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THE TOXICITY EFFECT OF SELECTED DRUGS IN ANIMALS

Abstract. *Therapeutic products quite often are causes of poisoning in both small and large animals. Drug poisonings in animals occur commonly due to off-label use of medicines, wrong dosage, negligence, accidental ingestion and deliberate poisonings. Toxicity of veterinary drugs may become evident also in therapeutic doses when adverse effects may occur. The aim of this review is to inform veterinary specialists about both veterinary and human drugs, specifically antiparasitics, non-steroidal anti-inflammatory drugs and other medicinal substances, which are most often reported to cause acute poisonings or adverse reactions in animals and to contribute to their broader knowledge and more accurate use of medicines, improving instructions to the animal owners and, hopefully, decrease the incidence of drug poisonings in animals.*

Much more is needed to be done to raise awareness of veterinarians, pharmacists and also pet owners to the problem of drugs adverse reactions, off-label use and inter-species differences. The treatment of poisoned or overdosed animal can be expensive, especially if an animal has to be hospitalised for several days, or if the treatment lasts for several weeks or months or the consequences of the health damage are irreversible and require further specific treatment, surgery, diet etc.

Many drug effects are not known or are considered unimportant as there is not a general knowledge of them and their frequency because these situations are under-reported. Cases may not be reported because the treating veterinarian does not require advice on treatment, does not think about reporting known facts or minor problems or does not have time to report the case immediately and forgets it later. In some cases the veterinarian is not sure about the identification of the causing agent. Also owners very often do not report the side effects or deaths to their veterinarian.

These misuse and accidents could be avoided through further education of veterinarians, pharmacists and general public, using modern and reliable sources of information available to everyone, by appealing on the importance of proper reports on poisoning cases and adverse effects to responsible authorities and publishing such cases in expert journals. Manufacturers should improve safety warnings and proper labelling of their products.

Key words: *poisoning, antiparasitics, analgesics, NSAIDs, pharmacovigilance, animals.*

Introduction. Medicines often are causes of poisoning in both small and large animals. Unfortunately, exact statistics cannot be given as in many countries no central register of poisoning cases in animals exists. Generally it is expected that drug intoxications can constitute 10-30% of poisonings in animals [54, 96]. Species affected are mainly dogs, cats and other companion animals, less is reported for farm animals [63]. Drugs most often reported as a cause of poisoning or adverse effects are antibiotics, antiparasitics and non-steroidal anti-inflammatory drugs [83, 96]. Antibiotics are not covered in this review due to the limited space and existence of many literature sources on this issue.

Drug poisonings in animals can have many causes. Very often it is an off-label use of medicines (application of veterinary product to a non-target animal species or application for a different indication than is mentioned in the summary of product characteristics, application of human drugs), wrong dosage (overdose), but also owner's negligence or unfamiliarity with the drug and proper drug handling. Another common reason of such poisonings is accidental ingestion of both human and veterinary medicines inappropriately stored in the reach of, especially, pet animals. In the worst cases deliberate poisonings of animals are revealed. Symptoms of poisoning reflect the type of the toxicity of the substance and mechanism of its action. Due to the fact that both veterinary and human drugs are responsible for toxic and adverse effects occurring in animals, both of the categories are ion mentioned in this article. The criterion for inclusion of the drug into this review was sufficient scientific data on its toxic properties and scientifically documented cases of poisonings/adverse reactions in animals.

Nowadays, cases of acute drug poisonings decrease in number, especially in large animals, but are still very important as they represent acute life-threatening situations and must be solved immediately, what imposes high requirements on the knowledge and abilities of veterinarians.

