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Pharmacokinetics and tissue residues of ivermectin in swine

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Abstract : Ivermectin is a widely used broad spectrum antiparasitic agent in veterinary medicine. In this work, we examined the pharmacokinetic parameters and the tissue residue profile of a new injectable formulation of ivermectin developed for pigs. The plasma ivermectin levels reached the peak at about 9 and 2 hours after the administrations in young and adult pigs, respectively. But the elimination half-life (3-3.5 days) and the C_{max} values (24~28 ng/ml) were not significantly different between young and adult pig groups. When compared to the reference formulation, the C_{max} of test formulation was higher and $T_{1/2}$ values were shorter than those of the reference formulation, respectively.

The tissue residue levels were dose- and time-dependent and were higher in the liver and fat, than in the other tissues such as the injection sites, the kidney, intestine, muscle, plasma (4~74 ng/g) at the 7th day after the administration of both formulations of ivermectin. Then, the mean tissue ivermectin levels at the 21st day after the administration in all the tissues decreased to 7.4 and 25% of the 7th day levels in the test and reference formulations, respectively. In general, the tissue levels of ivermectin in the animals treated with the test formulation decreased more rapidly than those with the reference formulation. The tissue to plasma distribution ratio (T/P ratio) of ivermectin was higher in the liver and fat than other tissues. The T/P ratio in the liver of animals treated with the test formulation was somewhat higher than that in the animals treated with the reference formulation.

Taken together, the results of pharmacokinetic and tissue residue studies indicate that the test formulation of ivermectin for subcutaneous injection is comparable to the reference formulation, but unique in that it has higher peak plasma concentrations, shorter elimination half-life and higher T/P ratio in the liver than the reference formulation.

Key words : ivermectin, pharmacokinetics, pig, tissue residue, withdrawal time.

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Introduction

The introduction of ivermectin in early 1980s revolutionized animal antiparasitic chemotherapy because of its potency, remarkably broader spectrum of activity and safety. Currently ivermectin is one of the most widely used veterinary drugs in the world. It is active against parasites of 3 classes: *nematoda*, *insecta*, *arachnida*[1,2]. Ivermectin is a member of the family of compounds produced by the soil microorganism *Streptomyces avermitilis* and known generically as avermectins. It is marketed as a mixture of 22,23 dihydroavermectin B_{1a} ($\rangle$ 80%) and 22,23 dihydroavermectin B_{1b} ($\langle$ 20%)[3].

Initially it was believed that ivermectin acts on susceptible *nematoda* and *arthropoda* by potentiating the release and binding of gamma aminobutyric acid (GABA) in certain nerve synapses, and thus blocking the transmission of nerve signals[4]. However, later evidences suggest that the parasiticidal action is likely to be mediated by interaction of avermectins with glutamate-gated chloride ion channels which have not yet identified in mammals[5~7].

The prolongation of drug action is frequently a therapeutic advantage in veterinary medicine because the drug treatment is labor intensive. Ivermectin is highly lipid soluble and is eliminated very slowly from the body compartments, especially liver and fat. Its biological half-life is rather long (0.5 to 2.8 days) when compared to most other drugs[8]. The volume of distribution is 4.6, 1.9 and 2.4 *l* /kg in sheep, cattle and dogs, respectively. Lo *et al*[8] reported that subcutaneous injection of the nonaqueous formulation containing 40:60% (v/v) polyethyleneglycol-glycerol formal showed a much longer elimination half-life (8~13 days) than that of the aqueous formulation in cattle (2 days). It was considered that the longer apparent biological half-life was due to the slow absorption process from this nonaqueous vehicle. In pigs, both the injectable products and premix formulation are available[2,9]. The current withdrawal period in the United States of America is set for 18 days in pigs for Ivomec, a subcutaneous formulation of Merck Sharp & Dohme B.V.

The aim of this work is to evaluate the pharmacokinetic properties and tissue residue profile of a new injectable formulation of ivermectin for pigs developed by LG Chemical Ltd (Taejon, Korea).

