BOOK OF ABSTRACTS

VETERINARY PHARMACY

The role of Pharmacist in the area of Animals' drugs

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We are pleased to present an ebook containing abstracts sent as part of the 1st edition of the Conference "Veterinary pharmacy - the role of a Pharmacist in the world of medicines for animals". The submitted abstracts are thematically related to the broadly understood pharmacy and veterinary medicine. The purpose was to promote science and the interdisciplinary cooperation of scientists from various fields of science.

We would like to thank the participants for their interest in the Conference and for submitting scientific works. We wish you further development, sucess and satisfacion in the field of science.

We encourage all of you to read the abstracts and broaden your knowledge also in areas that may not be of interest to you on a daily basis. We hope that both conference and this book of abstracts would be a great source of inspiration.

Conference Organizing Committee

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List of abstracts:

Microbiological safety of medicinal products for veterinary use

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Development of the pharmaceutical industry depends on the introduction of new, more effective medicinal products, as well as improving the quality of manufactured products. The safety of their use depends on compliance with good manufacturing practice (GMP) by manufacturers and following manufacturing procedures [2], [3], [5]. Quality control by both manufacturers and inspection bodies is also necessary. Undoubtedly, an important parameter of the quality control of a medicinal product is the appropriate microbiological quality.

In terms of microbiology, medicinal products are divided into sterile and non-sterile, i.e. products for which qualitative and quantitative criteria for accepting microbiological contamination have been established. The assessment of the microbiological quality is carried out on the basis of the results of test for sterility or microbiological examination and antimicrobial activity.

The test for sterility of medicinal products according to European Pharmacopoeia is performed by direct inoculation or membrane filtration [1], [4] – [7]. Antimicrobial activity of the product must be neutralised using an appropriate neutralising substance, by dilution in a sufficient quantity of culture medium in direct inoculation or washing with diluentin membrane filtration. The chosen testing method must be confirmedby method suitability test. The nature of the sterile medicinal product affects the choice of the test method.

Non-sterile medicinal products may contain specified number of microorganisms and should not contain specified bacteria and fungi[1], [4] – [7]. The purpose of microbiological examination of non-sterile medicinal products is both determination of the number of live aerobic microorganisms in the tested sample, as well as the exclusion of the presence of selected pathogenic microorganisms. Microbial enumeration tests allow quantitative enumeration of mesophilic bacteria and fungi growing under aerobic conditions. Product control can be performed using three methods, i.e. plate-count method, membrane filtration or most-probable-number (MPN) method. In turn, test for specified microorganisms allows determination of the absence or limited occurrence of specified microorganisms. In accordance with European Pharmacopoeiathese tests are performed aiming at detection of bile-tolerant Gram-negative bacteria, *Escherichia coli*, *Salmonella* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Clostridium* spp., *Candida albicans*.

Both in microbial enumeration test and in test for specifiedmicroorganisms, antimicrobial activity must be removed or neutralised. To prove that examined sample do not inhibit growth of microorganisms the suitability of the test method must be established. If sample preparation requires the use of surface-active substances, then absence of their toxicity for microorganisms, as well as their compatibility with inactivators must be confirmed. The

nature of the product and the requirements regarding maximum microbial count for the product should be taken into consideration for selecting the test method.

For the control of microbiological quality European Pharmacopoeia approves for use in addition to classical methods also faster alternative methods. Examples of such alternative methods are autofluorescence, flow cytometry or solid phase cytometry [1].

Microbiological quality of medicinal products for veterinary use is essential for the safety of animals. The presence of microorganisms in medicinal products may be the result of production faults, inadequate aseptic conditions of the production process, primary contamination of pharmaceutical raw materials or improper preservation. Another problem with the presence of microorganisms in medicinal products is the loss of therapeutic properties. Such a situation may result from the transformation or degradation of active substances due to impact of microorganisms. Therefore, it should be ensured that the medicinal products for veterinary use are not contaminated with microorganisms [3], [8].

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Key words: medicinal product, sterility, microbiological examination

The test for sterility for medicinal products using the isolator with hydrogen peroxide vapour technology

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The National Veterinary Research Institute (NVRI) in Pulawy is a member of General European OMCL Network (GEON). The NVRI as the Official Medicines Control Laboratory (OMCL) performs the batch release of immunological veterinary medicinal products and the quality control of medicinal products for veterinary use after introducing to the market.The NVRI is one of the few OMCLs in the European Union that perform tests of immunological veterinary medicinal products which are already on the market [4].

