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Ivermectin Pharmacokinetics, Metabolism, and Tissue/Egg Residue Profiles in Laying Hens

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ABSTRACT: The goals were to determine the ivermectin (IVM) plasma pharmacokinetics, tissue and egg residue profiles, and in vitro metabolism in laying hens. Experiments conducted were (1) 8 hens were intravenously treated with IVM and blood samples taken; (2) 88 hens were treated with IVM administered daily in water (5 days) (40 were kept and their daily eggs collected; 48 were sacrificed in groups (n = 8) at different times and tissue samples taken and analyzed); (3) IVM biotransformation was studied in liver microsomes. Pharmacokinetic parameters were AUC = 85.1 ng·day/mL, Vd_{ss} = 4.43 L/kg, and $T_{1/2el}$ = 1.73 days. Low IVM tissue residues were quantified with the highest measured in liver and skin+fat. IVM residues were not found in egg white, but significant amounts were quantified in yolk. Residues measured in eggs were greater than some MRL values, suggesting that a withdrawal period would be necessary for eggs after IVM use in laying hens.

KEYWORDS: *ivermectin, plasma pharmacokinetics, egg residue, tissue residue profiles, laying hens*

INTRODUCTION

Ivermectin (IVM) is an important broad-spectrum antiparasitic drug belonging to the macrocyclic lactone family. Since it was introduced in the veterinary market in 1981, it has been the most commonly used antiparasitic agent in cattle, horses, sheep, and pigs in many countries. Its spectrum of activity covers a wide variety of nematodes, microfilaria, and external parasites of domestic species.[1] The pharmacokinetic properties of IVM have been widely studied in domestic animals,[1] for which authorized veterinary medicinal products containing IVM are available. A huge number of IVM formulations such as slow-delivery systems, oral, topic, or injectable intended for domestic animals are available. The recommended doses range from 6 μg/kg for dogs (as prophylaxis for filariasis) to 200 μg/kg for ruminants (500 μg/kg for pour-on administration) and 300 μg/kg for pigs. In addition, the efficacy of this compound has also been investigated in other animal species such as nontraditional domesticated wild ruminants (reindeer, deer, buffaloes, camels, yaks, etc.), for which IVM extra-label use has been reported.[2] The remarkable utility of the macrocyclic lactones was also demonstrated in laboratory mammals, birds, fish, and reptiles many years ago.[3] IVM is reported to be effective against nematode infections in poultry, but it is not approved for use in avian species. IVM administered in water was effective in removing *Ascaris galli*, *Heterakis gallinarum*, and *Capillaria* in poultry.[4−6] The available data describing the pharmacokinetic behavior of IVM in avian species is scarce. In some countries, until recently there were some oral formulations to control internal and external parasites in pet or game birds and fighting cocks, but most of them are no longer on the market. In addition, no IVM formulations for avian production were available. However, extra-label use of this drug has been reported,[7] as evidenced in Web-based online discussion forums for avian producers. To our knowledge, IVM is used mainly to control internal and external parasites in chicks and hens, respectively. It is administered by applying available formulations in food, water, or topically in the cloaca in an empirical way. At present, there are some IVM formulations intended for avian production in some Latin American countries.

The European Commission adopted a regulation establishing maximum residue limits (MRLs) for IVM in all mammalian food-producing species. Extrapolation of MRLs to the relevant minor species has been considered. In addition, it is possible to further extrapolate the existing MRLs to other species and foodstuffs with a view to ensuring availability of veterinary medicinal products for conditions affecting food-producing animals while ensuring a high level of protection of human health. However, taking into account the current scientific knowledge, the extrapolation of MRLs to poultry (including eggs) was not recommended. The justification was based on metabolism patterns, which can be significantly different in poultry as compared with mammals. Consequently, species-specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety with regard to residues in poultry-derived food commodities.[8]

To contribute to the correct use of IVM in laying hens, the goals of the present work were (1) to investigate the pharmacokinetic behavior of IVM in laying hens following a single intravenous (IV) administration; (2) to describe the IVM tissue and egg residue profiles in laying hens after oral administration in water; and (3) to evaluate the IVM liver microsomal metabolism in hens in vitro.