A new type of drug poisoning is a chronic exposure to very low doses of medicines. This chronic intoxication or chronic action of drugs is possible due to the fact that the environment is contaminated with traces of hundreds of medicinal substances which are deposited in soil, sediments, occur in water and consequently enter food chain - can be found in plants and animals which serve as a food source. This contamination occurs due to an enormous consumption of drugs, improper knowledge of their behavior in the environment and inefficiency of waste water treatment processes to decompose or remove them from water [20, 28]. Of course, these chronic expositions to medicines rarely lead to death or highly significant health problems, but can alter animals health condition, can influence birth rates, weight gains and milk yield. And, last but not least, the presence of these substances (often inducers or inhibitors of many important enzymes) in the animal organism can lead to interactions with other medicinal substances administered to the animals or with internal biochemical processes.

Toxicity of veterinary drugs becomes evident also in cases when therapeutic doses for appropriate indication are used. Many drugs may have adverse effects ranging from mild health complications to life-threatening conditions. These effects occur upon individual sensitivity of animals and can be consequence of known toxicity of the drug or of individual or idiosyncrastic reaction. Monitoring of such effects, including off-label or wrong use of veterinary medicines, comes under the competence of state authorities responsible for pharmacovigilance. Unfortunately,

general experience is that veterinarians and general public do not cooperate well in this field although reporting of adverse effects to the responsible authorities is often decreed by the law.

The aim of this review is to inform veterinary specialists about possible toxic properties of both veterinary and human drugs, specifically antiparasitics, non-steroidal anti-inflammatory drugs and other medicinal substances, which are most often reported to cause acute poisonings or adverse reactions in animals.

Drugs most frequently involved in poisonings and adverse reactions

Antiparasitic agents

Benzimidazoles

Benzimidazoles are widely used popular anthelmintics used in various animal species which main negative effect is caused by their toxicity to bone marrow and gut mucosa. This toxicity occurs due to their inhibition of mitosis, even though differences between worm (target organism) and mammalian tubulin exist [36]. Bone marrow toxicity was described in several animal species, including dogs, cats, people, porcupines [32, 40, 94], and certain avian species appear to be especially sensitive [12, 36, 95].

In cats also mental changes were noted after overdose [74]. Moreover, oxfendazole shows testicular toxicity in laboratory animals [70]. Lethargy and hair loss are other adverse effects described after thiabendazole administration in dogs, a very rare complication might be also a toxic epidermal necrolysis. Dachshunds are reported to be particularly susceptible to it [74].

Benzimidazoles pose a risk if released into water as they show developmental toxicity to fish and aquatic invertebrates [16, 68]. Developmental damage was revealed for several substances also in laboratory animals [26, 89, 98] thus administration of benzimidazole dérivates to pregnant animals should be considered carefully.

Cytochrome P450 isoenzymes are influenced by benzimidazole anthelmintics [7, 75], so the pharmacological consequences of the possible induction or inhibition and complications in co-treatment with other substances must be taken into consideration.

Levamizole

Levamizole is used both as an anthelmintic and immunomodulator. It is considered a drug with narrow therapeutic index and many possible adverse and toxic effects. These negative effects are stimulation of nicotinic acetylcholine receptors and subsequent de creased convulsions threshold [76], paralysis of respiratory muscles, and asphyxia [40]. Toxic and adverse effects can develop in most of the animal species, mainly neurotoxicity has been reported. In dogs also pulmonary oedema and allergic skin reactions were described. In overdose even death due to respiratory failure is possible [74]. In higher doses it induces gastric haemorrhage, bloody vomiting and colic in dogs. Laboratory examinations revealed decreased number of erythrocytes, haematocrit, haemoglobin, increased activity of liver enzymes and urea level in the serum, as well as metabolic alkalosis [34]. In lower doses levamizole may have negative effect on pregnancy rates, probably by stimulating intrauterine immunity [72]. Its misapplication can have severe consequences as intravenous application leads to bradycardia and prolongation of QT interval [90].

Macrocyclic lactones - avermectins and milbemycins

Macrocyclic lactones are anti-endectoparasitic substances widely used in large animals and some of them also in the medicine of pet animals. Mainly ivermectin, but also the others, cause quite a broad spectrum of adverse effects and are very problematic if overdosed or applied in non-target species.

