Does the rate of fat deposition influence the pharmacokinetic disposition of subcutaneously administered moxidectin and ivermectin in pigs?

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Body condition has been shown to affect the pharmacokinetics of subcutaneously administered macrocyclic lactone anthelmintics but the underlying mechanism is unknown. This study examined the effect of different rates of fat deposition on the pharmacokinetics of moxidectin (MXD) and ivermectin (IVM). All animals initially received a diet with a high linoleic acid content for 7 weeks. One group of animals then received a normal grower diet while the other half received a maintenance ration. Within each diet group, animals were treated with either IVM (n = 4) or MXD (n = 4) or remained as untreated controls (n = 2).

There was no difference in the proportion of linoleic acid between the drug treated groups and the untreated controls at any time throughout the study. At 4 and 9 weeks after treatment there was a significantly lower proportion of linoleic acid in the pigs fed the normal ration indicating a greater fat deposition in these animals compared with those that received the maintenance diet. There was an increased persistence of MXD in the plasma of pigs fed the normal ration compared with those fed the maintenance ration. No differences were seen in the kinetic disposition of IVM between pigs fed the maintenance or normal ration.

Reducing the rate of fat deposition influenced the pharmacokinetic disposition of the highly lipophilic MXD but did not influence the pharmacokinetic disposition of the less lipophilic IVM.

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INTRODUCTION

The macrocyclic lactones are a highly efficacious group of anthelmintics that, in addition to removing existing parasites, provide some protection against re-infection. This period of protection is because of their high lipophilicity and extensive distribution in fat with the subsequent rate of release or exchange from this lipid reserve into the bloodstream considered to be a major determinant of the pharmacokinetic behavior of these compounds. The lipophilicity of moxidectin (MXD) is 100 times greater than that of ivermectin (IVM) (Hayes, 1994) and this would account for the longer half-life of MXD (Zulalian et al., 1994) compared with that of IVM (Chiu et al., 1987) in fat tissue. This longer half-life in fat correlates well with the significantly greater volume of distribution, smaller area under the plasma-time curve and longer mean residence time (MRT) observed in plasma for MXD compared with IVM or doramectin following s.c. injection to cattle (Lanusse et al., 1997).

The body condition of the host has been shown to influence the persistence of macrocyclic lactones. The efficacy of MXD against Ostertagia circumcincta was lower when administered 25 days after infection to sheep in poor body condition compared with sheep with a higher body condition score (Rolfe et al., 1995). The persistence of MXD and IVM was also reduced in pigs fed a restrictive diet compared with those fed a normal grower ration following s.c. drug administration (Craven et al., 2002). This reduction in persistence was correlated with the smaller fat depot in the animals in poor body condition. Following i.v. MXD administration differences in the rate of drug exchange between the tissue and central compartment and a greater recycling of the drug through the central compartment (Craven et al., 2001) suggested that the rate of fat turnover and/or deposition also has an impact on the kinetic disposition of these drugs.
The fatty acid composition of porcine fat is more reflective of the dietary fatty acid composition than that of ruminant fat and is readily influenced by feeding various quantities and types of oils or oilseeds (Dahl & Persson, 1965). Of these fatty acids linoleic acid is particularly sensitive to dietary alteration (Ellis & Isbell, 1926). As linoleic acid cannot be produced by the pig, the proportion of this fatty acid in fat tissue is solely of dietary origin. Following a period of feeding with a diet high in linoleic acid the proportion of this fatty acid increases dramatically (Smith et al., 1996). However, when the source of linoleic acid is removed the proportion of this fatty acid will fall as it is diluted in the fat by fatty acids from the new diet and those synthesized in adipose tissue, with the rate of this dilution reflecting the volume of fatty deposition in backfat (Rule et al., 1995). The volume of fat deposited is determined by the amount of fat absorbed from the diet, the amount of fat produced by lipogenesis and the amount of fat oxidized to meet the energy requirements of the pig. Pigs fed a restricted diet have a reduced deposition of fat as a result of reduced lipogenesis and increased oxidation of fat compared with animals fed at levels approaching ad libitum (Chwalibog & Thorbeck, 2000).

This study uses the proportion of linoleic acid in backfat as an indicator of fat deposition to determine whether the rate of fat deposition following treatment has an impact on the kinetic disposition of MXD and IVM.