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MATERIALS AND METHODS

Reagents and Chemicals. Pure reference standards (97−99% purity) of IVM and the internal standard (IS) abamectin (ABM) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Acetonitrile solvent used during the extraction and drug analysis was of HPLC grade and purchased from J. T. Baker (Phillipsburg, NJ, USA). The *N*-methylimidazole and trifluoroacetic anhydride used for derivatization reaction were from Aldrich (Milwaukee, WI, USA). Nicotinamide adenine dinucleotide phosphate ($NADP^+$) tris (base and acetate) was purchased from Sigma-Aldrich Chemical Co. Glucose-6-phosphate and glucose-6-phosphate dehydrogenase were purchased from Roche Applied Science (Buenos Aires, Argentina). Buffer salts (KCl, Na_2HPO_4, NaH_2PO_4, K_2HPO_4, KH_2PO_4, and $MgCl_2$) were purchased from J. T. Baker. Water was double-distilled and deionized using a water purification system (Simplicity; Millipore, Sao Paulo, Brazil).

Animals. One hundred healthy laying hens (Plymouth Rock Barrada), 6 months old and 2.2 ± 0.3 kg body weight (bw), were used in the experiment. The hens were monitored daily during a 2 week acclimatization period. They were housed with water and balanced commercial food ad libitum. Before the experiments, the hens were not medicated with any anthelmintic drug.

IVM Dosing. IVM treatments to laying hens were dosed using Ivomec 1% (Merial) diluted depending on the trial as follows: For the *intravenous treatment*, a 400 μg/kg dose was administered. Ivomec 1% was diluted to 0.2% (1:5) with 40% propylene glycol/ethanol (1:2) and 60% sterile physiological saline solution. For the *oral treatment*, a dose (400 μg/kg/day) was administered in water for 5 days. The daily volume of Ivomec 1% to be administered (1 mL per 25 kg bw) was diluted to 0.1% (1:10) with propylene glycol. Then, it was diluted in 25% of the total volume of daily water intake. To ensure uptake of medicated water, the regular drinking water was removed 2 h before administration.

Experimental Design. All of the experiments were carried out following ethical guidelines of the Animal Welfare Committee of the Faculty of Veterinary Medicine, Universidad Nacional del Centro de la Provincia de Buenos Aires (Internal Protocol 01/2014; approval date April 28, 2014).

Intravenous Administration. Eight animals were administered a single dose (400 μg/kg) of IVM by IV route using a catheter (MCM 24 G, China) previously placed into the right wing vein. After treatment, blood samples (1 mL) were taken by an IV catheter previously placed into the left wing vein as follows: 0 (blank) and 0.5, 1, 3, 6, 9, 12, 15, 24, 30, 36, and 48 h; and 3, 5, 8, and 10 days post-treatment. The volume of blood taken in each sample was replaced by sterile physiological saline solution (1 mL) by 10−15 s IV infusion. Blood samples taken in heparinized tubes were centrifuged at 3000 rpm for 10 min, and the plasma collected was placed into plastic tubes and frozen at −20 °C to be analyzed later.

Oral Therapeutic Treatment. Eighty-eight laying hens were treated with IVM administered daily in water at 400 μg/kg dose for a 5 day period. Animals were divided into two groups: Group 1 consisted of 40 hens; their daily eggs were collected from the beginning of the treatment to 20 days post-treatment. After collection, the eggs were opened, yolk and white separated, and samples placed into plastic tubes and then frozen at −20 °C to be analyzed by HPLC later. Group 2 consisted of 48 hens sacrificed (following ethical guidelines) in 6 groups of 8 at the following times: 1, 3, 5, 7, 10, and 15 days post-treatment. Samples of blood, muscle, liver, kidney, and skin and fat in natural proportions (skin+fat) were taken after sacrifice. Blood samples were centrifuged (3000 rpm for 10 min), and the plasma was collected. Tissue samples were wrapped with aluminum foil and labeled. All samples were frozen at −20 °C until analysis by HPLC.

