeding performance.

Many rumino-reticular delivery systems, as well as oral, topical, and injectable formulations of ivermectin, are currently available at the dosage recommended by manufacturers, namely, 200 µg/kg in ruminants (500 µg/kg for topical application) and equines, 300 µg/kg in pigs, and 6 µg/kg in dogs.

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 (Aranzazu *et al.*, 2009). All important gastrointestinal and lung nematodes are susceptible to the drug, including sensitive mites (Baggot, 1988), ticks (Marriner *et al.*, 1987), biting flies, and parasitic dipteran larvae (Timothy, 2005).

The pharmacokinetic parameters of Ivermectin vary extensively and in accordance with many factors that can all influence the drug's plasma concentration. These factors, which include the species, route of administration, vehicle used in the commercial formulation, bodyweight, body condition, physiological status, and amount and type of nutrition, create difficulties when extrapolating data from one species to another and should be considered in clinical practice in order to achieve effective levels that will last as long as possible.

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.

Materials and Methods

Experimental animals

The present study was conducted in four cross-bred male cattle calves (1.0-1.5 yrs in age, weighing 110±5 kg). Cross-bred male cattle calves for this study were procured from Instructional Dairy Farm (IDF), of 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.

Ethical approval

Institutional Animal ethics committee principles were followed strictly throughout the course of this study. Animals were handled gently and carefully. Deworming was done one month before the start of experimentation with the help of fenbendazole which was given at the rate 5mg/kg body weight.

Instruments used

HPLC system (Shimadzu Corporation, Kyoto, Japan, Model RF-10A_{XL}, LC10AT) comprised of double plunger pump, Rheodyne injector with 20 µl loop, Fluorescence detector, C_{18} reverse phase column (Lichrospher 100 RP-18, 5µm (125 mm x 4 mm) with a guard column (Lichrospher 100 RP-18e (5µm), Merck Kga A, 64271 Darmstadt, Germany, Hamilton

Syringe, Manufactured by Hamilton (Co., RE No. Nevada, USA) volume 20µl, to load the sample into the injector, Refrigeration Centrifuge machine

Drugs and Chemicals used

Pure technical standard Ivermectin (Sigma Aldrich Ltd), Methanol (HPLC grade), Acetonitrile (HPLC grade), Water (HPLC grade), Trifluoroacetic anhydride (Avra®), 1-methyl imidazole (HIMEDIA®), Heparin (Loba Chemie®), Acetic acid (HPLC grade)

Estimation of Ivermectin

Injectable formulation of Ivomec super® (M/s Merial Saude Animal 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 cattle. 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.

Preparation of Standard Curve

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.

Pharmacokinetic analysis of data

The plasma concentrations and pharmaco-kinetic 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 and Discussion

The plasma concentration-time profile following single dose (0.2 mg.kg^{-1}) subcutaneous administration of Ivermectin (Ivomec super®) in male cattle calves depicted in figure.1.

The plasma samples were collected up to 42 days. The concentration of Ivermectin could be detected only up to 30 days. The mean peak plasma concentration was 32.315 ± 0.64 ng.ml^{-1} attained at 4.44 days post administration which decreased slowly to a minimum of 2.165 ± 0.02 ng.ml^{-1} at 30th day. The pharmacokinetic parameters describing the disposition kinetics of Ivermectin (Noromectin®) following single dose (0.2 mg.kg^{-1}) subcutaneous administration are presented in Table 1. A two-compartment model adequately (r= 0.89) described the plasma concentration-time profile of Ivermectin in male cattle calves following single dose subcutaneous administration.