Materials and Methods

Drugs : The injectable formulations of ivermectin were from LG Chemical Ltd. (Taejon, Korea; IVM-LG) and the reference formulation from Merck Sharp Dohme B.V. (Haarlem, Netherlands ; IVM-MSD). IVM-MSD was purchased from local veterinary drug store. Each ml of IVM-LG or IVM-MSD contains 10 mg of ivermectin in the vehicle. Ivermectin from Sigma (St Louis, USA) was used in establishing the validity of analytical procedures such as standard curve, recovery rate and reproducibility. Drugs were administered subcutaneously to the neck of the pigs at the dose rate of 300 μg/kg or twice.

Animals and treatment groups : Crossbred white (Landrace-Yorkshire) gilts used in the present study were purchased from GP farm in Ehchon and the pigs of the same treatment group were housed together. The pigs were allowed free access to feed (Crumble Feed, Taihan Sugar Co., Korea) and water. For pharmacokinetic study, total of 20 pigs were allotted to 5 treatment groups and housed in the Experimental Animal Farm of College of Veterinary Medicine, Seoul National University from November, 1997 to January, 1998. During the experiments the temperature was below 10℃. For tissue residue study, 53 pigs were allotted to 4 treatment groups in a local pig farm in Eh-chon in February, 1998. The treatment groups for pharmacokinetic and tissue residue studies and sampling protocols are shown in Table 1.

Blood : Blood samples were collected from the external jugular vein by serial venipuncture with heparinized, disposable plastic syringes (10 ml, 24-gauge needle). Then, the blood samples were centrifuged for 10 min at 3,000 rpm within 1 hour after the collection. The plasma was collected and stored at -20℃ until assayed.

Tissues : Drugs were administered 7, 21, 28, and 35 days before the slaughter and tissue samples (about 100 gm) of liver, kidney, muscle, fat, small intestine, and injection site were taken during the carcass processing in the slaught-

Table 1. The treatment groups for pharmacokinetic and tissue residue studies and sampling protocols

Treatment groups		Drug treated	Dose (μg/kg)	Body weight (kg)	No. of pigs	Sampling times after administration
Pharmaco-kinetic study	Gruop Ⅰ (IVM-LG)	LG ivermectin	300	35~40	10	0, 4, 8, 18, 25, 32, 40 hrs, 2, 3, 4, 6, 8, 11, 14, 18, 26, 30 days
	Group Ⅱ (IVM-LG)	LG ivermectin	300	60~70	5	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 hrs, 3, 5, 8, 12, 18, 26, 32 days
	Group Ⅲ (IVM-MSD)	Ivomec	300	60~70	5	The same as above
Tissue residue study	IVM-LG	LG ivermectin	300	70~90	16	7, 21, 28, 35 days*
	IVM-LG2	LG ivermectin	600	70~90	16	The same as above
	IVM-MSD	Ivomec	300	70~90	16	The same as above
	Control	-	-	70~90	5	-

Drugs were administered subcutaneously to pigs. *In each sampling time, the tissue samples were collected from 4 pigs and blood were sampled before slaughtered.

er house. Control pigs without any treatment were simultaneously slaughtered together with treatment groups. The tissue samples were stored at -70℃ until assayed.

Pharmacokinetics

Determination of ivermectin : Plasma ivermectin was determined by HPLC according to the method of Montigny *et al*[10] using a solid phase extraction. The ivermectin extracts were derivatized by using 1-methylimidazole and trifluoroacetic anhydride. The mobile phase was 0.2% acetic acid : methanol : acetonitrile (4 : 32 : 64) and was pumped at a flow rate of 1.5 ml/min through Nova-Pak C_{18} (4 μm 3.9×150 mm; Waters, USA). The quantity of ivermectin was determined by HPLC (TSP P1000, USA) with a fluorescence detector (TSP F3000, USA) at an excitation wavelength of 474nm and emission wavelength of 374nm.

