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REVIEW SCIENTIFIC ARTICLE

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ANTIMICROBIAL AGENTS IN LAYING HENS

ABSTRACT: The European Union permitted 6 antimicrobial agents that can be used in laying hens. These are colistin, tyrosine, neomycin, oxytetracycline, chlortetracycline, and erythromycin. Antimicrobial drugs are used today primarily for the prevention and treatment of diseases in poultry and often (not in the EU) to stimulate growth. Because these drugs are often used irrationally, there are good chances that their residues will be found not only in poultry meat but also in the eggs within a certain period after the termination of treatment. In addition to the administration of authorised VMPs, the residues in eggs can be the result of erroneously applied medicated food, the contamination of the food with some antimicrobial drug in the mixing unit, as well as "extra-label" use of drugs in poultry. The antimicrobial agents are distributed in the body and deposited in the eggs, mainly in the yolk where they persist longer than in the albumen. Drugs that are poorly absorbed from the gastrointestinal tract (aminoglycosides, aminocyclitols, polymyxins) cannot be detected in the eggs, while the residues of some antimicrobial drugs can be detected for up to two months (chloramphenicol) after the last treatment. The rational use of drugs in veterinary medicine has manifold significance. When using drugs only when they are really necessary (indicated), in the right dose and route of administration, the potential damage can be reduced and efficiency increased, while the risk of microorganism resistance development would be significantly decreased. All of this becomes more important when these drugs are used in food animals.

KEYWORDS: antimicrobials, eggs, laying hens, residues, yolk, albumen

INTRODUCTION

In the clinical practice of human and veterinary medicine throughout the world, a large number of antimicrobial drugs are used. Likewise, many scientists

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intensively work on the discovery and synthesis of new drugs with a broader antimicrobial spectrum, stronger action, and a more satisfactory safety profile. Unfortunately, these drugs are often not rationally used. Despite permanent indications for all failures and harmful consequences of such use, it is present in everyday clinical practice (Ćupić and Dobrić, 2003).

Non-rational use of these drugs in veterinary medicine, as well as the need for control of their use, become greater problems regarding their use in food-producing animals. In that case, there is a possibility that minimal quantities of the drugs and their metabolites (residues), which remain in the edible tissues and animal products (meat, milk, eggs, honey) can induce some harmful effects in people as potential consumers of that food (Adams, 2001; Giguere et al., 2013; Ćupić and Živanov, 1990; Ćupić, 1997, Ćupić and Teodorović, 1997).

Because of their toxicity, both for animals (to whom are applied) and people as potential consumers of the products derived from these animals, the Food and Drug Administration (FDA) has banned the use of some antimicrobials, as well as some other drugs in food for animals. These are chloramphenicol, nitroimidazoles, nitrofurans, quinoxalines, fluoroquinolones, sulfonamides, glycopeptides, ionophores, cephalosporins, diethylstilbestrol, dipyrone, phenylbutazone, clenbuterol, and some antiviral drugs in poultry (Payne et al., 1999; Davis et al., 2009).

The use of antibiotics in laying hens has always been the subject of discussion because there are people who support their use and those who do not support it. In the Republic of Serbia and some neighboring countries, no antimicrobial drugs are used for the treatment of diseases in laying hens. However, antimicrobials are used in some countries. This relates mainly to those antibiotics that absorb from the digestive tract little or not at all (Goetting et al., 2011).

The European Union has approved 6 antimicrobial agents that can be used in laying hens. These are colistin, tylosin, neomycin, oxytetracycline, chlortetracycline, and erythromycin. In some countries of the European Union, USA, Australia, and Canada, the following antimicrobial drugs are approved: bacitracin, chlortetracycline, lincomycin and spectinomycin, neomycin, and tylosin (Australia); chlortetracycline, neomycin, oxytetracycline, and penicillin G (Canada); chlortetracycline, colistin, erythromycin, phenoxymethylpenicillin, tiamulin, and tylosin (Ireland); colistin, erythromycin, phenoxymethylpenicillin, tiamulin, and tylosin (England) and bacitracin, erythromycin, hygromycin B, nystatin, and tylosin (USA) (Goetting et al., 2011).