The mean values of zero time intercept of distribution phase (A) and elimination phase (B) in the present study were calculated to be 2487.436±263 ng.mL^{-1} and 0.304±0.03ng.ml^{-1}, respectively. The elimination rate constant of first phase (K_{10}) and second phase (β) were 0.221±0.002 and 0.04±0.001 day^{-1}, respectively, with an elimination half-life of first phase (K_{10}_HL) and second phase (Beta_HL) calculated as 3.115±0.03 and 16.92±0.79 day, respectively. The transfer rate constant from central to peripheral compartment (K_{12}) and from peripheral to central compartment (K_{21}) were 0.001±0.0002 and 0.041±0.001 day $^{-1}$, respectively. The volume of distribution of central compartment (V1_F; when fraction of drug absorption is not known), and volume of distribution of peripheral compartment (V2_F; when fraction of drug absorption is not known) were 2188.11 ± 50.7 and 116.236 ± 12.67 ml.kg^{-1} respectively. The clearance from central compartment (CL_F; when fraction of drug absorption is not known) and clearance from peripheral compartment (CLD2_F; when fraction of drug absorption is not known) were estimated as 486.558 ± 8.16 and 4.805 ± 0.47 ml.kg^{-1}.day^{-1} respectively. The rate constant of distribution phase (α) was 0.225±0.002day^{-1} with distribution half-life (Alpha_HL) of 3.078±0.029 day. The rate constant of absorption phase (K01) was 0.22 ± 0.002 day^{-1} with absorption half-life (K01_HL) of 3.115 ± 0.033 day. The mean area under curve (AUC) was 411.4 ± 7.06 ng.ml^{-1} day.

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

values of C_{max} in the present study were 33.38 $ng.ml^{-1}$ in cattle calves following SC administration of Ivomec super®. These findings could be well corroborated with C_{max} (33.1 ng/mL) in cattle (Echeverria *et al*., 1997), 32.7 ng/mL in cattle (propylene glycol: glycerol-formal vehicle 60:40 v/v) following SC route of administration. (Lifschitz *et al.*, 2004; Alvinerie *et al.*, 1998) have also reported C_{max} of 28.5 ng/mL in cattle by intraruminal route of administration. The C_{max} in the present study could also be compared with other species viz sheep (32.2 and 30 ng/ml; (Bogan, 1988) and (McKellar, 1991), respectively) and pigs (28.4 ng/mL; (Scott and McKellar, 1992)

A lower peak plasma concentration (C_{max}) as compared to the present study has been observed by other workers in cattle using different formulations (22.6, 12.2 and 16 ng/mL; (Lifschitz *et al.*, 1999b), (Gayrard *et al.*, 1999) and (Laffont *et al.*, 2001), respectively). Sheep (24.1, 25.8 and 12.5 ng/mL; (Echeverrı´a *et al*, 2002), (Barber *et al.*, 2003) and (Chiu *et al.*, 1990 a) respectively). Goats (21.8 and 9.3 ng/mL; (Gonzalez *et al.*, 2006) and (Escudero *et al.*, 1997), respectively).However, higher peak plasma concentration (C_{max}) level compared to present study has been reported in cattle (42.8, 133.2, 40 and 39 ng/mL; (Lanusse *et al.*, 1997), (Chiu *et al.*, 1990 a), (Lifschitz *et al.*, 2000) and (Laffont *et al.*, 2001), respectively). Pigs (39.6 ng/mL; (Lifschitz *et al.*, 1999a), horses (51.3 ng/mL; (Perez *et al.*, 2002) and dogs (44.3 ng/mL; (Daurio *et al.*, 1992).

