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Review

The pharmacokinetics and metabolism of ivermectin in domestic animal species

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Abstract

The pharmacokinetic properties of drugs are closely related to their pharmacological efficacy. The kinetics of ivermectin are characterised, in general terms, by a slow absorption process, a broad distribution in the organism, low metabolism, and slow excretion. The kinetics vary according to the route of administration, formulation, animal species, body condition, age, and physiological status, all of which contribute to differences in drug efficacy. Characterisation of ivermectin kinetics can be used to predict and optimise the value of the parasiticide effects and to design programmes for parasite control. This article reviews the pharmacokinetics of ivermectin in several domestic animal species.

Keywords: Ivermectin; Pharmacokinetics; Animal species; Absorption; Distribution; Metabolism; Excretion; Cattle; Sheep; Goat; Pig; Dog; Review

Introduction

The rational use of a drug requires knowledge of its basic pharmacokinetics in the target animal species, and this helps to optimise clinical efficacy. Ivermectin is probably one of the most widely used antiparasitic drugs worldwide, and its efficacy is well established. However, 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.

Ivermectin is a mixture of two chemically modified avermectins that contain at least 80% of 22,23-dihydroavermectin-B1a and >20% 22,23-dihydroavermectin-B1b (Fig. 1). 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.

Ivermectin is highly active against a wide spectrum of nematode species, including most larvae and adult forms; it is also highly effective against many arthropod parasites of domestic animals (Table 1). All important gastrointestinal and lung nematodes are susceptible to the drug, including sensitive mites, ticks, biting flies, and parasitic dipteran larvae (Campbell and Benz, 1984; Campbell, 1989; McKellar and Benchaoui, 1996). In dogs, ivermectin is also active against developing larvae of *Dirofilaria immitis* and is used in heartworm prophylaxis.

Toxicity to ivermectin is rare across animal species. The signs of toxicosis are mydriasis and depression, followed by

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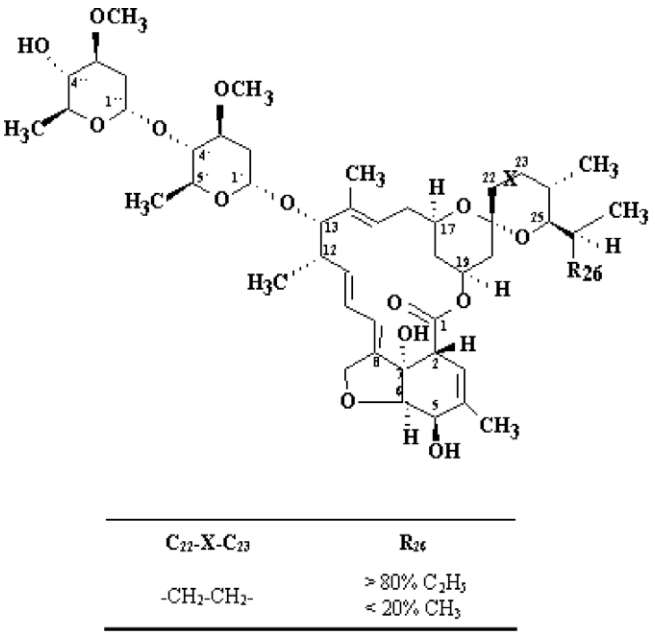

C_{22}-X-C_{23}	R_{26}
-CH_2-CH_2-	> 80% C_2H_5 < 20% CH_3

Fig. 1. Chemical structure of ivermectin.

ataxia, recumbency, and death. It has no adverse effects on breeding performance. Some Collie dogs and other herding breeds are remarkably susceptible, but even these animals will tolerate doses of 50 μg/kg, which are nearly 10-fold greater than the therapeutic dose in dogs. The central nervous system side-effects in sensitive Collie dogs have been linked to the absence or functional deficiency of P-glycoprotein, which functions as a transmembrane efflux pump and plays a central role in limiting drug uptake by the brain, thereby protecting against ivermectin neurotoxicity.

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. This paper reviews the most important aspects of ivermectin pharmacokinetics, including absorption, distribution, metabolism, and excretion (Fig. 2).

General overview of ivermectin pharmacokinetics and metabolism

Since its introduction in 1981, there have been numerous pharmacokinetic studies of ivermectin. The drug can be administered by oral, intramuscular (IM), subcutaneous (SC), or topical routes, depending on the species. The pharmacokinetic properties are dose-dependent, with a linear increase in the area under the curve (AUC) with increasing dose.

The route of administration and the formulation strongly affect ivermectin's pharmacokinetics. The greatest bioavailability is achieved with the SC injection, followed by the oral route. The lowest AUC values are obtained after topical administration, even if the dose is 500 μg/kg instead of 200 μg/kg. Parenteral administration delays ivermectin's absorption compared to the oral route, but leads to an overall higher availability in plasma, a longer duration of activity, and better efficacy. Molento et al. (2004) pointed out that the lower absorption of ivermectin after oral administration could be influenced by P-glycoprotein, which is also present on the intestinal epithelium; when ivermectin is co-administered with verapamil (a P-glycoprotein blocker), the maximum plasma concentration (C_{max}) and bioavailability increased, leading to an improvement in antiparasitic efficacy.

Ivermectin's extremely low water solubility and its precipitation in SC tissues favour slow absorption from the injection site, resulting in a prolonged presence in the bloodstream. On the other hand, the erratic SC absorption of ivermectin could relate to variability in pharmacokinetic parameters.

In ruminant species, intraruminal (IR) administration yields a lower systemic availability and could explain its lesser efficacy against ectoparasites (Benz et al., 1989; McKellar and Benchaoui, 1996) and shorter duration of activity against gastrointestinal nematodes.