Although laying hens lay eggs every day (every 24 h), each egg takes several days to develop *in vivo* (and some egg components several months). It is considered that the period from the 10th to 14th day before the egg is laid (this is the period of intensive development of the yolk) is the most suitable for the deposit of residues of drugs in eggs. Just during this period the largest amount of lipoproteins arrives from the liver with circulation and takes part

in the final stage of the formation of the yolk. If individuals are treated in this period, then the greatest chances are that lipoproteins are contaminated with drug residues (Goetting et al., 2011).

Depending on the physicochemical properties, the drugs are distributed in different concentrations in the body and deposited in the yolk and albumen. The largest number of drugs (probably because of the longer development of the yolk) achieve higher concentrations in the yolk than in the albumen. The retention length of certain antimicrobial drug residues in the eggs after the treatment is different (Goetting et al., 2011).

Drugs that are poorly absorbed from the gastrointestinal tract (aminoglycosides, aminocyclitols, polymyxins) cannot be determined in the eggs, while the residues of some antimicrobial drugs that are absorbed can be detected for up to two months (chloramphenicol) after the last treatment (Goetting et al., 2011).

This paper gives an overview of the pharmacokinetics of some groups of antimicrobial drugs: *aminoglycosides, amphenicols, tetracyclines, and macrolides*, with special emphasis on the possibility of depositing these drugs in eggs.

ANTIMICROBIAL DRUGS

Aminoglycosides

Aminoglycosides (like aminocyclitols) act on gram-negative and some gram-positive but not anaerobic bacteria. They are very poorly absorbed from the digestive tract. After oral administration, these drugs are mostly excreted in mammals by feces. In birds, aminoglycosides after oral administration, are eliminated by feces also (Botsoglou and Fletouris, 2001; Adams, 2001; Brown and Riviere, 1991).

Because of the poor absorption from the digestive tract, it is rare to find a residue of these drugs in the eggs after oral administration. When aminoglycosides are given parenterally for the treatment of systemic infections, the main route of elimination of these drugs in mammals is the kidney.

However, in mammals and birds, the systemic application is limited due to the toxic effects (nephrotoxicity, ototoxicity) of these drugs. Although in birds there are no data on the pharmacokinetics of systemically administered aminoglycosides, a nephrotoxic effect is also expected and it is believed that the main pathway of elimination is the kidney (Bennett et al., 2001).

When aminoglycosides are applied to laying hens intramuscular or subcutaneous, gentamicin and dihydrostreptomycin are deposited in yolks and albumen and the residues persist for a long time in the yolk (Roudaut, 1989b; Filazi et al., 2005) (Table 1).

The retention length of these drug residues in eggs is shown in Table 1.

Table 1. Residues of aminoglycosides in chicken eggs after parenteral and oral administration to laying hens (Goetting et al., 2011)

Drug	Status	Maximum residue limit	Dose and mode of application	Hen age (months)	Treatment duration (days)	The time from last treatment until the residue no longer detected (days)
Gentamicin	EU: Not approved	None	25 mg/kg b.w. (s.c.)	7,5	1	Y: 10 A: 4 WE: 10
			50 mg/kg b.w. (s.c.)	7,5	1	Y:12 A: 5 WE: 12
			10 mg/kg b.w. (i.m.)	7,5	1	Y: 7 A: 3 WE: 7
Neomycin	EU: approved USA: Not approved	500 µg/kg	0.25 g/l p.o. (in drinking water)	13-18	5	WE: 0
			25 mg/kg b.w. p.o. (in drinking water)	13-18	5	WE: 0
Kanamycin	EU: Not approved	None	20 mg/kg b.w., p.o. (in food)	10	7	Y: 0 A: 0 WE: 7
			1,000 mg/kg food, p.o. (in food)	10	7	Y: 0 A: 0
			4,000 mg/kg food, p.o. (in food)	10	7	Y: 0 A: 0
			8,000 mg/kg food, p.o. (in food)	10	7	Y: 0 A: 0

WE – whole egg; Y – yolk; A – albumen

This table shows that gentamicin persists longer in egg yolk than in albumen and the retention length is dependent on the dose.

