Pharmacokinetic Features of the Antiparasitic Macrocyclic Lactones

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Abstract: The macrocyclic lactones have pharmacokinetic properties which enhance their use against endo- and ectoparasites in animals and man. The most consistent physico-chemical feature of the group which contributes to their kinetic characteristics is high lipid solubility. This appears to be necessary for their pharmacodynamic action as well as common kinetic features such as large volumes of distribution and the influence of body fat composition on their disposition. They are used in all domestic animal species and are undoubtedly influenced by the anatomical and physiological differences in these species, however body fat composition also appears to exert a major influence on distribution, metabolism and persistence between species and between breeds and individuals. A myriad of formulations have been developed to enhance the convenience of administration in the different domestic animals and the macrocyclic lactones are delivered orally, subcutaneously and topically to good effect. Lipid based excipients have been developed in "depot" formulations to extend the period of effective prevention of parasite re-infection. Subtle structural changes have been made to the macrocyclic lactone molecules to reduce distribution to the central nervous system and mammary gland, thus allowing use of some compounds such as selamectin (SLM) in "toxicity sensitive" breeds of collie dog which lack P-glycoprotein efflux systems in their central nervous systems and the use of eprinomectin (EPM) in dairy cattle with a nil-milk withdrawal period. Gender differences exist in the pharmacokinetics of these compounds which may be associated with body (fat) composition or metabolism. Feeding may also reduce the availability of macrocyclic lactones which bind particulate digestive material and parasitism may impact the kinetics of the drugs because parasitized animals have altered pathophysiological processes, especially in the gastro intestinal tract but also because of the impact which parasitism may have on the body condition (and fat deposition) in animals. The pharmacokinetics of macrocyclic lactones may be affected by co-administration with compounds which interfere with P-glycoprotein transporters and these interactions have been explored as possible mechanisms for enhancing the effectiveness of these antiparasitics. The objective of this article is to provide a comprehensive review of the pharmacokinetics of macrocyclic lactones and to interpret where that information may prove clinically useful.

Keywords: Avermectins, lipid-solubility, macrocyclic-lactones, milbemycins, P-glycoproteins, pharmacokinetics.

INTRODUCTION

The macrocyclic lactones present a range of physico-chemical properties complemented by pharmaceutical formulations which confer desired delivery characteristics. They are active against diverse target species and interact with many host biological processes. Their pharmacokinetics are consequently varied, but for the most useful compounds can be characterised by high lipophilicity, large volumes of distribution and long persistence in the body at biologically active concentrations. The latter feature has proved particularly useful in agricultural and veterinary medicine where strategic control of parasites may be achieved by preventing re-infection for a significant time period.

Chemical modifications to the basic structure to confer desirable kinetic profile have been tempered by impact on potency and spectra of activity, nevertheless increased lipophilicity as a result of chemical alterations has in many instances both improved potency and conferred desired pharmacokinetics. The macrocyclic lactones currently marketed display a range of potencies, spectra of activity and pharmacokinetics, including persistent *in vivo* biological activity, transcuticular absorption or limited milk distribution. Changes to their physico-chemistry which confer an advantage in one characteristic may be disadvantageous in another giving each a tapestry of properties which, in relation to potency, spectra and dose limiting species has been coined their "spectral fingerprint" [1].

STRUCTURE : KINETIC RELATIONSHIP

Structurally the macrocyclic lactones are formed around a common 16-membered macrocycle with integral benzofuran (C-2 to C-8) and spiroketal (C-17 to C-25) groups and a disaccharide-oxy group on C-13 which is absent in the milbemycins Fig. (**1**) [2]. They do not contain strongly acidic or basic functional groups and pH partitioning is not a major feature of their kinetic characteristics.

The macrocyclic lactones are relatively large drug molecules with molecular weights ranging from about 650 [Moxidectin (MXD) 640] to 900 [Doramectin (DRM) 899] and with a radius of about 0.6 nm. It is unlikely that molecular size restricts permeability of capillary endothelium (capillary pore diameter is 4-8 nm) and the direct relationship between

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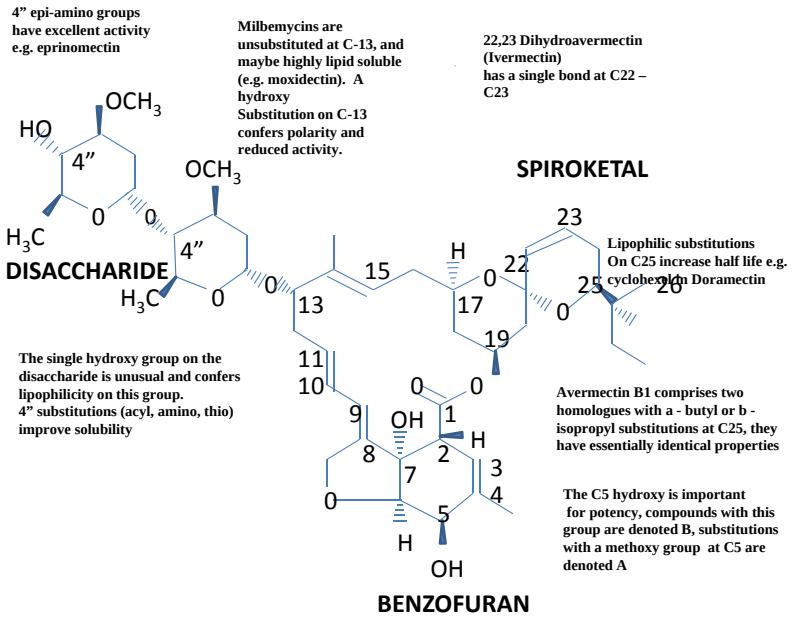

Fig. (1). Chemical Structure of Macrocyclic Lactones. Avermectin B1a with major sites of substitution shown. The natural products of streptomyces fermentation are mixtures

lipid solubility expressed as octanol : water partition coefficient, volume of distribution and accumulation in and depletion from fat (Table **1**) suggest that simple diffusion associated with lipid solubility is a major route of transmembrane movement. As a group the macrocyclic lactones are thought to be highly protein bound in plasma however their lipophilicity and association with circulating lipoproteins may be a more important determinant in their exchange between tissue and bloodstream [7].

Simple diffusion associated with lipid solubility probably applies to uptake by the parasite as well as the host animal species although transcuticular uptake by nematodes of macrocyclic lactones is slower than for smaller lipid soluble molecules and this may be associated with the collagen matrix of the cuticle acting as partial sieve [8]. It has been suggested that anthelmintic molecules with molecular weight < 350 [(radius 0.5 nm] and octanol : water partition coefficients of 1.5 – 3.0 will be most rapidly absorbed by parasites [9, 10].

The macrocyclic lactones have structural features which affect their pharmacokinetics. Perhaps the most striking difference exists between the avermectins which have a bisoleandrosyloxy disaccharide at C-13 and the milbemycins which do not. The disaccharide only has one hydroxyl group at C-4" and lacks the polarity and hydrophilicity normally associated with such sugar groups. Furthermore substitution of the C-4" hydroxy group with acyl, amino or thio groups improve the solubility and tissue distribution of avermectins and this feature has been embraced by the epi-acetyl amino substitution in EPM which retains/enhances the potency and spectrum of activity of this avermectin which is effectively absorbed percutaneously and possesses a very low plasma: milk partitioning ratio (0.17) permitting use in lactating dairy cattle [11]. The low plasma: milk partition coefficient of EPM suggests that structural conformation independent of absolute lipid solubility may be important in transfer between the mammary capillary vasculature and alveolar epithelium. The absence of the C-13 dissacharide characterises the milbemycin group, some of which (*e.g.* MXD) are highly lipophilic, however substitution at C-13 can either enhance (chloro, fluoro, methoxy) or abrogate (hydroxyl, amino) activity and this is directly associated with the lipophilicity or polarity respectively of the resultant molecules [12]. The spiroketal group from C-17 to C-25 has also proved receptive to substitutions which alter the kinetics of macrocyclic lactones.

The major fermentation product of *Streptomyces avermitilis*, Avermectin B_{1a} has a butyl group at C-25 (designated by $_a$) but a substantial minor metabolite Avermectin B_{1b} has an isopropyl at C-25, this appears to confer little difference in biological activity on the molecule. More radical alteration at C-25 has been achieved by mutational biosynthesis [13] and the 25 – cyclohexyl derivative (DRM) has a longer elimination half life and slower clearance than unsubstituted dihydro avermectin B_{1a} [the major component of ivermectin (IVM)] (Table **2**) [14].

Passive diffusion explains most of the pharmacokinetic characteristics of macrocyclic lactones and is governed principally by their lipid solubility. It cannot however fully explain the relatively poor penetration of the central nervous system and consequent lack of toxicity associated with macrocyclic lactones. Macrocyclic lactones act by increasing neuronal cell membrane permeability to chloride ions. They are thought to do so in parasites by activating glutamate gated channels [15] but are also known to stimulate gamma aminobutyric acid (GABA) – gated chloride channels at higher concentrations [16].

Selectivity is thought to be associated with lack of the target glutamate receptors in mammalian species [17] and relative restriction of GABA receptors to the central nervous system in mammals. Nevertheless toxicity following acute

Table 1. Relationship between Lipid Solubility, Volume of Distribution and Accumulation in and Depletion from Fat of Two Macrocyclic Lactones in Cattle

	Octanol : Water Partition Coefficient	Volume of Distribution	Total Residue (ppb)			Depletion $t_{1/2}$ (Days) from Fat
	Log P	(l/kg)	Days			Days
			7	14	28	
Ivermectin	4.8	2.2	270	83	29	4.3
Moxidectin	6.0	3.0	898	636	275	12.0-15.0

Volumes of distribution were determined following intravenous administration at 200 µg/kg [3] [4]. Total tissue residue levels and depletion half lives of unchanged drug were from cattle treated with ivermectin (300 µg/kg s/c) or moxidectin (200 µg/kg s/c) adapted from [5] [6]. Octanol : water partition coefficient (log P) are from [7].