Small differences in formulations may result in substantial changes in the antiparasitic activity of ivermectin. This property has been extensively studied in cattle. Absorption is greater and faster with an aqueous vehicle than with propylene glycol:glycerol-formal (60:40 v/v), and the drug's biological half-life is also longer, prolonging its clinical efficacy (Lo et al., 1985). Moreover, when using an oil-based formulation, absorption is faster after IM versus SC administration due to greater blood flow in muscle. SC absorption is delayed with an oil-based vehicle compared with propylene glycol:glycerol-formal due to slower release of the ivermectin from the SC depot (Lifschitz et al., 1999b).

Results do however vary. In one study, no differences were observed after SC administration of two commercial formulations with the same vehicle (propylene glycol:glycerol-formal 60:40 v/v) (Lifschitz et al., 1999a), whereas in another study from the same group there were significant differences in the absorption pattern (rate and extent) between four formulations with the same vehicle (Lifschitz et al., 2004).

Due to its high lipophilic nature, ivermectin is extensively distributed with broad volumes of distribution (V_d) in all species. It tends to accumulate in fat tissue, which acts as a drug reservoir and the highest levels of ivermectin are found in liver and fat, and the lowest in brain tissue. Binding studies in dogs have shown that ivermectin binds extensively to plasma albumin and lipoproteins (Rohrer and Evans, 1990), and this should be considered in undernourished animals or in diseases in which plasma proteins decrease, as there would be a higher free fraction of the drug. Ivermectin persists in the body for a prolonged period, due not only to low plasma clearance but also to this accumulation in fat tissue. Plasma clearance appears to be greater in pigs than in polygastric species (goats > sheep > cattle).

Table 1
Ivermectin spectrum of activity in several domestic animals

Animal species	Nematodes	Arthropods	Dose
Cattle	*Haemonchus* spp. *Ostertagia* spp. *Cooperia* spp. *Trichostrongylus* spp. *Strongyloides papillosus*; *Bunostomum* spp. *Nematodirus* spp. *Trichuris* spp. *Oesophagostomum* spp. *Dictyocaulus viviparus*	*Hypoderma* spp. *Sarcoptes bovis* *Psoroptes ovis* *Linognathus* spp. *Haematopinus* spp.	200 μg/kg subcutaneous and oral 500 μg/kg topical
Sheep	*Haemonchus* spp. *Chabertia ovina* *Ostertagia* spp. *Cooperia* spp. *Trichostrongylus* spp. *Strongyloides papillosus* *Bunostomum* spp. *Nematodirus* spp. *Trichuris* ovis *Oesophagostomum* spp. *Dictyocaulus filaria*	*Oestrus ovis* *Sarcoptes scabiei* *Psoroptes ovis* *Melanophagus ovinus*	200 μg/kg subcutaneous and oral
Goat	*Haemonchus* spp. *Chabertia ovina* *Teladorsagia* spp. *Cooperia* spp. *Trichostrongylus* spp. *Strongyloides papillosus* *Oesophagostomum* spp. *Dictyocaulus filaria*	*Sarcoptes* spp. *Psoroptes* ovis	200 μg/kg subcutaneous
Pig	*Ascaris suum* *Hyostrongylus rubidus* *Strongyloides ransomi* *Oesophagostomum* spp. *Metastrongylus* spp. *Stephanurus dentatus* *Trichinella spiralis* (intestinal)	*Sarcoptes scabiei* *Haematopinus suis*	300 μg/kg subcutaneous
Horse	*Strongylus* spp. *Parascaris equorum* *Oxyuris equi* *Draschia* spp. *Habronema* spp. *Trichostrongylus axei* *Parascaris equorum* (microfilaria) *Strongyloides westeri* *Dictyocaulus arnfieldi* *Onchocerca* spp.	*Gasterophilus* spp. *Sarcoptes scabiei*	200 μg/kg oral
Dog	*Dirofilaria immitis* (microfilaria and fourth-stage larvae) *Toxocara canis* *Toxascaris leonine* *Ancylostoma caninum* *Uncinaria stenocephala* *Trichuris vulpis*	*Sarcoptes scabiei* *Otodectes cynotis*	6 μg/kg oral

Ivermectin undergoes little metabolism; most of the dose is excreted unchanged. Metabolic studies have been performed in rats, cattle, sheep, goats, and pigs. The major metabolites isolated in vivo are 24-OH-H2B1a and 24-OH-H2B1b in cattle, sheep, and rats (Chiu et al., 1986), whereas in pigs *O*-demethylation derivatives are the major metabolites that have been isolated (3″-*O*-desmethyl-H2B1a and 3″-*O*-desmethyl-H2B1b); 3-*O*-desmethyl metabolite was found in goats (Alvinerie et al., 1994). In sheep and cattle, less polar metabolites have been found in fat tissue, suggesting that in both species liver metabolites are esterified with fatty acids and stored in fat as non-polar entities (Chiu et al., 1988). These non-polar metabolites have not been described in pigs, as their

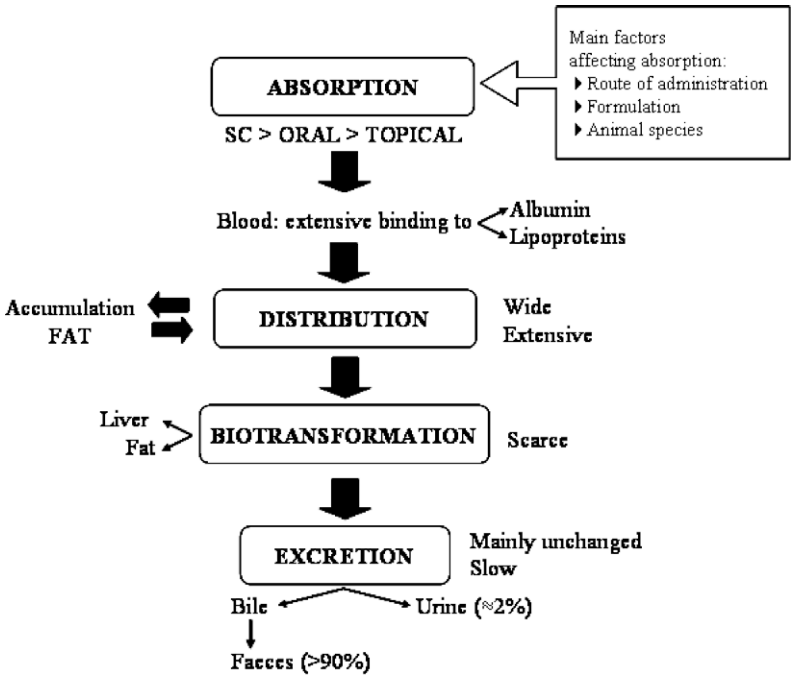

Fig. 2. Pharmacokinetics of ivermectin.

