RATIONAL USE OF DRUGS IN VETERINARY MEDICINE AND FOOD SAFETY

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Abstract

Rational use of drugs in veterinary medicine has manifold importance. Using drugs, only when they are really necessary (indicated), in the right dose and route of administration, the potential harm from their use would be reduced and efficiency increased, and the risk of development of resistant microorganisms (when are used antimicrobials) would be significantly reduced. All of this becomes more important when these drugs are used in food-producing animals.

Simultaneously with the intensification of livestock rearing and the exceptional increase in the productivity of animals, the number of used drugs unavoidably increases. There is almost any animal today, regardless of breeding system (intensive or extensive), which is not received at least one drug during their life cycle.

In the breeding of poultry, cattle and pigs as the main sectors for the production of foods of animal origin, the use of drugs has increased up to limits that can be considered as alarming to human health. Keeping in mind all of that, and also fact that there are no significant changes to better in the clinical practice, we must devote much more time and attention to follow and control the use of drugs to the animals [1].

Non-rational use of drugs in veterinary medicine, as well as need for control of their use become still higher problem, when they are used to the food-producing animals. In that case, there is possibility that minimal quantities of the drugs and their metabolites (residues), which remain in the edible tissues, i.e. in animal products (meat, milk, eggs, honey) can induce some harmful effects in people as potential consumers of that kind of food [2].

We are witnesses that productivity of the food-producing animals many fold increased during the last 50 years, first of all due to advancement 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, the animals became “real small factories” for food production. Simultaneously
with attaining of higher productivity of the animals, need for decreasing of their number was increased. Actually, only animals whose keeping is economic profitable in production are retained [3].

Evidences, how much productivity grows during the time, we can see on following examples: if in 1928 for grow poultry (broilers) with trade weight of 1.7 kg per one unit, duration of production process was about 112 days and animals had to eat in average about 22 kg of feed. In 1990 trade weight of 2 kg in broilers was reached for 42 days, and the feed consumption was just 4 kg per one unit/animal. When speaking for hens, the situation is following: in the thirtieth's years of last century hens were laying 93 eggs, in 1950 - 174, and in 1993 - 252 eggs per one [3].

Similar example exists in of cow’s milk production. In USA, for example, at the same time with decreasing of the number of milking cows, milk production raised thanks to the increasing of milk yield per one cow. In other words, in 1983 milk yield in the average in USA was 5.598 kg/per cow, and in 1995 milk yield increased to 7.478 kg/per cow [3].

One of measures, which (besides others), doubtless contributed to higher productivity of animals was veterinary-medical care. First of all, it refer to efficiency in prevention of different diseases in domestic animals, and understanding of use of different vaccines and others prophylactic remedies. Also, not less significant role have antibiotics, i.e. antimicrobial drugs, which are used mainly in therapy, but also for prevention of diseases, as well as drugs which are used as stimulators of growth, between which the most frequent are hormones and some antimicrobials [4 and 5].

Use of antimicrobial drugs in animals attracts special attention. In therapy of diseases from bacterial etiology, they are certainly indicated and in this cases their use is justified, or is better to say rational, regardless of all hazards which their residues brings to food products that people are consuming [6].

Namely, it is considered that risk in untreated animals could be much higher, than short disuse of the food products (obtained from those animals) in determined period after therapy, whose length depends from withdrawal period. Prophylactic use of antimicrobial drugs or use of these drugs with aim of animals growth stimulation, imply giving a smaller doses (than therapeutically doses) of antimicrobial drugs. Thereby, this kind of drugs use: decreases risk from diseases of bacterial etiology, improves feed utilization, and stimulates growth. However, simultaneously after this kind of antimicrobial drugs use, the possibility of unwanted effects appearance is increased multifold. First of all, the rate of development of resistance in bacteria where are used antimicrobial drugs is increased [7], and certainly risk from residues in animal products intended for human consumption is still higher, than when antimicrobials are used only in therapeutic purposes [8]; [9]. Therefore, in our country is undertaken maximal care that those antimicrobials will not be used in prophylactic, but only in therapeutic purposes, as well as that they will not be used for stimulation of growth in animals.

2. Antimicrobial Drugs

Antimicrobial drugs are compounds that in the body of animals will kill pathogenic microorganisms without to induce of adverse effects for the host. They are natural products of various species of fungi and bacteria that in low concentrations arouse death (bactericidal effect) or are causing growth inhibition (bacteriostatic effect) of microorganisms. These drugs are also including synthetic compounds that are structurally similar to the natural products and have similar mechanism of action [10 and 11].

The last 50 years may be considered as a “golden period” in the antibiotic development. In this period all so far known antibiotics were discovered and introduced in clinical practice. They led to the revolutionary changes in therapy of many diseases that in “preantibiotic era” were fatal. For an example, mortality from pneumonia in human medicine was in range from 30% to 40% till 1940s, and after clinical introduction of penicillin its incidence reduced to < 5% [12].

