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RESEARCH ARTICLE

Pharmacokinetics of ivermectin after oral and intravenous administration in Biłgorajska geese (*Anser anser domesticus*)

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ABSTRACT

Aims: To assess the pharmacokinetic profile of ivermectin in Biłgorajska geese (*Anser anser domesticus*) after single I/V or oral administration, in order to compare these routes of administration and assess the oral bioavailability.

Methods: Ten healthy male geese were used in a single-dose, two-phase study with a 3-month washout period between phases. In the first phase, all geese were given 0.2 mg/kg I/V ivermectin, while in the second phase they were treated orally with the same dosage. Blood samples were collected at selected time points up to 480 hours after each administration. Samples were purified using protein precipitation and drug concentration was quantified using HPLC. The analytical method was validated on blank goose plasma and was characterised by an optimal linearity and a limit of quantification of 0.025 µg/mL. The pharmacokinetic analysis was carried out using a non-compartmental approach.

Results: The drug was quantifiable up to 240 hours after I/V administration, while after oral treatment it was quantifiable up to 144 hours in most of the geese. The elimination half-life of ivermectin was approximately 3.8 (95% CI = 22.05–284.5; $p = 0.027$) times higher after I/V administration compared to oral administration. Moreover, the area under the curve from zero to the last detectable timepoint of ivermectin was 6.4 (95% CI = 13.82–17.17; $p < 0.001$) hours greater after I/V than oral administration. This difference led to a bioavailability of 20.38 (SD 5.92) %.

Conclusions: Following oral administration in geese, ivermectin has a bioavailability of approximately 20%. Further research on the action of ivermectin in the gastrointestinal tract is required along with assessment of tissue residues to allow calculation of withdrawal time to ensure consumer safety.

Abbreviations: AUC: area under the concentration-time curve; AUC_{last}: area under the curve from zero to the last detectable timepoint; AUMC: area under the first moment curve; C_{max}: maximum concentration; T_{max}: time at maximum plasma concentration

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Introduction

Geese (*Anser anser domesticus*) have long been domesticated and today are farmed in both large-scale breeding and urbanised settings. Breeding geese to produce meat and eggs with high nutritional value is undertaken mainly in Asia and Eastern European (Pingel 2004). Biłgorajska geese, a Polish breed, are characterised by a carcass with low fat and good muscularity (Pudyszak 2006).

Parasitic infestations frequently compromise health and productive performance in geese. The economic cost of parasite infections in poultry is one of the primary drivers for the development of specific antiparasitic drugs. Despite significant treatment advances, parasites remain a major threat to livestock farming, causing large deficits for the agricultural economy (Selzer and Epe 2021). Effective parasite control is thus essential for profitability in intensive livestock production. However, investment in control measures does not always result in the expected therapeutic success. Management strategies are often underrated and not well integrated with the use of antiparasitic drugs.

Ivermectin has been the most prevalent antiparasitic agent in cattle, horses, sheep and pigs in many countries (Lanusse *et al*. 1997; Sharun *et al*. 2019; Arisova 2020). Ivermectin is a highly lipophilic compound, characterised by long persistence in many species, including cattle, sheep and chickens, and a large volume of distribution after oral, I/M or S/C administration (Cerkvenik-Flajs and Grabnar 2002; Cirak *et al*. 2018). Its long half-life means infrequent administration can still achieve clinical effects (Lanusse *et al*. 2010; Laing *et al*. 2017).

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Ivermectin's spectrum of activity covers a wide variety of nematodes, microfilaria and external parasites of domestic species. Dosage regimens vary, depending on the species and parasite treated, and a huge number of pharmaceutical formulations are available, including oral, topical or injectable preparations (Lanusse *et al*. 2010). Despite the reputation for persistence, wide variations in half-life have been observed among the species mentioned above. For instance, the half-life after S/C administration in cattle is 6.3 days, while in chickens it is 1.45 hours (Cerkvenik-Flajs and Grabnar 2002; Cirak *et al*. 2018). Thus, species-specific studies are required to obtain precise information about the pharmacokinetic profile.