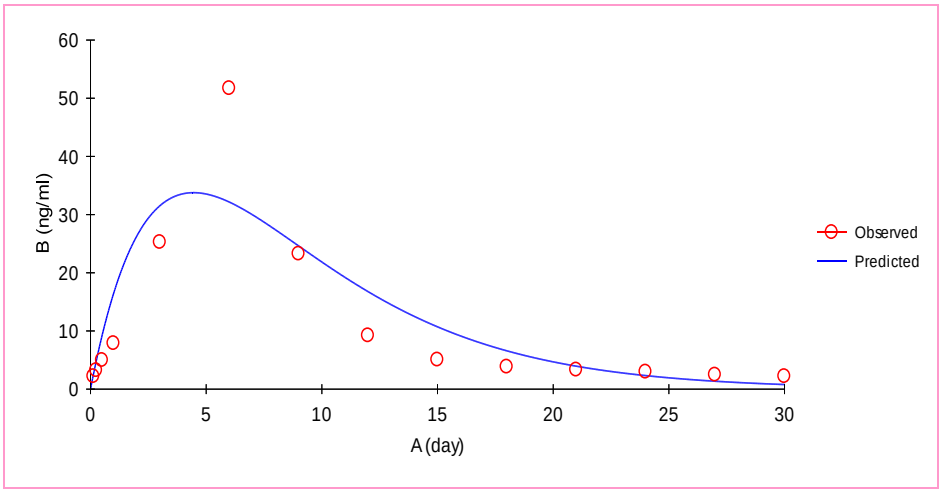
Table.1 Pharmacokinetic parameters of Ivermectin (Ivomec super®) in plasma following its single dose (0.2 $mg.kg^{-1}$) subcutaneous administration in cattle calves (n=4)

Parameters	Units	Calf Number				Mean±SE
		I	II	III	IV	I
V1_F	ml/kg	2141.514	2225.092	V1_F	ml/kg	2141.514
K01	1/day	0.220	0.215	K01	1/day	0.220
K10	1/day	0.226	0.223	K10	1/day	0.226
K12	1/day	0.001	0.002	K12	1/day	0.001
K21	1/day	0.045	0.039	K21	1/day	0.045
AUC	day.ng/ml	411.584	401.710	AUC	day.ng/ml	411.584
K01_HL	Day	3.140	3.212	K01_HL	Day	3.140
K10_HL	Day	3.054	3.097	K10_HL	Day	3.054
Alpha	1/day	0.229	0.226	Alpha	1/day	0.229
Beta	1/day	0.045	0.038	Beta	1/day	0.045
Alpha_HL	Day	3.026	3.063	Alpha_HL	Day	3.026
Beta_HL	Day	15.302	17.940	Beta_HL	Day	15.302
A	ng/ml	2482.658	1832.831	A	ng/ml	2482.658
B	ng/ml	0.270	0.2558	B	ng/ml	0.270
CL_F	ml/day/kg	485.926	497.870	CL_F	ml/day/kg	485.926
V2_F	ml/kg	79.408	119.654	V2_F	ml/kg	79.408
CLD2_F	ml/day/kg	3.630	4.675	CLD2_F	ml/day/kg	3.630
Tmax	Day	4.454	4.533	Tmax	Day	4.454
Cmax	ng/ml	33.768	32.322	Cmax	ng/ml	33.768

Table.2 Pharmacokinetic Parameters: Symbols & Units

V1_F	L.Kg-1	Volume of distribution of central compartment when fraction of drug absorption is not known
K01	day-1	Rate constant of absorbtion phase
K10	day-1	Elimination rate constant of first phase
K12	day-1	Transfer rate constant from central to peripheral compartment
K21	day-1	Transfer rate constant from peripheral to central compartment
AUC	ng.day.ml-1	Total area under the curve (from time zero to infinity)
K01_HL	Day	Absorption half life
K10_HL	Day	Elimination half life of first phase
α	day-1	First order rate constant; Regression coefficient for the distribution phase of the disposition curve
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)
Alpha_HL	Day	Distribution half-life
Beta_HL	Day	Elimination half-life of second phase
A	ng.ml-1	Zero time intercept of plasma concentration of distribution phase
B	ng.ml-1	Zero-time intercept of plasma concentration of elimination phase
CL_F	L.kg-1.day-1	The clearance from central compartment when fraction of drug absorption is not known
V2_F	L.Kg-1	Volume of distribution of 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

