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UNAUTHORISED USAGE OF VETERINARY DRUGS AS A POTENTIAL RISK TO HUMAN AND ANIMAL HEALTH *

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ABSTRACT

In the developed world the sustainable rearing of food producing animals depends a great deal on the use of veterinary medicines – pharmacologically active compounds. Their usage is fundamental to achieving a desirable level of animal and public health protection. This is particularly necessary in highly industrialized animal production systems. In addition, their use may be required to achieve acceptable welfare standards. It is important, therefore, that administration of veterinary prescription drugs (VPDs) is under the supervision and control of veterinarians. Veterinarians' role is also to raise awareness and educate farmers for the responsible use of veterinary drugs. Four randomly chosen agricultural stores in the east of Croatia were questioned as to whether they had sold the VPDs without prescriptions before the new law came in force (30 March 2007). The results showed that 15 different VPDs could have been purchased occasionally by farmers without veterinary prescription. These drugs may have not been administered appropriately to animals, which may result in short and long term effects on animals and humans. Products of animal origin (POAO) may contain residues above maximum residue limit (MRL) with a potential of developing antimicrobial resistance, therefore the risk to animal and human health may have been increased. In order to reduce such risks, and at the same time to enable farmers to use the VPDs responsibly, Croatia has recently enhanced the legislation in the field of food safety and veterinary medicine. Under this legal framework there is a requirement to implement the Veterinarian-Client-Patient Relationship (VCPR). This paper investigates the possible harmful effects of unauthorized usage of VPDs on human and animal health and the possibilities to enhance control and supervision of their purchase and usage.

Key words: veterinary medicine / drugs / unauthorized use / health risk

SAMOVOLJNA UPORABA VETERINARSKIH ZDRAVIL KOT VELIKA NEVARNOST ZA ZDRAVJE LJUDI IN ŽIVALI

IZVLEČEK

V razvitem svetu je sonaravna reja živali za hrano odvisna od uporabe veterinarskih zdravil – farmakološko aktivnih spojin. Njihova uporaba je nujna še posebno v visoko industrializiranih živinorejskih sistemih, če želimo zagotoviti ustrezno raven zdravstvene zaščite ljudi in živali. Poleg tega pa jih je potrebno uporabljati tudi za zagotovitev ustreznih standardov za dobro počutje živali. Zato morajo doziranje veterinarskih zdravil nadzorovati veterinarji. Naloga veterinarjev je, da ozaveščajo kmete in dvigajo zavest o odgovorni uporabi veterinarskih zdravil.

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V štirih naključno izbranih kmetijskih trgovinah na vzhodu Hrvaške smo povprašali, če so prodajali veterinarska zdravila na recept tudi brez recepta, preden je začel veljati nov zakon (30. marec 2007). Rezultati so pokazali, da je bilo občasno možno kupiti tudi do 15 različnih zdravil, ki se sicer dobijo samo na recept, brez recepta. Morda živali teh zdravil niso dobivale pravilno, kar bi lahko imelo kratkotrajne in dolgotrajne učinke na živali ali ljudi. Proizvodi živalskega izvora lahko vsebujejo ostanke zdravil nad najvišjo dovoljeno mejo, lahko se celo razvije odpornost na antibiotike, kar še dodatno ogroža zdravje ljudi in živali. Da bi zmanjšali takšno tveganje in omogočili kmetom, da bi odgovorno uporabljali veterinarska zdravila na recept, je Hrvaška nedavno zaostrila predpise s področja varnosti hrane in uporabe veterinarskih zdravil. Na tej zakonski osnovi se mora uveljaviti zahteva po odgovornem odnosu med veterinarjem, skrbnikom živali in živaljo – pacientom. Članek preučuje morebitne škodljive učinke samovoljne uporabe veterinarskih zdravil na recept na zdravje ljudi in živali ter možnosti poostritve nadzora nad nakupom in uporabo takih zdravil.

Ključne besede: veterina / zdravila / samovoljna uporaba / riziko / zdravje

INTRODUCTION

Food safety has to be considered by preventive approach and in a strategic way in order to bring reliable risk management decisions that could increase human and animal well-being (Antunović *et al*., 2006). All the food safety activities should take into consideration the need for the integration of Croatia into the EU and international organizations to follow and propose food safety standards, increase the export of food products and provide a better control of food (Antunović *et al.,* 2008).

Proper and authorized usage of veterinary drugs is one of the preconditions for preventive food safety approach by implementing the "From Farm to Fork" concept (EC, 2004).

Safety is an important part of veterinary drug assessment while user safety is a critical part of the overall safety assessment. In the European Union, user safety is addressed through preclinical studies and by relationships with exposure but a key part of the process is the user safety assessment (Woodward, 2008).