Standard curve, sensitivity and detection limit : Ivermectin is a mixture of 22,23-dihydroavermectin B_{1a} (H_2B_{1a}, 〉80%) and 22,23-dihydroavermectin B_{1b} (H_2B_{1b}, 〈 20%). The peak of H_2B_{1b} appears earlier and smaller than H_2B_{1a}[10]. In this work, the H_2B_{1b} was detected at 8 min 45 sec and H_2B_{1a} at 10 min 41 sec. The area of smaller peak was about 1/41 of that of larger peak (Fig 1) and was negligible in the plasma samples of pigs-treated ivermectin. Therefore the actual quantity of ivermectin in this work was primarily based on the slower and larger peak from H_2B_{1a}. Fig 1F is the standard curve for the HPLC measurement of ivermectin. Sensitivity was defined either as the minimal detectable concentration or the slope of the standard dose-response curve in radioimmunoassay[11]. The equation for the standard curve was : Peak area = 8959.6 × ivermectin concentration (ng) + 997.92, r = 0.998 (Fig 1F). The detection limit was as low as 125 pg in 1 ml of plasma. Signal to noise level (S/N) was about 2.

Recovery rate and reproducibility : The recovery rate was determined by comparing the amount of ivermectin detected from standard solution to that in the extracts from the plasma spiked with known amount of ivermectin at the concentrations of 0.125~50 ng/ml. The recovery rates in the 1 ml of plasma-spiked with 0.25, 0.5, 1, 2, and 4ng of ivermectin were 90.65±7.64, 96.23±15.46, 80.89±2.00, 78.58±2.00, and 86.13±2.39 ng/ml, respectively. The coefficient of variation (CV) calculated by the following equation, CV (%) = 100 × (standard deviation/mean), was 8.58±3.99% (n = 10). During the whole analysis period, the recovery rates in later period were somewhat higher that those in early period. Therefore, the calculation of ivermectin concentration in each sample was based on the recovery rate determined each day.

Pharmacokinetic analysis : The plasma concentration-time profiles of ivermectin were analyzed by a two compartment model including absorption and elimination phase according to the following equation[12].

$$C_p = (K_a * F/V_c)\{(K_{21} - a)e^{-a*t}/(K_{21} - a)(b - a) + (K_{21} - b)e^{-b*t}/(K_a - a)(a - b) + (K_{21} - K_a)e^{-Ka*t}/(a - K_a)(b - K_a)\} \quad (1)$$

Where C_p is the concentration of plasma ivermectin; t, time after administration; F, bioavailability; V_c, volume of the central compartment; K_{21}, fractional rate constant drug transfer from peripheral compartment to central one; K_a, absorption rate constant; a, intermediate elimination rate constant; b, terminal elimination rate constant, respectively.

AUC (area under the concentration-time curve) was obtained by the trapezoidal rule. The AUC from the last sampling point to infinite time was obtained by the following equation[13].

$$\text{Area} = C_p(t) / b \quad (2)$$

Where $C_p(t)$ is the plasma ivermectin concentration at the last time point and b, the terminal elimination rate constant.

Area under the first moment of the concentration-time curve (AUMC) was obtained by integrating the curve obtained by multiplying concentration-time data by time. Mean residence time (MRT) was obtained by dividing AUMC by AUC.

Absorption half-life and elimination half-life were obtained by dividing respective rate constant by 0.693. Terminal elimination half-life was estimated also by fitting the elimination phase of the concentration-time data after the peak with the equation (1). Total body clearance (Cl_B/F) was determined by dividing dose by AUC. The volume of distribution at steady-state (Vd_{ss}/F) was obtained by multiplying clearance by MRT. Actual non-linear curve fitting was done by using a graphic software Origin (Ver 4.0, Microcal Software Inc., Northhampton, MA, USA).

Tissue residue

Determination of ivermectin : Extraction of ivermectin from various tissues was based on the method of Tway *et al*[14] by serially extracting with acetone, isooctane, methanol, hexane and acetonitrile. Then, the extracts were subjected to the solid phase extraction. The other procedures were the same as those for plasma samples.