Ivermectin is contraindicated in pet animals. Poisonings have been described in many dog breeds and also in cats. Ivermectin is the drug probably most commonly associated with multi-drug resistance (MDR1) gene mutation in dogs. MDR1 gene codes P-glycoprotein responsible for the drug efflux from brain. This mutation appears mainly in collie and related lineage breeds [63]. The higher permeability of blood-brain barrier to certain drugs allows ivermectin to enter central nervous system and is responsible for the development of neurological adverse effects [40]. Collies suffering from ivermectin toxicity require very long time to recover - up to 3 weeks. Ataxia, disorientation, obtundation, bradycardia, mydriasis, and hypersalivation are common signs of poisoning in them. Stupor and coma were observed in severely affected dogs [39]. Temporary blindness can appear with retinal oedema being responsible for this transient condition in dogs [45]. Unfortunately, ivermectin toxicity was described even in dogs probably without mutation in MDR1 (German shepherd, Labrador retriever, greyhound, Chihuahua, pitbull terrier, dachshund, Jack Russell, beagle and others) [62]. In cats the signs differ a little bit. Paradoxically agitation, tremors, wall-climbing, limb paresis, decrease or absence of ocular reflexes and blindness were described. Ivermectin has to be given carefully to birds in which lethargy, anorexia and deaths were seen [74]. In horses depression, ataxia, muscle fasciculation, mydriasis, decreased pupillary reflexes were noted [86]. Ivermectin poisoning is described in zebra too, with signs similar to those in overdosed horses - ataxia, transient blindness, depression [38]. Treatment is complicated and administration of neostigmine is possible but is not always successful.

Doramectin is used off-label in dogs and in sensitive breeds and individuals with MDR1 mutation it has the same toxic effects as ivermectin [33, 97]. Moxidectin has been reported to cause severe clinical signs similar to other avermectins after its overdose in horses [46].

Fipronil

Fipronil from the group of phenylpyrazoles is considered quite a safe antiparasitic substance, but still cases of its toxicity are reported. Even though the substance itself has the affinity specific to insect γ-aminobutyric acid $GABA_A$ receptors, its metabolites generated by cytochrome P450 are more toxic and their toxicity partially loses its species specificity [37]. In dogs and cats, for which the products are registered, it often causes local alopecia at the place of administration, pruritus of skin and also neurological signs (www.apvma.gov.au).

Fipronil is contraindicated in rabbits as the fatalities and cases with adverse effects like severe lethargy, depression and inappetence occurred [95]. Guinea pigs seem to be very sensitive to fipronil too.

Apoptosis-inducing effect of fipronil was confirmed in vitro, with products of degradation or metabolism having even stronger effect [92]. In rats disturbances in thyroxine metabolism and elimination were observed, but the effect seems to be limited to this species, as in other animals this effect was only minimal [37]. In studies on rats, fipronil was confirmed to alter estradiol and progesterone levels and

cause adverse reproductive effects [69]. Fipronil has the potential to interact with a wide range of xenobiotics or endogenous chemicals that are cytochrome P450 3A4 substrates, thus there is a possibility of eliciting interactions with concurrently administered drugs [88].

Fipronil is highly toxic to fish and water invertebrates. Its lethal doses are very low. Fipronil accumulates in fish body and causes developmental toxicity [83]. Secondary toxicity of fipronil to lizards fed with contaminated insects was described [73].

Pyrethrins and pyrethroids

Pyrethrins are naturally occurring substances extracted from *Chrysanthemum cinerariifolium.* Pyrethroids are synthetic analogues of pyrethrins and both are neurotoxic. Their sites of action are mainly sodium channels in nervous tissue and muscle. We distinguish two types of pyrethroids - type I called also T (tremor) and type II called CS (choreoathetosis and salivation). Type II is considered more toxic [4].