In Vitro Metabolism Experiments. Samples of liver parenchyma were obtained from four untreated laying hens, slaughtered following the above-mentioned ethical guidelines. Liver samples were rinsed with ice-cold KCl 1.15%, covered with aluminum, and chilled in ice. Tissue samples were brought to the laboratory for subsequent procedures, which started within 1 h from sample collection and were carried out between 0 and 4 °C. The liver microsomes were prepared as previously described.[9] Microsomal suspensions were stored at −70 °C until used in the different biotransformation assays. Protein contents of each microsomal preparation were measured according to the method of Lowry et al.[10]

The enzymatic biotransformation of IVM was studied in liver microsomes by assessing the percentages of both unchanged parent drug and its formed metabolites. A typical reaction mixture contained (in a final volume of 0.5 mL) sodium phosphate buffer 0.1 M (pH 7.4) containing 5 mM $MgCl_2$ and 0.8 mM EDTA, 1.25 mg of microsomal protein, NADPH-generating system in phosphate buffer (0.32 mM $NADP^+$, 6.4 mM glucose-6-phosphate, and 1.25 U of glucose-6-phosphate dehydrogenase), and 250 ng (0.3 nmol) of IVM (dissolved in 5 μL of methanol). All incubation mixtures were prepared and allowed to equilibrate (1 min at 37 °C). Then, the reaction was started by the addition of 0.2 mL of the NADPH-generating system. Incubations (30 min at 37 °C) were carried out in glass vials in an oscillating water bath under aerobic conditions. Blank samples, containing all components of the reaction mixture except the NADPH-generating system, were also incubated under the same conditions. These incubations were used as controls for possible nonenzymatic drug conversion. All reactions were stopped by the addition of 0.2 mL of acetonitrile and stored at −20 °C until analysis.

Sample Analysis. All samples were analyzed by HPLC with fluorescent detection following an adapted version of the methodology previously described.[11]

Plasma Extraction. Samples (0.5 mL) were placed into a 5 mL plastic tube and spiked with 50 μL of the IS abamectin (2 ng/10 μL). Acetonitrile (1 mL) was added to the sample and then mixed for 10 min with a high-speed vortexing shaker (Multitube Vortexer, VWR Scientific Products, West Chester, PA, USA). After mixing, the sample was sonicated (Ultrasound Bath, Lab-line Instrument, Inc., Melrose Park, IL, USA) and centrifuged (BR 4i Centrifuge, Jouan, Saint Herblain, France) at 3000 rpm for 10 min at 5 °C. The clear supernatant was transferred to a tube and the procedure repeated. The total supernatant was transferred to C18 cartridges (100 mg/mL, Strata C18-T, Phenomenex) using a manifold vacuum (Baker spe-24G). The cartridges were previously conditioned with 2 mL of methanol (HPLC grade), followed by 2 mL of water (HPLC grade). All samples were applied and then sequentially washed with 1 mL of water and 1 mL of methanol/water (1:4), dried with air for 5 min, and eluted with 1.5 mL of methanol (HPLC grade). The eluted volume was evaporated at 60 °C to dryness in a vacuum concentrator (Speed-Vac, Savant, Los Angeles, CA, USA). The dry residue was dissolved in 100 μL of a *N*-methylimidazole/acetonitrile solution (1:1 v/v). To initiate the derivatization, 150 μL of trifluoroacetic anhydride/acetonitrile solution (1:2 v/v) was added,[12] and an aliquot of 100 μL was injected into the chromatographic system.