Table 2. Pharmacokinetics of Macrocyclic Lactones Administered Intravenously to Cattle at 200 µg/kg

	AUC (ng.h/ml)	$t_{1/2}$ (h)	V_{dss} (l/kg)	Cl (l/kg.d)	Reference
Ivermectin	6096	64.5	2.2	0.79	[3]
Doramectin	11640	89.0	1.7	0.32	[14]
Moxidectin	4680	71.3	3.0	1.10	[4]

overdose is attributed to neuro-intoxication and is thought to be associated with GABA receptor stimulation [18, 19]. Furthermore some animals (1 in 4 Collie breed dogs have this phenotype) appear to be particularly sensitive to macrocyclic lactones and intoxication in these animals is associated with high brain concentrations (Table **3**).

Brain concentrations are usually 1/10 or $1/100^{th}$ of the plasma or liver concentrations (see Table **4** for relative concentrations of IVM in cattle) however in these sensitive breeds of dog the concentrations in the brain were 2-31 times those found in liver and plasma [20]. The large molecular size of macrocyclic lactones and the tight junctions and absence of intercellular pores in the endothelial cells of the brain capillaries may reduce brain penetration, particularly by aqueous bulk flow. This cannot wholly explain the exclusion of such lipid soluble drugs as the macrocyclic lactones, nor the idiosyncratically high concentrations found in some Collies. The explanation was provided by the creation of genetically engineered mice lacking a multi-drug resistance (mdr) gene which encodes for a drug transporting P-glycoprotein. These mice were 100 times as sensitive to the intoxicating affects of IVM and had elevated brain concentrations (approximately 87 times that in normal mice) of IVM [21, 22].

P-glycoprotein carriers exist in other sites throughout the body, notably the intestine and hepatobiliary tract and have been shown to be deficient at these sites in the mdr knockout mice. They act at these sites to transport drugs out of cells into the biliary and intestinal lumen thus reducing plasma concentrations. They also act to reduce absorption of orally administered IVM and mdr knockout mice achieve concentrations 2.5 times higher in plasma than normal mice at 24 hours after administration [23].

Sensitive breeds of Collie have since been shown to possess a deletion mutation of the mdr 1 gene [24]. It is also apparent *in vitro* that different macrocyclic lactones have different affinity for the P-glycoprotein transporters with SLM and particularly MXD less potent competitors of verapamil – stimulated P-glycoprotein ATPase activity. The structure-affinity relationship reflected the integrity of the sugar moiety of the compound since SLM is a monosaccharide and MXD an aglycone [25]. The reduced affinity of SLM compared to IVM for P-glycoprotein has been confirmed *in vivo* utilising mdr - wild type (wt) and knockout mice where brain concentration ratios were ($mdr^{-/-}$ / wt) 4.9 for SLM and 59.2 for IVM following oral administration of SLM (1200 µg/kg b.w.) and IVM (200 µg/kg b.w.) [26]. This latter study also suggested that P-glycoprotein transporters were not the sole determinant in macrocyclic lactone tolerance since the absolute concentrations of SLM achieved in brain tissue were higher than those for IVM.

The impact which inherent physico-chemistry has on pharmacokinetics can be seen from Tables **2** and **5** in which kinetic characteristics are shown for several members of the group in cattle and dogs respectively following intravenous administration. Of note are the very large volumes of distribution of MXD in cattle and dogs.

It is likely that MXD distributes rapidly into fat (See Table **1** for fat residues following subcutaneous administration in cattle) and redistributes back into plasma over a prolonged period, explaining the very long plasma elimination half life in dogs. This characteristic may have had a bearing on the excipients used for MXD delivery (which are essentially aqueous – see later) which do not confer sustained delivery.

MXD persistent activity, utilised in parasite control strategies is thus a feature of the inherent physico-chemistry of the molecule and not a formulation characteristic.

Table 3. Concentrations (µg/ml or ppb) of Ivermectin in Tissues from Two Collies which became Intoxicated Following Administration of 200 µg or 600 µg of Ivermectin per Kilogram Body weight [20]

Dose	200 µg/kg	600 µg/kg
Brain	52	134
Spinal cord	34	95
CSF	0.0	0.0
Liver	27	53
Plasma	NA	4.3

Table 4. Total Radioactive Residue Levels (ng/ml or ppb) in Tissues and Fluids from Cattle Dosed Subcutaneously with 22, 23 - [^{3}H] Ivermectin at 0.3 mg/kg Body Weight. Adapted from [5]

Tissue	Days Post Dose			
	7	14	21	28
Brain	4	1	0	0
Liver	782	55	68	11
Plasma	45	11	6	3

Table 5. Pharmacokinetics of Macrocyclic Lactones Administered Intravenously to Dogs and Cats

		Dose (µg/kg)	AUC (ng.h/ml)	$t_{1/2}$ (h)	V_{dss} (l/kg)	Cl (l/kg.d)	Reference
Selamectin	Dog	200	3100	14.7	1.3	1.68	[27]
Selamectin	Cat	200	8526	74.5	2.2	0.67	[27]
Milbemycin Oxime (A4 homologue)	Dog	745	15422	95.5	0.4*	1.23	[28]
Moxidectin	Dog	200	4570*	334.0	5.7	1.05	[29]

*Estimated

SPECIES DIFFERENCES

Pharmacokinetic characteristics of IVM administered intravenously in cattle, horses, sheep, goats, pigs and dogs are given in Table **6**. Although volumes of distribution are large in all species they are substantially larger (at least double) in sheep, pigs and goats than in dogs and cattle. Clearance values are also larger (at least four times) in pigs and goats than in cattle and sheep. The differences in kinetics between species may reflect differences in body composition (relative fat content, presence or absence of a reticulo-rumen) and physiological differences (cardiac output and body fluid pH values) and also represent substantive differences in the metabolism of IVM in different species. In tissue residue and metabolism studies IVM is found in highest concentrations in liver (and bile) and in fat and has been shown to be metabolised in both tissues. Although the parent molecule remains the dominant residue during the immediate post administration period representing 64% at day 7 in cattle, 68% at day 5 in sheep and 51% at day 7 in swine of total liver recovery, polar 24 – hydroxyl metabolites are detected as the major liver metabolites in cattle and sheep and 3" – 0 desmethyl – metabolites as the major metabolite in pig liver [5]. In fat the parent drug also predominates in the immediate post administration period, however interestingly a less polar metabolite thought to be a fatty acid ester of 24 – hydroxy dihydro avermectin B_{1a} / B_{1b} is found in the fat of cattle and sheep [41]. In pig fat the major metabolites are the polar 3" 0-desmethyl derivatives of dihydro avermectin B_{1a} / B_{1b} and it is likely that this differs from cattle and sheep since the 3" 0-desmethyl derivatives are less favourable substrates for esterification than the 24-hydroxy substrates generated in cattle and sheep livers [42]. Excretion of IVM and its metabolites is principally enteric with only about 2% excreted in urine [5].

Differences in metabolism may also contribute to the differences in kinetics for the different macrocyclic lactones in the same species (Table **2**). The major metabolites of DRM in cattle are 3" – 0 – desmethyl, - 24 hydroxymethyl,

Table 6. Pharmacokinetic Paramaters of Ivermectin in Different Animal Species after Intravenous Administration

Species	Dose (µg/kg)	Weight (kg)	V_d (l/kg)	AUC (ng.h/ml)	MRT (h)	$t_{1/2}$ (h)	Cl (l/kg.d)	Reference
Cattle	200	-	2.2	6096	67	64	0.79	[3]
	300	-	1.9	-	-	67	-	[30]
	200	567 ± 24	-	18749	-	144	0.26	[31]
	70	688 ± 20	2.7	5064 (14468)*	194	187	0.35	[32]
Horse	200	510-610	3.7	8251	147	139	0.63	[33]
Sheep	300	28	4.6	-	-	65	-	[30]
	200	27.3 ± 4.3	3.9	2695	30	32	1.97	[34]
	200	25-30	5.3	346	23	23	3.9	[35]
	200	25-30	4.7	396	25	22	3.54	[36]
	200	-	5.3	8990	-	178	0.56	[37]
Goat	200	25-30	6.3	1461	45	65	3.39	[38]
Pig	300	41.7	5.3	1808 (1205)*	17	32	4.01	[39]
	300	-	7.9	2040 (1360) *	48	55	-	[40]
Dog	200	-	2.4	-	-	43	NA	[30]
Correlation with body weight (r^2)		-	-0.772	0.871	0.890	0.807	-0.917	

*Corrected for dose assuming proportionality

and 24 hydroxymethyl – 3" – 0 – desmethyl – DRM [43] and the major metabolites of MXD in cattle are C-29 hydroxymethyl, and C-14 hydroxymethyl MXD [44, 45]. Nevertheless for IVM, DRM and MXD the parent molecule is predominant and it is likely that metabolism makes a relatively minor contribution to the differences in pharmacokinetics for this group of compounds, particularly in the immediate post administration period.

Correlations of pharmacokinetic parameters with bodyweights in different animal species (cattle, horse, sheep, goat and pig) are shown in Table **6**. Although negative correlations were observed between bodyweight and volume of distribution (V_d) (r^2= -0.772) or clearance (Cl) (r^2= -0.917), the values of area under the concentration time curve (AUC) (r^2=0.871); mean residence time (MRT) (r^2=0.890) and elimination half life ($t_{1/2}$) (r^2=0.807) were positively correlated with the bodyweights of the different animal species. The plasma concentration of IVM is markedly lower and the clearance rate more rapid in sheep, goats and pigs that have relatively lower body weights because of its large distribution volumes compared to cattle and horses.

BREED DIFFERENCES

Studies have reported that the plasma disposition and systemic availability of macrocyclic lactones were substantially affected by breed differences. Significantly lower absorption and systemic availability of MXD was observed in Aberdeen Angus compared to Holstein cattle following topical administration [46]. It was suggested that histological and physiological differences in the skin between the two cattle breeds probably affected the different systemic availability of MXD. The pharmacokinetics of IVM following subcutaneous administration has also been investigated in two different cattle breeds, Holstein and Belgian Blue [47]. Although the plasma and tissue patterns of IVM were similar, AUC and maximum plasma concentration (C_{max}) values for plasma and skin were substantially higher in Belgian Blue cattle compared with Holstein cattle. The authors suggested that the difference observed between the two breeds may be attributable to their different body composition, since Holstein cattle's carcasses contain higher fat content compared with Belgian Blue cattle.