They are used as insecticides in agriculture, households and veterinary medicine. Their use as antiparasitic agents is broad, their toxicity to many animal species is low because of their rapid metabolism and excretion. But there are some exceptions, mainly for fish which are in danger if the agents are used near water sources in nature, or in spaces where uncovered aquarium is placed in households. Another species which is extremely sensitive to some pyrethrins and pyrethroids is cat, due to the lack of the metabolising enzyme glucuronosyl transferase [4, 40]. Cats are also at risk of secondary exposure after the contact with pyrethroid-treated dogs and other pets [85].

In cats poisoning by permethrin formulations used for dogs is probably the most common. Based on the retrospective studies, clinical signs of this poisoning may appear within 3 hours after exposure, but can be also delayed up to 72 hours, and involve tremors/muscle fasciculations, twitches, hyperaesthesia, seizures, pyrexia, ataxia, mydriasis and temporary blindness [11, 85]. During the treatment, complications such as hypothermia, electrolyte abnormalities, aspiration pneumonia, apnoea, cardiorespiratory arrest can appear. Care should be taken when administering benzodiazepines because of the reports on paradoxical reaction and increase in neurological signs in permethrin-poisoned cats. Pyrethroids cause extrapyramidal stimulation so the use of phenothiazine tranquilizers is prohibited. Death or euthanasia may be the consequence of permethrin poisoning in cats in up to 37% of cases [11].

Some of the pyrethroids show reproductive toxicity in both males and females [10] and some have negative effect on haematological and biochemical parameters [17]. They are also known to induce oxidative stress in animal tissues [64].

Amitraz

Amitraz is used as an acaricide and tickicide which influences (activates) α_2 receptors in mammals. Manufacturers do not recommend administration of amitraz-based products to cats and Chihuahua and other toy-breed dogs. Adverse effects, common for all mammals, mediated by its effect on adrenergic receptors are sedation (may be prolonged for up to 72 hours), ataxia, central nervous system (CNS) depression, bradycardia, hypotension, hyperglycaemia [74]. In cats, also respiratory depression, hypothermia, prolonged QT interval, arrhythmias were reported [5]. In

horses, besides the above mentioned general adverse effects, also difficulties in chewing and swallowing, diminished cutaneous sensibility, diminished reflexes, stridor and abdominal breathing were observed [24]. A survey in humans revealed miosis, decreased gastrointestinal motility and transient liver enzymes elevation as other possible adverse effects [91]. Hypothermia and torsades de pointes were recorded after amitraz suicidal intake in a man [41]. In tortoises, main adverse effects included inappetence, changed defecation intervals and eye irritation [15]. A combination of amitraz with metaflumizone should be administered carefully as pemphigus foliaceus-like reaction of both local and systemic character was described in dogs, especially in large breed females [67].

Metronidazole

Metronidazole, a drug from nitroimidazole group, is used as an antiprotozoic and antibacterial (especially for anaerobes) agent. It is registered, for pet animals and birds, but forbidden for the use\in animals used for food production. Metronidazole exhibits plenty of adverse effects, including anorexia, nausea, vomiting and diarrhoea, neurological symptoms - especially cerebellar and vestibular dysfunction, changes in blood count and toxic action on liver [40]. These symptoms may appear in acute, overdose, but also during the chronic treatment with therapeutic doses [74]. Reports on neurotoxicity are known for dogs, cats and also humans [18, 27, 54] but the mechanism of toxic action remains unclear. In overdose the spectrum of clinical signs involves also mydriasis, proprioception deficit, rigidity or seizures. Less common effects described in humans include pancreatitis, pseudomembranous colitis, peripheral neuropathy. Moreover, metronidazole was revealed as a potential teratogen in the studies on laboratory animals. It has not been proven in dogs and cats, but it is still not recommended to use this substance in pregnant animals [74]. In a study on cats its genotoxicity at therapeutic doses was reported [81].