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



The higher peak plasma concentration (C_{max}) in the present study may be attributed to the formulation (propylene glycol: glycerol-formal 60:40 v/v) as a vehicle in the injectable product (Ivomec 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 value of T_{max} in the present study was 4.49 days in cattle calves following SC administration of Ivomec super®. These findings could be well corroborated with T_{max} (4 days) in cattle (Lanusse *et al.,* 1997). A lower value of T_{max} compared to the present study has been reported in cattle (2.25 and 2.32 days; (Lifschitz *et al.,* 1999b) and **(**Echeverrı´a *et al.,* 1997**),** respectively), sheep (1.7 and 1.24 days; **(**Cerkvenik *et al.,* 2002**)** and **(**Barber *et al.,* 2003**),** respectively) and goats (3 and 2.85 days; **(**Gonzalez *et al.,* 2006**)** and **(**Alvinerie *et al.,* 1993**),** respectively). However, higher level of Tmax (15.1 day) compared to present study has been reported in cattle by sustained release bolus through intraruminal route (De montigny *et al.,* 1990).

The mean elimination half-lives in the present study were 16.93 days in cattle calves following SC route of administration of Ivomec super®. These findings could be well corroborated with mean elimination half-life of 17.2 days in cattle by subcutaneous route (Lanusse *et al.,* 1997). However, lower mean elimination half-lives compared to present study has been reported in sheep (9.6 days; (Gonzalez *et al.,* 2007), goats (7.4 days; (Gonzalez *et al.,* 2006) and pigs (1.18 days) (Craven *et al.,* 2001). The higher mean elimination half life in the present study could be due to low water solubility of Ivermectin and its precipitation in SC tissues favour slow absorption from the injection site, resulting in a prolonged presence in the bloodstream. Retention in the body is also increased due to slow absorption from the injection site.

Volume of distribution is a measure of extravascular distribution of a drug and higher values would always be advantageous for therapeutic purposes indicating excellent tissue penetration. In the present study, the volume of distribution (V1_F) was 2.18 $L.kg^{-1}$ in cattle calves following SC administration of Ivomec super®. These findings could be quite similar with volume of distribution (2.7 $L.kg^{-1}$) in cattle **(**Bousquet-Me´lou *et al.,* 2004**),** goats (2.8 $L.kg^{-1}$**;** **(**Gonzalez *et al.,* 2006**)** and pigs (2.7, $L.kg^{-1}$(Craven *et al.,* 2001). Due to its high lipophilic nature, Ivermectin is extensively distributed with wide volume of distribution (Vd) in all species. Inter-individual variation can also be attributed to differences in body condition, age, sex, and physiological status (Cerkvenik *et al.,* 2002). A lower Volume of distribution (1.2 $L.kg^{-1}$) compared to present study has been reported in cattle (Echeverrı´a *et al.,* 1997). However, higher volume of distribution (3.4 $L.kg^{-1}$) compared to present study has been reported in cattle (Lanusse *et al.,* 1997), sheep (5.3, 3 and 12.8 $L.kg^{-1}$; (Prichard *et al.,* 1985), (Gonzalez *et al.,* 2007) and (Cerkvenik *et al.,* 2002), respectively).

The AUC is the parameter that integrates both time and intensity of drug concentration. The area under the concentration time curve characterizes the relative availability of drug in the body (Dudley, 1991). The area under curve (AUC) in the present study was 411.4 $ng.ml^{-1}$day in cattle calves following SC administration of Ivomec super® respectively. These findings could be well corroborated with AUC (328.8 and 381.1 $ng.ml^{-1}$day; (Echeverrı´a *et al.,* 1997) and (Laffont *et al.,* 2001] respectively) in cattle. However, higher AUC compared to present study has been reported in cattle (459 and 595.1$ng.ml^{-1}$ day;

(Lanusse *et al.,* 1997) and (Laffont *et al.,* 2001) respectively), sheep (440 ng.ml^{-1} day; (Prichard *et al.,* 1985), horse (550.4 ng.ml^{-1} day; (Marriner *et al.,* 1987). A lower area under curve (AUC) compared to present study has been reported in cattle (189 and 278 ng.ml^{-1}day**;** (Lifschitz *et al.,* 1999b**)** and (Lifschitz *et al.,* 2000)**,** respectively).