Veterinary prescription drugs (VPDs) are labeled for use only by, or on the order of, a licensed veterinarian. Such drugs are labeled in Croatian market, as well as in other countries in the world, as "Prescription only medicine". The purpose of such labeling is having better control on the usage of active ingredients and avoiding possible mistakes in application, development of antimicrobial resistance, as well as exceeding dosage and residue limits.

Licensed veterinarian can dispense the VPDs to farmers who will administer drugs directly to animals, but only in quantities required for the treatment of the animals for which the drugs are dispensed. Before prescribing the product, the veterinarian must be satisfied that the person who will use the VPD is competent to do so safely and intends to use the product for the purpose for which it is authorized.

However, an increased cost of food production and self-confidence of some farmers in their knowledge about treating farm animals could lead to unauthorized usage of VPDs. This could result in increasing of risk to human or animal health, mainly due to possible exceeded MRLs in POAOs.

In order to enhance control on usage of VPDs by farmers, new Veterinary Act (O.G., 2007a) has taken into consideration a Veterinarian-Client-Patient Relationship (VCPR). The aim of this paper was to investigate possibilities that farmers could have purchased VPDs without prescriptions before the new Veterinary Act has been put into force and their potential risk to human and animal health.

MATERIALS AND METHODS

Four randomly chosen agricultural stores in the east of Croatia were interviewed about possibilities to sell VPDs without prescriptions before the new Veterinary Act (O.G., 2007) has been put into force (30 March 2007). The following data were statistically analyzed based on general prescriptions by drug manufacturer (Pliva®) that were following VPDs:

- Active ingredient;
- The prescribed route of administration;
- Kind of drug prescribed;
- Contraindication cautions;
- Possible additional effects;
- Slaughter withdrawal and/or milk and eggs withholding times;
- Specific cautions concerning drugs usage.

RESULTS

All of the four interviewed agricultural stores admitted selling on occasion certain VPDs without prescription in the period before the new Veterinary Act came into force on 30 March 2007. Fifteen different VPDs could have been sold without veterinary prescription. They contained the following 14 combinations of active ingredients:

- sulfadimidine,
- sulfaguanidine,
- trimethoprim + sulfafurazole,
- amoxicillin trihydrate + K clavulanate + prednizolone,
- oxytetracycline + chlorhexidine gluconate,
- enrofloxacine,
- tylosin tartrate,
- cloxacilline + ampicillin,
- ampicillin trihydrate + vitamine A, D_3, B_1, B_2, B_3, B_5, B_6, B_{12}, C, E, K_3 + methionine, Na-sulfate, Fe, Mn, Zn, Cu, Co,
- amoxicillin + clavulanic acid + prednizolone,
- dihydrostreptomycin,
- ivermectin,
- diazinon,
- vitamins A, D_3, E.
-

The VPDs were prescribed by the manufacturer for administration in five different ways, most common *per os* administration (Fig. 1).

The VPDs fall into seven pharmacological groups, most commonly in chemotherapeutics and antibiotics groups (Fig. 2).

Contraindication cautions by the drugs manufacturer were related to 12 from the total number of 15 VPDs (Table 1).

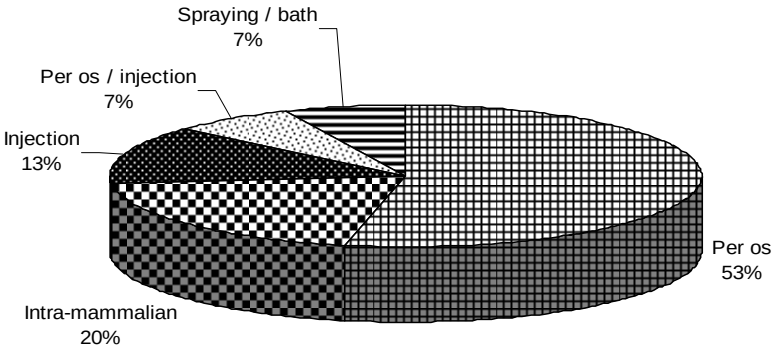

Figure 1. The route of VPDs administration according to the manufacturer's subscriptions.

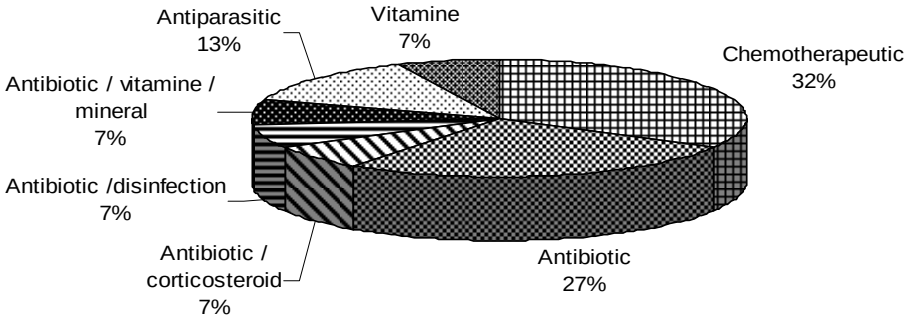

Figure 2. Pharmacological groups of VPDs.