OMCL in the NVRI carrying out quality control of medicinal products for veterinary use performs i.a. evaluation of microbiological quality. The test for sterility is required for immunological veterinary medicinal products manufactured in aseptic conditions and sterilised in immediate packaging at the end of production cycle. Such medicinal products in accordance with European Pharmacopoeia requirements must be sterile and microorganisms or their spores must not be found in the test for sterility [1], [7]. The method of testing for sterility of immunological veterinary medicinal products has been confirmed and obtained attestation of European Directorate for the Quality of Medicines & HealthCare (EDQM).

The test for sterility of medicinal products can be performed by direct inoculation or membrane filtration according to European Pharmacopoeia [1], [2], [5], [6]. The choice of the test method depends on the nature of the medicinal product. Direct inoculation can be used for medicinal products that do not show inhibitory effect on the growth of microorganisms, as well as when inhibitory factors can be inactivated by dilution in a sufficient quantity of culture medium or by adding a suitable neutralising substance. In turn, membrane filtration can be used for medicinal products which show inhibitory effect on the growth of microorganisms and when the nature of the product allows it. In this method, in order to eliminate antimicrobial activity neutralising substances can be added to diluent or washing with diluent can be applied. The method suitability test must be performed for confirmation of adequacy of the chosen testing method.

Aseptic working conditions are required to conduct the test for sterility. Testing of medicinal products for which sterility is required must be performed in grade A zone. In standard cleanroom the test for sterility requires maintaining grade B environment in surrounding of grade A zone.Appropriate hygiene standards, proper protective clothing for staff and regular monitoring of the working area are required. It results in significant expenses, increased risk of contamination and reduced comfort of work [3].

OMCL in the NVRI uses the isolator with hydrogen peroxide vapour technology in order to assure appropriate conditions for performing the test for sterility. This device provides decontamination with hydrogen peroxide vapour. An isolator is a device designed for aseptic procedures in grade A zone, which can be also placed in lower grade environment. The isolator provides also monitoring of environment conditions required for the test for sterility. Using the isolator results in reduced costs of preparation and monitoring of laboratories which are maintained in lower grade. Decreased risk of contamination and better comfort of work for staff are other beneficial effects.

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Key words: medicinal product, sterility, isolator

Restrictions on the use of pharmacologically active substances in food-producing animals.

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Food-producing animals means animals bred, raised, kept, slaughtered or harvested for the purposes of producing food (according to Regulation (EC) No 470/2009).

Not all pharmacologically active substances can be administered to food-producing animals. Drugs which are considered to be allowed to use in food-producing animals are evaluated in terms of a risk analysis of harmful effects of the substance in case of its human consumption in tissue or any other products of animal origin. In food-producing animals the substances can be used, which only were evaluated favourably .For some substances maximum residue limits (MRLs) were established. In the case of other substances there is no need to establish a safe limit. MRL means maximum level of residues of a drug or its metabolites in tissues of animal origin allowed for human consumption. However, there are also active substances for which MRL cannot be determined, as any residue of such substances may constitute a hazard to human health. Such substances are prohibited to use in food-producing animals.

MRL is the point of reference for establishment of withdrawal period in marketing authorisation for veterinary medicinal product to be used in food-producing animals. Withdrawal period can be defined as time needed after the last administration of veterinary medicinal product until slaughter of the animal or in the case of milk, eggs or honey until the beginning of acquiring of these products for food.This time must elapse so that tissues and other products do not contain residues of drug in excess of MRL.

In order to public health protection,pharmacologically active substances were classified in four Annexes (Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin).Annex I - substances with established MRL,Annex II - substances which can be used without determination of MRL,Annex III – substances with temporarily established MRL, conditionally approved for use in animals intended for food for a certain period and Annex IV - substanceswith undetermined MRL- they cannot be used in food-producing animals.

For reasons of simplification, according to Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (which replaced the previousone)

pharmacologically active substances are classified in one Annex in alphabetical order, in 2 separate tables:

Table 1 – substances which are approved for use in food-producing animals (equivalent of annexes I,II,III of Regulation (EEC) No 2377/90).

Table 2 – substances which are not allowed for use in food-producing animals (equivalent of annex IV of Regulation (EEC) No 2377/90).

The examples of drugs which are not allowed to use in food-producing animals are chloramphenicol due to idiosyncratic aplastic anemia in human or nitrofurans and nitroimidazoles due to mutagenic and procarcinogenic potential.