Furthermore the pharmacokinetic profiles of DRM and MXD in Zebu Gobra cattle after subcutaneous administration were similar to those observed in other cattle breeds [48], whereas the plasma disposition of IVM [49] and EPM [50] were considerably different. Faster absorption and elimination processes generated much lower plasma availability of IVM and EPM in Zebu Gobra after subcutaneous and topical administration. Substantial differences in the plasma disposition of EPM and MXD have also been demonstrated after topical administration between buffaloes and other cattle breeds [51]. Although the AUC and C_{max} values for MXD obtained in buffaloes treated with a pour-on at 500 µg/kg were similar to those reported for two different cattle breeds, Aberdeen-Angus and Holstein [47], the time until maximum

plasma concentration (t_{max}) and MRT were significantly shorter. Furthermore, significantly lower plasma availability of EPM in buffalos was observed compared to dairy cattle [52] and Zebu Gobra cattle [50]. It was hypothesized that the faster absorption and elimination processes of MXD were probably due to a reduced storage in fat since the animals were in lactation during which rapid fat turnover may result in more rapid drug release [51]. A closely related species difference in the pharmacokinetics of IVM has been demonstrated between yak (*Bos grunniens*) and other species of cattle [53], a faster rate of absorption but lower plasma availability were observed in the yak and this may be associated with a low fat storage in these animals.

Breed-related differences in the pharmacokinetics of macrocyclic lactones have been observed in sheep. The peak plasma concentration of IVM observed in Senegalese sheep [54] after subcutaneous administration was lower than that reported in Merino sheep [55] and Suffolk sheep [56]; and higher than that obtained in Istrian Pramenka sheep [57]. Similar variations have been also demonstrated for DRM in Awassi and Pampinta sheep [58, 59] and for MXD in Laucune and Australian Merino sheep [55, 60]. Breed-related differences have also been observed in the plasma disposition of IVM between Kilis and Damascus goats following subcutaneous administration [61]. The elimination process of IVM was notably different between the two goat breeds as indicated by time until last measurable concentration (t_{last}) (38.33 days *vs.* 22.5 days, respectively) and elimination half-lives (5.65 days *vs.* 3.81 days, respectively). The plasma disposition of IVM is also breed-depended in different horse breeds. The C_{max} 43.99 ng/ml, AUC 3185 ng.h/ml and MRT 115 h obtained in Chilean criollo horses [62] were all substantially larger than in thoroughbreds and hunters (C_{max} 21.4 ng/ml, AUC 1106 ng.h/ml and MRT 55h) [63]. Breed-related body condition of the animals may have been responsible for these differences since Perez and colleagues [62] used Chilean criollo horses weighing 390-446 kg whereas a mixed group of thoroughbreds and hunters weighing between 560 kg and 690 kg were administered IVM in the other study.

In conclusion, the breed-related differences in the pattern of absorption, systemic availability and plasma residence time can be substantial and should be taken into account for rational usage of macrocyclic lactones. While metabolic and excretory processes may contribute to breed differences the most likely causes of differences relate to fat content and where the macrocyclic lactones are applied topically to skin histology.

DIFFERENCES IN BODY COMPOSITION

The high lipophilicity of the macrocyclic lactones, large fat residues (See Table **1**) and the important role of fat metabolism suggest that fat composition of administered animals may impact on the pharmacokinetics of these drugs.

Differences in body condition substantially affect the plasma kinetic disposition of macrocyclic lactones in animals. There was a high correlation ($r^2 = 0.922$) between body weight and time until MXD was no longer detectable in lambs [64]. Similarly a correlation ($r^2 = 0.703$) was found between body weight and time until concentrations fell below the limit of detection of DRM in horses [63]. The lightest horse (490 kg) demonstrated the last detectable plasma concentration of DRM at day 8 whereas; the heaviest horse (880 kg) reached the last detectable plasma concentration at day 39. In addition, a more rapid absorption of IVM with a reduced AUC has been observed in sheep in poor body condition as a result of mange infestation compared with healthy animals [65]. This is in agreement with the observation that a variation in body condition significantly influenced the plasma disposition of IVM and MXD in pigs and the persistence of the drugs was reduced in thin pigs compared with the heavier or fat animals (Table **7**) [39, 66, 67]. It has also been observed recently that plasma kinetic disposition of IVM was markedly affected by body weight of sheep after subcutaneous administration [68]. Significantly longer terminal half-life and MRT and lower C_{max} values of IVM were obtained in heavier sheep and the authors hypothesized that this was caused by increased tissue distribution due to greater adipose tissue content in fat sheep compared to sheep with lower bodyweight. Perez and colleagues [69] have demonstrated that changing body condition because of a parasitic infection is associated with significant changes in plasma disposition of IVM when it is administered subcutaneously to parasitized lambs. The AUC and MRT values of IVM were significantly reduced in lambs with parasitic infection compared to the parasite-free animals.

Other physiological conditions may also affect the plasma disposition of macrocyclic lactones in animals. The MRT values of IVM in pregnant sheep were significantly longer compared to those observed in non-pregnant animals with lower body weight [70]. This difference may be attributable to the larger volume of distribution and longer persistence of IVM associated with the higher body fat content in pregnant animals. It has been shown that the C_{max} and AUC obtained after oral administration was greater in lambs compared to ewes [71] and this probably reflects differences in body composition (especially fat content) and impaired elimination (reduced metabolism) in lambs.

It has been suggested that variations in body condition should be taken into account when planning anthelmintic treatment with macrocyclic lactones since the animals in poorer body condition probably need to be treated more often because of reduced bioavailability and persistence of the drugs [66]. They are also likely to be the animals with highest parasite burdens.

DIFFERENCES IN ROUTE OF ADMINISTRATION

Route of administration in domestic animals is greatly influenced by the practicalities of delivery, thus in cattle pour-on (transcutaneous [t/c]) and subcutaneous injection (s/c), in sheep oral drench (*Per os* [p/o]) or s/c injection, in horses oral paste or intramuscular injection (i/m), in dogs oral tablet or spot on (t/c) and in pigs in-feed or s/c are routes often selected. Injectable preparations of IVM for horses resulted in occasional adverse reactions (Clostridial spp infections and anaphylactoid reactions) and were withdrawn in 1984 [72] but all other routes indicated above are utilised for delivery of macrocyclic lactones.

Route of administration may substantially affect the pharmacokinetics of macrocyclic lactones as can be seen by comparison of the kinetics of different members of the group

Table 7. Pharmacokinetic Results from fat and Lean Pigs Administered Ivermectin or Moxidectin Intravenously at 300 µg/kg Bodyweight [39]

	Ivermectin		Moxidectin	
	Fat	Lean	Fat	Lean
Vd (l/kg)	5.3	5.1	17.9	18.7
Cl (l/kg.d)	4.0	4.2	1.1	1.2
MRT (h)	19.3*	12.9*	317	314
$t_{1/2\ \beta}$ (h)	31.8	28.3	336	303

*Significantly different ($p < 0.05$)

administered by either the subcutaneous or oral route in sheep (Table **8**).

IVM and DRM have been shown to become highly associated with ruminal particulate material and it has been suggested that they are partially degraded in the reticulo-rumen and abomasal fluids [37, 74] although there is conflicting evidence on their degradation (see below). This may account for the lower C_{max} and AUC values obtained following oral administration. In one study in sheep MXD achieved higher C_{max} following oral administration than subcutaneous, however the elimination half life was shorter and it produced a smaller AUC [59]. In more recent work higher C_{max} and AUC values have been determined following subcutaneous administration [75]. The fast oral absorption of MXD in sheep has been attributed to its lipophilicity [76].

In sheep, it has been shown that systemic bioavailability of IVM was 25% following intraruminal administration compared with almost 100% after intra-abomasal injection. This marked difference was attributed to degradation or metabolism of the drug within the rumen [37]. In cattle, similar biodegradation has been suggested for the higher bioavailability of IVM obtained after subcutaneous compared to intraruminal treatment [77]. Nevertheless *in vitro* studies have indicated that no metabolism or degradation of macrocyclic lactones occurred in rumen and abomasal contents [78, 79]. An alternative explanation for the low bioavailability of orally or intraruminally administered IVM may be adsorption or binding to the particulate phase of the digesta which has been shown to influence the pharmacokinetics of some drugs [79]. Although, a significant first-pass metabolism of macrocyclic lactones is not apparent in ruminant species [37], oral administration confers relatively lower bioavailability of these endectocides because of binding with the organic gut content in sheep [74] and cattle [80].

The rumen affects the bioavailability of anthelmintics by acting as a metabolic compartment for foreign compounds. Mariner and Bogan [81] reported that the oral administration of benzimidazole anthelmintics resulted in higher and more sustained plasma concentrations of parent drug and its metabolites than when the anthelmintic was given by the intra-abomasal route. In sheep, it was shown that partial or complete oesophageal groove closure or reflex occurred in 42% of animals treated with an oral benzimidazole preparation and this caused a reduction in bioavailability and efficacy [82]. In addition, it has been reported that significantly lower C_{max} and smaller AUC values but almost six-times longer t_{max} value were observed following intraruminal administration of IVM compared with the inraabomasal route in sheep [37]. In order to reduce the possibility of rumen by-pass and thus prolong plasma persistence of macrocyclic lactones, it has been recommended that oral drench formulations should be applied over the tongue and not deposited in the buccal cavity where they could stimulate oesophageal groove closure [83].