Plasma clearance of drug is the volume of the blood or plasma cleared of drug by metabolism and excretion per unit of time. It is a better index of efficiency of drug elimination than half-life as it gives the clearance of drug from blood per unit of time (Baggot, 1988). The value of clearance in this study was 0.48 L.kg^{-1} day^{-1} in cattle calves following SC administration of Ivomec super®.

These findings could be well corroborated with plasma clearance (0.48 L.kg^{-1}.day^{-1}) in cattle (Lanusse *et al.,* 1997) and in sheep (0.56 L.kg^{-1}.day^{-1}; (Prichard *et al.,* 1985). However, higher plasma clearance compared to present study has been reported in sheep (1.11 and 3.24 L.kg^{-1}.day^{-1}; (Gonzalez *et al.,* 2007) and (Cerkvenik *et al.,* 2002) respectively), goats (1.56 L.kg^{-1}.day^{-1}; (Echeverrı´a *et al.,* 2002) and pigs (4.15 L.kg^{-1}.day^{-1}; Craven *et al.,* 2001). A lower plasma clearance compared to present study has been reported in cattle (0.27 and 0.35 L.kg^{-1}.day^{-1}; (Laffont *et al.,* 2001) and (Bousquet-Me´lou *et al.,* 2004) respectively).

Ivermectin persists in the body for a prolonged period, not only due to low plasma clearance but also due to the accumulation in fat tissue. Plasma clearance appears to be greater in pigs than in (goats > sheep > cattle) polygastric species (Ara´nzazu *et al.,* 2009).

References

Alvinerie, M., Sutra, J.F. and Galtier, P. (1993). Ivermectin in goat plasma and milk after subcutaneous injection. *Annales de Recherches Ve´te´rinaires.* 24: 417–421.

Alvinerie, M., Sutra, J.F., Galtier, P., Lifschitz, A., Virkel, G., Sallovitz, J., and Lanusse, C. (1998). Persistence of Ivermectin in plasma and faeces following administration of a sustained-release bolus to cattle. *Research in Veterinary Science.* 66: 57-61.

Ara´nzazu, G.C., Ana, M.S.P., Jose, D.L.B., Nelida F.M., Matilde S.V., Vieitez, J. G. (2009). The pharmacokinetics and metabolism of Ivermectin in domestic animal species. *The Veterinary Journal.* 179: 25-37

Baggot, J.D. (1988). Veterinary pharmacology and therapeutics. Ed. 6th. Boothe, N.H. and Mc. Donald, L.E., The Lowa State Univ. Press, pp. 36-39.

Barber, S., Bowles, V., Lespine, A., Alvinerie, M. (2003). The comparative serum disposition kinetics of subcutaneous administration of doramectin, Ivermectin and moxidectin in the Australian merino sheep. *Journal of Veterinary Pharmacology and Therapeutics.* 26: 343-348.

Bogan, J.A. and McKellar, Q.A. (1988). The pharmacodynamics of Ivermectin in sheep and cattle. *Journal of Veterinary Pharmacology and Therapeutics.* 11: 260-268.

Bousquet-Me´lou, A., Mercadier, S., Alvinerie, M., Toutain, P.L. (2004). Endectocide exchanges between grazing cattle after pour-on administration of doramectin, Ivermectin and moxidectin. *International Journal of Parasitology.* 34: 1299-1307.

Cerkvenik, V., Grabnar, I., Skubic, V., Doganoc, D.Z., Beek, W.M., Keukens, H.J., Drobnic, M. and Pogacnik, M. (2002). Ivermectin pharmacokinetics in lactating sheep. *Veterinary Parasitology.* 104: 175-185.