Most of the antibiotics were developed after World War II as a consequence of strong development of chemical industry. In the last two or three decades, in clinical practice were introduced antimicrobial drugs with already known chemical structure, but with better pharmacokinetic properties and wider spectrum of action [12 and 13]. These drugs mainly are members of IV generation of cephalosporin’s (e.g. cefquinom, cefepime and cefpirome), glycopeptides antibiotic teicoplanin as well as newer carbapenems (meropenem) and macrolides (claritromycine, tuluathromycine) [14 and 15].

Some of them, as well as members of III and IV generations of cephalosporin’s (ceftiofur, cefpodoxime, cefixime, and cefquinom), macrolides (tulathromycine) or carbapenems (imipenem) also are used in veterinary medicine today [6].

2.1 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 that these drugs are rather
non-rational used. Despite permanent indications for all failures and harmful consequences of such use, it is present in everyday clinical practice.

Most mistakes during antimicrobial therapy may occur when the pathogen microorganism is unknown and therapy starts empirically. Most often combinations of two or more antibiotic drugs are used. With aim to avoid these mistakes, clinically confirmed and effective antibiotic combinations should be used. These combinations are useful in treating of serious infections, like as mixed bacterial infections, when the resistance (enzymatic destruction of the drug) occurs, in order to reduce toxicity [6].

2.2 Unwanted effects of antimicrobial drugs

Unwanted effects of antimicrobial drugs can be quite mild and to pass in a form of quite slight disturbances, but also unexpected reactions may occur (as are idiosyncratic or allergic reactions, even anaphylactic shock), as well as different organs functions damages. Sometimes, non-rational drugs use can provoke the most serious disturbances, as are mutagenesis, carcinogenesis and teratogenesis. Therefore, today in clinical practice we must undertake care about frequency and dose of these drugs, and also about possible side effects, which some of these drugs could provoke, and especially about those drugs whose use (because of proved toxicity) is banned [1 and 6].

2.3 Forbidden antimicrobial and other drugs for use in food animals

Because of their toxicity, how for animals (to whom are applied) and also for the people, potential consumers of the products, which derived from those animals, Food and Drug Administration (FDA) has banned the use of some antimicrobials, as well as some other drugs in food for animals. Those are: chloramphenicol, nitroimidazoles, nitrofurans, quinoxalines, fluoroquinolones, sulfonamides, glycopeptides, ionophors, cephalosporins, diethylstilbestrol, dipirone, phenylbutazone, clenbuterol and some antiviral drugs in poultry (Payne et al. [16]; Davis et al. [17]).

Some of the mentioned drugs (the majority), FDA prohibits completely, and some of them are drugs prohibited for extra label use in food animals. What does it mean extra label use of drugs? That means, when some drug is used in a manner that is not in accordance with the FDA-approved label, or instructions. This includes use for a species or for a disease or condition which is 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. In accordance with Animal Medicinal Drug Use Clarification Act (AMDUCA) from 2010, all above aforementioned drugs are now completely prohibited for use in food-producing animals [18].

Chloramphenicol - This drug was forbidden in 1984, because it can causes (although rarely) idiosyncratic (non dose dependent, irreversible) aplastic anemia in people. Likewise, the use of all pharmaceutical forms including ophthalmic ointments, or spray for wounds in food-producing animals is forbidden. However, the newer members of amphenicols like florfenicol or tiamphenicol are allowed. Florfenicol is available for use in cattle, swine, and some aquatic species (Davis et al. [17]; Payne et al. [16]).

Nitrofurans - These drugs are also forbidden because of carcinogenicity and mutagenicity (Payne et al. [16]; Batas et al. [19]). The use of these drugs for therapy of systemic infections in human medicine was withdrawn in 1974, and for therapy of systemic infection in veterinary medicine in 1991. Later studies showed that the topical application of these drugs for therapy of eye or surface wounds to cattle, sheep and goats, also result with their residues in the milk and meat. Because of that, the FDA has banned the topical use of nitrofurans intended for human and veterinary medicine (Smith et al. [20]). Since 2002 whole systemic and topical use of nitrofuran products has been prohibited (US FDA [21]).

Quinoxalines - Has long been known that quinoxalines (carbadox, olaquindox and cydox) are carcinogenic compounds. Because of that, in many countries their use is forbidden or these drugs are withdrawn from use (Payne et al. [16]).

Fluoroquinolones - These drugs become interesting, because it was shown that they stimulate development of resistance of bacteria. The best example are resistant Salmonellosis infections in humans. Therefore, the use of fluoroquinolones intended for humans, in 1997 is forbidden for use in food-producing animals. So, enrofloxacin is banned for use for all food-producing animals, except for calves and heifers. Specifically, this drug may not to be used in period of lactation or dry period in cows, heifers, dairy calves, ewes, goats and deer. Also, this drug may not be stored in dairy farm drug cabinets [16].