Tissue and Egg Extraction. Tissue samples (muscle, liver, kidney, and skin+fat) were thinly sliced, and 1 g was placed into a 5 mL plastic tube and spiked with 10 μL of the IS abamectin (4 ng per 10 μL). A volume (500 μL) of water was added to egg white or yolk samples (500 mg) before extraction. After fortification with the IS, 1 mL of acetonitrile was added to each sample and mixed for 10 min on a high-speed vortexing shaker. After mixing, the sample was sonicated and centrifuged at 2000*g* for 10 min at 5 °C. The clear supernatant was transferred to a tube and the procedure repeated. The total supernatant was transferred to C18 cartridges for solid phase extraction following the procedure described for plasma. An aliquot (100 μL) of the derivatized sample was injected in the HPLC system.

Microsomal Sample Extraction. Ten nanograms of ABM (internal standard), dissolved in 25 μL of methanol, was added to each microsomal incubation. Then, samples were mixed with 0.5 mL of acetonitrile, shaken for 5 min, and centrifuged (10000*g*, 10 min). An aliquot (100 μL) of the clear supernatant was evaporated to dryness and, after derivatization, injected into the HPLC system.

HPLC Quantification. A Shimadzu chromatography system (Shimadzu Corp., Kyoto, Japan) was used to quantify IVM by HPLC. A mobile phase of water/methanol/acetonitrile (6:40:54, v/v) was pumped into the system through a C18 column (Kromasil 100-5C18, 5 μm, 4.6 × 250 mm) placed in an oven at 30 °C. Fluorescence

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detection (spectrofluorometric detector RF 10; Shimadzu) was performed at 365 nm excitation and 475 nm emission wavelengths.

Validation Procedure. A complete validation of the analytical procedures for the extraction and quantification of IVM in the different matrices (plasma, muscle, liver, kidney, skin+fat, egg white, egg yolk of hens) was performed. The linearity of the method was tested after elaboration of analytical calibration curves. Blank tissue samples were fortified with IVM in different ranges of calibration: plasma, 0.2−200 and 200−800 ng/mL; muscle, 0.2−10 ng/g; liver, kidney, and skin +fat, 0.5−10 ng/g; egg white, 0.2−10 ng/g; egg yolk, 0.2−100 ng/g. The extraction efficiency of the analytes was determined by comparison of the peak areas from fortified blank samples with the peak areas from direct injections of equivalent quantities of standards. Precision and accuracy (intra- and interassay) of the method were determined by evaluation of replicates of drug-free samples (n = 5) fortified with each compound at different concentrations (0.2, 5, 50 ng/g) depending on the matrix. Precision was expressed as coefficient of variation (% CV). The limit of quantification (LOQ) was calculated as the lowest drug concentration (n = 5) on the standard curve that could be quantitated with precision not exceeding 20% and accuracy within 20% of nominal. The linear regression lines for IVM showed correlation coefficients ≥0.995. Mean absolute recovery percentages ranged between 74.8 and 97.1%. The interassay precision of the analytical procedures obtained after HPLC analysis of IVM on different working days showed CV between 0.90 and 14.1%. The LOQ values were established at 0.2 ng/mL for plasma; 0.2 ng/g for muscle, egg yolk and egg white; and 0.5 ng/g for kidney, liver, and skin+fat.

Data Analysis. Tissue and egg concentrations were expressed as nanograms per gram. The pharmacokinetic parameters and concentration data are reported as the mean ± SEM. The pharmacokinetic analysis of the plasma concentration (ng/mL) versus time curves for IVM for each animal after IV administration was carried out using PK Solution 2.0 software (Summit 10 Research Services, Montrose, CO, USA). Pharmacokinetic analysis of the experimental data was performed using noncompartmental (area) and compartmental (exponential terms) methods without presuming any specific compartmental model. The concentration−time profile for IVM in plasma after its IV administration was best fitted to a biexponential equation: $Cp = A^{-\alpha \cdot t} + B^{-\beta \cdot t}$, where A and B are primary and secondary disposition intercepts, α and β sre the primary and secondary disposition rate constants (h^{-1}), and Cp is the plasma concentration of IVM at time t. Regression parameters from this equation were then used to calculate the presented pharmacokinetic parameters. The elimination half-live ($T_{1/2el}$) was calculated as ln 2 divided by β rate constant. The estimated plasma concentration of IVM at time zero (C_0) was the sum of the extrapolated time zero concentrations of the coefficients A and B. The area under the concentration−time curve (AUC), clearance (Cl_{area}), and apparent volume of distribution at steady-state (Vd_{ss}) were calculated according to the equations of Gibaldi and Perrier.[13] Statistical moment theory was applied to calculate the mean residence time (MRT) in plasma.[13]