Ionophores

Ionophores are a group of substances (e.g. salinomycin, lasalocid, monensin, maduramicin, semduramicin etc.) with similar properties which are used mainly as coccidiostatic agents. One of their important properties is their ability to bind with monovalent and divalent cations thus influencing and enhancing their movement across membranes and impairing their balance. This principle is responsible for both their efficacy in coccidia control and adverse effects occurrence. Electrolyte imbalances, changes in K^+, Na^+ and especially Ca^{2+} concentrations in cells lead to disturbances in muscle contractility, which might be fatal if cardiac muscle is affected. Another result of excessive calcium in cells can be induction of apoptosis. Calcium overload moreover contributes to the activation of phospholipase A_2, endonucleases and proteases, and enhances intracellular signalling and release of neurotransmitters which is connected with possible cytotoxic effect [47]. The species extremely sensitive to the ionophores action are horse and other equids [40], but the cases of poisonings in cattle, sheep, turkeys, cats, dogs and rabbits were also described [1, 9, 31, 60, 71]. The off-label use is the main reason of these situations, followed by exchange of feed. Clinical signs - anorexia, dyspnoea, tachycardia, ataxia, recumbency and others are described. In cats salinomycin was described to cause peripheral polyneuropathy with paresis and paralysis. Very often the poisoning is severe and leads to the death of affected animals. The attention should be paid also

to the combination of these substances with other medicines. It is really dangerous to combine them with tiamulin which is a potent inhibitor of cytochrome P450 3A, enzyme necessary for the metabolism of many ionophores, or the combination with macrolide antibiotics [8].

Analgesics and non-steroidal anti-inflammatory drugs

Acetaminophen (syn. paracetamol)

Acetaminophen is one of the most common drugs used in human medicine, and unfortunately also one of the drugs most commonly involved in both off-label administration and accidental poisoning of small animals. It belongs to the group of analgesics and antipyretics. Though there are acetaminophen preparations registered for animals (e.g. for pigs), the substance is generally not recommended for use in pet animals and in cats and ferrets it is contraindicated. Cats lack glucuronidation capacity necessary for the detoxification of acetaminophen metabolites, ferrets activity of glucuronosyl-transferase is also low [51]. Dogs metabolize it less than humans too, so even in them it is not recommended [74].

In animals with the low capacity of glucuronidation there is an increased reliance on the sulfation for acetaminophen detoxification. The sulfation pathway is also of limited capacity and if becomes saturated, an alternate cytochrome P450 pathway of acetaminophen metabolism is used. This pathway produces highly reactive acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified by glutathione conjugation. When the NAPQI is produced as the main metabolite of acetaminophen in large quantities, it overwhelms glutathione availability which leads to severe oxidative injury [56].

NAPQI binds to liver cellular proteins, disturbs their function, increases oxidative stress and leads to cell death. NAPQI also causes oxidation of ferrous iron to ferric iron, this leads to the formation of met-haemoglobin. Cats are very sensitive to this type of damage as they have decreased amount of met-haemoglobin-reductase in their red blood cells. Not only haem is affected by this metabolite, but also are sulfhydryl groups of protein part of haemoglobin. Cats have more (8) sulfhydryl groups in their globin part which again makes them more susceptible to erythrocyte injury compared to other species [2]. The degree of the damage is influenced by pre-existing glutathione levels and selenium concentration in the organism [59].

Typical signs of acetaminophen poisoning are anorexia, vomiting, salivation, apathy, dyspnoea, facial oedema. Recumbency, bleeding tendencies, icterus, and hypothermia were described too. In cats, due to the susceptibility to oxidative stress, also methaemoglobinaemia, Heinz bodies formation, hypoxia and cyanosis or brownish colour of mucosa occur. Death comes as a result of hypoxia or due to hepatic failure.