Previous studies have also shown that subcutaneous injection of macrocyclic lactones is a more efficient route for administration in terms of drug bioavailability in cattle, goats and horses compared with pour-on or topical administration [31, 33, 84, 85, 86, 87, 133]. Although macrocyclic lactones were administered topically at a higher dose rate than orally or subcutaneously in all studies, the C_{max} observed were lower than those reported after subcutaneous or oral administrations. It has been suggested in cattle that after pour-on administration, the lower bioavailability maybe due to wastage (run off) or the drug being trapped in the skin and released very slowly over a longer period of time [88]. Licking or grooming affects erratically the bioavailability of macrocyclic lactones administered topically and may result in subtherapeutic concentrations in untreated animals which lick their stable mates [31]. In goats, following pour-on administration of IVM at 500 µg/kg, more persistent but much lower plasma concentrations were observed than after oral administration at 200 µg/kg [83, 86, 89], but it has been reported that both subcutaneous and pour-on routes were 100% effective against *Melophagus ovinus* in goats [90]. It may be that topical delivery confers both systemic and cutaneous spread whereby the drug is absorbed into the bloodstream and redistributed to the skin, and also spreads radially from the topical site of administration in sebum or other skin/hair substance. In horses, a recent study indicated that the plasma concentration and systemic availability of IVM was lower but the plasma persistence was prolonged after pour-on administration compared with oral [33]. Moreover, IVM paste formulation administered orally reduced the eggs per gram of faeces (a marker of anthelmintic efficacy) by >95% for 10 weeks, whereas the reduction in a pour-on administered group varied from 82 to 97%. It is likely that IVM binds physically to the haircoat at the application site further preventing absorption or that IVM becomes trapped in the skin or precipitated at the skin surface of the application site and is very slowly released from there after pour-on administra-

Table 8. Pharmacokinetics of Ivermectin, Doramectin and Moxidectin when Administered by the Subcutaneous (s/c) and oral Routes to Sheep at a Dose Rate of 200 μg/kg Bodyweight

	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2el}$ (h)	Reference
Ivermectin					
s/c	31	60	5718	88	[73]
Oral	22	16	2039	61	[73]
Doramectin					
s/c	23	180	9696	274	[58]
Oral (150 μg/kg)	7	27	797	129	[74]
(Oral*)	9		1063		
Moxidectin					
s/c	37	4	6080	427	[75]
Oral	13	13	1262	433	[75]

*Oral dose corrected (200μg/kg b:w) assuming proportionality.

tion. Although the plasma concentration is much lower after pour-on administration in animals, the values of terminal half-life and MRT are significantly longer and these differences suggest slow absorption from skin which limits later elimination of IVM. It has been shown that absorption was the rate-limiting kinetic process for pour-on formulations and the terminal half-life represents the half-life of absorption of macrocyclic lactones in cattle thus conferring a flip-flop effect in which the disposition of the drug in the body and its elimination is controlled by the absorption process [88].

Although there is considerable variability in systemic availability as assessed by AUC, in most species and for most of the macrocyclic lactones subcutaneous administration confers the greatest availability and might be expected to deliver greatest antiparasitic efficacy. Nevertheless high concentrations achieved locally (on the skin following t/c administration and in the gastro intestinal tract following p/o administration) could confer high activity against parasites where the skin or gut are predilection sites.

EFFECT OF FORMULATION

Oral (drench, tablet, paste, feed additive and sustained-release delivery), topical or transdermal (pour-on and spot-on) and subcutaneous formulations of macrocyclic lactones which allow convenient administration have been developed to increase the antiparasitic efficacy and to extend the persistence at the site of parasite location. The physico-chemical properties of macrocyclic lactones may account for differences in formulation flexibility, in their kinetic behaviour, and in the potency and persistence of their antiparasitic activity [91]. The nature of the formulations used to deliver the active macrocyclic lactones have substantially changed the plasma disposition of the parent drugs [2, 30, 92] (Table **9**) and the persistence of the antiparasitic activity of macrocyclic lactones depends on their disposition kinetics and pattern of plasma/tissue exchange in the host [96]. Even small modifications in the pharmaceutical formulation of macrocyclic lactones account for changes to the plasma disposition [30, 97] and their concentration and residence time at the parasite locations [98].

ORAL FORMULATIONS

After oral administration of the aqueous micelle and propylene glycol solutions, no significant difference was observed in the bioavailability of IVM in sheep. The maximum plasma concentrations of both formulations were achieved within 24 h, and elimination half-life ranged between 72 h and 120 h [93]. In horses, a paste formulation and an aqueous formulation of IVM were administered at the 200 μg/kg dose rate [99]. Although the peak concentration was observed within 4-5 h for the liquid formulation, a delay of 15 h occurred before C_{max} was reached for the paste form. In addition, after treatment of horses with a liquid form of IVM via nasogastric tube, 20% higher bioavailability was obtained than for the oral paste form. Nevertheless, the efficacy of the two formulations was similar in reducing faecal egg count [99]. In dogs, after dosing with a beef-based chewable preparation better absorption was reported than after dosing with a tablet formulation [100] and in man, 50% greater bioavailability was observed for an aqueous IVM solution than for a capsule or tablet form [93]. While, in cattle, a non-aqueous formulation of MXD provided a slower rate of absorption, lower peak plasma levels and longer residence time compared to the aqueous form [101]. In addition, it has been shown that a tablet formulation of IVM displayed a slower absorption process compared with the solution after oral administration in sheep [102]. The oral tablet formulation of IVM displayed lower plasma concentration [84, 103] compared with the drench formulation in goats. The slower dissolution rate of the tablet probably delays its absorption compared with the drench or solution formulations.

Table 9. Effect of Excipient on the Pharmacokinetics of Ivermectin given by the Subcutaneous Route to Cattle at 200 µg/kg

	C_{max} (ng/ml)	$t_{1/2el}$ (h)	AUC(ng.h/ml)	Reference
Aqueous Micellar formulation* Polysorbate 80 glycerol formol	84	48	5904	[30]
Mixed aqueous micellar (50%) Glycerol formol (50%)	25	88	4464	[30]
Propylene glycol (60%) glycerol Formal (40%) (commercial product)	44	199	8028**	[93]
Propylene glycol (60%) glycerol Formal (40%) (commercial product)	35	96	4968	[94]
Oil Formulation	20	141	4944	[91]

*For formulation see [95]

**Estimated from graph

ORAL ADMINISTRATION

Following oral administration, systemic availabilities and plasma dispositions of macrocyclic lactones display wide variation between animal species. Considerably lower systemic availability and shorter persistence are generally observed compared to subcutaneous administration. Shorter MRT following oral compared to subcutaneous administration suggests a more rapid absorption process. After oral administration, IVM was absorbed from the gastrointestinal tract and reached peak plasma concentrations faster and the AUC values were higher in monogastric animals compared with ruminants. Slower gut transport and high level of binding of active compounds to solid rumen contents [79] probably reduced the systemic availability of IVM in ruminants. Previous studies have indicated that the systemic availability and plasma concentrations of IVM, DRM and MXD in horses were greater than those reported for ruminants following oral administration (Tables **10**-**12**). Moreover, the plasma concentrations of IVM were higher and more rapidly achieved in horses compared to sheep after oral administration [73], probably because of the absorption delay associated with reticulo-rumen transit in ruminant species.

The plasma disposition of IVM and DRM in donkeys differ substantially from those reported for in horses [62, 63, 73, 113] at same dose rate and administration route. In donkeys, larger AUC (2863 ng.h/ml) and longer MRT (156 h) of both molecules in plasma and faeces reflect longer drug persistence and greater absorption from the gastrointestinal tract compared to horses (AUC: 1106 ng.h/ml, MRT: 55 h – [63]). In contrast Marriner and colleagues [73] observed a much larger AUC (4822 ng.h/ml) with a higher C_{max} (82.3 ng/ml) for IVM in horses. Both IVM and DRM reached peak plasma concentration at 24 h (t_{max}) after oral administration in donkeys and this was considerably later compared to t_{max} in horses (3.1-7.9 h for IVM and 4.8-8.0 h for DRM, Tables **10** & **11**). These differences are probably associated with diet, breed and anatomic characteristics in donkeys compared with horses. In the donkey study, the animals were kept indoors and fed a hay-based diet. The horses were yarded for the period during and immediately (4 h) after drug administration and were then returned to a grass paddock [63].

After oral administration the systemic availability of IVM and DRM were much greater in dogs than ruminants or horses (Tables **10** & **11**) [115]. The absorption of IVM was faster in dogs than in ruminant species, and was similar to horses. In contrast to ruminants and equine species, DRM generated a relatively lower plasma concentration and bioavailability than IVM following oral administration in dogs. No significant difference was observed between these molecules following subcutaneous administration in dogs. These differences may be attributable to the use of different injectable formulations of IVM and DRM for oral administration and to physiological or body composition differences between dogs and the other animals [96, 97, 107].

Goats generally display lower systemic availability and plasma disposition profiles of macrocyclic lactones regardless of the administration routes compared with sheep and cattle (Tables **10**-**13**) [61, 84, 87, 89, 103, 109, 110, 127, 139, 140]. The origin of the low systemic availability is unclear. Previous studies have indicated that IVM reached relatively lower C_{max} and was more rapidly eliminated from blood in goats compared to sheep following oral administration [73, 84, 103]. The AUC value for MXD following oral administration in goats (881 ng.h/ml) is similar to that obtained for IVM [127] but is lower compared to that obtained in sheep of 2373 ng h/ml [60]. The systemic availability of MXD following oral administration was considerably lower in goats compared to other ruminant species and horses [127] (Table **12**). However, the plasma disposition of MXD after subcutaneous administration in goats was similar to that obtained in sheep but lower than that obtained in cattle. In ruminants and equine species, DRM produced greater bioavailability and longer persistence compared with IVM when administered by same route of administration [55, 58, 88, 96, 107, 142].