RESULTS

Intravenous Administration. The mean (±SEM) plasma concentrations (ng/mL) versus time profile after IVM administration (400 μg/kg) by IV route to laying hens is plotted in Figure 1. The highest IVM concentration (739.6 ± 50.2 ng/mL) was quantified at 30 min (first sampling time), decreasing until the lowest concentration (0.38 ± 0.06 ng/mL) attained at day 10, showing a typical IV profile. Pharmacokinetic parameters obtained for IVM after its administration are shown in Figure 1. The plasma availability represented by AUC was 85.1 ± 4.9 ng·day/mL. The clearance was 4.8 ± 0.1 L/day/kg, with a $T_{1/2el}$ and MRT of 1.73 ± 0.08 and 0.95 ± 0.11 days, respectively.

Oral Therapeutic Treatment. The tissue residue concentrations (mean ± SEM) quantified after IVM administration in water to hens for 5 days are shown in Table 1. Residues were

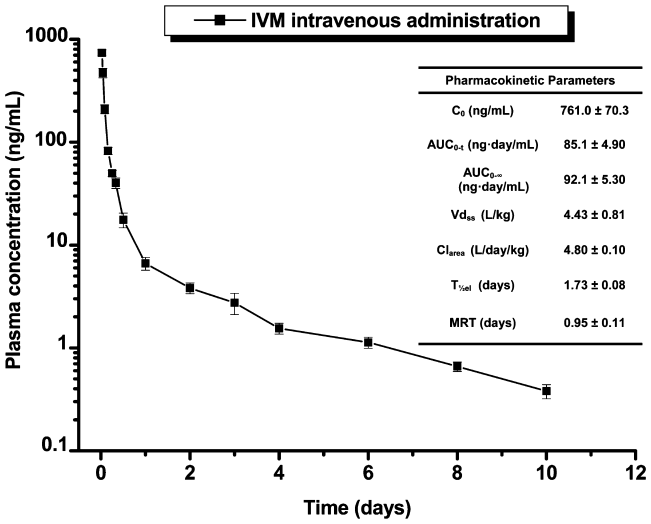

Figure 1. Mean (±SEM) plasma concentrations (ng/mL) versus time profile and pharmacokinetic parameters after ivermectin (IVM) administration (400 μg/kg) by the intravenous route to laying hens. C_0, initial concentration extrapolated to time zero; AUC_{0-t}, area under the concentration versus time curve from time 0−10 days; $AUC_{0-\infty}$, area under the concentration versus time curve extrapolated to infinity; $T_{1/2el}$, elimination half-life; MRT, mean residence time; Vd_{ss}, apparent volume of distribution at steady state; Cl_{area}, total body clearance.

quantified for a longer time in skin+fat until 15 days post-treatment. Plasma, muscle, and liver residues were quantified until 7 days after the end of treatment, whereas IVM kidney residues were quantified only until 3 days post-treatment. The residue levels were low, with the highest concentration measured the first day post-treatment in all tissues. The tissue with the highest concentration was liver, followed by skin+fat, kidney, plasma, and muscle.

After IVM oral administration in water to laying hens for 5 days, residues were found in eggs. Yolk and egg white were analyzed separately. Although IVM residues were not found in egg white, significant residues were quantified in yolk (Figure 2). The residue levels were higher than those found in tissues. IVM residues were quantified in yolk from the second day of treatment to 17 days post-treatment. The maximum concentration of residues was nearly 50 ng/g quantified 3 days post-treatment.