Detection limits for the tissue samples were 1 ng/g for kidney and 0.5 ng/g for liver, fat, muscle, small intestine and the injection site.

Recovery rate and reproducibility : Recovery rates of iver-

Table 2. Recovery rate of ivermectin in tissues and reproducibility

Spiked concentration of ivermectin (ng/g)	Recovery rates (%)						
	Fat	Injection site	Intestine	Kidney	Liver	Muscle	Plasma
0.25							90.65
0.5							96.23
1							80.89
2							78.58
4	41.26	47.26	56.90	56.42	45.72	46.21	86.13
16	57.79	72.93		50.98	45.39	45.88	
48	44.99	56.95		46.05	45.86	45.63	
Overall	47.12±3.12	56.10±6.69	56.90±9.21	51.79±3.11	46.66±1.14	45.94±2.01	86.49±1.61
Mean±SE	(n = 11)	(n = 4)	(n = 4)	(n = 8)	(n = 6)	(n = 8)	(n = 10)
CV (%)	21.99	23.87	32.39	16.97	5.98	12.39	8.58

Values of recovery rate and coefficent of variation (CV) were expressed as mean±SEM.

mectins from various tissues were determined by comparing the ivermectin in standard solution to that in the extracts from the tissues spiked with known amount of ivermectin at the concentrations of 4~48 ng/g. As shown Table 2, The recovery rates in muscle, fat, liver, small intestine, kidney and the injection site were 45.94±2.01 (n = 8), 47.12±3.12 (n = 11), 46.66±1.14 (n = 6), 56.90±9.21 (n = 4), 51.79±3.11 (n=8) and 56.10±6.69% (n = 4), respectively. The respective coefficient of variations were 12.39, 21.99, 5.98, 32.39, 16.97 and 23.87 %, respectively.

Statistics : All the parameter values are presented as mean±standard error of mean. The statistical significance was determined by *t*-test at p values less than 0.05.

Results and Discussion

Pharmacokinetics : Fig 1 illustrates the typical chromatograms of ivermectin in plasma and muscle. Although both 22,23-dihydroavermectin B_{1a} (H_2B_{1a}) and 22,23-dihydroavermectin B_{1b} were detected, H_2B_{1a} was predominant and H_2B_{1b} was negligible in the plasma and tissue samples. Therefore, we used the area of H_2B_{1a} peak for the determi-nation of