Ivermectin is used in an off-label manner in broiler poultry, due to its effectiveness against nematodes (e.g. *Ascaris galli*, *Heterakis gallinarum*, *Capillaria spp.*) and ectoparasites (e.g. *Menopon gallinae, Menacanthus Stramineus*) after topical (in the cloaca) or oral (medicated food or water) administration (Geary 2005; Wolstenholme and Rogers 2005; Moreno *et al*. 2015; Arisova 2020). As oral administration is easier than parenteral routes, oral administration of ivermectin is important for the management of many farmed species. Published studies mainly report pharmacokinetics and tissue/egg residues in broiler chickens and laying hens (Moreno *et al*. 2015; Mestorino *et al*. 2017; Cirak *et al*. 2018), but no information has been reported for waterfowl. The incorrect use of anthelmintic drugs due to insufficient knowledge of their pharmacological features in the target species may lead to ineffective therapy and/or to development of resistance (Schweizer *et al*. 2005; Charlier *et al*. 2020). Thus, the present study aims to describe the pharmacokinetic profile of ivermectin in geese after a single oral and I/V administration (0.2 mg/kg) to compare the two routes of administration and to assess the oral bioavailability.

Material and methods

Chemicals, reagents and solutions

Ivermectin and the internal standard (moxidectin), both with a standard purity of >99.0%, were purchased from Sigma-Aldrich (Milan, Italy). HPLC-grade acetonitrile was purchased from VWR International Bvba (Leuven, Belgium), while deionised water was produced using a Milli-Q Millipore Water System (Millipore, Darmstadt, Germany).

Animals

The animal experiment was approved (nr. 77/2021) by the Institutional Animal Care and Use Committee of the University of Lublin (Poland) and carried out in accordance with European law (2010/63/UE).

Ten adult male Biłgorajska geese were selected randomly from a wider group of 100 subjects using randomiser software (Research Randomizer, www.randomizer.org) and enrolled in this study. They were judged to be in good health based on serum chemistry, haematological analyses and physical examination by a supervising veterinarian (B Ł-W) and were acclimatised for 1 week in a 60 m^2 enclosure with an indoor shelter of 8 m^2 before the commencement of the study. Animals were able to graze freely during the day, as a ring with an identity code was applied to the left leg for easy identification. The geese were fed with a drug-free pelleted diet (Purina Animal Nutrition, Gray Summit, MO, USA) twice a day and water was supplied *ad libitum*. Geese were monitored daily through observation of behaviour and appetite.

Treatment and sampling

A two-phase study design with a washout period of 3 months was used for this study. In the first phase, the 10 geese were orally administered a single dose of 0.2 mg/kg ivermectin (Vetamectin 10 mg/mL; Vet-Agro Sp. z.o.o., Lublin, Poland) via crop gavage by a rounded-tip metal catheter. In the first phase the geese had a mean body weight of 5.0 (min 4.35, max 5.7) kg. After a washout period of 3 months the animals were treated I/V (Vetamectin 10 mg/mL) at the same single dosage using a sterile 20-gauge 3.75 cm needle in the left-wing vein. By the end of the study each goose had received both the oral and I/V dose. In the second phase, the mean body weight of the animals was 4.8 (min 3.1, max 6.1) kg. Blood (approximately 3 mL per time point) was collected from the right ulnar vein by direct venipuncture at 1, 3, 6, 12, 24, 48, 96, 120, 144, 192, 240, 360 and 480 hours after both treatments. Blood was collected in heparinised tubes and centrifuged at 1500*g*. The harvested plasma was stored at −20°C and analysed within 30 days of collection.

Analytical method

HPLC instrumentation and analytical conditions

An HPLC system from Jasco (Como, Italy) was used, consisting of a ternary gradient system (PU 980), in line degasser (DG-2080-53), autosampler (AS-2055) and an ultraviolet, multiple wavelength detector (MD-1510). The chromatographic separation assay was performed with a Gemini C18 analytical column (250 × 4.6 mm inner diameter, 5 µm particle size; Phenomenex, Torrance, CA, USA) maintained at 30°C using a Peltier system (CO-4062; Jasco). The mobile phase consisted of acetonitrile:water (90:10% v:v) at a flow rate of 1 mL/min and the optimal wavelength for the quantification was set at 242 nm.