Chiu, S.H.L., Green, M.L., Baylis, F.P., Eline, D., Rosegay, A., Meriwether, H. and Jacob, T.A. (1990a). Absorption, tissue distribution, and excretion of tritium-labeled Ivermectin in cattle, sheep, and

rat. *Journal of Agricultural and Food Chemistry*. 38: 2072-2078.

Chiu, S.H.L., Green, M.L., Baylis, F.P., Eline, D., Rosegay, A., Meriwether, H. and Jacob, T.A. (1990a). Absorption, tissue distribution, and excretion of tritium-labeled Ivermectin in cattle, sheep, and rat. *Journal of Agricultural and Food Chemistry*. 38: 2072-2078.

Craven, J., Bjørn, H., Hennesy, D., Friis, C. and Nansen, P. (2001). Pharmacokinetics of moxidectin and Ivermectin following intravenous injection in pigs with different body compositions. *Journal of Veterinary Pharmacology and Therapeutics.* 24: 99-104.

Daurio, C.P., Cheung, E.N., Jeffcoat, A.R. and Skelly, B.J. (1992.) Bioavail-ability of Ivermectin administered orally to dogs. *Veterinary Research Communications.* 16: 125-130.

De montigny, P., Shim, J.S.K. and Pivinichny, J.V. (1990). Liquid chromatographic determination of Ivermectin in animal plasma with trifluoroacetic anhydride and N-methylimidazole as the derivatization reagent. *Journal of Pharmaceutical and Biomedical Analysis.* 8: 507-511.

Dudley, M.N. (1991). Pharmacodynamics and pharmacokinetics of antibiotics with special reference to the fluroquinolones. *Am. J. Vet. Med.* 91: 455-505.

Echeverrı´a, J., Mestorino, N., Errecalde, J. (2002). Comparative pharmacokinetics of Ivermectin after its subcutaneous administration in healthy sheep and sheep infected with mange. *Journal of Veterinary Pharmacology and Therapeutics.* 25: 159-160.

Echeverrı´a, J., Mestorino, N., Giorgieri, S., Turic, E., Alt, M., Errecalde, J. (1997). Pharmacokinetics of Ivermectin after its intravenous and subcutaneous administration to cattle. *Journal of Veterinary Pharmacology and Therapeutics.* 20: 77-78.

Escudero, E., Carceles, C.M., Galtier, P. and Alvinerie, M. (1997). Influence of fasting on the pharmacokinetics of Ivermectin in goats. *Journal of Veterinary Pharmacology and Therapeutics.* 20: 71-72

Fisher M.H , H. Mrozik. Chemistry. In W. C. Campbell (ed.), Ivermectin and abamectin: Springer, New York, (1989) pp. 1–23.

Gayrard, V., Alvinerie, M. and Toutain, P.L. (1999). Comparison of pharmacokinetic profiles of doramectin and Ivermectin pour-on formulations in cattle. *Veterinary Parasitology*, 81: 47-55.

Gonzalez, A., Sahagun, A., Diez, M.J., Fernandez, N., Sierra, M. and Garcia, J.J. (2007). Bioavailability of a commercial formulation of Ivermectin after subcutaneous administration to sheep. *American Journal of Veterinary Research.* 68: 101-106

Gonzalez, A., Sahagun, A.M., Diez, M.J., Fernandez, N., Sierra, M. and Garcia, J.J., (2006). Pharmacokinetics of a novel formulation of Ivermectin after administration to goats. *American Journal of Veterinary Research*. 67: 323-328.

Laffont, C.M., Alvinerie, M., Bousquet-Me´lou, A. and Toutain, P.L., (2001). Licking behaviour and environmental contamination arising from pour-on Ivermectin for cattle. *International Journal of Parasitology*, 3: 1687-1692.