As already said, neomycin belongs to a group of antimicrobials that are approved in the EU. Because of that, a maximum residue limit is determined. However, this drug is poorly or not absorbed and consequently, it cannot be determined in eggs.

This table shows that kanamycin persists longer in egg yolk than in albumen regardless of the dose and retention length is dependent on the dose.

Amphenicols

Amphenicols effectively act against rickettsia, chlamydia, anaerobic and gram-positive aerobic bacteria, as well as intestinal bacteria. Since it can cause irreversible bone marrow suppression in humans, the use of chloramphenicol

is banned or restricted in animals which are used for human consumption in many countries (Ćupić et al., 2003, 2019). Amphenicols are given orally in food or drinking water to poultry (Bishop, 2001; Papich and Riviere, 2001; Botsoglou and Fletouris, 2001; Dorrestein et al., 1984).

After oral administration to chickens, absorption is rapid but incomplete. They are rapidly distributed throughout the body, and the pathways of excretion vary depending on the drug. Studies performed in most mammalian species have shown that chloramphenicol is metabolized in the liver and excreted via the urine and the bile. The pathways of chloramphenicol excretion in birds are not described. In chickens, thiamphenicol is eliminated through both systems (bile and kidney). Florfenicol and its metabolite florfenicol amine are deposited in significant amounts in the liver and kidneys (Anadon et al., 1994a; Bennett et al., 2001).

A small number of studies carried out in laying hens, examining the elimination of amphenicol residues, showed that the residue can be found in the yolk and the albumen a few days (and more) after oral administration.

The persistence of residues of these drugs in eggs is shown in Table 2.

Table 2. Residues of amphenicols in chicken eggs after oral administration to laying hens (Goetting et al., 2011)

Drug	Status	Maximum residue limit	Dose and mode of application	Hen age (months)	Treatment duration (days)	The time from last treatment until the residue no longer detected (days)
Chloramphenicol	Not approved	None	40 mg/l p.o. (in drinking water)	Not specified	5	Y: > 5 A: 4
			500 mg/l p.o. (in drinking water)	3	8	WE: > 17
			1,000 mg/l p.o., (in drinking water)	3	6	WE: > 19
			60 mg/kg b.w., p.o., (in drinking water)	10	10	WE: > 72
Thiamphenicol	Not approved	None	40 mg/kg t.m., p.o. (in capsules)	6	1	Y: 10 A: 2
			40 mg/kg t.m., p.o. (in capsules)	6	5	Y: 8 A: 1

WE – whole egg; Y – yolk; A – albumen

Table 2 shows that chloramphenicol persists in eggs for a very long time, even more than 72 days.

Unlike chloramphenicol, the residues of thiamphenicol remain much shorter in eggs.

Tetracyclines

Tetracyclines are a typical example of antimicrobials with a broad spectrum of action. They are used to prevent and treat diseases, as well as to improve growth in animals whose products are used to feed people in countries where such use is legal (Giguere et al., 2013). They are effective against a large number of gram-positive and gram-negative bacteria, mycoplasmas, chlamydia, and rickettsia. The most common mode of using tetracycline in poultry is oral (in food or drinking water) (Botsoglou and Fletouris, 2001; Chopra and Roberts, 2001).

Generally, tetracyclines are moderately absorbed from the digestive tract in mammals, but absorption is incomplete in birds. Tetracyclines have a high affinity for ionic metals, such as calcium, iron, magnesium, and zinc, which hinder absorption if present in the food or digestive system (Anadon et al., 1994b; Botsoglou and Fletouris, 2001).

When tetracyclines are absorbed, they are distributed throughout the body and concentrated in the liver and kidneys. Tetracyclines are also deposited in egg-laying hens. After administration, the residues of these drugs appear more rapidly in the albumen than in the yolk but the concentrations in the yolk are higher and persist longer. The achieved levels of residues and the degree of their decrease in eggs depend on the mode of administration, the dose, and the drug that is applied (Frazier et al., 1995; Yoshida et al., 1973c).