Table 1. Frequency of prescribed contraindication cautions in VPDs

Contraindication cautions following VPDs	VPDs with prescribed caution (n)
1/ Kidney or liver damage	6
2/ Hemathopoetic stem cell damage	4
3/ Laying hens	3
4/ Adult ruminants	2
5/ Ruminants in lactation	2
6/ Hypersensitivity in cows	2
7/ Cows in dry period	1
8/ Hypersensitivity on streptomycin and dihydrostreptomycin	1
9/ Hypersensitivity on penicillins and cephalosporins	1
10/ Damages of auscultatory and balance organs	1
11/ Low conditional and nutritional status	1
12/ Horses	1

Cautions on possible additional effects by the drugs manufacturer were pointed out in subscriptions following nine from the total number of 15 VPDs (Table 2).

Table 2. Frequency of prescribed cautions on possible additional effects of VPDs

Possible additional effects of VPDs	VPDs with prescribed caution (n)
Hemorrhagic syndrome in poultry	2
Diarrhoea in calves	2
Disturbances in cellulose digestion in cows	2
Allergic reaction in cows	1
Kidney damage	1
Damages of auscultatory and balance organs	1
Decreased appetite and milk yield	1
Diarrhoea	1
Sedative effect	1

Cautions on necessary withdrawal period were pointed out by the drugs manufacturer in 14 prescriptions from the total number of 15 VPDs (Table 3).

Table 3. Number of days prescribed by drug manufacturers needed for excretion of active substances from different animals or animal products after application of VPDs (slaughter withdrawal and/or milk and eggs withholding times)

Animal or product	VPDs with prescribed withdrawal caution (n)	Withdrawal days prescribed (x_{min}–x_{max})
Cow	13	1–30
Swine	10	3–30
Goat	7	7–28
Sheep	8	7–28
Horse	2	5–10
Poultry	7	5–14
Eggs	5	1–14
Milk (cow)	6	3–53
Milk (goat)	3	4–5
Milk (sheep)	3	3–5

Furthermore, various specific cautions concerning drugs usage were pointed out in the VPDs prescriptions by the drugs manufacturer:

- Water has to be available to the animal;
- Dosage has to be decreased in animals with kidney failure;
- Other sources of food should not be available to cured animals;
- Drug should not be used in healthy animals;
- Drug is not suitable for curing of systematic infections in adult ruminants;
- Drug should be completely dissolved;
- Bacteriostatic antibiotic should not be given together with drug;
- Other pharmaceutics should not be dissolved together with drug;

- Drug should not be mixed with milk, swill or silage;
- Drug should not be given to animal in the last third of gravidity;
- Results of the therapy should be monitored by laboratory trials (mastitis test);
- Dosage should be determined individually before administration;
- Faeces should be removed from animal;
- Special attention should be taken while caring out therapy of thin or dehydrated animals;
- Application in highly pregnant or lactating animals should be avoided;
- Animals could easily perish if dosage has been exceeded;
- Drug should be used only externally;
- Animals should not be treated more than four times per year.

DISCUSSION

The usage of VPDs without proper veterinary supervision and control raises many questions of concern. These may relate to an increased risk to human and/or animal health. As presented in Fig. 1, some farmers administered drugs in several ways; *per os*, intramammalian or spraying/bath administration, even injection application. As most of the VPDs found to be occasionally available on free market fall in two groups; chemotherapeutics and antibiotics (Fig. 2), potential risks of their usage without veterinary control are related to hazards coming from these two pharmacological groups. Unauthorized person could make mistake by not recognizing damage of certain organs in cured animals (Table 1, points 1, 2, 10), which could lead to serious consequences for the animal, including death, especially in cases of overdosing. Furthermore, VPDs could be given to the wrong species of animals or just exhausted animals resulting in specific reactions or damage of digestive micro flora (Table 1, points 4, 7, 12). Administration of VPDs to food producing farm animals (Table 1, points 3, 5) could result in exceeding residue limits in the uration of withdrawal or withholding period (Table 3). The fact that necessary withdrawal/ withholding periods were pointed out by the drug manufacturer in 14 prescriptions from the total number of 15 VPDs reveals necessity of better control on the usage of these drugs.

Antimicrobial resistance in human or animals is considered as one of the most significant potential harmful effects as a result of inadequate usage of antibiotics. Large worldwide surveillance studies report that resistance to nearly all classes of antimicrobials are increasing, as is the emergence of what have been termed pan-drug–resistant and extremely drug-resistant pathogens (Owens, 2008). Changes of bacteria in a way that reduces or eliminates the effectiveness of antibiotics result in the survival and multiplication of resistant bacteria causing more harm, such as longer illness, more medical visits, and a need for more expensive and toxic antibiotics.