Table 10. Plasma Pharmacokinetic Parameters of Ivermectin in Different Animal Species

Species	Route	Dose (μg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
Cattle	s/c	200	42.8	96	11016	412.8	176.4	[96]
	s/c	200	46.1	72				[104]
	s/c	200	46.4	50.9	6384	132	129	[94]
	s/c	200	40	24	6672		67.2	[98]
	s/c	200	33.1	55.9	7891.2	137.3		[105]
	s/c	200	54.6	34.8	10790		156.9	[106]
	s/c	200	31.7	95.5	8664	103.7	216	[107]
	s/c	200	46.3	21.6	4444.8	67.2	74.4	[49]
	T	500	12.2	81.6	2916	127.2	201.6	[88]
	T	500	28.2	48				[104]
	T	500	39	147	14282.4	363		[31]
	T	500	16	191	9146.4	154		[31]
Sheep	s/c	200	30	46	2440			[56]
	s/c	200	11.9	40.8	1536	68.4		[57]
	s/c	200	24.1	64.1	4980	134.4	206.4	[65]
	s/c	200	41.2	21.6	4320	132	160.8	[65]
	s/c	200	30.8	60	5712	88.4		[73]
	s/c	200	25.76	29.76	1969.4	40.1		[55]
	s/c	200	16.3	62.4	6744	168.5	141.1	[58]
	s/c	200	19.6	3.1	4576.8	264	247.2	[108]
	s/c	200	14.3	62.4	2121.6		127.2	[70]
	O	200	14.7	24	871.2			[71]
	O	200	23.6	36	2248.8			[71]
	O	200	29	19.3	1790.4			[56]
	O	200	21	20	2131.2			[56]
	O	200	17.6	23.5	2260	101.9		[37]
	O	200	11.3	31.9	1072.8	87.12	82.8	[102]
	O	200	8.5	43.9	1248	88.8	90.72	[102]
	O	200	22	16.4	2040	61.1		[73]
	IR		12.5	24				[77]
	IR		17.6	23.5	2260.8			[37]
	IAB		60.6	4.8	10560			[37]
Goat	s/c	200	21.8	72	3456	134.4	199.3	[109]
	s/c	200	6.1	68.4	1440	189.6	96.72	[110]
	s/c	200	18.16	21.12	1062.48	26.16	47.28	[103]
	s/c	200	10.83	66	2646.24	135.6	223.44	[61]

(Table 10) contd….

Species	Route	Dose (µg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
	s/c	200	10.15	55.92	1761.12	91.44	152.4	[61]
	O	200	15.9	24	516			[84]
	O	200	10.33	13.68	292.32	16.08	27.12	[103]
	T	500	3.9	48	316.8			[84]
	T	500	3.75	46.08	552.48	56.4	114.72	[87]
	T	500	3.92	43.92	408.72	34.08	85.2	[87]
	T	500	2.27	30.27	248.64	56.78	92.52	[89]
	T	500	1.97	34.29	315.01	88.73	141.30	[89]
	T	1000	4.51	39.43	639.45	65.70	110.24	[89]
	T	1000	4.2	37.68	820.1	119.52	180.24	[89]
Pigs	s/c	300	28.4	27.2	1713.84	35.2		[111]
	s/c	300	39.6	22.6	3168	91.2	138.7	[94]
	s/c	300	13.5	74	2712	100.8	187.2	[40]
	s/c	300	9.7	33.2	2056.8		194.4	Thin [66]
	s/c	300	7.4	71.9	2680.8		235.2	Fat [66]
	s/c	300	8	75.1	1692	54.72	201.6	Grower [67]
	s/c	300	7.2	48	2104.8	61.2	230.4	Maintenance [67]
Horse	s/c	200	60.7	80	13209.6	88.2	114.7	[73]
	im	200	31.4	84	7245.6	108.5	206.4	[112]
	T	200	4.29	103.92	1438.3	172.32	283.2	[33]
	O	200	82.3	3.1	4821.6	66.3		[73]
	O	200	21.4	7.9	1106.4	51.6	55.2	[63]
	O	200	44	2.2	3184	102	114.7	[62]
	O	200	51.32	3.6	3290.4	69.36	100.8	[112]
	O	200	61.28	4.08	3959	156.72	176.16	[33]
Donkey	O	200	23.6	24	2863.2	177.6	156.0	[113]
Dog	O	6	2.97	5.3	108			[100]
	O	100	44.3	4.2	1034.4			[100]
	O	200	132.6			80.3		[114]
	O	200	116.8	5.52	5682.96	79.68	104.4	[115]
	s/c	200	66.8	33.6	8380.32	76.56	127.68	[115]
Cat	s/c	200	16.75	29.28	2359.44	60.72	-	[116]
Rabbit	s/c	300	32.02	26.4	4598.9	66	113.5	[117]
	s/c	400	42	37.2	3543.1			[118]
	s/c	300	20.82	27.12	1764.5	48.48	66	[119]
Deer	s/c	200	15.8	19.8				[120]

(Table 10) contd….

Species	Route	Dose (µg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
Camel	s/c	200	1.79	295.9	723		456.7	[121]
	s/c	200	3.24	144	1591	365	516	[122]
Elephant	O	100	5.41-8.49		410.4-487.2	74.88-107.28		[123]

IR – Intraruminal
IAB - Intraabomasal

Table 11. Plasma Pharmacokinetic Parameters of Doramectin in Different Animal Species

Species	Route	Dose (µg/kg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
Cattle	s/c	200	73.5	60.0	12182.0			[97]
	s/c	200	27.8	141.6	10968.0			[124]
	s/c	200	37.5	144.0	15048.0	150.0	218.2	[96]
	s/c	200	32.6	127.4	12264.0	129.4	283.2	[107]
	im	200	33.1	112.8	11400.0	156.0		[124]
	T	500	12.2	103.2	4334.0	235.7	307.2	[88]
Sheep	s/c	300	26.3	43.2	6342.0	112.2		[125]
	s/c	200	34.9	43.0	4753.2	66.5		[55]
	s/c	200	22.7	129.6	9696.0	273.6	155.8	[58]
	s/c	200	33.9	64.8	5510.4	96.0	158.4	[126]
	s/c	200	38.4	39.4	3432.0	48.0	81.6	[126]
	im	300	25.4	55.8	5722.0	106.6		[125]
	O	150	5.4	29.4	753.0	155.9		[74]
Goat	s/c	200	16.8	41.1	2455.0	62.4	17.6	[127]
Pigs	s/c	300	22.9	62.4	5472.0	115.2	206.4	[40]
Horse	im	200	33.3	69.6	9446.4	223.2	319.2	[128]
	O	200	51.6	4.8	4286.4	124.3	185.3	[128]
	O	200	21.3	8.0	1279.2	93.8	72.0	[63]
Donkey	O	200	33.9	24.0	5493.6	266.4	218.4	[113]
Dog	O	200	86.5	2.9	4403.5	90.0	111.8	[115]
	s/c	200	54.8	40.8	7010.4	74.2	121.7	[115]
Rabbit	s/c	300	34.1	74.4	6201.0	107.5	180.5	[117]
	s/c	400	29.0	33.6	2359.0	39.8		[129]
Alpaca	T	500	4.2	132.0	1209.6	120.0	360.0	[130]
Lama	T	500	3.8	139.2	1214.4	163.2	336.0	[130]

Table 12. Plasma Pharmacokinetic Parameters of Moxidectin in Different Animal Species

Species	Route	Dose (μg/kg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
Cattle	s/c	200	35.6		3816.0	213.6	165.6	[131]
	s/c	200	39.4	7.7	5208.0	348.0	340.0	[96]
	s/c	200	18.3	20.9	6717.0	69.6	393.6	[121]
	s/c	200	18.3	37.4	6719.0	347.3	615.8	[132]
	T	500	3.9	168.0		68.9		Non-licker [133]
	T	500	8.7	67.2		92.6		Licker [133]
	T	500	2.3	32.2	520.3	214.8	306.7	Aberdeen Angus [46]
	T	500	5.1	12.7	988.8	316.1	375.4	Holstein [46]
Buffalo	T	500	5.5	28.8	567.8		126.5	[51]
Sheep	s/c	200	8.3	21.1	2696.0	237.6	403.2	[60]
	s/c	200	36.6	4.3	6080.6	427.2	260.2	[75]
	s/c	200	65.1	3.6	4746.5	191.0		[55]
	O	200	13.2	13.2	1261.9	432.7	190.8	[75]
	O	200	27.1	5.3	2373.0	504.9	301.2	[60]
Pig	s/c	300	91.3	1.0	2712.0		126.0	Thin [66]
	s/c	300	72.1	0.8	5330.0		190.1	Fat [66]
Goat	s/c	200	24.3	8.6	3280.0		297.6	[127]
	O	200	15.5	9.1	880.8	288.0	247.2	[127]
Horse	O	200	30.1	7.9	2227.0	534.5	420.0	[63]
	O	400	70.4	8.9	8726.0	554.6	442.1	[62]
Dog	O	200	123	2.0				[29]
Rabbit	s/c	300	27.4	4.1	1996.1	195.8	215.3	[117]
Camel	s/c	200	8.5	31.4	1760.0		400.1	[134]
	s/c	200	8.7	24.0	1695.0		330.2	[121]

Table 13. Plasma Pharmacokinetic Parameters of Eprinomectin in different Animal Species

Species	Route	Dose (μg/kg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
Cattle	T	500	43.8	48.5	5789.0	48.7	99.9	[135]
	T	500	8.8	31.2	735.1	46.8	81.1	[50]
	s/c	200	44.0	39.0	7916.0	164.0	221.0	[136]
Buffalo	T	500	2.7	34.6	274.3		107.8	[51]
Sheep	T	500	2.2	52.8	326.4	129.6	184.8	[137]
	T	1000	5.3	36.0	808.8	292.8	216.0	[137]
Goat	s/c	200	10.0	22.6	1644.0		158.6	[138]
	T	500	5.6	61.2	1735.4	179.0	226.1	[139]

(Table 13) contd….