hepatic metabolites lack a primary hydroxyl functional group, and would be less favourable substrates for esterification in fat.

Ivermectin is mainly eliminated in the faeces in all species regardless of the route of administration, and faecal excretion accounts for 90% of the dose administered with <2% of the dose excreted in urine. Bile is the main route of excretion. As P-glycoprotein is also present in biliary canalicules, it could contribute to the drug's high faecal excretion (Laffont et al., 2002). Ivermectin is also excreted by the mammary gland in dairy cows, sheep, and goats; this mode of excretion is related to its high lipophilicity. After intravenous (IV) administration, the plasma elimination half-life appears to be longer for ruminant species than for monogastric animals.

Excretion is also affected by the formulation and is slower in cattle treated SC with non-aqueous vehicles compared with aqueous vehicles (Table 5); retention in the body is also increased due to slow absorption from the injection site (elimination half-lives are 2.0, 3.7, and 8.3 days with aqueous, aqueous:glycerol-formal 50:50 v/v, and propylene glycol:glycerol-formal 60:40 v/v formulations, respectively) (Lo et al., 1985). Furthermore, excretion is slower with an oily solvent compared with propylene glycol:glycerol-formal (Lifschitz et al., 1999b). Even with the same vehicle, however, the elimination half-life varies depending on the pharmaceutical preparation (Lifschitz et al., 1999a). The half-life of the non-aqueous formulation of ivermectin is longer after SC than IV administration, reflecting the rate-limiting effect of the absorption process on the drug's overall kinetics (Lo et al., 1985; Echeverría et al., 1997).

There are large interspecies and inter-individual variations in ivermectin pharmacokinetics. Regarding interspecies variability, the AUC values after SC and oral administration are almost 2.5 times less in sheep compared to horses, and the time to reach the maximum plasma concentration (t_{max}) is longer (Marriner et al., 1987). On the other hand, the V_d could influence plasma concentrations, as after IV administration the V_d increases in the following manner: cattle < sheep and pigs < goats. Inter-individual variation can also be attributed to differences in body condition, age, sex, and physiological status (McKellar and Marriner, 1987; Bogan and McKellar, 1988; Scott et al., 1990; McKellar et al., 1991; Scott and McKellar, 1992; Lanusse et al., 1997; Gayrard et al., 1999; Cerkvenik et al., 2002; Barber et al., 2003).

The effect of malnutrition on ivermectin kinetics has been studied in cattle (Lifschitz et al., 1997). When administered SC, plasma availability was greater in calves with a restricted diet for 21 days compared to cattle fed ad libitum, (undernourished: AUC = 443 ng day/mL, C_{max} = 53.9 ng/mL; ad libitum: AUC = 286 ng day/mL, C_{max} = 48.5 ng/mL). Lifschitz et al. (1997) hypothesised that due to the lipid solubility of ivermectin, the mobilisation of free fatty acids from adipose tissue could modify the plasma-adipose tissue exchange pattern. Moreover, ivermectin elimination is delayed in undernourished (elimination half-life: 9.7 days; clearance: 0.465 L/kg day) versus regularly fed calves (elimination half-life: 5.6 days; clearance: 0.733 L/kg day), with significant differences in the elimination half-life and clearance. Lifschitz et al. (1997) proposed that dietary restrictions could reduce bile flow and, subsequently, biliary excretion of ivermectin.

Table 2
Pharmacokinetic models followed by ivermectin in different animal species after the administration of the drug by various routes

Animal species	Route	Model	References
Cattle	Intravenous	Two-compartmental	Lo et al. (1985); Bousquet-Mélou et al. (2004); Echeverria et al. (1997)
	Subcutaneous	One-compartmental	Lifschitz et al. (1999b); Toutain et al. (1988)
		Two-compartmental	Lanusse et al. (1997)
	Intraruminal	Two-compartmental	Alvinerie et al. (1998)
	Topical	One-compartmental	Gayrard et al. (1999)
Sheep	Intravenous	Two-compartmental	Lo et al. (1985); Gonzalez et al. (2007)
	Subcutaneous	One-compartmental	Cerkvenik et al. (2002); Barber et al. (2003); Echeverría et al. (2002)
		Two-compartmental	Marriner et al. (1987); Atta and Abo-Shihada (2000)
Goat	Intravenous	Two-compartmental	Gonzalez et al. (2006)
	Subcutaneous	One-compartmental	Alvinerie et al. (1993)
	Intraruminal	One or two-compartmental[a]	Escudero et al. (1997)
Pig	Intravenous	Two-compartmental	Craven et al. (2001)
Horse	Subcutaneous	Two-compartmental	Marriner et al. (1987)
	Oral	Two-compartmental	Perez et al. (2002)
Dog	Intravenous	Two-compartmental	Lo et al. (1985)

[a] Depending on the individual animal.