Lanusse, C., Lifschitz, A., Virkel, G., Alvarez, L., Sanchez, S., Sutra, J.F., Galtier, P. and Alvinerie, M. (1997). Comparative plasma disposition kinetics of ivermectin, moxidectin and doramectin in cattle. *Journal of Veterinary Pharmacology and Therapeutics.* 20: 91-99.

Lifschitz, A., Pis, A., Alvarez, L., Virkel, G., Sanchez, S., Sallovitz, J., Kujanek, R. and Lanusse, C., (1999a). Bioequivalence of Ivermectin formulations in pigs and cattle. *Journal of Veterinary Pharmacology and Therapeutics.* 22: 27-34.

Lifschitz, A., Sallovitz, J., Imperiale, F., Pis, A., Lorda, J. and Lanusse, C. (2004). Pharmacokinetic evaluation of four generic formulations in calves. *Veterinary Parasitology*, 119: 247-257.

Lifschitz, A., Virkel, G., Pis, A., Imperiale, F., Sanchez, S., Alvarez, L., Kujanek, R. and Lanusse, C. (1999b). Ivermectin disposition kinetics after subcutaneous and intramuscular administration of an oil-based formulation to cattle. *Veterinary Parasitology*, 86: 203-215.

Lifschitz, A., Virkel, G., Sallovitz, J., Sutra, J.F., Galtier, P., Alvinerie, M. and Lanusse, C. (2000). Comparative distribution of Ivermectin and doramectin to tissues of parasite location in cattle. *Vet. Parasitol*. 87: 327–338.

Marriner, S.E., McKinnon, I. and Bogan, J.A. (1987). The pharmacokinetics of Ivermectin after oral and subcutaneous administration to sheep and horses. *Journal of Veterinary Pharmacology and Therapeutics.* 10: 175-179.

McKellar, Q.A., Jackson, F., Coop, R.L., Jackson, E. and Scott, E. (1991). Effect of parasitism with *Nematodirus battus* on the pharmacokinetics of levamisole, ivermectin, and netobimin. *Veterinary Parasitology*. 39: 123-136.

Na-Bangchang, K., Banmairuroi, V. and Choemung, A. (2006). High performance liquid chromatographic method for the determination of Ivermectin of Ivermectin in plasma. *Southeast Asian J. Trop. Med. Public. Health.* 37(5): 848-858

Perez, R., Cabezas, I., Godoy, C., Rubilar, L., Mun˜oz, L., Arboix, M., Castells, G. and Alvinerie, M. (2002). Pharmacokinetics of doramectin and Ivermectin after oral administration in horses. *The Veterinary Journal*. 163: 161-167.

Perez, R., Palma, C.,Nunez, M.J, Cox, J, Arboix, M, (2007). Pharmacokinetics of Ivermectin in pregnant and nonpregnant sheep. *J. vet. Phamacol. Therap*. 31: 71-76.

Prichard, R.K., Steel, J.W., Lacey, E. and Hennessy, D.R. (1985). Pharmacokinetics of Ivermectin in sheep following intravenous, intra-abomasal or intraruminal administration. *Journal of Veterinary Pharmacology and Therapeutics.* 8: 88-94.

Scott, E.W. and McKellar, Q.A. (1992). The distribution and some pharma cokinetic parameters of Ivermectin in pigs. *Veterinary Research Communications*, 16: 139-146.

Steel, J.W., (1993). Pharmacokinetics and metabolism of avermectins in livestock. Veterinary Parasitology 48, 45–47.

Timothy G.G. (2005). Ivermectin 20 years on: maturation of a wonder drug. *Trends in parasitology.* 21: 11 -12.

How to cite this article:

Sakthikarthikeyan, S., A. H. Ahmad and Kannan, K. 2020. Disposition Kinetics of Ivermectin (Ivomec Super®) Following Single Dose Subcutaneous Administration in Cattle Calves. *Int.J.Curr.Microbiol.App.Sci.* 9(06): 4222-4231. doi: https://doi.org/10.20546/ijcmas.2020.906.495