Sulfonamides - Sulfonamides have been banned in adult dairy cows. Adult dairy cows are defined as any dairy cow with 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 on the market. Currently, use of any sulfonamide other than SDM in dairy cattle older than 20 months is illegal. Additionally, extra label use of SDM in lactating dairy cattle (for example use of a higher dose or slow-release SDM boluses in dairy cattle) is prohibited (Payne et al. [16], Davis et al. [17]).

Glycopeptides - The only glycopeptides antibiotic available in the United States is the vancomycin for human use. Vancomycin is often used antibiotic for the treatment of methicillin-resistant Staphylococcus aureus infections in humans. Avoparcin, a compound chemically similar to vancomycin, has been used in feed for animals in Europe as a growth promoter since the middle of 70's. FDA in 1977 issued an order for prohibiting the extra label use of all glycopeptides in food-producing animals. The restriction of use of fluoroquinolone and glycopeptides drugs represents a novel exercise of FDA discretion in the enforcement of mandatory use. In this case, the restriction was imposed on its potential for increasing human pathogen resistance (Jung et al. [22]; Klare et al. [23]; Song et al. [24]).

Ionophors - The use of ionophore antibiotics, such as monensin and lasalocid, is banned in lactating in cows. This is valid also for ewes and goats in period of lactation [16].

Cephalosporins - In July 2008, FDA proposed prohibition on extra label use of cephalosporins in food-producing animals, because of the increased emergence 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 [25]).

Diethylstilbestrol - This drug is forbidden for use in food-producing animals in 1979, because of its carcinogenic potential. Namely, it is showed that in pregnant women who is treated with diethylstilbestrol, provokes development of abnormalities in reproductive tract and tumors in female offspring (Newbold [26]).

Dipyrene - It is known that dipyrene is drug which belongs to big group of nonsteroidal-antiinflammatory drugs. However, it is showed that this drug besides, anti-inflammatory, antipyretic and analgesic act, provokes very toxic effects in humans (non-dose dependent teratogenic effects, prolonged bleeding times and agranulocytosis). Because of that FDA abolish its use and withdraw this drug from the market in 1977, while its use in veterinary medicine first abolished in small non-food-producing animals 1995, with suggest that this must be made in food-producing animals also. Today, use of dipyrene in any food-producing animals is considered illegal [27].

Phenylbutazone - Phenylbutazone (as sulfonamides) in dairy cattle over 20 months of age was prohibited in 2003. This made on the basis of the 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 dyscrasia (such as aplastic anemia, leukopenia, agranulocytosis and thrombocytopenia) and causes 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 [28].

Clenbuterol - This drug is known bronchodilator which acts on the β-adrenergic receptors in bronchial tree. As that kind of drug it allowed to use in horses, but in cattle and sheep for provoke relaxation of uteri miometrium. Also, it has secondary anabolic effects. Just, because of this anabolic effect it was used illegally for stimulation of growing in food animals intended for humans and for increase lean body mass and weight gain in humans. But it is showed, for attaining 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 from treated of cattle and lambs. So far many people hospitalized, and some of them death (Payne et al. [16]; Salinas et al. [29]; Barbosa et al. [30]; Brambilla et al. [31]).

Antiviral drugs in poultry - Two classes of antiviral drugs currently marketed for use in humans have been added to the list of prohibited drugs [32]. These are the adamantane 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 [33]; He et al. [34]; Cyranoski [35]).

2.4 Forbidden antimicrobial drugs for use in food animals (state in Serbia)

In according to propose of Agency for drugs and medical device of Republic of Serbia following antimicrobial drugs are prohibited: quinaxalines, nitrofurans, nitro-
imidazoles, glycopeptides, sulfonamides in adult dairy cows and fluoroquinolones) [36].

3. Conclusions

On the basis of all mentioned before we can concluded and proposed following:

- Non-rational and frequent use of drugs is long-existing problem, how in human medicine also in veterinary medicine.
- Between all, antimicrobial drugs are the most common drugs which are used in the clinical practice.
- Because of that, many adverse effects of these drugs, easier and faster are exert.
- Besides development of resistance, the most important adverse effects are allergic reactions, and anaphylaxis, and sometimes it can arise even mutagenesis, carcinogenesis and teratogenesis.
- When drugs are used in animals which are intended for humans, then there is possibility for exert of adverse effects in humans as potential consumers of food which origin from treated animals.
- In the goal of arise of adverse effects on the smallest possible measure, it is need maximally rationally are used of drugs, and used then only when they are really indicated (therapy bacterial infections), in the right way, true time and in the right dose.
- Respect withdrawal period.
- Permanently follow, register and announce all about adverse effects after use of any drug.
- Establish regularly control of sensitivity of bacteria, on determined antimicrobial drugs in defined region.
- Establish regularly control of residues of some antimicrobials or at least some, which are common used in determined region.

4. References