Taking into consideration all aspects mentioned above, the most important practical information for veterinary surgeons is that only pharmacologically active substances from Table 1 are allowed to use in food-producing animals.

Key words: food-producing animals, MRL, Table 1

Maropitant – off-label use in medicine of rodents and rabbits

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Abstract: This clinical case review brings to the attention off-label use of maropitant in rodents and rabbits who not have the ability to vomit. Maropitant is used in cats and dog as an anti-emetic drug, but in small mammal practice it can be used to ensure safer isoflurane anesthesia and better visceral analgesia.

Introduction: There is a common use of cascade of drugs in veterinary medicine. [6] However shortage of drugs approved for rodents and rabbits often results in use of drug registered for cats and dogs or humans. Maropitant is being used in cats and dogs as an antiemetic drug, but it found it's use in medicine of rodents and rabbits. [4,5] As those species do not have ability to vomit on account of a strong esophageal sphincter maropitant is not used as an antiemetic, but rather an anti-inflammatory, analgesic drug or part of general anesthesia.

Material and methods: This is an retrospective stadu reviewing clinical cases and practical use of maropitant solution. Maropitant is a neurokinin-1 (NK1) receptor antagonist, which acts in the central nervous system by inhibiting Substance P, the key neurotransmitter involved in vomiting. [1] By inhibiting substance P, maropitant acts as an anti-emetic. [4,5] Used solution for injection contains 10 mg/ml maropitant (as maropitant citrate), sulphobutylether-beta(β)-cyclodextrin sodium (SBECD) and metacresol, made to 20 ml final volume with water for injections. [1] The review took into consideration otherwise healthy female rabbits and guinea undergoing surgical ovariohysterectomy in general anesthesia adn hospitalized guinea pigs presenting with pancreatitis. Animals undergoing surgery were divided into 2 groups: rabbits whose anesthetic protocol did not include use of maropitant (group A), rabbits whose anesthetic protocol did include use of maropitant 2mg/kg (group B). Signs of anorexia, apathy, peristalsis disorder and flatulence up to 10 days after the surgery were taken into consideration. Patients presenting with pancreatitis were divided into 2 groups: those whose protocol of hospitalisation included maropitant 2mg/kg sc and those whose protocol of hospitalisation did not include maropitant. Visceral pain, in scale from 1 being the lowest to 3 being the highest, overall apathy, anorexia and duration of treatment in days were taken into consideration.

Results: The results from the sugical group are presented in the table I. The results from the group presenting with pacreatitis are presented in the table II.

Group	A	B
Species	Rabbits	Rabbits
Use of maropitant	Yes (2mg/kg)	No
Number of patients in the group	46	34
Number and percentage of patients with no signs of disscomfort	45 [98%]	27 [79%]
Number and percentage of patients presenting with anorexia	1 [2%]	7 [21%]
Number and percentage of patients presenting with apathy	0 [0%]	7 [21%]
Number and percentage of patients presenting with peristalsis disorder	0 [0%]	6 [18%]
Number and percentage of patients presenting with flatulence	0 [0%]	2 [6%]

Tabl. I The results in surgical group

Group	Protocol of hospitalisation included maropitant 2mg/kg	Protocol of hospitalisation did not include maropitant
Number of patients in group	6	2
Number and percentage of patients presenting with anorexia	6 [100%]	2 [100%]
Number and percentage of patients presenting with apathy	5 [83%]	2 [100%]
Number and percentage of patients with visceral pain scored at 1	1 [17%]	0 [0%]
Number and percentage of patients with visceral pain scored at 2	4 [67%]	0 [0%]

Number and percentage of patients with visceral pain scored at 3	1 [17%]	2 [100%]
Average duration of treatment	4 days	4,5 days

Tabl. II The results in group of patients with pancreatitis

Discussion: Off-label use of maropitant in rabbits undergoing surgery with interference in the abdominal cavity is showing promising results in regard to anorexia, apathy and working of digestive tract after the surgery. Painkillers, NSAIDS and opioids used during general anestesia can compromise peristatics of digestive tract witch in rodents and rabbits is an important factor in general well being as well as convalescence after the surgery. Off-label use of maropitant in rabbits and rodents presenting with pancreatitis is believed to have some positive effect on hospitalized patients by reducing visceral pain. There seems to be no significant difference in duration of treatment with or without maropitant. The next step in those considerations should be off-label use of maropitant solution as an anti inflammatory drug for treatment of purulent, ulcerative, persistent dermatitis in mice to break the cycle of self-harm, as substance P (SP) has recently been demonstrated as an important neuropeptide linked to the itch-scratch cycle. [3] Other off-label use would be as an intranasal solution in treatment of purulent, persistent nasal discharge in case of Pasteurella multocida infection in rabbits. [2]

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Key words: maropitant, off-label use, rodent

Monoclonal antibodies – new possibilities for therapy in Veterinary Medicine.