**MATERIAL AND METHODS**

**Animals**

Twenty Danish Landrace × Yorkshire × Duroc pigs (10 male, 10 female) from three litters (weaned at 4 weeks of age) were initially housed together and fed a diet containing 10% sunflower oil from 9 until 16 weeks of age.

One week before treatment the pigs were allocated to one of six groups and moved to individual pens. Three of the groups were fed a low fiber/high fat ‘grower’ ration (Grower; G). One group was to be given IVM (IG; n = 4), another was to be given MXD (MG; n = 4) and the third group was an untreated control group (UG; n = 2). The other three groups were fed a low fat/high fiber ‘maintenance’ ration (Maintenance; M) based on a commercial dry sow maintenance diet, and were similarly allocated into an IVM treated group (IM; n = 4), a MXD treated group (MM; n = 4) and an untreated control group (UM; n = 2). The quantity of the grower ration was adjusted weekly from a minimum 2 kg/pig/day to a maximum of 2.8 kg/pig/day, whereas the maintenance ration was given ad libitum. Details of the two diets are given in Table 1. Water was available ad libitum.

**Treatment protocol**

At approximately 16 weeks of age the animals were weighed and the treated groups received a s.c. injection of either MXD (Cydectin vet., 10 mg MXD/mL, Cyanamid, Copenhagen, Denmark) or IVM (Ivomec vet., 10 mg IVM/mL, MSD Agvet, Haarlem, Holland) at a dosage of 300 μg/kg bodyweight. Blood samples were taken from the jugular vein of all treated pigs into heparinized tubes immediately prior to and at regular intervals following treatment. The blood was centrifuged for 10 min at 2000 g to separate the plasma, which was then stored at −18 °C until analysis.

Fat biopsies were taken from all animals at 0, 1, 2, 4, and 9 weeks after treatment using a spring-loaded biopsy instrument (Biotech PPB-U, Nitra, Slovakia) using a 10-mm cannula set at a depth of 2 cm. The biopsy wound was immediately filled with a wide spectrum antibiotic and the animals were observed for signs of infection until their wounds had healed. Fat biopsies were taken 3–4 cm lateral to the midline from above the last rib and 5 and 10 cm distal to the last rib on either side of the midline. The order of sampling from these six potential sites was randomized but at each time point samples were taken from the same site on each pig. The amount of fat collected per biopsy sample was 50–120 mg.

**Analytical methods**

Fat biopsy samples were divided to allow fatty acid determination and, where there was sufficient material, high-pressure liquid chromatography (HPLC) determination of MXD or IVM concentration. The fatty acid profile of each biopsy sample was determined using gas–liquid chromatography (GLC) (Gulati et al., 1999) following acid-catalyzed trans-esterification of the lipids into their respective methyl esters (Christie, 1989).

Moxidectin or IVM was extracted from fat tissue samples by first mixing 20 mg of fat tissue with 25 μL of internal standard (1 μg/mL) before adding 2 mL of acetonitrile and homogenizing with an ultraturrax for 30 sec. After centrifugation at 2000 g for 10 min the supernatant was removed and diluted with 2 mL of water. The fat tissue was resuspended in 2 mL of acetonitrile and vortexed for 15 sec prior to being centrifuged again. The second supernatant was added to the first and the pooled supernatant was then added to a C18 cartridge (Isolute, International Sorbent Technology, Glamorgan, UK), preconditioned by the addition of 6 mL acetonitrile and 6 mL water. The cartridge was washed with 3 mL of acetonitrile:water (1:2) and the analytes were eluted with 6 mL of acetonitrile and evaporated at 50 °C under a stream of air. Ivermectin and MXD were derivatized by resuspending them in 100 μL of triethylamine:acetonitrile (1:1), mixing for 15 sec, adding 150 μL of

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**Table 1. Composition of the grower and sow maintenance diets as a percentage of dry matter**

<table>
<thead>
<tr>
<th>Diet component</th>
<th>Grower diet</th>
<th>Maintenance diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Matter (%)</td>
<td>88.2</td>
<td>89.9</td>
</tr>
<tr>
<td>Gross energy (MJ/kg)</td>
<td>18.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Crude fiber</td>
<td>4.67</td>
<td>15.65</td>
</tr>
<tr>
<td>Crude fat</td>
<td>3.15</td>
<td>1.47</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>3.14</td>
<td>2.01</td>
</tr>
<tr>
<td>Ash</td>
<td>5.37</td>
<td>7.18</td>
</tr>
</tbody>
</table>

trifluoroacetic anhydride:acetonitrile (1:2) and again mixing. The sample was concentrated to approximately 75 µL at 50 °C prior to the addition of 250 µL of 2 m ammonia in methanol. The samples were again mixed and concentrated at 50 °C before the addition of 100 µL acetonitrile. Approximately 150 µL of the sample was transferred to a wisp vial for HPLC analysis.