Sample extraction

Samples were thawed and processed using a modified version of the method described by Elazab and Hsu (2021). Sample purification was performed using protein precipitation. Briefly, 0.5 mL of plasma was spiked with 100 µL of internal standard (10 µg/mL) solution in methanol. After the addition of 1 mL of acetonitrile, each sample was vortexed, shaken and centrifuged at 4000*g* for 10 minutes. The supernatant was transferred into a clean tube and dried at 40°C under a gentle nitrogen stream. The residue was dissolved in 100 µL of mobile phase, vortexed, sonicated and centrifuged at 4000*g* for 10 minutes. An aliquot of 50 µL was injected onto the HPLC system. CromNav 2.0 (Jasco) software was used to extract and analyse chromatograms.

Validation of the analytical method

The quantitative HPLC method was fully validated for goose plasma in terms of linearity, intra-day and inter-day precision, recovery, limit of detection and limit of quantification according to the European Medicines Agency guidelines (Anonymous 2012). Ivermectin (1 mg/mL) and internal standard (1 mg/mL) stock solutions and dilutions were prepared in methanol. Linearity was assessed with a 6-point calibration curve using goose plasma spiked at different concentrations (0.025, 0.05, 0.1, 0.5, 1, 10 µg/mL). Intra- and inter-day precision were calculated after analysis of six plasma samples spiked with ivermectin at three different concentrations (0.05, 1 and 10 µg/mL), and expressed as CV%. Sample recovery was evaluated by comparing the response (in area) of high (10 µg/mL), middle (1 µg/mL) and low (0.05 µg/mL) concentration spiked samples, and the internal standard to the response of equivalent standards. Recovery was expressed as mean and SD. The limit of detection was estimated as the plasma drug concentration that produced a signal-to-noise ratio of 3, and limit of quantification was determined as the lowest plasma concentration that produced a signal-to-noise ratio of 10. The mean concentration was within 20% of the nominal values.

Pharmacokinetic analysis

The data obtained after I/V and oral administration was analysed using a non-compartmental approach (ThothPro software; ThothPro, Gdansk, Poland). The maximum concentration (C_{max}) and time to achieve it (T_{max}) were determined directly from the concentration-time curves. The elimination half-life was calculated using least squares regression analysis of the concentration-time curve, and the area under the concentration-time curve (AUC) was calculated by linear log trapezoidal and the linear-up log-down rule to the final concentration-time point (AUC_{last}) for I/V and oral administration, respectively. From these values, the volume of distribution (dose x AUMC/AUC^2) and systemic clearance (dose/AUC) were calculated, where AUMC is the area under the first moment curve of time *vs.* the product of time and concentration.

Statistical analysis

The normality of the data was assessed using a Shapiro–Wilk normality test. The pharmacokinetic parameters are reported as mean and SD, except T_{max}, which is expressed as median and range (Julious and Debarnot 2000). The paired Student t-test was used for the statistical comparison of pharmacokinetic data between the two routes of administration (Powers 1990). Data were analysed with GraphPad Prism v 5.0 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Analytical method validation

The analytical method showed an optimal linearity ($R^2 = 1.000$; $y = 0.372x-0.0064$) in the range of 0.025–10 µg/mL. The recovery was found to be 94 (SD 3.2)%. The inter- and intra-day precision were (CV%) <4.02, while the limit of detection and limit of quantification were 0.01 and 0.025 µg/mL, respectively.

Pharmacokinetic analysis

The animals did not show any adverse effects during or after treatment. After I/V administration, ivermectin was above the limit of quantification for 240 hours in all 10 geese and remained above the limit of quantification for 144 hours in 8/10 geese after oral administration (Figure 1). The plasma concentrations were characterised by a low inter-subject variability (oral SD 0.012; I/V 0.02).