Species	Route	Dose (μg/kg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Reference
	T	500	2.2	18	197.76	58.6	64.1	[140]
	T	1000	2.98	23.8	376.3	73	88.6	[140]
Camel	T	500	1.8	36.0	150.2		127.2	[141]

SUBCUTANEOUS FORMULATIONS

The plasma dispositions of macrocyclic lactones in different animal species are significantly affected by the solvent vehicle of the drug formulation for subcutaneous administration. Since macrocyclic lactones are highly lipophilic compounds with poor water solubility, an appropriate vehicle is required to ensure that these drugs are released from the injection site. DRM which is formulated with an oily based vehicle, has a greater bioavailability and a longer persistence compared to IVM following SC administration in sheep [55, 58] and cattle [88, 96, 107]. The formulations of IVM and DRM differ since the original IVM is formulated in propylene glycol/glycerol formal (60:40) whereas; DRM contains sesame oil/ethyl oleate (90:10) as vehicle.

The aqueous solubility of the active molecule may affect its bioavailability, which depends on the rate and extent of absorption of the drug from the site of injection into the bloodstream [143]. Although the antiparasitic spectrum and efficacy of the different endectocide molecules are similar, different physico-chemical properties of macrocyclic lactones may account for differences in kinetic behaviour, potency and persistence of their antiparasitic activity [144] and in compatibility with excipients for formulation. It has been demonstrated that plasma disposition of IVM [30, 94], DRM [97] and MXD [101, 145, 146] in cattle is markedly affected by the solvent vehicle of the drug formulation. IVM, administered in non-aqueous injectable form (60% propylene glycol/40% glycerol formal), was absorbed more slowly from the site of subcutaneous injection than when the drug was administered as an aqueous solution in cattle, and the elimination half-life of the non-aqueous form of IVM was much longer than that obtained with an aqueous preparation [30]. The long persistence of the non-aqueous injectable formulation for cattle is reflected in the persistence of its clinical effect [147].

Due to difficulties in discovery and development of new anthelmintic drugs, the existing pharmaceutical preparations and delivery systems have been improved as an alternative for the control of parasites in livestock [148, 149]. The subcutaneous route has been shown to confer a higher bioavailability of macrocyclic lactones in sheep, cattle and goats, when compared to oral or topical administrations [31, 88, 103, 132] and several different formulations for subcutaneous administration have been developed. Novel long-acting formulations for macrocyclic lactones are currently used to provide longer protection against reinfestation with nematodes and ectoparasites compared to previous formulations in some markets. After expiry of the original patent of the 1% formulation of IVM, several different generic formulations including long-acting oil-based formulations for subcutaneous administration in cattle have been introduced. It has been demonstrated that following SC administration, oil-based formulations of IVM confer significantly slower absorption from the injection site and provide more prolonged persistence in the systemic circulation compared to the original non-aqueous formulation in cattle [91]. Recently, concentrated (3.15%) long-acting (LA) IVM preparations were developed and introduced in some markets for subcutaneous administration to cattle at a dose of 630 μg/kg. These preparations were developed to provide much longer antiparasitic persistent efficacy following a single administration and to reduce the labour costs for practitioners or farmers. Lifschitz and co-workers compared two different long-acting (LA) IVM formulations with the conventional preparation (1%) in cattle [150]. Although there were no differences in the plasma persistence of IVM after the administration of IVM 1% formulation at the two different dose levels (200 and 630 μg/kg), higher C_{max} and shorter MRT were obtained for IVM 1% given at 630 μg/kg compared to the treatments with both IVM-LA preparations [150]. It has been shown that the LA formulations containing 2.25% IVM for subcutaneous injection at a dose rate of 450 μg/kg and 3.15% IVM administered at a dose rate of 630 μg/kg displayed delayed t_{max} and significantly longer $t_{1/2}$ and MRT compared to 1.0% IVM at a dose rate of 200 μg/kg in cattle [151]. Another novel formulation of IVM displayed relatively higher plasma availability and longer residence time [109] compared to the conventional formulation in goats [84, 103, 110]. An aqueous injectable formulation of IVM with solid-dispersion suspension displayed dramatically longer MRT with much longer terminal half-life compared with the conventional formulation and could be considered as a sustained-release formulation in sheep [152]. In addition, a long-acting biodegradable drug delivery matrix for IVM has been developed for prevention of heartworm disease and studied in dogs after subcutaneous administration [153]. The results demonstrated sustained release of IVM during at least 287 days and prevention of heartworm disease for at least 6 months after treatment in dogs.

Furthermore, a novel LA oil-based formulation of MXD (10%) has been developed for parenteral administration in cattle and the plasma disposition of this formulation was evaluated after subcutaneous administration in cattle at the recommended dose of 1 mg/kg [146]. The AUC for plasma (0–120 days) obtained after administration of the LA formulation of MXD was more than 4.5 times greater compared with that obtained after subcutaneous administration at 200 μg/kg body weight [96].

It has been demonstrated that although the plasma bioavailability of both formulations were similar, a liposo-

mal formulation of IVM generated significantly higher C_{max} with faster absorption compared with the conventional IVM formulation in rabbits after subcutaneous administration [119].

These LA formulations may have some disadvantages; prolonged drug residence and anthelmintic persistence is likely to extend the withdrawal period for food-producing animals. A reduction in the acquisition of natural immunity by preventing parasite development and thus immune response and the more rapid selection of resistant parasites by extending their exposure to sub-therapeutic concentration are also risks [154].

Subcutaneous Administration

The systemic availability of macrocyclic lactones was lower in sheep compared to cattle after subcutaneous or intramuscular administrations (Tables **10 - 13**) this is thought to reflect the large body fat:body weight ratio with larger volume of distribution in sheep and is due to substantial deposition into adipose tissue, which acts as a drug depot [37]. The plasma concentration of IVM is markedly lower and the clearance rate more rapid in sheep because of its large distribution volume [155]. In addition, in sheep, IVM concentrations in milk were similar to those in plasma [71], and only 0.71% of a subcutaneous dose was excreted through milk and this ratio was lower compared to cattle, probably due to species differences in the volume and fat content of milk. The peak plasma concentrations and AUC values of IVM and DRM were relatively lower in pigs after subcutaneous administration at 1.5 times higher dose rate compared to cattle (Tables **10** & **11**). This is most probably related to the higher distribution and deposition of the drug in fat tissue, which diminishes plasma levels in this animal species [94]. In contrast MXD reached peak plasma concentration earlier in pigs (t_{max} : 1.0 h [66]) compared to cattle (t_{max}: 7.7 h [96]) or sheep (t_{max}: 21 h [60]) following subcutaneous administration and the corresponding C_{max} was also higher in pigs compared with cattle or sheep (Table **12**).

Limited information is available in the literature on the pharmacokinetics of macrocyclic lactones after parenteral administration in horses, since parenteral preparation of IVM has been shown to cause adverse reactions including anaphylaxis [147]. Although no authorised macrocyclic lactones are now available for parenteral administration, the plasma dispositions of IVM and DRM have been investigated after subcutaneous or intramuscular administration in horses [73, 112, 128]. Parenteral administration of IVM and DRM resulted in greater bioavailability than oral administration (Tables **10** & **11**). The maximum plasma concentration (C_{max}: 33.3 ng/ml), systemic availability (AUC: 9446 ng.h/ml) and terminal elimination half-life ($t_{1/2:}$ 223 h) of DRM in horses were greater and longer at a dose rate of 200 µg/kg compared to sheep at a 1.5 times higher dose rate (C_{max}: 25.4 ng/ml, AUC: 5722 ng.h/ml and $t_{1/2}$: 107 h), respectively, however were similar to those in cattle [124] after intramuscular administration. In addition, the AUC value after subcutaneous administration was almost 2.5 times less and the time to reach the maximum plasma concentration (t_{max}) was longer in sheep compared to horses [73]. The systemic availability (AUC: 7245 ng.h/ml) of IVM in horses observed after intramuscular administration [112] was also higher than that reported in cattle (AUC: 6384 ng.h/ml, [94]) and sheep (AUC: 1969 ng.h/ml, [55]) after subcutaneous administration at the same dose rate.

The plasma disposition of IVM and MXD following subcutaneous administration in camels differed substantially compared to other ruminant species [121, 122]. The systemic availabilities and peak plasma concentrations of IVM (1.79-3.24 ng/ml) and MXD (8.5-8.7 ng/ml) were much lower and achieved much more slowly (144-296 h for IVM and 31.4-24.0 h for MXD) in camels compared to other ruminant species (Tables **10** & **12**). The MRT of MXD was similar whereas MRT of IVM was much longer in camels compared to cattle. In camels, lower AUC (1760 ng.h/ml) and C_{max} (8.51 ng/ml) were reported following subcutaneous injection of MXD at 200 µg/kg [134] compared to cattle (AUC: 5208 ng.h/ml, c_{max}: 39.4 ng/ml) at same dose rate [96]. It has been suggested that the lower C_{max} and later t_{max} of IVM and MXD in camels after subcutaneous administration is related to the slower lipid turnover in this species [83]. The AUC of EPM was also much lower in camels (150 ng.h/ml) compared to cattle (735 ng.h/ml) when administered topically at the same dose (500 µg/kg) [50, 141, 156].

The plasma disposition of IVM in cats has been investigated after subcutaneous administration at 200 µg/kg bodyweight [116]. This study indicated that the absorption half-life ($t_{1/2ab}$) in cats (6.48 h) was faster than in ruminant species such as sheep (20 h [65]) and cattle (104 h [107]), but similar to dogs, since the time taken to maximum concentration (t_{max}) in cats and dogs [115] was 29.8 h and 33.6 h, respectively. The C_{max} (16.75 ng/ml) and AUC (2359.4 ng.h/ml) values in cats were lower than those reported in dogs (66.8 ng/ml and 8380.3 ng.h/ml [115]). Chittrakarn and coworkers [116] have suggested that these differences could be due to the actual extent of absorption or could be an artefact associated with the time of blood collection during the absorption phase. The elimination half-life ($t_{1/2}$) in cats was 60.7 h which was similar to that found in dogs (76.6 h [116]; 80.4 h [114]). Moreover, the volume of distribution of IVM in cats was 9.77 L/kg which was larger than in cattle (3.4 L/kg [96]), sheep (8.76 L/kg [65]) and dogs (5.35 L/kg [114]).