In humans other unusual complications of this poisoning may occur. It is probable that similar adverse effects can be seen in animals too. Metabolic acidosis may appear early after the poisoning or during the hepatic failure. In severe form of intoxication with fulminant hepatic failure, cardiotoxicity (bradycardia, tachycardia, endocarditis), pulmonary toxicity (alveolar damage), thrombocytopaenia and abnormal platelet function, severe hypoglycaemia and renal toxicity (acute tubular necrosis and kidney failure) can appear [43].

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesic substances in both human and veterinary medicine. In the management of animal pain they gained their position in 1990s. Acute pain in quite easy to recognise, but chronic pain is often under-diagnosed in animals. Choice of a proper substance, dosage and application regimen can be a hard task for a veterinarian, as many adverse effects and interspecies differences in most of the NSAID substances exist among animals. The treatment is especially problematic in cats, as there are no data supporting safety during the chronic use of these substances in them [56].

NSAIDs work predominantly by inhibiting cyclooxygenases (COX) thus decreasing the production of prostaglandins (PGE). In general, it is believed that COX1 is the constitutive form of the enzyme, necessary for the regulation of physiological functions, while COX2 is the inducible form of the enzyme synthesised at the place of inflammation. However, there is evidence that COX2 is also a constitutive enzyme in CNS, kidney and reproductive system [56]. Moreover, the drug selectivity for different COX forms can differ between animal species [14]. Both desired analgesic and anti-inflammatory effects and toxic/adverse effects are caused by the usually reversible (and in acetylsalicylic acid irreversible) inhibition of COX. Leukotrienes, produced in higher amounts from arachidonic acid by lipoxygenase due to COX inhibition, can contribute to the gastrotoxicity of NSAIDs [3].

Big interspecies differences in pharmacokinetics of NSAIDs have been reported. Some of NSAIDs (acetylsalicylic acid, carprofen) are metabolised in liver and excreted after conjugation with glucuronides. Based on the knowledge of decreased capability of glucuronidation in cats and ferrets [51], it is clear that those substances will be contraindicated in them. On the other hand, substances metabolised via oxidation as meloxicam and piroxicam do not cause any elimination problem in cats. Interestingly, some of the substances verifiably metabolised by glucuronidation in dogs (flunixin, ketoprofen) are metabolized via different mechanisms in cats [56].

The most common toxic effects connected with NSAIDs administration involve gastrointestinal effects, renal effects, hepatic effects and influence on clotting function.

Gastrointestinal ulceration occurs due to the inhibition of PGE_2 synthesis and decrease in the production of mucosal protective substances as bicarbonates and mucus. Adverse vascular effects (vasoconstriction) may contribute to the situation. Elevated gastrin appears in cats with NSAID-induced renal failure and this increases the risk of ulceration [56].

Nephrotoxicity is related to the inhibition of prostaglandins present in kidneys, which are necessary for the regulation of salt and water balance, vascular tone, blood flow and renin secretion. Prostaglandins under physiological conditions promote vasodilatation, and their effect is required especially in hypovolaemia and decreased blood pressure. NSAIDs (including new generation of COX2 selective inhibitors) effect on prostaglandin synthesis may result in the increase of blood pressure and this effect causes that they interfere with most of the anti-hypertension drugs [19]. Vasoconstriction of the renal vessels and decreased renal blood flow can consequently lead to acute renal failure and death [56].

Hepatotoxicity induced by NSAIDs is rare, but serious adverse effect which may occur. In dogs, it has been described after repetitive administration of carprofen.

Its mechanism is not clear, but some studies suggest immunological background as acyl glucuronide metabolites of NSAIDs can form adducts with liver proteins [6].

Decreased coagulation is the result of the lack of thromboxane A_2 in the platelets (which cannot aggregate) after the administration of COX1 inhibitors. On the other hand, inhibition of prostacyclin production by selective COX2 inhibitors (coxibs) may lead to opposite effect which is increased intravascular coagulation and higher risk of infarction [22, 32].