McKellar et al. (1991) showed that infestation with *Nematodirus battus* did not modify the kinetics of ivermectin administered SC or orally to sheep. Nevertheless, Echeverría et al. (2002) observed that infestation with *Psoroptes* spp. resulted in faster absorption with a higher C_{max} value after SC treatment, probably due to the smaller amount of body fat compared to healthy animals.

The pharmacokinetic model describing the kinetics of ivermectin varies according to the animal species and route of administration (Table 2). The choice of one model over another involves a consideration of pharmacokinetic parameters and the ways in which they are calculated.

Species considerations

Cattle

Table 3 summarises the pharmacokinetic parameters calculated for different routes of administration in cattle. SC administration is the most studied, and the results show a high degree of variability, which may be due to differences in breed, body condition, number of samples or data points, methods of quantification, and kinetic treatment of the data, or to erratic absorption from the injection site.

Despite this variability, Campbell and Benz (1984) and Benz et al. (1989) showed that the plasma concentrations achieved in cattle are clinically effective against some species of endo- and ectoparasites. It is known that ivermectin administered SC has persistent anthelmintic activity against most gastrointestinal nematodes, lasting for approximately 10 days, and it is active against *Dictyocaulus viviparus* for 21 days (Barth, 1983; Bremner et al., 1983; Armour et al., 1985). In cattle, plasma concentrations of 0.5–1 ng/mL are required for optimal anthelmintic activity against most gastrointestinal and lung nematodes (Lifschitz et al., 1999b); plasma concentrations of 0.5 ng/mL also control *Hypoderma* spp. flies (Alvinerie et al., 1994).

Intra-ruminal administration has also been tested in cattle and results in a lower and earlier plasma peak concentration and reduced bioavailability. With a single IR dose, the bioavailability was 26% of that following SC administration (Chiu et al., 1990a). However, a sustained-release bolus (SRB) that delivered 12 mg/day to the cattle rumen for 135 days yielded a high steady-state concentration (20 ng/mL) between days 4 and 120 after treatment, offering a desirable drug-release profile for parasite control throughout an entire grazing season (Alvinerie et al., 1998).

Pour-on formulations are used in cattle, as their application is less stressful for handlers and animals. Bioavailability is low and does not exceed 15% of that for SC injection possibly due to wastage or the drug being trapped in the skin and released very slowly over a longer period of time (Gayrard et al., 1999). Thus, the choice of a SC or pour-on route could be important clinically, as topical formulations (with a longer action) would be more effective against most sensitive parasite species (*D. viviparus* or *Oesophagostomum radiatum*), whereas SC administration should be considered for less sensitive nematodes (*Nematodirus helvetianus* or *Trichostrongylus colubriformis*).

With topical application, attention should be paid to the animal's licking behaviour. Laffont et al. (2001) observed that the bioavailability of ivermectin was lower in calves when licking was prevented (19%) compared to when it was not (33%). Thus, with licking, a substantial amount of topically applied ivermectin could access the systemic circulation via oral consumption resulting in subtherapeutic concentrations in untreated and licked animals, which can contribute to the development of resistance. Bousquet-Mélou et al. (2004) reported that 6.3–80.4 μg/kg

Table 3
Absorption pharmacokinetic parameters obtained after ivermectin administration to ruminants

Reference	Route	C_{max} (ng/mL)	t_{max} (h)	AUC (ng day/mL)	F (%)
Cattle					
Lifschitz et al. (1999b)[a]	IM	22.6[p]	54[p]	189[n,p]	–
Lanusse et al. (1997)[e]	SC	42.8	96	459[n]	–
Lo et al. (1985)					
Formulation A[b]	SC	84	24	246$^{(0–4d)}$	55
Formulation B[c]	SC	25	48	186$^{(0–4d)}$	41
Formulation C[d]	SC	13	48	149$^{(0–4d)}$	33
Lifschitz et al. (1999b)					
Formulation 1[a]	SC	19.9[o,p]	96[o,p]	206[n,o,p]	–
Formulation 2[d]	SC	35.4[o]	39.1[o]	207[n,o]	–
Lifschitz et al. (1999a)[d]					
Formulation 3	SC	40.5	48	244[n]	–
Formulation 4	SC	46.4	50.9	266[n]	–
Lifschitz et al. (2004)[d]					
Formulation D	SC	23.6	27.4	231	–
Formulation E	SC	32.7	62	308	–
Formulation F	SC	22	103	262	–
Formulation G	SC	28.4	44.6	242	–
Chiu et al. (1990a)[f]	SC	133.2	24	–	–
Lifschitz et al. (2000)	SC	40	24	278[n]	–
Echeverria et al. (1997)[g]	SC	33.1	55.9	328.8	–
Toutain et al. (1988)	SC	54.6	34.8	–	–
Alvinerie et al. (1998)[r]	IR	28.5	364	247.6 $^{(0–160d)}$	–
Gayrard et al. (1999)[g]	T	12.2	81.6	121.5$^{(0–50d)}$	–
Laffont et al. (2001)					
Lickers	T	39[o]	147	595.1[o]	–
Non-lickers	T	16[o]	191	381.1[o]	–
Sheep					
Prichard et al. (1985)	IV			375	
Gonzalez et al. (2007)	IV			197	
Bogan and McKellar (1988)	SC	32.2	36	–	–
McKellar et al. (1991)					
Healthy animals	SC	30	46	101.7	–
Parasitized animals	SC	35	38.2	175	–
Cerkvenik et al. (2002)[g,h]	SC	11.9	40.8	64[n]	–
Barber et al. (2003)[g]	SC	25.8	29.8	82.1$^{(0–15d)}$	–
Lo et al. (1985)[f]	SC	–	12	–	22
Echeverría et al. (2002)[g]					
Healthy animals	SC	24.1[o]	64.1[o]	207.5[o]	–
Parasitized animals	SC	41.2[o]	21.6[o]	180[o]	–
Marriner et al. (1987)[e]	SC	30.8	60	238	–
Atta and Abo-Shihada (2000)[e]	SC	16.3	62.4	281[n]	–
Gonzalez et al. (2007)	SC	19.6	3.1	190.7	98.2
Bogan and McKellar (1988)					
Ewes	O	14.7	24	36.3$^{(0–7d)}$	–
Lambs	O	23.6	36	93.7$^{(0–7d)}$	–
McKellar et al. (1991)					
Healthy animals	O	29	19.3	74.6	–
Parasitized animals	O	21	20	88.8	–
Mestorino et al. (2003)					
Solution	O	11.3	31.9	44.7	–
Tablets	O	8.5	43.9	52	–
Marriner et al. (1987)[e]	O	22	16.4	85	35.7[l]
Chiu et al. (1990a)[f]	IR	12.5	24	–	–
Prichard et al. (1985)	IR	17.6	23.5	94.2	25.1[m]
Prichard et al. (1985)	IAB	60.6	4.8	440	–
Goat					
Gonzalez et al. (2006)[e]	IV	–	–	153	–
Gonzalez et al. (2006)	SC	21.8	72	144	91.8