The elimination half-life value of ivermectin was found to be approximately 3.8 (95% CI = 22.05–284.5; $p = 0.027$) times higher after I/V than oral administration (Table 1). Moreover, the AUC_{last} of ivermectin was 6.4 (95% CI = 3.82–17.17; $p < 0.001$) hours higher after I/V than oral administration (Table 1). This difference led to a bioavailability after oral treatment of 20.38 (SD 5.92)%. After oral treatment the C_{max} was found to be 0.09 (SD 0.02) µg/mL and was achieved 3 hours after administration (Table 1).

Discussion

This is the first study describing the pharmacokinetics of ivermectin in Biłgorajska geese. Ivermectin was characterised by a long persistence in this species;

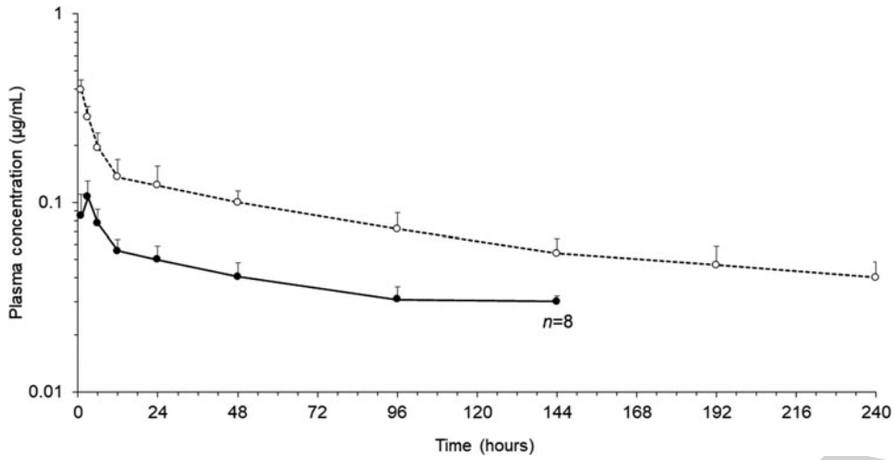

Figure 1. Semi-logarithmic curve of the mean concentrations in plasma of ivermectin (±SD) *vs.* time after a single I/V (—○—) or oral (—●—) dose of 0.2 mg/kg in geese (*Anser anser domesticus)* (n = 10, except where otherwise indicated).

the drug was quantified in goose plasma up to 240 hours (10 days, n = 10/10) and 144 hours (6 days, n = 8/10) after I/V and oral administration, respectively.

A significant difference between the AUC_{last} following oral and I/V administration was found in geese; a similar ratio between these two parameters has been reported in laying hens (Cirak *et al*. 2018) (geese, 0.16; hens, 0.12). Consequently, in both studies low bioavailability after oral treatment was found (20.38% in geese; 11.9% in laying hens). It should be noted that the geese used in the present study and the hens in the study by Cirak *et al.* (2018) were both fed before the treatment. The presence of food in the gastrointestinal tract may have caused a decrease in the absorption rate of orally administered drugs. Moreover, it is well known that the gastrointestinal tract of birds is not only a site for drug absorption but can act also as a metabolic and immunological organ (Adedokun and Olojede 2019). Thus, it can be speculated that metabolic interactions in the gastrointestinal tract may occur in poultry, compromising the drug absorption process. In addition, the retention time in the digestive tract of poultry is remarkably short (~5 hours; Svihus and Itani 2019) compared to other mammals or ruminants, and this is likely a contributor to the low oral bioavailability of ivermectin in poultry. A further explanation may be absorption or binding to the particulate phase of the digesta which has been shown to influence the pharmacokinetics of some endectocides (McKellar and Gokbulut 2012).

Table 1. Mean and SD of the pharmacokinetic parameters of ivermectin in plasma after I/V or oral administration (0.2 mg/kg) to geese (*Anser anser domesticus*; n = 10) at a dose of 0.2 mg/kg bodyweight.