Plasma samples were prepared by mixing 2 mL of plasma with 25 µL of internal standard (1 µg/mL) and then 5 mL of acetonitrile. After centrifugation at 2000 g for 10 min the supernatant was diluted in 4 mL of water and the sample was loaded on a preconditioned C18 cartridge (see above). The supernatant was diluted in 4 mL of water and the sample was analyzed whereas fat samples were analyzed after the addition of 100 µL acetonitrile. The proportion of each fatty acid present in the backfat samples from pigs treated with IVM was reversed for pigs treated with MXD. Duplicate plasma samples were analyzed whereas fat samples were analyzed singly.

Both drugs were resolved on a 150 × 5 mm C18, 5 µm column eluted with acetonitrile, tetrahydrofuran and water (52.25:23) at a flow rate of 1 mL/min. The fluorescent analyte derivatives of IVM and MXD were detected at an excitation wavelength of 370 nm and emission wavelength of 470 nm (Waters 470 fluorescence detector. Waters Associates, Milford, MA, USA) after 8 and 10 min, respectively. The injection volume was 50 µL.

Determination of the correlation coefficient of each standard curve by linear regression analysis resulted in r-values > 0.980. The coefficient of variation was 7.5 ± 1.9% for assays of plasma samples and 13.2 ± 3.5% for assays of fat tissue. Recovery of analytes from plasma was constant over the tested concentration range at 86 ± 7 and 89 ± 6% for IVM and MXD, respectively. Recovery of IVM and MXD from fat tissue was 60 ± 8 and 69 ± 7%, respectively. The limit of quantitation for both drugs was 0.3 ng in assays of fat samples and 0.2 ng for assays of plasma samples. The limit of detection was set as the lowest tested standard concentration for each drug.

Data analysis

The proportion of each fatty acid present in the backfat samples was calculated by integrating the area under the peaks identified by GLC.

Concentrations of IVM or MXD in the plasma of individual animals were evaluated by noncompartmental analysis. The area under the concentration–time curve (AUC) was calculated using the trapezoidal rule (Gibaldi & Perrier, 1982). The area under the first moment curve (AUMC) was calculated as the AUC of the product of time and plasma concentration. The MRT of the drug was calculated as the ratio of AUMC to AUC and the body clearance (Cl) was calculated as the dose divided by AUC as the bioavailability of subcutaneously administered macrocyclic lactones is 100% (Friis & Bjørn, 1996). The elimination half-life (T1/2) was calculated from the slope of the concentration–time curves over the last five time points. The peak concentration (Cmax) and the time taken to reach this concentration (Tmax) were read from the individual plasma concentration curves.

Results are presented as mean ± SD for each of the four groups. Apparent differences between groups were examined for significance using t-tests.

RESULTS

The average daily weight gain for pigs on the maintenance ration were 389, 392, and 406 g/day for groups IM, MM, and UM, respectively. The average daily weight gain was significantly higher for pigs on the grower ration with groups IG, MG, and UG gaining an average of 731, 749, and 767 g/day, respectively.

The average weights of the treated pigs are shown in Table 2. The lowest mean weight was recorded in group IG and the