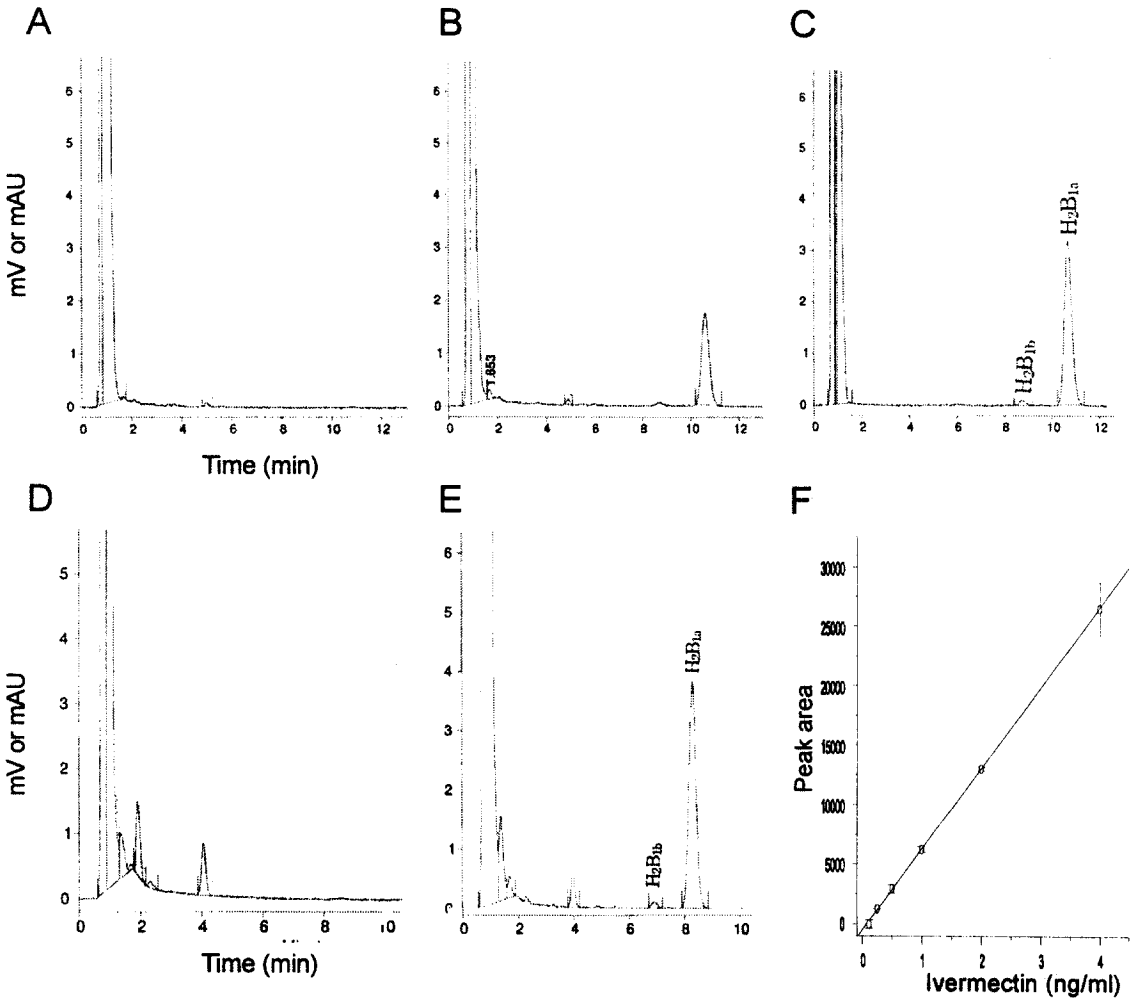

Fig 1. Typical HPLC chromatograms and standard curve of ivermectin chromatograms of plasma blank (A), plasma-spiked with ivermectin (5 ng/ml) (B), ivermectin (5 ng/ml) standard (C), muscular tissue blank (D) and muscular tissue-spiked with ivermectin (20 ng/g) (E) are illustrated. F, Standard curve of ivermectin.

ivermectin in plasma and tissues.

Fig 2 shows the plasma concentration-time profiles of LG ivermectin injection in young pigs (35~40 kg) (Group Ⅰ). The plasma ivermectin reached the peak at about 9 hours after the administration and the peak level (C_{max}) was 27.99± 4.88 ng/ml (n = 9). The patterns of concentration-time profiles were similar in 9 animals (Fig 2A). Terminal elimination half-life was 3 days. The C_{max} was higher, but the time to peak (T_{max}) was much faster than the results by Scott and McKellar[9] in young pigs treated with Ivomec injection of Merck Sharp and Dohme B.V. (MSD). Since this discrepancy was rather large, we further tried to examine the concentration-time profiles of ivermectin with shorter sampling intervals during the first 24 hours after the administration in pigs weighing 60~70 kg (Group Ⅱ and Group Ⅲ) to compare the concentration-time profiles of two preparations under our experimental conditions

