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Doctoral thesis

Pharmacokinetic profile and residue depletion of selected antibacterial drugs in domestic geese.

Goose meat production is an important component of the poultry sector in Poland, which is among the largest producers and exporters of goose meat in Europe. However, the intensification of poultry production increases the risk of bacterial diseases, which may lead to significant economic losses. Antibiotics are commonly used in the treatment of bacterial infections in poultry, yet the number of medicinal products specifically registered for geese is limited. Consequently, veterinary practice often relies on drugs authorized for other poultry species in accordance with the cascade principle. Such an approach requires a thorough understanding of the pharmacokinetics and pharmacodynamics of the active substances used, as interspecies physiological differences may affect drug absorption, distribution, metabolism, and elimination.

Understanding the pharmacokinetics of antibiotics is essential for developing effective dosing regimens that ensure adequate therapeutic concentrations at the site of infection while minimizing the risk of adverse effects and antimicrobial resistance. Additionally, in food-producing animals, the evaluation of drug residues in edible tissues is of particular importance, as their presence may pose a risk to consumer health.

The aim of this study was a comprehensive analysis of the pharmacokinetics of selected antibiotics (tilmicosin, colistin, and lincomycin) in domestic geese. The study enabled the determination of key pharmacokinetic parameters, evaluation of bioavailability, distribution, and elimination, as well as analysis of residue depletion in the context of establishing withdrawal periods.

The study was conducted on healthy adult Biłgoraj geese divided into three experimental groups (tilmicosin, n = 15; colistin, n = 16; lincomycin, n = 16). In the tilmicosin group, a three-stage design was applied: a single intravenous administration (5 mg/kg b.w.), followed by subcutaneous administration at a dose of 10 mg/kg b.w., and in the final stage, multiple oral (25 mg/kg b.w.) administration for 5 days, after which, in addition to blood, tissue samples (muscle, kidney, liver, and fat with skin) were collected between 24 and 120 hours. In the colistin group, a similar three-stage design was used: a single intravenous administration (1 mg/kg b.w.), followed by oral administration (30 mg/kg b.w.), and finally repeated oral dosing for 5 days (2.5 mg/kg b.w.). After the last stage, in addition to blood samples, tissues were also analyzed at time

intervals of 6–36 hours. In the lincomycin group, four stages were implemented, including a single intravenous administration (15 mg/kg b.w.), intramuscular administration at the same dose, oral administration (50 mg/kg b.w.), and subsequent repeated oral dosing for 7 days (5 mg/kg b.w.). After completion of the final stage, both blood and tissue samples were collected (10–72 hours). A one-month washout period was applied between successive stages.

Validated chromatographic methods, including HPLC and UHPLC-MS/MS, were used for analysis, enabling quantitative determination of the investigated antibiotics in plasma and tissues. Method validation included the assessment of linearity, precision, accuracy, recovery, and limits of quantification. All developed methods complied with current EMA analytical standards.

Based on the obtained data, key pharmacokinetic parameters were determined, including maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration–time curve (AUC), elimination half-life ($t_{1/2}$), volume of distribution (V_d), and clearance (Cl). Pharmacokinetic analyses were performed using non-compartmental methods.

In the case of tilmicosin, relatively rapid absorption after oral administration and pronounced distribution into tissues, including the respiratory system, were observed, which may explain its effectiveness in treating respiratory infections in poultry. However, oral bioavailability was low (4%) compared to subcutaneous administration (nearly 90%). The highest concentrations were observed in highly perfused organs such as the liver, kidneys, and lungs. The elimination half-life suggested relatively prolonged persistence of the drug in the body, which may be relevant for therapeutic efficacy, dosing intervals, and the application of relatively long withdrawal periods (6–8 days). However, precise optimization of dosing regimens is necessary to maintain therapeutic concentrations for an adequate duration.

In the case of colistin, following oral administration, its absorption from the gastrointestinal tract was very limited, resulting in low plasma concentrations and minimal distribution into tissues. This confirms that the therapeutic effect of colistin in poultry is primarily local and associated with its presence in the intestinal lumen. Pharmacokinetic parameters also indicated a small volume of distribution and no tendency for accumulation, suggesting a low likelihood of consumer exposure.

Lincomycin, in contrast, was characterized by very high bioavailability following both oral and intramuscular administration (approximately 100%). The obtained C_{max} and AUC values indicated substantial systemic exposure. The calculated volume of distribution suggested extensive tissue penetration, which may enhance efficacy in the treatment of systemic infections. However, PK/PD analysis suggests that the applied lincomycin doses may not

always ensure adequate exposure above the minimum inhibitory concentration (MIC) for certain clinically relevant pathogens, indicating the need for dose optimization, while maintaining a low risk of residue accumulation in tissues and a relatively short withdrawal period (1–4 days).

The results indicate that the pharmacokinetics of antibiotics in geese may differ significantly from those observed in other poultry species, such as chickens or turkeys. These differences may arise from distinct physiological characteristics, including metabolic rate, gastrointestinal structure, and differences in fat distribution and organ blood flow. The findings also highlight the importance of PK/PD analysis in designing therapeutic regimens. Appropriate adjustment of dosing to the pharmacokinetic properties of the drug and the susceptibility of microorganisms can improve treatment efficacy and reduce the risk of antimicrobial resistance, in line with the One Health approach.

Keywords: tilmicosin, colistin, lincomycin, geese, pharmacokinetics, tissue residues.