| Table 2. Pharmacokinetic parameters (mean ± SD) measured after s.c. injection (300 µg/kg) of ivermectin (IVM) or moxidectin (MCD) to animals receiving a maintenance (M) or grower (G) diet |
|----------------------------------|---------------|---------------|---------------|---------------|
| Parameter                        | IM (n = 4)    | IG (n = 4)    | MM (n = 4)    | MG (n = 4) |
| Weight (kg)                      | 60.0 ± 8.78   | 51.1 ± 7.05   | 54.9 ± 6.71   | 58.9 ± 1.34  |
| AUC (ng·d/mL)                    | 87.7 ± 22.6   | 70.5 ± 18.3   | 274 ± 123     | 436 ± 273    |
| AUMC (ng·d²/mL)                  | 820 ± 171     | 600 ± 220     | 6309 ± 344    | 8503 ± 597   |
| Tmax (h)                         | 48.0 ± 0.04   | 75.1 ± 53.9   | 5.81 ± 0.025  | 5.83 ± 0.057 |
| Cmax (ng/mL)                     | 7.16 ± 2.61   | 7.89 ± 3.63   | 26.0 ± 16.8   | 29.1 ± 21.9  |
| MRT (days)                       | 9.57 ± 1.58   | 8.41 ± 1.36   | 22.3 ± 3.26   | 18.7 ± 8.57  |
| T1/2 (days)                      | 2.55 ± 1.17   | 2.28 ± 0.452  | 6.76 ± 1.02   | 5.46 ± 1.55  |
| Cl (L/kg/day)                    | 3.64 ± 1.15   | 4.47 ± 1.11   | 1.29 ± 0.580  | 1.06 ± 0.865 |

For each parameter significant differences (P < 0.05) between groups are indicated by different letters. Calculated parameters: area under the concentration–time curve (AUC); area under the first moment curve (AUMC); maximum concentration (Cmax); time to maximum concentration (Tmax); mean residence time (MRT); half-life of elimination (T1/2); clearance (Cl).
highest in group IM but there was no significant difference in bodyweight between these groups at the time of treatment. Despite the higher growth rate seen in group IG there was no significant difference in the weights of the two IVM-treated groups throughout the study. In the control and MXD-treated groups, pigs fed the grower diet were significantly \((P < 0.05)\) heavier than those receiving the maintenance ration from day 28 until the end of the study.

**Fatty acid composition of backfat**

The seven most prolific fatty acids accounted for 94–97% of total fatty acids. Table 3 shows the average proportions of these fatty acids at each of the sampling times. Small amounts of other fatty acids (e.g. eicosapentaenoic acid) were found but have not been included in the observations. Treatment with either MXD or IVM had no significant effect on the fatty acid composition of animals receiving either the grower or maintenance diet so these groups and the controls have been pooled within each diet.

The proportions of myristic acid (14:0), palmitic acid (16:0), stearic acid (18:0), oleic acid (18:1), and linoleic acid (18:2) were significantly higher \((P < 0.01)\) in the backfat of pigs fed the grower ration 4 and 9 weeks after treatment compared with the level at the time of treatment. The proportion of linoleic acid (18:2) was significantly lower \((P < 0.001)\) at these time points but there was no significant change in the proportion of palmitoleic acid (16:1) throughout the study in these pigs. The backfat of the pigs fed the grower diet was significantly \((P < 0.002)\) more saturated at 4 and 9 weeks after treatment compared with the time of treatment.

In the pigs fed the maintenance diet the proportion of linoleic acid was significantly higher \((P = 0.02)\) at the time of treatment compared with 9 weeks after treatment. The proportion of linolenic acid increased significantly \((P < 0.0001)\) from the time of treatment to 4 and 9 weeks after treatment, but there was no significant change in the proportions of the other fatty acids in these pigs.

Between the two diet groups (maintenance and grower) there were significant differences in the proportions of oleic acid at 4 weeks after treatment, stearic acid at 9 weeks after treatment and myristic, linoleic and linolenic acids at 4 and 9 weeks after treatment.

**Plasma pharmacokinetics**

Ivermectin was detected in the plasma of all IVM-treated animals from the first sample at 6 h until day 21 after treatment. The concentration of IVM in plasma over this time period is shown in Fig. 1. There was no significant difference in any of the calculated pharmacokinetic parameters following IVM administration into pigs fed the maintenance or grower diet (Table 2).

Moxidectin was detected in the plasma of all MXD-treated pigs from the first sample 6 h after treatment until the end of the trial at day 63. The MXD concentration in plasma was above 2 ng/mL for 49 days in the pigs fed the maintenance diet but remained above this level at the end of the study in those fed the grower ration (Fig. 2). There was no significant difference between the pigs fed the grower or maintenance diet for any of the calculated pharmacokinetic parameters following treatment with MXD (Table 2).