Table 3 (*continued*)

Reference	Route	C_{max} (ng/mL)	t_{max} (h)	AUC (ng day/mL)	F (%)
Alvinerie et al. (1993)[g,h]	SC	6.1	68.4	60	–
Scott et al. (1990)[h]	O	15.9	24	21.5	–
Escudero et al. (1997)[h,p,i]	IR	9.3	31.2	34.4	–
Escudero et al. (1997)[h,k]	IR	10.6	29	34.6	–
Scott et al. (1990)[h]	T	3.9	48	13.2	–

C_{max} = maximum plasma concentration; t_{max} = time to reach C_{max}; AUC = area under the plasma concentration–time curve; F = bioavailability; d = day(s); – = unknown data.
IM = intramuscular; SC = subcutaneous; IR = intraruminal; T = topical; IV = intravenous (200 μg/kg); O = oral; IAB = intra-abomasal. Doses are always those recommended by manufacturers, except if indicated.

[a] Oily vehicle.
[b] Aqueous vehicle.
[c] Aqueous-glycerol-formal vehicle (50:50, v/v).
[d] Propyleneglycol:glycerol-formal vehicle (60:40, v/v).
[e] Two-compartmental model.
[f] 300 μg/kg.
[g] One-compartmental model.
[h] Lactating animals.
[i] Animals fasted for 36 h before ivermectin administration.
[k] Animals fed ad libitum.
[l] Relative to subcutaneous.
[m] Relative to intra-abomasal.
[n] $AUC_{0-\infty}$; if other, it is indicated as superscript in brackets.
[o] Significant differences within the study.
[p] Significant differences within the study.
[r] Sustained release bolus.

(1.3–16.1% of a pour-on dose) was ingested by untreated cattle licking treated cattle.

The distribution of ivermectin is slow in cattle but broad, as demonstrated by the high V_d and the high mean residence time (MRT) (Table 5). When administered SC and IR, [3H]ivermectin was detected in all sampled tissues: the highest concentrations were found in liver and fat; high levels were also recorded in the kidney and muscle (Chiu et al., 1990a). Availability was higher in tissues where parasites usually reside than in plasma at 167%, 163%, and 244% in lungs, intestinal mucosae, and abomasal mucosae, respectively, and persisted in most organs for 48 days (Lifschitz et al., 2000). This could explain the strong efficacy of ivermectin against parasites in these locations.

As in other species, ivermectin metabolism is minimal. In studies using radiolabelled ivermectin, unchanged drug represented 52% of the radioactivity in liver and fat (day 14 after SC treatment). Twenty-eight days after administration, these levels decreased to 40% in liver and 19% in fat (Chiu et al., 1986). Liver metabolites were hydroxylated derivatives of ivermectin (Chiu et al., 1986), whereas non-polar metabolites were detected in fat tissue (Chiu et al., 1988). In another study, such non-polar derivatives represented 64% of the radioactivity detected in fat on day 28 after treatment, and lengthened the depletion time of the residues in fat compared to residues in liver (Chiu et al., 1990a).

After SC injection, Chiu et al. (1990a) found that on day 7 after treatment, 1.5% and 62% of ivermectin was found in urine and faeces, respectively (Chiu et al., 1990a). Toutain et al. (1988) found that 5.5% of a SC dose was secreted via the mammary gland and because of these high concentrations milk from dairy cows treated with ivermectin must be excluded from human consumption.

Chiu et al. (1990a) found that with IR treatment, the percentage of ivermectin excreted in faeces and urine 7 days after administration was 79.7% and 0.5%, respectively, and its concentration in bile was high (273 ng/mL). Alvinerie et al. (1998) reported that 80–90% of drug delivered via SRB systems was excreted faecally and the drug was detected in faeces until day 160. This persistent excretion could pose a threat to the ecosystem (through, for example, dung-breeding/dung-feeding invertebrates).

Following topical application, ivermectin has a longer plasma half-life in cattle prevented from licking (15.1 days) than in those that are permitted to lick themselves (6.4 days); the half-life is also longer than after IV injection (6 days) reflecting slow absorption through the skin, which limits later elimination. Laffont et al. (2001) measured 69% of the dose in faeces from lickers after 28 days of treatment, and only 6.6% of the dose in faeces from non-lickers. These results are consistent with ivermectin transiting directly through the digestive tract into faeces, which contributes greatly to the drug's faecal output (Laffont et al., 2001).

Sheep

Plasma levels of ivermectin are lower in sheep than in cattle. The SC bioavailability is highly variable, ranging from 22% (Lo et al., 1985) to 98.2% (Gonzalez et al., 2007). Plasma concentrations are lower after oral versus

SC administration (McKellar and Marriner, 1987). Thus, as in other animal species, oral administration yields poorer efficacy and a shorter duration of action.