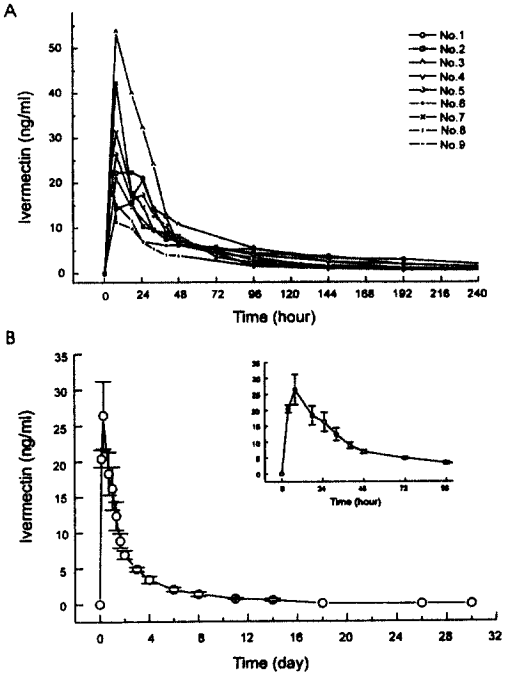

Fig 2. Concentration of ivermectin (IVM-LG) in plasma of young pigs (Group Ⅰ, 35~40 kg) after subcutaneous injection at a dose rate of 300 μg/kg. Individual (A) and mean (B) plasma concentration-time profiles of ivermectin. Symbols in A represent individual pigs. Insert of B depicts the rapid distribution phase.

Fig 3 illustrates the plasma concentration-time profile of ivermectin from the adult pigs treated with both preparations from LG and MSD. Tmax of LG ivermectin was 2 hours which was shorter than that obtained in the young pigs (Group Ⅰ) (Fig 2) and the Tmax was 24.45±3.75 ng/ml. The terminal elimination half-life was 3.5 days. The T_{max} and C_{max} for IVM-MSD were about 1 hour and 10.37 ng/ml with the terminal elimination half-life of 5 days. The observed C_{max} of MSD ivermectin was about half of that reported by Scott and McKellar[9].

Available T_{max} values of subcutaneous ivermectin preparations of MSD range 27 to 95 hours in the animals including cattle, sheep, pig, deer and rabbit[13-18]. Above results indicate that the fast kinetics of LG formulation is not unique because, as illustrated in Fig 3, MSD formulation also showed rapid absorption pattern and Tmax values were similar to both preparations under our experimental conditions.

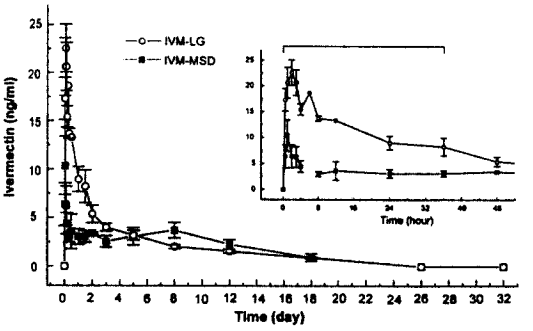

Fig 3. Mean concentration-time profiles of ivermectin (IVM-LG and MSD-LG)) in plasma of adult pigs (Group Ⅱ and Ⅲ, 60~70 kg) after subcutaneous injection at a dose rate of 300 μg/kg. Insert depicts rapid distribution phase for the first 48 hours. *p < 0.05.

Presently we are not sure why MSD-ivermectin formulation in our hands behaved differently from that reported by Scott and Mckellar[9]. However, one valuable conclusion we can draw from these results is that LG formulation has higher Cmax and shorter terminal elimination half-life than MSD formulation.

Table 3 summarizes the pharmacokinetic properties of ivermectin in Group Ⅰ~Ⅲ. C_{max}, AUC, Vd_{ss} (volume of

Table 3. Pharmacokinetic parameters for ivermectin obtained after subcutaneous administration to pigs at 300 μg/kg

Kinetic parameters	Groups		
	I (n = 7)	II (n = 3)	III†
$t_{1/2ab}$	77.30±13.81	1.51±0.35*	
C_{max} (ng/ml)	27.99±4.88	24.45±3.75	10.37
T_{max} (h)	9.21±0.62	1.88±0.43*	1.33
AUC (ng · h/ml)	1,448.37±156.46	1324.28±142.02	1229.35
AUMC (ng · h^2/ml)	118,873.43±26,128.28	216,408.20±65,263.44	243,882.35
$t_{1/2a}$ (h)	4.94±0.65	1.06±0.33*	
$t_{1/2b}$ (h)	75.79±9.58	82.92±31.92	121.79
MRT (h)	79.55±14.91	161.79±39.97*	198.06
Vd_{ss}/F (L/kg)	13.38±2.25	17.28±4.44	
Cl_B/F (L/h/kg)	0.18±0.02	0.10±0.01	

