tehnologija mesa
Osnivač i izdavač: Institut za higijenu i tehnologiju mesa, Beograd
UDK: 64.9:615.3.07
BIBLID: 0494-9846

The significance of rational use of drugs in veterinary medicine for food safety*

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A b s t r a c t: Rational use of drugs in veterinary medicine has manifold significance. By using each drug, only when it is really necessary (indicated), in right dose and route of administration, the potential damage of their use is reduced, efficiency increased, and the risk of microorganisms resistance development (in case of antimicrobials) significantly decreased. All of this becomes more important when these drugs are used in food producing animals.

Simultaneously with the intensifying of cattle breeding and exceptional increase of animal productivity, the number of used drugs is unavoidably increased. There are almost no animals today in intensive as well as in extensive production/rearing system, which haven't received at least one drug during their life.

In poultry, cattle and pig production, which are main sectors for production of food stuffs of animal origin, the use of drugs has increased and reached the limits which are considered alarming for health of people.

On the first place are antibiotics, or antimicrobial drugs, which are used very often in therapy or prevention of bacteria diseases, and also, very often, as growth stimulator. In addition to antibiotics, many other drugs are used, with proven numerous harmful effects, even with carcinogenic and teratogenic features, whose residues in food intended for human consumption can very seriously endanger the health of people, as potential consumers of this kind of food. Therefore, the control of use of antimicrobial, and other drugs in livestock production is exceptionally significant.

***Key words**: non-rational use of drugs, antimicrobials, side effects, food producing animals.*

Introduction

Non-rational use of drugs is a problem, which already existed for a long time in the clinical practice in human and veterinary medicine. Although this issue was on many occasions subject of discussion on numerous Symposiums and Congresses, it is still very current, maybe even more than before. First of all, such use of drugs can easier cause certain harmful effects and damages in treated animals. Bearing this in mind, and also the fact that there aren't any significant improvements in the clinical practice, we must devote much more time and attention to follow and control use of drugs on animals (*Ćupić and Živanov*, 1990).

Non-rational use of drugs in veterinary medicine, as well as the need for control of their use becomes even bigger problem when used on food producing animals. In that case, there is the possibility that minimal quantities of drugs and their metabolites (residues) which remain in edible tissues, i.e. in animal products (meat, milk, eggs, honey) induce certain harmful effects in people as potential consumers of such food (*Ćupić,* 1997).

We are witnesses that productivity in food producing animals has manifold increased during the last 50 years, first of all due to improvement of selection, veterinary-medical care, as well as improvement of diet and good organization of production. With the help of these measures, which are permanently corrected and amended, even in the countries where they were brought to the perfection), animals became "real small factories" for production of food. Simultaneously with attaining of higher productivity of animals, the need for the decrease of their number occurred. Actually, only animals whose keeping is economic profitable in production are retained.

**Plenary paper on International 56th Meat Industry Conference held from June 12-15th 2011. Tara mountain;*
**Plenarno predavanje na Međunarodnom 56. savetovanju industrije mesa, održanom od 12-15. juna 2011. godine na Tari.*

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Evidence of increase of animal productivity over time can be illustrated in the following example: in 1928 year, in poultry rearing (broilers), in order to reach the commercial weight of 1,7 kg per unit, 112 days were necessary and birds needed to consume about 22 kg of food, in average; in 1990, broiler reach the weight of 2 kg in 42 days by consuming only 4 kg of food per one unit/animal. In the 1930-ties, hens laid 93 eggs per year, in the 1950-ties 174, and in 1993 252 eggs yearly.

Similar example exists in production of cow milk. In USA, for example, with the decrease of dairy cows, there was the increase of milk production, due to the increase of milk yield per cow. In comparison to year 1983, when milk yield in USA amounted to 5.598 kg/cow in average, in 1995, milk yield increased to 7.478 kg/cow, etc.

One of measures, which besides others, no doubt, contributed to higher the productivity of animals was veterinary-medical care in animal production. First of all, it is reflected in the efficiency of prevention of different animal diseases, and understanding of the use of different vaccines and others prophylactic remedies. Also, not less significant was the role of antibiotics, i.e. antimicrobial drugs and anti-parasitic drugs, which are used mainly in therapy, but also for prevention of diseases, as well as drugs which are used as growth stimulators, among which the most frequent are hormones and some antimicrobials (*Adams, 2001; Brander et al.,* 1991).

The use of antimicrobial drugs in animals attracts special attention. In therapy of diseases of bacterial etiology they are certainly indicated and in those kinds of cases their use is justified, it is better to say rational, regardless of all hazards due to residues of these drugs in food stuffs consumed by humans (*Giguere et al.,* 2006).