As expected, absorption of ivermectin is faster after oral administration of a solution versus tablets (Mestorino et al., 2003). The C_{max} and AUC obtained after oral administration was greater in lambs versus ewes, probably reflecting differences in body composition (especially fat content) and to impaired elimination in lambs (Bogan and McKellar, 1988). Ali and Hennessy (1996) demonstrated that reducing feed intake for 24 h before IR administration could be a valid option to ensure the efficacy of ivermectin, as it should increase the drug's bioavailability and extend its residence time.

Distribution in the sheep (Table 5) is faster and broader than in cattle or dogs (Lo et al., 1985) due to substantial deposition into adipose tissue, which may act as a drug depot (Prichard et al., 1985). The larger fat reservoir in sheep compared to cattle could contribute to not only the more extensive distribution but also the greater persistence in plasma at lower concentrations, probably because less blood is supplied to fatty tissues (Atta and Abo-Shihada, 2000). Likewise, the higher V_d in sheep versus cattle correlates well with the lower plasma concentrations observed in sheep.

As with cattle, Chiu et al. (1986) reported that unchanged ivermectin represented >50% of the radioactivity in liver and fat, but in this case on day 3 after IR administration. Ivermectin levels decrease faster in sheep than in cattle (Chiu et al., 1986). The main metabolites isolated in the liver are the same in the two species and accounted for 55% of the radioactivity on day 7 after IR treatment. A significant first-pass effect was not evident in sheep, as intra-abomasal bioavailability was 100% (Prichard et al., 1985).

Prichard et al. (1985) reported that IR administration in sheep resulted in a low bioavailability (25%), similar to that obtained in cattle. They also proposed that the ruminal microflora metabolise ivermectin, as 50% disappeared from the rumen fluid after 2-h incubation. Andrew and Halley (1996) however attributed this disappearance to the high level of binding to solids and surfaces. More recently, Lifschitz et al. (2005) confirmed that ivermectin was thoroughly bound to solid ruminal contents (> 90%) without suffering degradation.

The IV half-life of ivermectin is similar in sheep and cattle (Table 5); thus, the lower plasma levels in sheep are due to a broader distribution rather than to faster elimination (Lo et al., 1985). In sheep, concentrations in milk are similar to those in plasma (Bogan and McKellar, 1988), and only 0.71% of a SC dose was excreted through milk (less than in cattle, probably due to species differences in the volume and fat content of milk). However, Cerkvenik et al. (2001) observed that ivermectin remains stable following thermal treatment, confirming that residues in dairy products would be an issue for consumers.

Indirect exposure of untreated sucking lambs to ivermectin via milk ingestion is negligible; Cerkvenik et al. (2002) found that only 2.1% of the dose was transferred by treated ewes; this is lower than the oral value (10%). Furthermore, the plasma concentration derived from treated dams was only 4% of that found in the same lambs treated orally. Although this seems low, it could have beneficial effects for lambs due to the high efficacy of ivermectin at a low dosage. On the other hand, treatment of ewes over the periparturient period has been recommended to reduce faecal egg output and after only one SC dose this reduced faecal output persists for approximately 1 week.

Goats

Studies in goats are limited but plasma levels tend to be lower than those obtained in cattle and in sheep (Table 3). The SC bioavailability is very high (91.8%) (Gonzalez et al., 2006) and Scott et al. (1990) demonstrated that the bioavailability of topically administered ivermectin was 61.5% of that found when the drug was orally administered; persistence in plasma was, however, more prolonged following the percutaneous route.

Ivermectin associates with lipoproteins in goats, preferentially high density lipoprotein (88.1%), with binding percentages of 7.3% for low density lipoprotein, 1.8% for very low density lipoprotein, and 2.7% for albumin and α-1 glycoprotein (Bassissi et al., 2004). This extensive binding to lipoproteins could affect the delivery of ivermectin to fat tissue and consequently relate to its extended presence in the body.

Total body clearance after IV administration (Table 5) demonstrated the slow elimination process in goats (Gonzalez et al., 2006). Excretion in milk is even lower than in sheep with only 0.31% of the dose recovered in milk 25 days after SC treatment (Alvinerie et al., 1993). Scott et al. (1990) observed that the concentrations excreted in milk were similar after oral and topical administration.

Pigs

In pigs treated SC (Table 4), the C_{max} and AUC are significantly lower than in calves; this could be related to the higher distribution and deposition of the drug in fat tissue, which diminishes plasma levels in this animal species (Lifschitz et al., 1999a). The influence of body fat levels on ivermectin kinetics has been investigated in pigs, but the results are not clear. Craven et al. (2001) reported that fat content had no detectable influence on ivermectin disposition and they found no significant differences in the pharmacokinetic parameters representative of the distribution process between two groups of pigs with different body conditions (Table 6). In another study, these workers compared two groups of animals differing in back-fat thickness and weight (71.6 and 38.3 kg) and found that absorption was slower and availability higher in fat pigs. Plasma levels were >2 ng/mL until 18 days after treatment in fat pigs and 11 days in thin pigs, suggesting a longer period of drug efficacy (Craven et al., 2002a). When animals with an inter-

Table 4
Absorption pharmacokinetic parameters obtained after ivermectin administration to monogastric species