Values are presented as mean±SEM. †Kinetic parameters of Group III were calculated significantly different from those obtained for Group I. $t_{1/2ab}$ and $t_{1/2a}$ of Group III were not calculated by the equation of Meterials and Methods because of the appearance of main peak following small peak. *$p < 0.05$. $t_{1/2ab}$ absorption half-life; C_{max} peak plasma concentration; T_{max}, time to peak plasma concentration; AUC area under the concentration-time curve extrapolated to infinity; AUMC, area under the first moment of the curve; $t_{1/2a}$, intermediate half-life; $t_{1/2b}$: terminal half-life; MRT, mean residence time; Vd_{ss}, volume of distribution at steady-state: Cl_B/F, total body clearance.

distribution at steady state) and terminal elimination half-life of LG ivermectin between young and mature pigs were not significantly different, but Tmax occurred earlier in group II, suggesting a possibility of more rapid absorption in the mature animals.

Tissue residues : Table 4 summarizes the tissue levels of ivermectins in three groups after administration of LG and MSD preparations in 7 different tissues. In general, the residue levels were higher in the liver and the fat than other tissues in all three treatment groups. The mean tissue residue levels were highest in IVM-LG×2 group (48 ng/g), and followed by IVM-MSD (38 ng/g) and IVM-LG (18 ng/g). At the 21st day after the administra-tion, tissue levels of ivermectin rapidly decreased 10, 4, and 1 ng/g in the groups of IVM-MSD, IVM-LG×2 and IVM-LG, respectively. At the 35th day after the adminstration, the tissue ivermectin levels in all three groups were below 1ng/g. All the tissue levels examined on the 7th day were below the safety levels set by Food and Drug Administration of the United State of America (FDA)[19] except two tissues: fat of IVM-LG×2 and the injection site of IVM-MSD groups. On 21 days, none of tissues tested exceeds FDA safety levels.

The tissue levels of ivermectin were lower in the animals treated with LG formulation of ivermectin than in the animals treated with MSD preparation (Table 4). This result is in good agreement with the pharmacokinetic data showing lower C_{max} and longer terminal elimination half-life in the animals treated with MSD formulation than those with the LG formulation (Table 3). At 7 days, ivermectin levels in fat and injection site of IVM-MSD group pigs were significantly higher than those in IVM-LG group.

Such trend is also evident in Table 5 which shows tissue-to-plasma (T/P) ratio of ivermectin at the 7th day after administration of ivermectin formulations from LG and MSD. Among tissues, the T/P ratios of the liver and the fat were 5~12 times higher than those in other tissues. The T/P ratio of MSD formulation was significantly higher in fat, but lower in liver than those of LG formulation. The difference of T/P ratio between two formulations is more likely due to the difference in their formulations. In contrast, ivermectin level in liver was higher in IVM-LG group than in IVM-MSD group.

Table 4. Concentration of ivermectin in various tissues at 7, 21, 28 and 35 days after subcutaneous injection of ivermectins