Namely, it is considered that damage in untreated animals could be much higher, than short-term inability to use food stuffs (obtained from such animals) in determined period subsequent to therapy, depending on the withdrawal period. Prophylactic use of antimicrobial drugs or use of these drugs for the purpose of growth stimulation in animals understands giving of smaller doses than therapeutic of antimicrobial drugs. Thereby, with this kind of drug use, the risk from incidence of diseases bacteria etiology is decreased and utilization of food improved and growth stimulated. However, subsequent to such use of antimicrobial drugs simultaneously the risk of incidence of undesirable effects increases considerably. First of all, rate of development of resistance of bacteria to used antimicrobial drugs is increased (*Ašanin et al.,* 2005) and certainly risk from residues in animal food stuffs intended for human consumption is higher than when antimicrobials are used only in therapeutic purposes (*Sanders,* 2007*; Spirić et al.,* 2007). Because of this reason, in our country, maximum care is taken so that antimicrobials are not used in prophylactic purposes, but only in therapeutic, as well as that they are not used for stimulation of growth in animals (*Ćupić et al.,* 1997).

Rational use of antimicrobial drugs

Nowadays, in the clinical practice of human and veterinary medicine throughout the world a large number of antimicrobial drugs are used. Likewise many scientists intensively work on discovery and synthesis of new drugs with broader antimicrobial spectrum, stronger action and more satisfactory safety profile. Unfortunately we are witnesses of rather non-rational use of these drugs. Despite constant indicating of all failures and harmful effects of such use, it is present in every-day clinical practice.

Most mistakes during antimicrobial therapy may occur when pathogenic microorganism is unknown and therapy starts empirically. Most often combinations of two or more antibiotic drugs are used. To avoid these mistakes, clinically confirmed, effective antibiotic combinations should be used. These combinations are useful in treating serious infections, mixed bacterial infections, when resistance occurs enzymatic destruction of a drug, and in order to reduce toxicity (*Giguere et al.,* 2006*)*.

Unwanted effects of antimicrobial drugs

Unwanted effects of antimicrobial drugs can be quite mild and pass in a form of quite slight disturbances, then also unexpected reactions may appear, (such as idiosyncratic or allergic reactions, even anaphylactic shock), as well as different damages to the function of organs. Sometimes, non-rational use of drugs, can provoke the most serious disturbances, as are mutagenesis, carcinogenesis and teratogenesis. Because of all of this, today, in clinical practice we must be very careful and consider frequency of application and dose of these drugs, and also possible side effects, which some of these drugs can provoke, and especially in case of those drugs which are banned (because of proved toxicity), (*Ćupić and Živanov,* 1990*; Giguere et al.,* 2006*; Ćupić and Dobrić,* 2003).

Forbidden antimicrobial and other drugs for use in food producing animals

Because of their toxicity, for animals alone (to whom they are applied), and also for people, potential consumers of products, which derived from

such animals, Food and Drug Administration (FDA) banned the use of some antimicrobials, as well as other drugs in food animals. Those are: *chloramphenicol, nitroimidazoles, nitrofurans*, *quinoxalines, fluoroquinolones, sulfonamides, glycopeptides, ionophors, cephalosporins, diethylstilbestrol, dypirone, phenylbutazone, clenbuterol and some antiviral drugs in poultry* (*Payne et al.,* 1999*; Davis et al.,* 2009).

Some of the mentioned drugs (majority) FDA prohibited completely, and some of them are prohibited as extra label drugs, which means that when a drug is used in a manner that is not in accordance with the FDA approved label, or Instruction. This includes use in a species or for a disease or condition not listed on the label; use at dosages, frequencies or routes of administration that differ from those stated on the label; or deviation from the labeled withdrawal time. According to AMDUCA (Animal Medicinal Drug Clarification Act) from the year 2010, all of the aforementioned drugs now are completely prohibited for use in food animals (*AMDUCA,* 2010).

Chloramphenicol - This drug is forbidden since the year 1984, because it can cause (although rarely) idiosyncratic (non dose dependent, irreversible) aplastic anemia in people. Likewise, the use of all preparations including ophthalmic ointments, or spray for wounds in food producing animals is forbidden. However, the newer members of amphenicols like florfenicol or tiamfenicol are allowed. Florfenicol is available for use in cattle, swine, and some aquatic species (*Davis et al,* 2009; *Payne et al.,* 1999).

Nitroimidazoles - All members of this group (including dimetridazole, metronidazole, ronidazole, tnidazole and ipronidazole) are forbidden because of their *in vitro* and *in vivo* carcinogenic properties. Although they are used in humans and companion animals, the use of any drug from this group in food producing animals is illegal (*Payne et al.,* 1999*)*.