When administered in the same dose and in the same way, doxycycline is deposited in eggs at higher concentrations than tetracycline, and tetracycline achieves higher concentrations than oxytetracycline. Variations in the persistence of residues in eggs are a direct consequence of the difference in drug absorption. Doxycycline can be detected in eggs for almost a month after discontinuation of the drug, while after a similar dosage regimen, oxytetracycline residues can be detected within 4–10 days after administration (Nogawa et al., 1981; Roudaut et al., 1989).

The persistence of residues of these drugs in eggs is shown in Table 3.

Table 3. Residues of tetracyclines in chicken eggs after oral and parenteral administration to laying hens (Goetting et al., 2011)

Drug	Status	Maximum residue limit	Dose and mode of application	Hen age (months)	Treatment duration (days)	The time from last treatment until the residue no longer detected (days)
Oxy-tetracy-cline	EU: Approved USA: Not approved	200 µg/kg	0.1 g/l (10 mg/kg b.w.) p.o. (in drinking water)	Not specified	5	Y: 0 A: 0
			0.25 g/l (25 mg/kg b.w.) p.o. (in drinking water)	–	5	Y: 4 A: 3
			0.4 g/l p.o. (in drinking water)	12	7	Y: 3 A: 0
			30 mg/kg b.w., i.m.	Not specified	3	Y: 11 A: 9
			200 mg/kg b.w., i.m.	Not specified	5	Y: 12 A: 5
Chlor-tetracy-cline	Approved in EU and USA	200 µg/kg (EU) 0.4 mg/kg (USA)	0.5 g/l p.o. (in drinking water)	Not specified	7	WE: 6
Doxycy-cline	EU: Not Approved USA: Not Approved	None	0.5 g/l p.o. (in drinking water)	Not specified	7	Y: 27 A: 25

WE – whole egg; Y – yolk; A – albumen

Table 3 shows that the residues of doxycycline (when compared to chlortetracycline and oxytetracycline) remain the longest in eggs.

Macrolides

These antibiotics are effective against mycoplasmas and gram-positive microorganisms (streptococci and staphylococci), while they are less active against gram-negative bacteria. The oral route is the most common route of administration of these drugs to chickens. After the absorption, in birds and mammals macrolides are widely distributed in the body and penetrate everywhere into the tissues and cells, deposited mostly in the yolk (Adams, 2001; Papich and Riviere, 2001; Anadon and Reeve-Johnson, 1999; Botsoglou and Fletouris, 2001; Ćupić et al., 2019).

The persistence of residues of these drugs in eggs is shown in Table 4.

Table 4. Residues of macrolides in chicken eggs after oral administration to laying hens (Goetting et al., 2011)

Drug	Status	Maximum residue limit	Dose and mode of application	Hen age (months)	Treatment duration (days)	The time from last treatment until the residue no longer detected (days)
Tylosin	Approved in EU and USA	200 µg/kg (EU and USA)	0.5 g/l p.o. (in drinking water)	5	5	WE: 8
			0.5 g/l p.o. (in drinking water)	7–16	5	Y: 0 A: 0
			0.5 g/l p.o. (in drinking water)	Not specified	7	Y: 6 A: 3
			0.529 g/l p.o. (in drinking water)	Not specified	3	WE: 6
Spira-micin	EU: Not Approved	None	100 mg/kg b.w., p.o. (in food)	10	7	WE: 2
			200 mg/kg food, p.o. (in food)	10	7	WE: 1
			400 mg/kg food, p.o. (in food)	7–16	7	Y: 7 A: 15

WE – whole egg; Y – yolk; A – albumen

Table 4 shows that the length of retention of residues of the tylosin and spiramycin in chicken eggs depends on the length of treatment and the age of the animals being treated with the drug.

CONCLUSIONS

The wide and irrational use of drugs in animals whose products are used for human consumption (in addition to all other adverse effects) inevitably leads to an increased risk that a certain amount of these drugs remains in foods of animal origin.