The **AUC** of MXD was significantly larger than that of IVM (Table 2). The peak MXD plasma concentration was higher and occurred earlier in comparison with that of IVM. The greater persistence of MXD in plasma was reflected in a longer **MRT** and a slower clearance of MXD from the body compared with IVM.

**Drug concentrations in fat**

Biopsy samples from at least three of the four pigs in each group were analyzed at each time point and the concentrations of IVM or MXD detected in these samples are shown in Figs 3 and 4, respectively. Ivermectin was detectable in biopsy samples taken 1 and 2 weeks after treatment but not at 4 or 9 weeks. The maximum IVM concentration in fat was 55 ng/g recorded 1 week after treatment. Moxidectin was detectable at 1, 2, and 4 weeks but not at 9 weeks with a maximum concentration of 296 ng/g fat 2 weeks after treatment. Despite large numerical differences between mean drug concentrations there were no statistical differences in IVM or MXD backfat concentrations between pigs fed the grower or maintenance diet at any time.

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**Table 3.** Proportions (mean ± SD) of the major long-chain fatty acids in the backfat of animals fed either a maintenance (M) or grower (G) diet at various times points after treatment

<table>
<thead>
<tr>
<th>Diet</th>
<th>Weeks after treatment</th>
<th>C14:0</th>
<th>C16:0</th>
<th>C16:1</th>
<th>C18:0</th>
<th>C18:1</th>
<th>C18:2</th>
<th>C18:3</th>
<th>Percent unsaturated</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>0</td>
<td>1.0 ± 0.08</td>
<td>17.5 ± 1.0</td>
<td>1.9 ± 0.45</td>
<td>8.8 ± 1.6</td>
<td>35.5 ± 2.2</td>
<td>30.0 ± 3.4</td>
<td>0.71 ± 0.13</td>
<td>68.2 ± 2.7</td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>1.1 ± 0.14</td>
<td>18.1 ± 1.4</td>
<td>1.9 ± 0.35</td>
<td>9.4 ± 1.6</td>
<td>36.1 ± 1.7</td>
<td>29.5 ± 2.3</td>
<td>0.85 ± 0.08</td>
<td>68.1 ± 2.5</td>
</tr>
<tr>
<td>G</td>
<td>2</td>
<td>1.0 ± 0.08</td>
<td>17.6 ± 0.81</td>
<td>1.8 ± 0.37</td>
<td>9.2 ± 1.4</td>
<td>36.1 ± 1.5</td>
<td>29.1 ± 1.9</td>
<td>0.90 ± 0.10</td>
<td>68.0 ± 2.4</td>
</tr>
<tr>
<td>G</td>
<td>4</td>
<td>1.2 ± 0.08</td>
<td>19.5 ± 1.2</td>
<td>1.9 ± 0.27</td>
<td>11.0 ± 1.6</td>
<td>38.5 ± 1.9</td>
<td>23.0 ± 2.2</td>
<td>0.84 ± 0.09</td>
<td>64.2 ± 2.1</td>
</tr>
<tr>
<td>G</td>
<td>9</td>
<td>1.2 ± 0.10</td>
<td>19.4 ± 0.82</td>
<td>1.6 ± 0.35</td>
<td>11.2 ± 1.6</td>
<td>38.6 ± 1.9</td>
<td>22.1 ± 2.1</td>
<td>0.94 ± 0.11</td>
<td>63.3 ± 2.3</td>
</tr>
<tr>
<td>M</td>
<td>0</td>
<td>0.98 ± 0.11</td>
<td>17.3 ± 1.1</td>
<td>1.7 ± 0.33</td>
<td>9.2 ± 1.2</td>
<td>34.1 ± 2.0</td>
<td>31.6 ± 4.4</td>
<td>0.70 ± 0.14</td>
<td>68.2 ± 3.5</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>0.99 ± 0.11</td>
<td>17.5 ± 1.2</td>
<td>1.7 ± 0.25</td>
<td>8.9 ± 2.1</td>
<td>33.2 ± 1.3</td>
<td>32.0 ± 3.3</td>
<td>0.78 ± 0.19</td>
<td>67.7 ± 3.6</td>
</tr>
<tr>
<td>M</td>
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<td>0.93 ± 0.07</td>
<td>16.6 ± 1.1</td>
<td>1.9 ± 0.22</td>
<td>8.4 ± 1.3</td>
<td>33.2 ± 2.3</td>
<td>32.2 ± 4.1</td>
<td>0.81 ± 0.18</td>
<td>68.0 ± 5.9</td>
</tr>
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<td>M</td>
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<td>29.1 ± 4.6</td>
<td>1.1 ± 0.20</td>
<td>66.8 ± 6.0</td>
</tr>
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<td>M</td>
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<td>17.7 ± 1.5</td>
<td>1.8 ± 0.37</td>
<td>10.3 ± 2.0</td>
<td>33.5 ± 3.3</td>
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<td>63.1 ± 7.9</td>
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<td>G</td>
<td>0</td>
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<td>17.5 ± 1.0</td>
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<td>63.3 ± 2.3</td>
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</tbody>
</table>