Nitrofurans - These drugs are also forbidden because of carcinogenicity and mutagenicity (*Payne et al.,* 1999; *Batas et al.,* 2007). The use of these drugs for therapy of systemic infections in human medicine was withdrawn in 1974 and for treatment of systemic infection in veterinary medicine was banned in 1991. Later studies have documented that topical application of these drugs for therapy of eye or surface wounds in cattle, sheep and goats, also results in milk and meat residues. Because of that, FDA prohibited the use of topical nitrofurans intended for human and veterinary medicine in food producing animals (*Smith et al.,* 1998). Since year 2002, all systemic and topical use of nitrofuran products has been prohibited (*US FDA Web site,* 2009).

Quinoxalines - It has been known for a long time that quinoxalines (carbadox, olaquindox and cydox) are carcinogenic compounds. Because of that, many countries have forbidden or withdrawn these drugs from use (*Payne et al.,* 1999*)*.

Fluoroquinolones - These drugs became interesting, because it was shown that they stimulate development of bacterial resistance. The best instance are resistant salmonellosis infections in humans. Therefore, the use of fluoroquinolones intended for humans is banned since 1997, as well as their use in food producing animals. So, the use of enrofloxacin is banned in all food producing animals, except in calves and heifers. Precisely this drug may not be used in cows in period of lactation or dry period, heifers, dairy calves, ewes, goats and deer. Also, because of that, enrofloxacin may not be stored in dairy farm drug cabinets (*Payne et al.,* 1999*)*.

Sulfonamides - Sulfonamides have been banned in adult dairy cows. Adult dairy cows are defined as any dairy cow over 20 months of age, regardless of milking status. This ban was instituted because of the concern over carcinogenic effects detected in laboratory animals, which coincided with reports of sulfonamide residues detected in up to 73% of commercial milk samples. Only 1 of the 3 sulfonamides that have label indications for lactating cows, sulfadimethoxine (SDM) is currently being marketed. Currently, use of any sulfonamide other than SDM in dairy cattle older than 20 months is illegal. Additionally, extralabel use of SDM in lactating dairy cattle is prohibited (for example use of a higher dose or slow-release SDM boluses in dairy cattle is not permitted), (*Payne et al.,* 1999*; Davis et al,* 2009*)*.

Glycopeptides - The only glycopeptide antibiotic available in the United States is the human product vancomycin. Vancomycin is often used for the treatment methicillin-resistant *Staphylococcus aureus* infections in humans. Avoparcin, a compound chemically similar to vancomycin, has been used in European animal feeds as a growth promoter since the mid 1970s. FDA in 1977 issued an order prohibiting the extra label use of all glycopeptides in food producing animals. The restriction of fluoroquinolone and glycopeptide use represents a novel exercise of FDA discretionary authority: restriction based not on the drugs direct toxicity, but on its potential for increasing human pathogen resistance (*Jung et al.,* 2007*; Klare et al.,* 2003*; Song et al.,* 2005).

Ionophors- The use of ionophore antibiotics such as monensin and lasalocid is banned in lactating dairy. This is valid also for ewes and goats in period of lactation (*Payne et al.,* 1999).

Cephalosporins - In July 2008, FDA proposed prohibition on extra label use of cephalosporins in food producing animals, because of the increased incidence of cephalosporin-resistant food-borne pathogens, particularly *Salmonella spp*. Monitoring system revealed an increase in resistance of *Salmonella* isolates from both humans and food-producing animals to ceftiofur, a member of third-generation cephalosporin drug marketed for use in cattle, sheep, dairy goats, and swine as multiple injectable formulations as well as intramammary preparations for lactating and non-lactating cows (*US FDA Web site,* 2009).

Diethylstilbestrol - This drug is forbidden in food producing animals since 1979, because of its carcinogenic potential. Namely, it was recorded that in pregnant women it provokes development of reproductive tract abnormalities and tumors in female offspring of diethylstilbestrol treated patients (*Newbold,* 2008).

Dipyrone- It is known that dipyrone is drug which belongs to the large group of Nesteroidal-anti-inflammatory drugs. However, it was recorded that this drug, in addition to the anti-inflammatory, antipyretic and analgesic action, also induces very toxic effects in humans (non-dose dependent teratogenic effects, prolonged bleeding times and agranulocytosis). Because of that FDA abolished its use and withdrew this drug from the market in 1977, while its use in the veterinary medicine was first abolished in small non-food-producing animals in 1995, with suggestion that this must be instituted in all food-producing animals also. Today, use of dypirone in any food producing animal is considered illegal (*Center for food Safety and Applied Nutrition Web Site,* 2009).

Phenylbutazone - Phenylbutazone (as sulfonamides) in dairy cattle over 20 months of age was prohibited in 2003. This was based on detection of phenylbutazone residues in culled dairy cattle and the discovery of phenylbutazone products on dairy farms. It is considered that phenylbutazone in humans can induce blood dyscrasis (such as aplastic anemia, leucopenia, agranulocytosis and thrombocytopenia) and cause death. It is also considered a carcinogen. Because of that, currently phenylbutazone use is strictly prohibited only in dairy cattle over 20 months of age (*New animal drugs*, 2003).