Since residues of antimicrobial drugs can also be deposited in eggs, special attention should be devoted to the use of these drugs in poultry, especially laying hens.

In the European Union, 6 antimicrobial drugs were approved for laying hens. These are neomycin, erythromycin, tylosin, oxytetracycline, chlortetracycline, and colistin.

In the Republic of Serbia and some neighboring countries, no antimicrobial drugs are used for the treatment of diseases in laying hens. However, there are cases when antimicrobials are used. This relates mainly to the antibiotics that are very poorly absorbed from the digestive tract.

The question arises whether we are fully aware of the real situation in the field and whether the prohibition on the use of antimicrobial drugs is being respected.

We suppose it is not being fully respected. That was the reason for the presentation of this paper.

Therefore, we think that this issue should be dealt with properly and that some of the drugs approved in the EU should be also approved in Serbia, in the first place those that are not absorbed from the digestive tract.

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REFERENCES

Adams HR (2001): *Veterinary Pharmacology and Therapeutics*. Iowa State University Press/ Ames. 8th Edition.

Anadon A, Bringas P, Martınez-Larranaga MR, Diaz MJ (1994a): Bioavailability, pharmacokinetics and residues of chloramphenicol in the chicken. *J. Vet. Pharmacol. Ther.* 17: 52–58.

Anadon A, Martınez-Larranaga MR, Diaz MJ, Bringas P, Fernandez MC, Fernandez-Cruz, ML, Iturbe J, Martinez MA (1994b): Pharmacokinetics of doxycyline in broiler chickens. *Avian Pathol.* 23: 79–90.

Anadon A, Reeve-Johnson L (1999): Macrolide antibiotics, drug interactions and micro somal enzymes: implications for veterinary medicine. *Res. Vet. Sci.* 66: 197–203.

Bennett M, Elliott J, Sommerville LM, Taylor MA (2001): Drugs used in the treatment of bacterial, fungal, viral, and protozoal infections. In: *The Veterinary Formulary*, 5th edn. Ed. Bishop, Y., Cambridge: Pharmaceutical Press, 135–218.

Bishop Y (2001): *The Veterinary Formulary*, 5th edn., London: Pharmaceutical Press, 692 p.

Botsoglou NA, Fletouris DJ (2001): *Drug Residues in Food*. New York: Marcel Dekker, Inc.

Brown SA, Riviere JE (1991): Comparative pharmacokinetics of aminoglycoside anti biotics. *J. Vet. Pharmacol. Ther.* 14: 1–35.

Chopra I, Roberts M (2001): Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol. Mol. Biol. Rev.* 65: 232–260.

Ćupić V (1997): *Zaostaci lekova u jestivim tkivima životinja*. Subotica: Sitoprint.

Ćupić V, Teodorović V, Simić I (1997): Ostaci lekova u namirnicama animalnog porekla. Šabac: Veterinarski fakultet u Beogradu i Društveno preduzeće „Unifarm".

Ćupić V, Dobrić S (2003): Sadašnje stanje i perspektive u razvoju antimikrobnih lekova. *Vet. ž. Repub. Srp.* 2: 36–42.

Ćupić V, Živanov D (1990): Sporedna i neželjena dejstva lekova. *Vet. Glas.* 46: 513–517.

Ćupić V, Muminović M, Kobal S, Velev R (2019): *Pharmacology for Students of Veterinary Medicine*. Belgrade–Sarajevo–Ljubljana–Skoplje: Naučna KMD.