Reference	Route	C_{max} (ng/mL)	t_{max} (h)	AUC (ng d/mL)
Pigs				
Scott and McKellar (1992)	SC	28.4	27.2	71.41
Lifschitz et al. (1999a)[a]				
Formulation 1	SC	33.3	66[d]	165[c]
Formulation 2	SC	39.6	22.6[d]	132[c]
Craven et al. (2002a)				
Animals weighing 38.3 kg	SC	9.7	33.2[d]	85.7[d]
Animals weighing 71.6 kg	SC	7.4	71.9[d]	111.7[d]
Craven et al. (2002b)				
Animals weighing 51 kg	SC	8	75.1	70.5
Animals weighing 60 kg	SC	7.2	48	87.7
Horse				
Marriner et al. (1987)[b]	SC	60.7	80	550.4
Marriner et al. (1987)	O	82.3	3.1	200.9
Gokbulut et al. (2001)	O	21.4	7.9	–
Perez et al. (2002)[b]	O	51.3	3.6	137.1[(0-30d)]
Donkey				
Gokbulut et al. (2005)	O	23.6	24.0	119.3
Dog				
Daurio et al. (1992)				
Standard tablet	O	2.97	5.3	4.5
Chewable tablet	O	3.37	8.5	5.5
Daurio et al. (1992)[e]				
Standard tablet	O	44.3	4.2	43.1
Modified tablet (crystalline)	O	48.4	3.8	41.7

C_{max} = maximum plasma concentration; t_{max} = time to reach C_{max}; AUC = area under the plasma concentration–time curve; – = unknown data. SC = subcutaneous; O = oral; d = day(s). Doses are always those recommended by manufacturers, except if indicated.
[a] Propyleneglycol:glycerol-formal vehicle.
[b] Two-compartmental model.
[c] $AUC_{0-\infty}$; if other, it is indicated as superscript in brackets.
[d] Significant differences within the study.
[e] 100 μg/kg.

mediate bodyweight were used, no differences in kinetic disposition were observed (Craven et al., 2002b).

A higher V_d after IV administration was observed in pigs when compared to sheep or cattle. Ivermectin also distributed widely in this species after SC administration, with the highest levels in liver and fat (Chiu et al., 1990b). Twenty-four hours after injection, a large amount remains at the injection site, indicating a slow release process. Ivermectin has been detected at all levels of the gastrointestinal tract (contents and mucus), with high concentrations in the lungs, skin, and also earwax (accounting for its effectiveness against ectoparasites, particularly ear mites) (Scott and McKellar, 1992).

Chiu et al. (1990) reported that on day 7 the parent drug represented 45% of radioactivity in the liver and the percentage was slightly higher in fat tissue (63%). These levels decreased to 30% and 35%, respectively, on day 14 after drug administration. Differences with respect to other domestic species have been found in hepatic and fat metabolism; *O*-demethylation products were the metabolites found in liver. In contrast to other species, the same derivatives were also present in fat, accounting for the similar elimination half-lives (5 days) of residues from liver and fat in swine (Chiu et al., 1990).

Taking into account the half-life, the disappearance of ivermectin from plasma (Table 6) is faster in pigs than in cattle or sheep (Lo et al., 1985), suggesting briefer protection against parasites in this animal species. Clearance is also higher than in ruminant species, which correlates well with the shorter half-life in pigs. On the other hand, body condition does not affect clearance when ivermectin is administered IV (Craven et al., 2001) or SC (Craven et al., 2002a,b). Chiu et al. (1990b) reported that on day 7 after SC treatment, the concentrations excreted in faeces and urine were half those found in cattle (30% and 0.6% of the dose, respectively). One day after treatment, high concentrations were found in bile (210 ng/mL) and faeces (178.5 ng/g) (Scott and McKellar, 1992).

Horses

In contrast to ruminants, the absorption process in horses is faster after oral versus SC administration. Moreover, although SC injection results in greater bioavailability than does oral administration ($AUC_{oral} = 36.5\%$ of the AUC_{sc}), the oral route is preferred, as parenteral administration can produce local swelling and other adverse reactions (Anderson, 1984). Plasma concentrations are higher and more rapidly achieved in horses compared to sheep (Marriner et al., 1987) (Table 4), probably because the rumen delays absorption in ruminant species. Nevertheless, the elimination half-lives after SC and oral treatment are 3.7 and 2.8 days, respectively, and similar to sheep (Marriner et al., 1987).

In horses, the MRT is also longer after oral administration (4.2 days) (Pérez et al., 2002) versus SC injection (3 days) (Gokbulut et al., 2001); it is longer still in donkeys treated orally with ivermectin (6.5 days) (Gokbulut et al., 2005), where the elimination of ivermectin is slower, with a half-life of 7.4 days (Gokbulut et al., 2005). In horses treated SC, most of the dose (90%) is faecally excreted in 4 days. The higher concentrations found in equine faeces compared to cattle faeces have been attributed to a lower production of more concentrated faeces (Pérez et al., 2001).

Dogs

In dogs, the oral route is preferred for heartworm prevention. Absorption of ivermectin is faster in dogs than in ruminants and pigs, and similar to horses. Peak plasma levels are attained in 3–5 h (Table 4). Oral bioavailability is greater if the tablets are chewable. The amount absorbed follows a linear dose-relationship, as C_{max} and AUC increase proportionally with dose (Daurio et al., 1992). The Vc (volume of distribution in the central compart-

Table 5
Distribution and elimination pharmacokinetic parameters obtained after ivermectin administration to ruminants