Drug	Sample	Concentration of ivermectin (ng/g)				Note
		Sampling time after administration				
		7 day	21 day	28 day	35 day	
IVM-LG	liver	47.09±3.79	1.75±1.23	0.34±0.34	0.06±0.06	Safety concentration (ppb)[19] muscle : 25, liver : 75, kidney : 100, fat : 100
	kidney	6.56±2.18	0	0.35±0.25	0	
	fat	37.5±10.12	1.36±0.69	0	0	
	muscle	7.68±2.66	0.52±0.52	0.22±0.12	0	
	injection site	8.05±0.85	1.95±0.42	0.39±0.11	0	
	intestine	9.97±3.79	3.28±3.06	0.51±0.29	0	
	plasma	6.80±0.34	0.21±0.16	0	0	
	mean±SEM	17.66±3.39	1.30±0.87	0.26±0.16	0.01±0.10	
IVM-LG×2	liver	97.20±12.32[a]	7.96±0.12	0.68±0.68	0.19±0.19	
	kidney	30.05±4.68[a]	1.72±0.54	0.29±0.29	0	
	fat	137.3±33.77[a]	8.18±3.07	1.30±0.65	0	
	muscle	6.21±1.57[a]	1.53±0.53	0.39±0.14	0.69±0.23	
	injection site	35.99±13.11	3.89±1.83	0.43±0.09	0.54±0.41	
	intestine	15.21±2.94	3.62±3.10	0.57±0.35	0	
	plasma	15.05±2.43	1.22±0.31	0	0	
	mean±SEM	48.19±10.12	4.02±1.36	0.52±0.31	0.20±0.12	
IVM-MSD	liver	24.53±6.51[a,b]	12.44±3.24	2.13±0.33	1.49±0.86	
	kidney	9.61±4.24	1.50±0.29	0.47±0.47	1.44±0.73	
	fat	74.86±7.90[a,b]	13.81±3.78	1.81±1.16	0.79±0.47	
	muscle	8.37±0.92	1.67±0.71	0.38±0.24	0.69±0.23	
	injection site	124.7±45.76[a]	19.88±11.36	1.11±0.58	0.57±0.45	
	intestine	19.88±4.44[a]	15.79±7.32	0.54±0.22	0	
	plasma	4.42±1.36	1.97±0.46	0.14±0.08	0	
	mean±SEM	38.05±10.16	9.58±3.88	0.94±0.44	0.71±0.39	
Control	liver 0.17±0.17, kidney 0.01±0.01, fat 0, muscle 0.06±0.03, injection site 0.3±0.3, intestine 0, plasma 0 (mean 0.07±0.04)					

Values were expressed as mean±SEM. [a] and [b] $p < 0.05$ when compared with the values from IVM-LG and IVM-LG×2 at the same kind of tissue and sampling time, respectively.

The tissue levels in the pigs at 7, 21 and 28 days were much lower compared to the tissue levels at 7, 14 and 28 days in the liver, muscle and fat of cattle[20]. This difference could be due to the interspecies variation[2].

Table 5. Tissue-to-plasma ratio (%) in ivermectin concentration at 7 days after subcutaneous injection of ivermectin

Tissues	IVM-LG	IVM-LG×2	IVM-MSD
Liver	7.02±0.77	6.60±0.37	3.16±0.48[a,b]
Kidney	0.98±0.34	2.26±0.68[a]	1.64±1.25[a]
Fat	5.79±1.56	9.49±2.80	12.17±1.61[a]
Muscle	1.17±0.42	1.14±0.16	1.31±0.11
Small intestine	1.41±0.48	1.18±0.21	3.47±1.33[a,b]

Values of tissue to plasma ratio were expressed as mean±SEM. [a] and [b] $p < 0.05$ when compared with the values from IVM-LG and IVM-LG×2, respectively.

Taken together, the results of pharmacokinetic and tissue residue studies indicate that the LG formulation of ivermectin for subcutaneous injection in pigs is unique in that it has higher peak plasma concentrations (C_{max}), shorter elimination half-life ($t_{1/2}$) and higher T/P ratio in liver than the reference formulation from MSD. At the 7th day after administration, tissue residue levels in pigs treated with a proposed clinical dose of ivermectin were already below the safety levels set by FDA (Table 4). At 21, 28, and 35 days after administration, tissue residue levels in pigs of all treatment groups were further decreased. The withdrawal period of this new formulation of ivermectin from LG Chemical Ltd. could be set as 18 days, which is equal to that of MSD formulation, or shorter.

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