In Vitro Hepatic Biotransformation of IVM. After 30 min of incubation, mean IVM concentrations decreased (27.8 ± 4.4%, $p < 0.001$) from 0.61 ± 0.03 nmol/mL (control incubations without NADPH) to 0.44 ± 0.03 nmol/mL (experimental incubations in the presence of NADPH). Thus, the metabolic rate of IVM disappearance was 0.14 ± 0.02 nmol/h per mg of microsomal protein. An additional chromatographic peak (a supposed IVM metabolite), with a retention time of 6 min, was detected when liver microsomes were incubated in the presence of NADPH (Figure 3). Therefore, the unchanged parent drug was 99.9 ± 0.02% in control liver microsomes incubated without NADPH, but represented 84.1 ± 1.4% when IVM was incubated in the presence of NADPH. In these experimental incubations, the additional chromatographic peak represented 14.9 ± 1.4% of the total measured area.

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Table 1. Ivermectin (IVM) Tissue Residues (Mean ± SEM) Quantified after Its Oral Administration in Water (400 μg/kg) for a 5 Day Period to Laying Hens

	IVM tissue concentration (ng/g·mL)				
time (days) post-treatment	plasma	muscle	kidney	liver	skin+fat
1	1.07 ± 0.24	0.22 ± 0.02	0.84 ± 0.18	2.96 ± 0.52	1.84 ± 0.88
3	0.21 ± 0.01	0.28 ± 0.02	0.53 ± 0.17	0.94 ± 0.23	0.94 ± 0.17
5	0.80 ± 0.10	0.23 ± 0.03		0.56 ± 0.11	1.04 ± 0.29
7		0.20 ± 0.02		0.77 ± 0.25	0.98 ± 0.22
10					0.89 ± 0.33
15					0.54 ± 0.18

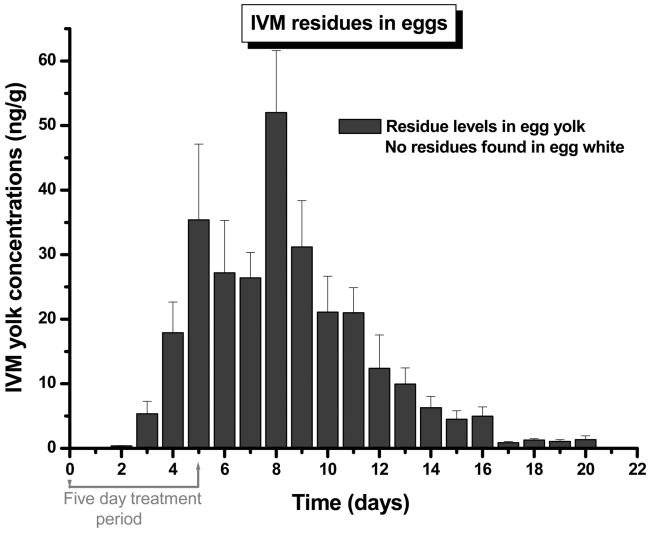

Figure 2. Mean (±SEM) ivermectin (IVM) residue concentrations (ng/g) in egg yolk and white after its daily administration (400 μg/kg) for 5 days in water to laying hens.

DISCUSSION

The disposition of the avermectin compounds is characterized by their long persistence in the body and large volume of distribution, the significant effects of formulation and/or route of administration on their bioavailability, and the large interspecies and interindividual variations.[14] Owing to its high lipophilicity, IVM distributes largely to the tissues and is eliminated slowly from the body compartments.