Hypersensitivity to antibiotics in animals is also question of concern while using VPDs (Table 1, points 6, 8, 9). Such status could be unrecognized by unauthorized persons and lead to anaphylactic shock and death of the animal. Furthermore, active ingredients from VPDs can cause additional unwanted effects in animals that can range from decrease of production to serious health disturbances (Table 2). Beside contraindications, possible additional effects and withdrawal/withholding time, the person who treats the animals has to be aware of many specific cautions related to the ways of dispensing drugs, dosage limits in low conditioned animals, antagonistic effects between certain drugs, gravidity, monitoring of effectiveness after therapy, frequency of therapy etc.

In order to increase control in the field of food safety, Croatia has recently aligned its veterinary legislation with EU as pre-accession country. The control on usage of VPDs has been enforced by a concept of Veterinarian-Client-Patient Relationship (VCPR) within the new

Veterinary Act (O.G., 2007a), and the new Act on veterinary-medicine products (O.G., 2008a), which upgrade previous legislation on veterinary drugs (O.G., 1998). The previous legislation was considered to be an obstacle in the period of the Croatian accession to EU in the process of adjusting legislation to the *Acqui communautaire* (EC, 2001). According to the new rules, farmers must keep records on the administration of all veterinary drugs in food-producing animals. They have to respect subscribed preventive measures and the number of days prescribed for excretion of active substances after application. Only animals that have completed the withdrawal period can be slaughtered for human consumption and used for food production (O.G., 2007b). The control of caring out these preventive measures has been enforced by better traceability rules in swine, cow, sheep and goat husbandry (O.G. 2007c; O.G. 2007d; O.G, 2007e), program of monitoring of residues in live animals and food of animal origin (O.G., 2004) followed with new rules on maximum residue limits (MRL) in food of animal origin (O.G., 2008b), as well as by better labeling of food products (O.G., 2008c). This system should enable faster recognition of animal husbandry practices producing food products with excessive residue limits.

The VCPR still have to be developed further in Croatia by providing the Guidiance for farmers and veterinarians. EU user safety guidelines are available and these make certain recommendations but in places they lack detail and clarity (Woodward, 2008). The European Medicine Agency defines a user as any person that may come into contact with the veterinary medicinal product or its components before, during or after its administration. This extends therefore to veterinarians and other veterinary health-care workers, to farmers, members of the animal owning public, animal beauticians, bystanders and animal breeders (EMA, 2003). This contribution seeks to examine the practical aspects of user safety assessment.

The system in the USA could be good example of how it should work in praxis. According to the USA guideline (AVMA, 1998), orders issued by licensed veterinarians authorize drug distributors to deliver VPDs to a specific client, or authorize pharmacists to dispense such drugs to a specific client. Adequate treatment records must be maintained by the veterinarian for at least two years (or as otherwise mandated by law), for all animals treated, to show that the drugs were supplied to clients with whom a VCPR has existed. Food animal owners must also keep treatment records, which have been developed by several producer organizations and are available in conjunction with quality assurance programs. Such records must include the information set forth under Basic Information for Records (R), Prescriptions (P), and Labels (L) as follows:

- Name, address, and telephone number of veterinarians (RPL)
- Name (L), address, and telephone number of clients (RP)
- Identification of animal(s) treated, species and numbers of animals treated, when possible (RPL)
- Date of treatment, prescription, or dispensing of drug (RPL)
- Name, active ingredient, and quantity of the drug (or drug preparation) to be prescribed or dispensed (RPL)
- Drug strength (if more than one strength available) (RPL)
- Dosage and duration
- Route of administration (RPL)
- Number of refills (RPL)
- Cautionary statements, as needed (RPL)
- Expiration date if applicable
- Slaughter withdrawal and/or milk withholding times, if applicable (RPL)
- Signature or equivalent (P)

An important stipulation is that VPDs should be securely stored, with access limited to key personnel.

CONCLUSION

Unauthorized or inappropriate use of veterinary prescription drugs (VPDs) in food producing animals-carries an increased risk to treated animals and humans. Animals may show unrecognized side effects and in the most extreme cases die. On the other hand humans, through consumption of products of animal origins from those animals, may suffer short and long term effects

The result of our investigations showed that farmers were purchasing VPDs, prior to March 2007. However, it was difficult to establish a reliable link between the usage of these drugs and ill- effects on animals and humans.

Veterinarian-Client-Patient Relationship (VCPR), within the legal framework, will need to be developed further to protect animals and humans from unauthorized usage of VPDs.

An effective implementation of such toolkit (VCPR) will help to mitigate the risk of irresponsible use of VPDs.

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