In guinea pigs, after subcutaneous, oral and topical treatments, the bioavailability of IVM at 500 µg/kg was much lower than in other species given equivalent and lower doses [118]. Similarly, relatively lower AUC of IVM and MXD was observed in rabbits after subcutaneous administration at 300 or 400 µg/kg level compared with other animal species [117, 118, 119]. In addition, it has been reported that DRM displayed a faster absorption and elimination in rabbits after subcutaneous administration at a dose rate of 400 µg/kg bodyweight compared with cattle and sheep [129]. The t_{max} (33.6 h) and $t_{1/2}$ (39.8 h) values of DRM in rabbits are considerably shorter than those reported in cattle (t_{max}: 144 h; $t_{1/2}$: 150 h) [96] and sheep (t_{max}: 43 h; $t_{1/2}$: 66.5 h) [55]. The differences may be attributed to the physiological, metabolic or body fat composition in rabbits [129]. Although several different formulations have been developed for different routes of administration of macrocyclic lactones so far, subcutaneous injection is still the most effective route, in respect

of the plasma availability and antiparasitic efficacy compared to other routes of administration.

Topical Administration

There are large variations between different studies conducted after pour-on administration of macrocyclic lactones in the same animal species, due to inherent variation between animals and irregular absorption of drug from the site of application associated with different coat lengths and environmental conditions such as rainfall during application (Tables **10**-**14**). In cattle, self-licking or licking between animals makes the systemic availability and plasma disposition variable and unpredictable. Large differences between lickers and non-lickers have been observed after pour-on administration of IVM or DRM [31, 85, 158]. Prevention of licking resulted in an extended terminal plasma half-life and in a lower systemic availability and faecal excretion of IVM.

The systemic availability of MXD obtained in buffalos [51] after pour-on administration at 500 μg/kg was similar to that reported in two different cattle breeds [46] although, the peak plasma concentration (C_{max}) was equivalent to the Holstein breed and higher than Aberdeen-Angus. The MRT was lower (126 h) in comparison with other cattle (375 h for Holstein and 307 h for Aberdeen-Angus) [46]. Considerably different plasma disposition of EPM has been demonstrated between buffalo and other animal species following pour-on administration [51] with the systemic availability significantly lower [50, 139], but close to that reported in dairy goats [140] and greater than that reported in camels [141] (Table **13**). Dupuy and co-workers [51] have suggested that limited absorption of the drug through the buffalos' skin and/or retention of a reservoir in the fatty histological structures of the skin, could account for the low systemic availability of EPM in buffaloes compared to cattle.

The plasma availability of EPM and IVM following pour-on administration at a bovine dose rate (500 μg/kg) was much lower in goats compared with cattle [84, 86, 87, 89, 138, 140]. It has been reported that C_{max} and AUC values of EPM (5.60 ng/ml and 1735 ng.h/ml) were significantly lower in goats compared to cattle (43.76 ng/ml and 5738 ng.h/ml) after pour-on administration, but the MRT of EPM pour-on was about 3 times longer in goats (226.1 h) than in cows (99.8 h) suggesting a slower absorption and longer retention in hair and skin or slower elimination process in goats [139]. The plasma concentrations of IVM in goats are also lower compared with those in non-licking cattle [31] at same dose rate (500 μg/kg). The peak plasma concentration (C_{max}) and the time taken to reach the peak plasma concentration (t_{max}) in young (y) and old (o) goats (2.27 (y)-1.97(o) ng/ml and 30(y)-34(o) h, respectively) were considerably lower and shorter [89] compared to those reported in non-licking cattle (16.00 ng/ml and 191 h, respectively). In addition, the terminal elimination half-life in goats was almost 5 times shorter than that reported in cattle. These results indicate that IVM was absorbed and eliminated more rapidly, and thus conferred lower bioavailability in goats compared to cattle. It has also been demonstrated that the systemic availability of IVM after pour-on application in horses was lower compared to cattle given the same dose rate [33]. Although the C_{max} value in horses (4.29 ng/ml) was similar to the value observed in goats (3.75-4.2 ng/ml), the AUC, t_{max}, $t_{1/2}$ and MRT values were considerably greater and longer, respectively in horses compared to goats after pour-on administration of IVM (Table **10**). The systemic bioavailability of EPM was also poorer in sheep compared to cattle [137]. Wool and wool grease in the hair coat of sheep probably generate a relatively impenetrable barrier for the active compound [83]. The reason for the lower plasma availability of IVM in goats and horses compared with cattle is unclear. Differences in the physiological and histological structure of skin between animal species are most likely. The quantitative prediction of the rate and extent of percutaneous penetration (into skin) and absorption (through skin) of topically applied chemicals is complicated by the biological variability inherent in skin across animal species [159]. Moreover, hair follicle density and/or length of hair coat and the secretion of sweat and sebaceous glands are important variables for drug absorption from skin between animals. A correlation was observed between length of hair coat and plasma concentrations of IVM following pour-on administration in young and old goats [89]. The longer hair coat may hold more molecules at the application site and/or different fibre type of hair may cause lower plasma availability of endectocides.

The systemic availability of SLM in dogs after topical administration at a dose rate of 6000 μg/kg was only 4.4% and considerably lower (74%), than in cats, probably due to ingestion of drug during grooming or self-licking in cats. Moreover, plasma disposition of SLM following intravenous administration indicated a slower elimination in cats compared to dogs reflecting a slower clearance and longer $t_{1/2}$ in cats, probably because of species-related differences in metabolism and excretion [27]. The systemic availability of SLM was almost two times greater in female dogs after topical administration compared with male animals [157]. The terminal half-lives in male (288 h) and female (264 h) dogs were much higher than those obtained previously in dogs (14 h) following intravenous administration [27]. This difference was probably due to the long process of absorption at the site of administration [157].

The topical route of administration for macrocyclic lactones has some advantages such as prolonged plasma persistence, of injury for both user and animal and convenience for farmers who apply the products. This route also displays some disadvantages such as lower systemic availability, large inter-species and inter-individual variations, reduced plasma availability during adverse weather conditions such as rainfall and unpredictable plasma concentration due to licking behaviour. There are clearly substantial effects on pharmacokinetics which can be attributed to route of administration, formulation in which the active is delivered and species to which it is being delivered. Nevertheless the compounds have been developed in formulations which optomise their delivery by the target route and in the specified species and each has its place dependent upon husbandry and management situations in which its use is required.

EFFECT OF GENDER

Gender-related differences in the plasma disposition of some macrocyclic lactones have been observed in different animal species following different routes of administration.

Dupuy and colleagues observed sex-related differences in plasma disposition of SLM in dogs after topical administration; the AUC values in females were significantly greater compared to those in male Beagles [157]. Similarly significantly larger (68.7%) AUC of IVM was observed in females compared with male sheep after subcutaneous administration [54]. These results are in agreement with those of Toutain and colleagues [107], who reported remarkable sex-related differences in plasma disposition of IVM and DRM in cattle, the bioavailability was 10% higher in heifers than steers for both drugs. These differences may be related to the quantity of adipose tissue in males and females [146]. The high lipid solubility of the endectocide agents facilitate their storage in the adipose tissue, which then acts as a drug reservoir that contributes to the persistence of these compounds in the body [83, 131, 160]. Metabolism of drugs may also differ in females compared to males owing to hormonal influences on physiological functions and metabolic processes. Sex-dependent differences in pharmacokinetics including metabolism and clearance of drugs are important [161] and sex-related differences have been shown for phase I (cytochrome P450) as well as phase II (especially glucuronidation) reactions [162-164]. However, Dupuy and colleagues demonstrated no significant differences between males and females in the *in vitro* metabolism of IVM by hepatic microsomal preparations from cattle [165].

In contrast to sheep and cattle, IVM produced larger AUC, longer $t_{1/2}$ and extended persistence in male goats compared with females after pour-on administration at the same dose rate [87]. The origins of these observed sex-related pharmacokinetic differences are unclear. It seems unlikely that they are directly related to skin histology since male goats have thicker back skin than females, but could be associated with more subtle differences such as coat thickness or sebum production. Differences in body conditions could also be important since the mean body weight of male animals (39.5±2.4 kg) was significantly greater than that of females (32.5±1.6 kg). It has been shown that there is a high correlation between body weight and time for the last detectable MXD concentration in sheep and horses [63, 64].

The major route for the elimination of macrocyclic lactones is P-glycoprotein-mediated intestinal secretion and the activity or distribution of P-glycoprotein in the gastrointestinal system could be different between males and females. It has been shown that substantial sex-related differences in P-glycoprotein-mediated IVM disposition were observed in the gastrointestinal tract of rats [166]. Co-administration with itraconazole, a modulator for P-glycoprotein, resulted in significantly higher IVM concentrations in the wall tissues from different portions of the gastrointestinal tract in males compared to female rats [166].

EFFECT OF FEEDING

The plasma dispositions of macrocyclic lactones are substantially affected by alteration in the quality and quantity of feed consumed and this affects the efficacy of the drugs [2, 167]. The macrocyclic lactones are widely eliminated in the faeces regardless of the target animal species, or the macrocyclic lactones molecule or the route of administration, with less than 2% excreted in the urine [6, 74, 168, 169]. It had been assumed that biliary secretion was the major pathway of elimination of the parent drug [73]. However, recent studies have demonstrated that the major route for the elimination of IVM in the gastrointestinal system is not biliary but P-glycoprotein-mediated intestinal secretion [36, 170, 171].

The AUC of IVM in housed lambs was larger compared with grazing lambs [167]. This may be attributed to shorter gastrointestinal transit time and relatively less absorption of IVM in the grazing animals. Moreover, different diet has been shown to affect the faecal excretion pattern of subcutaneously administered IVM which was more than 5 times higher in the faeces of grain-fed cattle compared with pasture-fed (grazing) cattle [172].