The plasma pharmacokinetic behavior of IVM after IV administration to laying hens is reported for the first time in the present work. In agreement with the described properties, after IVM IV administration in laying hens, the drug was measured for an extended period of time (10 days) and was widely distributed to tissues (4.4 L/kg). This large volume was similar to that found in mammalians such as sheep and pigs.[15,16]

In most species, IVM undergoes little metabolism and most of the dose is excreted unchanged in the feces (90%) with <2% excreted in urine. Bile is the main route of excretion, with the transporter P-glycoprotein present in biliary canalicules contributing to the drug's high fecal excretion.[17] According to the results obtained in the current work, hens could apparently metabolize IVM nearly 15%. The half-life in hens was similar to that in pigs[16] and shorter than those reported in ruminant species.[15,18−21] In fact, the shorter half-life in pigs compared to other species was associated with a higher rate of metabolism.[22]

IVM absorption was described to be proportional to the administered dose in ruminants.[23] As a consequence, a lineal AUC increment was observed when the dose was increased. In the present work, the IVM dose was twice as much as that used in other animal species. However, the IVM AUC obtained in hens corrected by dose (AUC/2) was lower (42.5 ng·day/mL) compared to that in pigs (50 ng·day/mL),[16] goats (153 ng·day/mL),[24] horses (343 ng·day/mL),[25] and sheep (375 ng·d/mL).[15] Then the systemic IVM exposure (measured as AUC) was lower in hens than that in mammalian species.

Overall, we can conclude that IVM pharmacokinetic behavior in laying hens is characterized by a long persistence and a large apparent volume of distribution; however, the half-life was shorter and plasma disposition lower than those in other species, the pig being the species that most resembles the hen from the IVM pharmacokinetic point of view.

The available information reporting tissue residue profiles after IVM treatment is scarce in poultry compared with other species. When administered subcutaneously (SC) and intraruminally (IR) in cattle, IVM was recovered in all sampled tissues. High levels were recorded in kidney and muscle, but the highest concentrations were found in liver and fat.[26] IVM levels decrease more quickly in sheep than in cattle.[27] IVM bioavailability after intra-abomasal administration in sheep was 100%; otherwise, a significant first-pass effect was associated with the low bioavailability (25%) obtained after IR administration similar to that in cattle.[15] However, Lifschitz et al.[28] demonstrated that IVM was thoroughly bound to solid ruminal contents (>90%) without suffering degradation. IVM is widely distributed in pigs after SC administration, with the highest levels in liver and fat.[22]

We evaluated the IVM residue profiles in egg and tissues of laying hens, after IVM administration (400 μg/kg) by oral route in water for 5 days. The IVM concentrations quantified in hen plasma were low, demonstrating a poor IVM bioavailability by this route, which could be associated with a poor absorption or significant first-pass effect. IVM tissue residue levels in hens were also low, with the highest level in liver and skin+fat, with very low residues in kidney and muscle. Consistent with reports on mammals, due to its high lipophilicity, IVM tends to accumulate in tissues with the highest fat content. In fact, when IVM residues were measured in eggs, they were not found in egg white, which contains fat at trace levels, whereas significant IVM residues were quantified in egg yolk, which is very rich in lipids. Plasma IVM and liver lipoproteins would reach the follicles during the rapid growth phase in the process of egg formation in hen ovary, allowing the IVM accumulation in yolk.

In contrast, when adult pigeons brooding squab were treated with IVM in drinking water (3.3 μg/mL) for 3 days, high IVM residue concentrations were quantified in both liver (58.5 ng/g) and breast muscle (43.1 ng/g) at the end of treatment.[7] On the other hand, Miller[29] fed IVM to broiler chickens in the diet (2 μg/g of diet) for 5 weeks and found no residues in liver tissue, even without a withdrawal period.