Clenbuterol - This drug is known bronchodilatator which acts on the β-adrenergic receptors in bronchial tree. As that kind of drug, its use is allowed in horses, but in cattle and sheep it can provoke relaxation of uteri miometrium. Also, it has secondary anabolic effects. Because of this anabolic effect it was used illegally for stimulation of growth in food animals intended for humans, and for increase of lean body mass and weight gain in humans. However, in order to attain these effects, high doses of this drug are needed. High doses usually provoke adverse effects in humans. There are reports from Spain, France, Italy, Portugal and other countries in humans who consumed liver of treated cattle and lambs, and many people were hospitalized, and some of them died (*Payne et al.,* 1999; *Salleras et al,* 1995*; Barbosa et al.,* 2005*; Brambilla et al.,* 2000).

Antiviral drugs in poultry - Two classes of antiviral drugs currently marketed for use in humans have been added to the list of prohibited drugs in poultry (*US FDA Web Site*, 2009). These are the adamantine inhibitors, rimantadine and amantadine, as well as the neuraminidase inhibitors, oseltamivir and zanamivir. These antiviral drugs have been used in countries outside the United States to treat or prevent the development and spread of avian influenza in poultry. The prohibition extends specifically to chickens, turkeys, and ducks. The prohibition order is based on the potential for the development of resistance to these compounds (*Parry,* 2005*; He et al.,* 2008*; Cyranoski,* 2005).

Forbidden antimicrobial drugs for use in food animals (present situation in Serbia)

According to the proposal of the Medicines and Medical Devices Agency, (published in *Official Journal,* No. 96/09), the following antimicrobial drugs are prohibited in Republic of Seriba: quinaxalines, nitrofurans, nitroimidazoles, glycopeptides, sulfonamides in adult dairy cows, fluoroquinolones) (*Official Journal of RS*, 2009).

Conclusions

When drugs are used in animals which are intended for humans, then there is possibility for producing adverse effects in humans as potential consuments of food, orginating from treated animals. To prevent this possibility it is necessary to rationally use drugs, i.e. to use them only when they are really indicated, in the right way, right time and in the right dose. Also, it should respect withdrawal period, permanently follow, register and announce all about adverse effects after use of any drug, regularly control sensibility of bacteria to antimicrobial agents, and regularly control residues of antimicrobials common used in clinical practice.

Finally, having in mind that our country is in transition, and aspiring to become EU member, as soon as possible justifies further discussions and studies of this topic.

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Značaj racionalne primene lekova u veterinarskoj medicini za bezbednost hrane

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R e z i m e: Racionalna primena lekova u veterinarskoj medicini ima višestruk značaj. Korišćenjem lekova samo kada su stvarno neophodni (indikovani), u pravoj dozi i na pravi način, smanjuje se potencijalna šteta od njihovog korišćenja, a ujedno se povećava delotvornost, i smanjuje rizik od nastanka rezistentnosti mikroorganizama (odnosi se na antimikrobne lekovei). Sve navedeno postaje još važnije kada se veterinarski lekovi koriste u lečenju farmskih životinja, odnosno životinja čiji se proizvodi koriste za ishranu ljudi.

Istovremeno sa intenziviranjem stočarske proizvodnje i povećanjem produktivnosti životinja, povećava se i broj lekova koji se koriste. Danas ne postoji skoro nijedna životinja, u intenzivnom, kao i ekstenzivnom uzgoju, koja nije primila barem jedan lek tokom svog života.

U živinarstvu, govedarstvu i svinjarstvu, kao glavnim sektorima gde se proizvode prehrambeni proizvodi životinjskog porekla, upotreba lekova je dostigla granice koje se mogu smatrati alarmantnim za zdravlje ljudi.

Na prvom mestu su antibiotici, ili antimikrobni lekovi, koji se veoma često koriste u terapiji ili prevenciji bakterijskih bolesti, a ne tako retko i kao promotori rasta. Osim antibiotika, koriste se i mnogi drugi lekovi, koji imaju dokazano štetno dejstvo, pa čak i kancerogene ili teratogene osobine/svojstva. Njihove rezidue u proizodima životinjskog porekla koji se koriste u ljudskoj ishran, mogu veoma ozbiljno da ugroze zdravlje ljudi, koji su potencijalni konzumenti ove vrste hrane. Zbog toga je kontrola primene antimikrobnih lekova, kao i ostalih lekova u stočarstvu, od izuzetne važnosti.

***Ključne reči**: neracionalna primena lekova, antimikrobni lekovi, neželjeni efekti, životinje čiji se proizvodi koriste za ishranu ljudi.*

Paper recieved: 4.05.2011.