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Monoclonal antibodies (mAbs) are one of the biotherapeutics used in biological therapy based on the use of knowledge about normal immune responses to treat diseases or protect against adverse effects [1].

Monoclonal antibodies therapy mimics normal immune response by administering recombinant mAbs directly to a patient. Therapeutic mAbs target a single antigen of interest and arise from a single plasma cell line, so they are essentially identical to natural occurring antibodies produced and secreted by plasma cells in the body. The production of mAbs consists in immunizing mice, isolation the desired B-lymphocytes and fusing them with an immortal myeloma cell line (the hybridoma technique). Recombinant DNA techniques allow designed and production of therapeutic mAbs that will be tolerated by targed species for injection for human, dog and cat. Those mAbs we called humanized, caninized and felinized. This speciation decrease the risk of adverse effect [3,4].

mAbs exert their biological effect by 3 types of mechanism of actions (predominantly by one of these): 1) is through the binding or “soaking up” of soluble extracellular targets (i.e. cytokines) to prevent this molecules to binding with and activating their receptor; 2) is to simply bind a target receptor on the cell surface and block activation of signal transduction; mAbs that act through this pathway are classified as antagonistic; 3) is to bind to an infectious agent or cancer cell and either activate cell lysis (via complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity) or enhance clearance of the foreign agent by antibody-dependent phagocytosis [1,2].

In human medicine, among the available biotherapies, it is mAbs that have brought the greatest successes in the treatment of neoplasms (eg. Rituximab) or autoimmune diseases (eg. Adalimumab).

To date, two mAbs are approved by EMA in veterinary, as fully licensed, commercially available products. This is lokivetmab – categorized as other dermatological preparations and bedinvetmab – categorizes as other analgesics and antipyretics.

Lokivetmab is a caninized mAb specifically targeting canine interleukin-31 (IL-31). The blocking of IL-31 by lokivetmab prevents IL-31 from binding to its co-receptor and thereby inhibits IL-31 mediated cell signalling, providing relief from Atopic Dermatitis-related pruritus and anti-inflammatory activity. Indication to use is treatment of clinical manifestations of

atopic dermatitis in dogs. mAb is injected subcutaneously in recommended doses once a month [5,6,7].

Bedinvetmab is a canine monoclonal antibody (mAb) targeting Nerve Growth Factor (NGF). The inhibition of NGF mediated cell signalling has demonstrated to provide relief from pain associated with osteoarthritis. Indication to use is alleviation of pain associated with osteoarthritis in dogs. Drug is administered in subcutaneous injection in recommended doses once a month [3,8].

The major advantages of mAbs over traditional drugs are the agents' specificity (precise action) and their long half-lives (infrequent dosing). Also mAbs do not need to undergo biotransformation and unlikely to goes adverse drug-drug interaction (inactivation pathway by intracellular catabolism), it is easier to predict adverse effects, based on the expected blockade of the target [1].

Several new mAbs are currently being tested (ranevetmab, frunevetmab, blontuvetbam, tamtuvetmab) for the treatment of arthritic pain and oncological disorders [3,9]. It is likely that the biological medicines market in the veterinary market will increase the availability of new products for clinical use. Biologics open up exciting new therapy options.

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Key words: monoclonal antibodies, lokivetmab, bedinvetmab

„Anatomical structure of rostral epidural rete mirabile and its role in retrograde transfer of neurotransmitters in selected species of Bovidae and Cervidae”

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The rostral epidural rete mirabile is not fully characterized. Available research on it sheds more and more light on its physiological role. They described new mechanism of retrograde transfer of neurotransmitters to the brain which provides novel possibilities for the treatment disorders of reproductive system [1].