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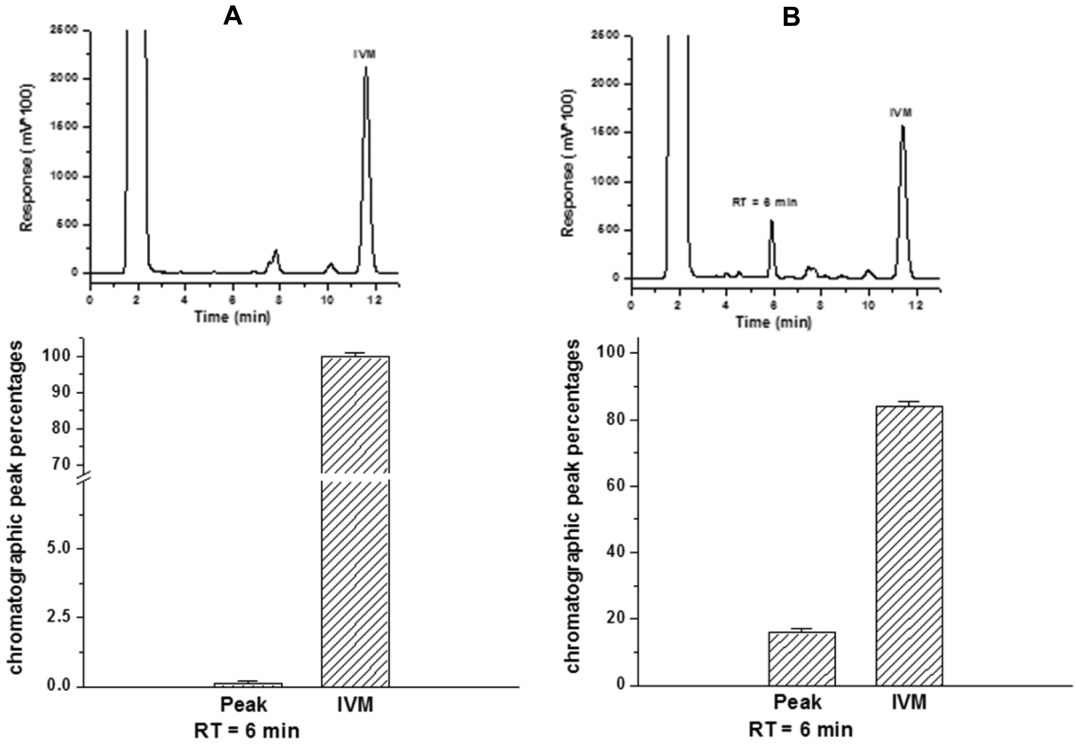

Figure 3. Ivermectin (IVM) biotransformation by liver microsomes from hens: percentages (mean ± SEM) of unchanged parent drug and its supposed metabolite observed after incubation of IVM, both in control incubations (without NADPH producing system) (A) and in experimental incubations (B). The insets show representative chromatograms obtained under both incubation conditions. Data represent the mean ± SEM of four livers.

IVM was evaluated at the 58th JECFA (Joint FAO/WHO Expert Committee on Food Additives) meeting. According to this, the Codex Alimentarius established MRLs for IVM of 100, 40, and 10 μg/kg, for liver, fat, and milk, respectively. In the EU, maximum residue limits of 100 (fat and liver) and 30 μg/kg (for kidney and muscle) are established for IVM in all mammalian food-producing species.[8] Withdrawal time periods of 35, 28, and 18 days are recommended after IVM administration (Ivomec, Merial) by subcutaneous route in cattle, sheep, and pig, respectively. As mentioned before, there are some IVM commercial formulations for use in avian production in some Latin American countries. They are usually administered in water or food for 2, 3, 5, or 21 days. Withdrawal times are recommended in only some of these products (2 or 7 days for meat and 0 for egg). In the present work, the IVM tissue residues quantified in laying hens were not greater than the MRLs (reported for other species) in any case. Otherwise, the IVM residues quantified in egg were greater than some established MRLs values. These results would suggest that an IVM withdrawal period after its oral administration at 400 μg/kg in laying hens should not be required for meat, whereas it could be necessary for eggs produced by IVM-treated hens.

The scientific information shown in the present work based on IVM pharmacokinetic behavior and tissue residue studies in laying hens is an original contribution to the rational use of this drug in poultry. Overall, we conclude that it would be necessary to establish an MRL value for IVM in eggs of laying hens, to determine the appropriate withdrawal period that guarantees the safety of this animal food product for human consumption.

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