Reference	Route	V_d (L/kg)	$t_{1/2\alpha}$ (d)	$t_{1/2\beta}$ (d)	MRT (d)	$t_{1/2}$ (d)	Cl (L/kg d)
Cattle							
Lo et al. (1985)[a,b]	IV	1.9[l]	–	–	–	2.8	–
Echeverría et al. (1997)[b]	IV	1.2[m]	–	–	–	3.4	–
Laffont et al. (2001)	IV	–	–	–	–	6	0.27
Bousquet-Mélou et al. (2004)[c]	IV	2.7[m]	–	–	8.1	7.8	0.35
Lifschitz et al. (1999b)[d]	IM	–	–	–	–	5.2[k]	–
Chiu et al. (1990a)[a]	SC	–	–	–	–	4.3	–
Echeverría et al. (1997)[d]	SC	–	–	–	–	5.7	–
Lanusse et al. (1997)[b]	SC	3.4[m]	4.2	17.2	7.4	–	0.48[i]
Lifschitz et al. (1999b)	–	–	–	–	–	–	–
Formulation 1[d]	SC	–	–	–	–	5.9[i]	–
Formulation 2[e]	SC	–	–	–	–	3.99[i,k]	–
Lifschitz et al. (1999a)[e]							
Formulation 3	SC	–	–	–	–	5.3	–
Formulation 4	SC	–	–	–	–	6.3	–
Lifschitz et al. (2000)	SC	–	–	–	5.8	–	–
Toutain et al. (1988)[f,g]	SC	–	–	–	6.5	–	–
Chiu et al. (1990a)	IR	–	–	–	–	3.7	–
Gayrard et al. (1999)	T	–	–	–	8.4	–	–
Sheep							
Lo et al. (1985)[b]	IV	4.6[l]	–	–	–	2.7	–
Prichard et al. (1985)	IV	5.3[m]	–	–	–	7.4	0.56
Gonzalez et al. (2007)	IV	3.0[l]	0.7	9.6	10.3	–	1.11
Marriner et al. (1987)[b]	SC	–	–	–	–	3.7	–
Atta and Abo-Shihada (2000)[b]	SC	–	–	–	5.9	7	–
Cerkvenik et al. (2002)[f,g]	SC	12.8[m]	–	–	5.2	2.9	3.24[i]
Echeverría et al. (2002)[f]							
Healthy animals	SC	8.8[n]	–	–	8.6	5.6	–
Parasitized animals	SC	6.5[n]	–	–	6.7	5.5	–
Barber et al. (2003)[f]	SC	–	–	–	–	1.7	–
Gonzalez et al. (2007)	SC	17.6[n]	–	–	10.3	11	1.11
Marriner et al. (1987)[b]	O	–	–	–	–	2.6	–
Atta and Abo-Shihada (2000)	O	–	–	–	–	2.1	–
Mestorino et al. (2003)							
Solution	O	–	–	–	3.45	3.6	–
Tablets	O	–	–	–	3.78	3.7	–
Chiu et al. (1990a)[a]	IR	–	–	–	–	2.4	–
Prichard et al. (1985)	IR	–	–	–	–	4.3	–
Goats							
Gonzalez et al. (2006)[b]	IV	2.8[l]	0.7	7.4	–	–	1.56
Gonzalez et al. (2006)	SC	12.8[n]	–	–	8.3	5.6	1.43
Alvinerie et al. (1993)[m,g]	SC	–	–	–	7.9	4.03	–
Escudero et al. (1997)[g]	IR	–	–	–	2.6–2.8	1.18–1.24	–

V_d = volume of distribution; V_{ss} = volume of distribution at steady state; $t_{1/2\alpha}$ = half-life associated with α phase; $t_{1/2\beta}$ = half-life associated with β phase; MRT = mean residence time; $t_{1/2}$ = half-life; Cl = total body clearance; – = unknown data. IV = intravenous; IM = intramuscular; SC = subcutaneous; IR = intraruminal; T = topical; O = oral; d = day. Doses are always those recommended by manufacturers, except if indicated.

[h] V_{SS}/F.

[a] 300 μg/kg.

[b] Two-compartment model.

[c] 70 μg/kg.

[d] Oily vehicle.

[e] Propyleneglycol:glycerol-formal vehicle (60:40, v/v).

[f] One-compartment model.

[g] Lactating animals.

[i] Significant differences within the study.

[k] Significant differences within the study.

[l] V_c (volume of distribution in the central compartment).

[m] V_{ss}.

[n] V_a (volume of distribution of the area).

Table 6
Distribution and elimination pharmacokinetic parameters obtained after ivermectin administration to pigs

Reference	Route	V_c (L/kg)	$t_{1/2\alpha}$ (d)	$t_{1/2\beta}$ (d)	MRT (d)	$t_{1/2}$ (d)	Cl (L/kg d)
Craven et al. (2001)[a]							
Animals weighing 28.5 kg	IV	2.7 (5.1*)	0.14	1.18	0.5[b]	–	4.15
Animals weighing 41.7 kg	IV	2.1 (5.3*)	0.15	1.33	0.7[b]	–	4.01
Lo et al. (1985)	SC	–	–	–	–	0.5	–
Scott and McKellar (1992)	SC	–	–	–	–	1.5	–
Lifschitz et al. (1999a)	SC	–	–	–	–	3.5–3.8	–
Craven et al. (2002a)							
Animals weighing 38.3 kg	SC	–	–	–	8.1	–	3.55
Animals weighing 71.6 kg	SC	–	–	–	9.8	–	2.75
Craven et al. (2002 b)							
Animals weighing 50 kg	SC	–	–	–	8.4	2.28	4.47
Animals weighing 60 kg	SC	–	–	–	9.6	2.55	3.64

V_c = volume of distribution in the central compartment; $t_{1/2\alpha}$ = half-life associated with α phase; $t_{1/2\beta}$ = half-life associated with β phase; MRT = mean residence time; $t_{1/2}$ = half-life; Cl = total body clearance.
[a] Two-compartmental model.
[b] Significant differences within the study; – = unknown data. IV = intravenous; SC = subcutaneous. Doses are always those recommended by manufacturers, except if indicated.
* V_{ss} = volume of distribution at steady state.

ment) is 2.4 L/kg in dogs injected IV, intermediate between values obtained in cattle and sheep (Lo et al., 1985). On the other hand, excretion is more rapid in dogs versus cattle or sheep (IV elimination half-life = 1.8 days) (Lo et al., 1985).

Conclusions

Although the efficacy of ivermectin has been established across a variety of domestic species, its pharmacokinetic properties differ between them, and the factors responsible for modifying ivermectin's pharmacokinetics should be taken into account to ensure its clinical efficacy, prevent subtherapeutic levels, and minimise the development of resistance.

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