Davis J, Smith GW, Baynes RE, Tell LA, Webb AI, Riviere JE (2009): Update on drugs prohibited from extralabel use in food animals. *J. Am. Vet. Med. Assoc.* 235: 528–534.
Dorrestein GM, Vangogh H, Rinzema JD (1984): Pharmacokinetic aspects of penicillins, aminoglycosides and chloramphenicol in birds compared to mammals – a review. *Vet. Quart.* 6: 216–224.
Filazi A, Sireli UT, Cadirci O (2005): Residues of gentamicin in eggs following medication of laying hens. *British Poultry Science*. 46: 580–583.
Frazier DL, Jones MP, Orosz SE (1995): Pharmacokinetic considerations of the renal system in birds: part II. Review of drugs excreted by renal pathways. *J. Avian Med. Surg.* 9: 104–121.
Giguere S, Prescott JF, Dowling MP (2013): *Antimicrobial Therapy in Veterinary Medicine*. Fifth Edition. Iowa State University Press/Ames.
Goetting VK, Lee KA, Tell LA (2011): Pharmacokinetics of veterinary drugs in laying hens and residues in eggs: a review of the literature. *J. Vet. Pharmacol. Therap.* 34: 521–556.
Nogawa H, Nagura S, Tsuchiya M, Yonezawa S (1981): Residues of tetracycline antibiotics in eggs laid by hens given drinking water medicated. *Ann. Rep. Nat. Vet. Assay Lab.* 18: 25–30.
Papich MG, Riviere JE (2001): Chloramphenicols and derivatives, macrolides, lincosami des, and miscellaneous antimicrobials. In: *Veterinary Phamacology and Therapeutics*, 8th ed., Ed. Adams HR, Iowa State University Press, Ames, IA, 868–917.
Payne MA, Baynes RE, Sundlof SE, Craigmill A, Webb AI, Riviere JE (1999): Drugs prohibited from extralabel use in food animals, *J. Am. Vet. Med. Assoc.* 1: 28–32.
Roudaut B (1989b): Residues of aminoglycosides antibiotics in eggs after medication of laying hens. *British Poultry Sci.* 30: 265–271.
Roudaut B, Moretain JP, Boisseau J (1989): Excretion of tetracycline and chlortetracycline in eggs after oral medication of laying hens. *Food Addit. Contam.* 6: 71–78.
Yoshida M, Kubota D, Yonezawa S, Nakamura H, Yamaoka R, Yoshimura H (1973c): Transfer of dietary chlortetracycline into eggs and its disappearance from eggs and from the liver. *Japan. Poultry Science* 10: 261–268.

ПРЕГЛЕДНИ НАУЧНИ РАД

АНТИМИКРОБНИ ЛЕКОВИ КОД КОКА НОСИЉА

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РЕЗИМЕ: Европска унија је одобрила шест антимикробних лекова који се могу користити код кока носиља конзумних јаја. То су: колистин, тилозин, неомицин, окситетрациклин, хлортетрациклин и еритромицин. Антимикробни лекови се данас користе првенствено за превенцију и лечење болести код живине, а

често (не у ЕУ) за стимулацију раста. Узимајући у обзир чињеницу да се ови лекови често користе нерационално, постоје велике шансе да ће се њихови остаци наћи не само у месу перади већ и у јајима у одређеном периоду након престанка лечења. Поред примене одобрених лекова, остаци у јајима могу бити резултат погрешно примењене лековите хране, контаминације хране неким антимикробним леком у мешаонама хране, као и „ехтра-лабел" коришћења лекова код живине. Антимикробни лекови се дистрибуирају у организму и депонују у јајима, углавном у жуманцету где се задржавају дуже у односу на беланце. Лекови који се слабо апсорбују из гастроинтестиналног тракта (аминогликозиди, аминоциклитоли, полимиксини) не могу се утврдити у јајима, док се остаци неких антимикробних лекова који се апсорбују могу детектовати и до два месеца (нпр. хлорамфеникол) након последњег третмана. Рационална употреба лекова у ветеринарској медицини има вишеструки значај. Употреба сваког лека, само када су заиста неопходни (индиковани) у правој дози и начину примене, потенцијална штета од њихове употребе би се смањила, а ефикасност повећала, те би се ризик од развоја резистенције код микроорганизама значајно смањио. Све ово постаје још важније када се ови лекови користе код животиња чији се производи користе за исхрану људи.

КЉУЧНЕ РЕЧИ: антимикробни лекови, јаја, коке носиље конзумних јаја, резидуе, жуманце, беланце