The aim of this study was to analyze in detail the structure of the rostral epidural rete mirabile. There were two methods used in this study. The first method consisted of passing liquid stained latex LBS 3060 into both common carotid arteries, leaving to set in 5% formalin solution for 2 weeks, then preparing the blood vessels manually using surgical instruments during dissection. In the second method, the both common carotid arteries were filled with a solution of chemo-setting acrylic material DURACRYL® PLUS and macerated enzymatically for about a month. The study was condicted of 30 specimens from the deer family belonging to the species: European roe deer, red deer and fallow deer, and those belonging to the bovine family: domestic cattle, domestic sheep and domestic goat.

The rostral epidural rete mirabile is well developed in the analyzing species. It consists of small arteries anastomosing with each other, embedded in the venous blood of the cavernous sinus. The main component of the rostral epidural rete mirabile in Bovidae family is the maxillar artery which is an extension of the external carotid artery. Moreover in domestic cattle rostral epidural rete mirabile is connected with caudal epidural rete mirabile. In the Cervidae family, besides maxillar artery there is additionally the condylar artery which is the second component of the rostral epidural rete mirabile.

Except knowledge of the descriptive and comparative anatomy of this rete, a physiological role is also important. Venous blood flows to the cavernous sinus from areas of the brain, pituitary gland, and parts of the nose and eye, via the sinus opthalmicus[2]. Due these connections, a retrograde transfer of neurotrasmitters between the venous blood of the cavernous sinus and the arterial blood of the rostral epidural rete mirabile is possible [2]. Studies of this phenomenon by some authors was performed on isolated head of swine and sheep models or on anesthezided animals by infusion into nasal cavity or cavernous sinus of radioactive neurohormones or pheromones like dopamine [3] oxitocine [4], progesteron [5]. This mechanism offers innovative possibilities in the context of treatment disorders of the reproductive system and the regulation by humoral pathway of the estrous cycle [6].

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Key words: rostral epidural rete mirabile, retrograde transfer of neurotransmitters, blood

A study of the brachial plexus anatomy of the Steppe caracal (Caracal caracal) for local anesthesia of the thoracic limb in the cats (*Felidae*)

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Abstract: The brachial plexus (*plexus brachialis*) is a structure made up of interconnected nerve fibers originating from the ventral branches of the cervical and thoracic nerves. It is the most common composed of the C6-8 and Th1-2 nerves[1]. The nerves of the brachial plexus are responsible for the innervation of the thoracic limb and chest. The brachial plexus also communication with the autonomic nervous system through fibers to the sympathetic nervous system ganglia from the cervical and thoracic regions and with the parasympathetic nervous system through fibers originating from the spinal ganglia[2]. The clinical importance of this structure is underlined by the number of scientific studies conducted on laboratory animals from a physiological point of view, but also on species in which this structure is anatomically undescribed. One such species is the steppe caracal, in which the brachial plexus has not been anatomically described. Despite the high similarity the cat group, there are differences in structure between species, as indicated by studies on great ocelots (*Leopardus pardalis*)[3] or fawn cougar (*Puma concolor*)[4]. However, there is a lack of work in the literature on species variation in the steppe caracal. Therefore, obtaining such information on the brachial plexus would be valuable to veterinarians caring for zoo animals. It is a naturally occurring animal in Africa, Asia and the Arabian Peninsula. The animal has been known since 1776 but its nervous system is not well understood. Knowledge of the topography and detailed anatomy of the plexus is a prerequisite for successful thoracic limb anaesthesia procedures using injections in the region of the plexus body or individual plexus nerves branching to the thoracic limb and chest wall. The aim of this study was to analyse the brachial plexus to assess whether the use of injection sites on the thoracic limb to anaesthetise it in cats could also be used in steppe caracals. Placing animals or parts of their bodies in a state of painlessness enables a number of procedures to be performed. Developed topographical access sites to specific parts of the nervous system allow for rapid and accurate application of anaesthetics to the nerve in question. The possibility of using access sites used in closely related cats would allow, if necessary, rapid anaesthesia of the thoracic limb in the steppe caracal. A study was carried out on a male steppe caracal to determine the similarity between these species. The study material was fixed in 10% formic aldehyde solution. The study was based on macroanatomical preparation of the thoracic limb and thorax. The neural structures were visualized with 2% hydrogen peroxide and through 3% acetic acid solution. Pharmaceuticals used to anesthetize nerves, such as lidocaine, should be deposited as precisely as possible to anesthetize the structure. Proper use of anesthetics allows the procedure to be carried out safely for the animal and under well-behaved conditions. Therefore, data on the course of brachial plexus nerve fibres and

the location of the main part of the brachial plexus of the steppe caracal are valuable for veterinarians dealing with exotic animals.

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