DISCUSSION

Under typical production conditions porcine backfat consists of approximately 60% unsaturated fatty acids with oleic palmitic, and linoleic acid accounting for up to 43, 26, and 15% of total fatty acids (Wood et al., 1989), respectively. In comparison, feeding a diet rich in sunflower oil for 7 weeks in this study increased the percentage of linoleic acid in backfat to approximately 30% of total fatty acids while the proportions of oleic and palmitic acids were reduced to approximately 35 and 17.5%, respectively, with unsaturated fatty acids accounting for 68% of total fatty acids. Similar changes in the proportions of these fatty acids have been reported previously following the feeding of diets high in linoleic acid (Hartman et al., 1985; Whittington et al., 1986) and show the preferential deposition of dietary polyunsaturated fatty acids (Dahl & Persson, 1965).

Reducing the fat content of the diet increases the rate of lipogenesis (Allee et al., 1971) and results in the deposition of more saturated and monounsaturated fatty acids (Rule et al., 1995) and therefore a decrease in the proportion of the
polyunsaturated fatty acids such as linoleic and linolenic acid. Feeding a restricted diet reduces the amount of fat deposited as the animals receiving this diet must oxidize fat to meet energy requirements whereas those on a full diet can meet energy requirements by oxidizing carbohydrates (Chwalibog & Thorbek, 2000). The higher proportion of linoleic acid in the biopsy samples from the pigs on the maintenance diet is indicative of this reduced fat deposition compared with the backfat of those receiving the grower diet which had significantly higher proportions of saturated fatty acids (myristic and palmitic acids).

There was a large variation in the concentration of either IVM or MXD in the backfat of animals within each group. Differences in the structure of the analyzed fat samples (e.g. amount of connective tissue) are a likely source of this variation. Normally this variation would be controlled by averaging the mean of replicated samples but the small amount of fat available for the HPLC analysis in this study did not permit such replication.

While the results presented in Figs 3 and 4 are similar to those previously reported (Prabhu et al., 1991; Zulalian et al., 1994; Craven et al., 2002) the large degree of variation between animals within each group makes further interpretation of this data unreliable.

Differences in the time to reach peak IVM plasma concentration and in the persistence of IVM and MXD in plasma have been observed between pigs in differing body condition (Craven et al., 2002). In the current study, the plasma MXD concentration remained above 2 ng/mL 63 days after treatment in pigs fed the grower ration compared with only 49 days in those animals fed the maintenance diet. As these animals were of similar body condition at the time of treatment the reduced plasma persistence of MXD must be a result of the reduced fat deposition in the pigs fed the maintenance diet compared with those that received the grower diet.

The AUC of MXD in the current study was higher (10464 vs. 5310 ng/h/kg) and the MRT longer (19 vs. 8 days) than that obtained in a previous study (Craven et al., 2002). Pigs in this previous study were significantly lighter at the time of treatment (29 vs. 59 kg) suggesting that the volume of the fat depot at the time of treatment also has a major impact on the pharmacokinetics of MXD.

In the current study there were no differences in IVM plasma pharmacokinetics between animals on the maintenance or grower ration. This suggests that the differences in IVM persistence observed in the former study (Craven et al., 2002) are as a result of differences in the volume of fat in the animal at the time of treatment. However, the lack of difference in IVM plasma persistence observed in the current study may be because of the relatively short persistence of this drug in plasma.

A reduction in the rate of fat deposition, as indicated by a higher proportion of linoleic acid in the backfat, reduced the plasma persistence of MXD but had no measurable effect on the pharmacokinetics of IVM.

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