	I/V		Oral	
Parameter	Mean	SD	Mean	SD
AUC_{last} (µg/mL.hours)	18.35[x]	2.44	2.86[y]	0.96
Kel ($hours^{-1}$)	0.005[x]	0.003	0.014[y]	0.004
Elimination half-life (hours)	208.37[x]	181.65	55.12[y]	16.64
Clearance (mL/g.hours)	0.011	0.002	N/A	N/A
Volume of distribution (mL/g)	0.98	0.15	N/A	N/A
C_{max} (µg/mL)	N/A	N/A	0.09	0.02
T_{max}[a] (hours)	N/A	N/A	3.00	3.00–3.00
Bioavailability (%)	N/A	N/A	20.38	5.92

[a]Median and range.
[x,y]Significant difference within rows evaluated using paired Student t-test ($p < 0.05$).
AUC_{last} = area under the curve from zero to the last detectable timepoint; C_{max} = maximum concentration; k_{el} = elimination rate constant; N/A = not applicable; T_{max} = time at maximum plasma concentration.

Although geese and laying hens had a similar ratio between AUC_{last} for I/V and oral administration, the individual AUC values in geese (I/V, 18.35 µg/mL.hours; oral, 2.86 µg/mL.hours) were approximately 20-fold higher compared to those found by Cirak *et al.* (2018) (I/V, 0.9 µg/mL.hours; oral, 0.1 µg/mL.hours). The large variation between the AUC (and C_{max}, geese 0.09 µg/mL; hens 0.01 µg/mL) values found in geese and laying hens might be explained by the different pharmaceutical formulations used. Indeed, the presence of specific excipients may have altered the drug absorption (Panakanti and Narang 2012). In the present study, the formulation Vetamectin 10 mg/mL was used for both routes of administration, while in Cirak's (2018) study of laying hens, the drug was diluted in propylene glycol for I/V administration, and an oral pharmaceutical formulation from a different manufacturer was used for the oral treatment. Regardless, physiological and anatomic species-specific differences between laying hens and geese at the gastrointestinal level are likely to be relevant. In addition, waterfowl have been shown to have physiological differences in renal morphology compared to galliform birds, which may result in species differences in renal elimination and/or reabsorption of drugs (Warui 1989).

We observed faster elimination after oral treatment: the elimination half-life after oral treatment was significantly lower compared to I/V administration (I/V, 208.37 hours; oral, 55.12 hours, p = 0.0268), and a

similar trend can be observed in laying hens (I/V, 8.88 hours; oral, 5.52 hours, $p < 0.01$) (Cirak *et al*. 2018). As elimination half-life is a hybrid parameter between the clearance and volume of distribution, the difference between the two treatments may relate to a change in these parameters during the two phases of the study. A possible explanation is that during the washout period of 3 months, the muscle–fat body composition of the geese may have changed without any variation in body weight (Poźniak *et al*. 2020). Moreover, as mentioned above, the presence of food in the gastrointestinal tract as well as tissue properties, may have bound the drug, affecting the volume of distribution (Di 2021).

The elimination half-life value was lower in laying hens (5.52 hours) compared to that found in geese (55.12 hours). This may reflect the differences in clearance. Clearance was slower in chickens (0.27 mL/g.hours, Cirak *et al*. 2018) than in geese (0.011 mL/g.hours). This may be due to the different size of the animals (in Cirak *et al,* (2018), the body weight of chickens was 1.7–2.2 kg; body weight of geese in this study, 4.35–5.7 kg), and consequently in the cardiac output (higher in laying hens compared to geese).

There may be some limitations to this study. The plasma concentrations found after oral administration remain under the limit of quantification for the last two time points (up to 144 hours), while the elimination slope after the I/V dose was based on more time points (up to 240 hours). A more sensitive analytical method may be able to quantify for a longer period the concentration of ivermectin after oral administration. Another limitation may relate to the study design, as a cross-over study would be more appropriate for this research. However, this was not performed due to practical issues during study development.

In conclusion, the present findings show that after oral administration, the bioavailability of ivermectin in Biłgorajska geese is low. Further research on ivermectin action in the gastrointestinal tract should be performed, as well as assessment of tissue residues to evaluate the withdrawal time to ensure consumer safety.

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Disclosure statement

No potential conflict of interest was reported by the author (s).

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