A reduction of feed intake resulted in greater availability, an extended residence time and higher efficacy after oral administration of IVM in sheep [169]. The anthelmintic efficacy of IVM was significantly improved when feed intake was reduced from 800 g/day to 400 g/36 h prior to and 36 h after IVM administration. Fasting enhanced the plasma bioavailability of MXD in the horse after oral administration; significantly higher AUC values with longer absorption process were obtained in the fasted horses compared to those in fed animals [173]. It was suggested that fasting decreased intestinal transit time, and prolonged the time for absorption of MXD. Since biliary excretion and intestinal secretion are major elimination routes for macrocyclic lactones, fasting may have also reduced bile flow and intestinal secretion [173]. IVM probably binds onto digesta following oral administration to horses just after feeding and food withdrawal is likely to improve absorption [73]. Fasting or feed withdrawal before treatment is therefore useful for improving the anthelmintic efficacy in animals [173].

It has been demonstrated that malnutrition also affected the plasma availability of IVM in cattle after subcutaneous administration [174]. Substantially greater plasma availability (AUC: 10632 ng.h/ml, C_{max}: 53.9 ng/ml) with longer terminal half-life ($t_{1/2}$: 9.7 days) was observed in calves fed with a restricted diet compared to calves fed *ad libitum*, (AUC: 6864 ng.h/ml, C_{max}: 48.5 ng/ml, $t_{1/2:}$ 5.6 days) and the authors suggested that due to the lipid solubility of IVM, the mobilisation of free fatty acids from adipose tissue modified the plasma-adipose tissue exchange pattern, furthermore dietary restrictions could also reduce bile flow and, subsequently biliary secretion of IVM.

EFFECT OF PARASITISM

The plasma kinetics of IVM were not altered by infection with the intestinal nematode, *Nematodirus battus* after subcutaneous or oral administration in sheep [56] and although faster absorption and smaller AUC of IVM were observed after subcutaneous administration in sheep with mange infection compared with parasite-free animals, the changes were not significant [65]. Nevertheless, gastrointestinal nematode infection significantly altered the plasma disposition of MXD in lambs; 54% and 46% lower plasma availability with shorter mean residence time for MXD were observed in infected lambs compared to controls following subcutaneous and oral administrations, respectively [75]. Gastrointestinal nematode infections considerably altered the plasma disposition of IVM and DRM following subcutaneous administra-

tion in lambs [69, 126, 175] whereby the AUC values of infected lambs were significantly lower compared to parasite-free animals. This difference was associated with a shorter terminal half-life and higher clearance in infected lambs. Gastrointestinal parasite burden is associated with serious physiopathological changes such as intestinal dysfunction and poor body condition [75, 176]. Host physiopathological changes induced by parasitism on gastrointestinal mucosa and tissues may alter the gastrointestinal passage time of digesta and rate of drug absorption and elimination in comparison with non-parasitised animals. Gastrointestinal helminth infections produce pathological changes including diarrhoea in the horse [177] and ruminants [176, 178] and these changes may have a major impact on the plasma, tissue and gastrointestinal disposition of anthelmintic drugs and consequently on their anthelmintic efficacy [126].

POTENTIATION OF MACROCYCLIC LACTONES

Different strategies associated with pharmaceutical formulation of anthelmintic drugs have been developed to increase drug potency and to provide higher treatment efficacy for more effective parasite control.

In vivo and *in vitro* studies have demonstrated that multidrug resistance transporters (mdrs) such as P-glycoproteins (P-gp) play an important role in the disposition kinetics of some chemotherapeutics including macrocyclic lactones and the kinetics of the parent molecules can be affected by modification of P-gp by inhibitors or reversing agents such as verapamil, ketaconazole or itraconazole, loperamide and fumagillin which modify secretion or efflux of drugs from the bloodstream to the gastrointestinal tract [4, 36, 166, 179-183]. IVM is a substrate for P-gp [184] and the involvement of P-gp in the intestinal secretion of IVM has been demonstrated [36, 170, 171] (Table **15**). Verapamil which is widely used as a P-gp substrate or inhibitor in drug transport studies considerably increased the plasma availability of IVM and MXD when co-administered in sheep [183]. Alvinerie and colleagues [185] observed an increased plasma concentration and decreased elimination of pour-on IVM following co-administration with verapamil in rats. Verapamil also inhibited by 50% the metabolism of MXD in rat microsomes [180].

Furthermore, subcutaneous administration of IVM or MXD in combination with verapamil enhanced the efficacy against a MXD resistant strain of *Haemonchus contortus* in jirds [186, 187]. The co-administration of IVM with ketoconazole or itraconazole, which are also P-glycoprotein competitors increased the plasma concentrations of IVM in sheep [36, 179] and dogs [182] and tissue concentration in different parts of the gastrointestinal tract in rats [166]. Loperamide, a P-gp modulating agent, significantly enhanced the plasma concentration and decreased the body clearance of MXD after co-administration in cattle [4] and in rats, the presence of Loperamide conferred a significantly higher plasma concentration of IVM compared with IVM alone [187]. It was demonstrated that co-administration of loperamide elevated the plasma concentration of IVM by modifying its P-glycoprotein-mediated intestinal and bile secretion and enhanced its anthelmintic efficacy against resistant nematodes in lambs [35]. It has been shown that the plasma concentration of MXD was increased significantly by quercetin, a natural flavonoid, following co-administration in lambs [188]. Recently, the effect of phenobarbital and rifampicin on the disposition kinetics of IVM has been investigated in rats [189]. Although, the plasma and tissue disposition of IVM was significantly altered by the phenobarbital treatment, but not by rifampicin the concentration of IVM metabolites recovered from plasma was not affected. The authors suggested that the increased P-glycoprotein-mediated intestinal transport activity induced by phenobarbital in pre-

Table 14. Plasma Pharmacokinetic Parameters of Selamectin in Different Animal Species

Species	Route	Dose (µg/kg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng.h/ml)	$t_{1/2}$ (h)	MRT (h)	Cl (l/kg.d)	V_d (l/kg)	Reference
Dog	IV	50			761	13.8	19.0	1.71	1.14	[27]
	IV	100			1534	14.2	18.9	1.70	1.22	[27]
	IV	200			3100	14.7	19.9	1.68	1.26	[27]
	T	24000	86.5	72	16104	266.6	270.3			[27]
	T	6000	12.72	116.64	4609.9	291.36	301.4			[157]
	T	6000	22.65	124.8	8903.3	257.5	301			[157]
	O	24000	7630	8	227985	45.7	31.3			[27]
Cat	IV	50			2045	58.9	85.2	0.73	2.1	[27]
	IV	100			4756	78.2	110.0	0.62	2.26	[27]
	IV	200			8526	74.5	93.7	0.68	2.22	[27]
	T	24000	5513	15	767695	198	219.3			[27]
	O	24000	11929	7	1116916	97.7	136.8			[27]

Table 15. Mean Kinetic Parameters for Ivermectin (IVM) and Moxidection (MXD) in Plasma Obtained after its Administration (200 µg/kg) Either Alone or with Verapamil (VRP) Ketoconazole (KTZ) or Loperamide (LPD)

Species	Route	Drugs	$t_{1/2\ ab}$ (d)	C_{max} (ng/ml)	t_{max} (d)	AUC (ng.h/ml)	MRT (d)	$t_{1/2\ el}$ (d)	References
Sheep	Oral	IVM / IVM+VRP	0.29 / 0.34	6.88 / 12.6	0.86 / 0.91	463 / 713	2.85 / 29.7	2.14 / 2.90	[183]
	Oral	MXD / MXD+VRP	0.20 / 0.17	7.2 / 12.3	0.79 / 0.53	2278 / 1495	17.7 / 19.7	15.4 / 16.2	
	s/c	IVM / IVM+KTZ	0.21 /0.26	5.4 /10.6	0.62 /0.71	382 / 672	2.6 /2.36	3.35 /3.30	[179]
	Oral	IVM / IVM+ITZ	0.23 / 0.35	2.09 / 6.85	1.25 / 1.00	1677 / 636	3.46 /4.54	2.10 / 2.76	[36]
Cattle	s/c	MXD/ MDX+LPD	0.07/ 0.06	33.5 / 47.7	0.37 / 0.35	3888 / 5352	12.2 / 12.9	10.3 / 9.88	[4]

treated rats probably accounted for the dramatic decrease in IVM disposition. Since the P-glycoprotein transport system is responsible for removing macrocyclic lactones from the CNS serious side effects such as neurotoxicity may occur when P-gp modulating agents or inhibitors are co-administered with macrocyclic lactones [190].

CONCLUSIONS

The macrocyclic lactones have pharmacokinetic properties which contribute to the diverse strategies available for their use. They have absorption characteristics which allow delivery by oral, parenteral and topical routes offering flexibility and economy to their use in a variety of animal species.

Their distribution characteristics confer access to the major sites of animal parasitic pathogens including gut and skin and can be manipulated to reduce access to potential organs of intoxication (central nervous system) or residue transfer (milk). Inherent characteristics (lipid solubility) or formulations confer sustained residence on many members of the group which are thus effective in preventing parasitic reinfection for prolonged periods as well as direct therapy.

These pharmacokinetic properties, together with pharmacodynamic activity against a broad range of nematodes and arthropods have made the macrocyclic lactones the most popular group of antiparasitics in global animal health markets for the last thirty years.

CONFLICT OF INTEREST

None declared.

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ABBREVIATIONS

AUC = Area under the concentration time curve

b.w. = Bodyweight

Cl = Clearance

C_{max} = Maximum Plasma Concentration

CSF = Cerebrospinal fluid

DRM = Doramectin

EPM = Eprinomectin

GABA = Gamma amino butyric acid

i/m = Intramuscular

IAB = Intra abomasal

IR = Intraruminal

IVM = Ivermectin

KTZ = Ketaconazole

LA = Long acting

LPD = Loperamide

mdr = Multi drug resistance

MXD = Moxidectin

MRT = Mean Residence Time

O = Oral

p/o = Per os/oral

SLM = Selamectin

s/c = Subcutaneous

T = Topical

t/c = Transcutaneous

$t_{1/2}$ = Half life of elimination

$t_{1/2}$ab = Absorption half life

t_{last} = Time until last detectable concentration

t_{max} = Time until C_{max}

V_d = Volume of distribution

VRP = Verapamil

wt = Wild type

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