Acetylsalicylic acid is a traditional substance used for its antipyretic and analgesic properties. This substance should be used cautiously, as it shows many drug interactions. Its irreversible effect on COX causes especially bleeding complications, because platelets cannot synthesise new enzymes and thrombocytes have to be completely renewed for the restoration of coagulation balance [56]. In an overdose, hyperthermia, initial alkalosis followed by a profound metabolic acidosis, muscular weakness, pulmonary and cerebral oedema, seizures and. mineral imbalance appear [74]. Salicylates are suspected teratogens. In **carprofen**, a risk of hepatic and renal damage exists mainly in geriatric patients, in dogs 1/3 of hepatic damage cases was described in Labrador retriever [74]. Also gastric lesions and increased bleeding time were observed after chronic treatment in dogs [58]. **Ibuprofen** in dogs typically causes renal impairment and gastrointestinal ulceration to which especially German shepherds are sensitive. Ferret is another species very susceptible to ibuprofen intoxication. The pathophysiology of ibuprofen toxicity is unknown in ferrets, but the clinical signs after the ingestion are usually severe and involve depression, ataxia, recumbency, tremors, further gastrointestinal effects and renal damage [77]. **Phenylbutazone** belongs to the older NSAIDs. It is registered for the use in dogs and horses, but banned in food-producing animals. Foals and ponies are very sensitive to it, and often develop hypoproteinaemia and gastrointestinal ulceration after its administration. Decreased mineral apposition rate and bone healing rate [78], and neutropenia [61] were detected in horses treated with phenylbutazone. In humans, phenylbutazone is described to cause aplastic anaemia, hypersensitivity reactions and neurological effects. Blood dyscrasias have been observed also in dogs. In overdose, except all common toxic effects, also metabolic acidosis, seizures and hypotension crisis have been described [74]. **Nimesulide** is a new substance from the group of NSAIDs which is not registered for the use in animals in the Czech Republic. It has been reported to cause severe to fatal non dose-related hepatotoxicity in humans [8, 93]. Biliary injury and renal failure after the administration of high doses of this substance were described also in a cat [13]. **Diclofenac** is approved for the use in horses. Its toxicity to birds, especially renal adverse effects, was reported. This toxicity is highly species-dependent with some of the species being very susceptible and doses even lower than therapeutic can be fatal to them. Surprisingly, even secondary poisoning by diclofenac in carrion eaters has been revealed [66]. New COX2 specific drugs are called **coxibs** and their second generation is considered safe with minimal toxic properties and risk of adverse effects. Despite their generally positive profile they were reported to cause gastrointestinal adverse effects, especially in higher doses [17, 35, 55], and occasionally to cause liver injury [25]. In laboratory animals their possible hepatotoxicity and nephrotoxicity was revealed [49].

Others

Antifungal agents belonging to azole group are now commonly used for the therapy of both topical and systemic mycoses. Imidazoles usually undergo very

strong "first pass effect" and do not reach therapeutic concentrations in the body, so they are preferably used for topical mycoses. Triazoles serve as a systematic treatment. Most of the substances influence cytochromes P450 [82] and some of them also P-glycoprotein and may exhibit many drug interactions [53]. Toxicity and adverse effects are often connected with gastrointestinal tract and liver damage and teratogenic properties. Itraconazole in higher doses may lead to the manifestation of hepatotoxicity in dogs, also skin lesions and vasculitis were observed. In cats, hepatotoxicity and depression may be seen. Ketoconazole inhibits the production of testosterone and can cause infertility. Hepatotoxicity, both idiosyncrastic and dose-related is possible and cats are very sensitive to the hepatic damage caused by ketoconazole [74].

Loperamide is an opioid substance with peripheral effect which is generally not approved for the use in animals. Its off-label use by veterinarians is infrequent, but in the literature available the substance is recommended for veterinary practice by several, authors who describe its advantages [30, 48]. On the other hand, there are also reports on its adverse effects and poisonings in animals. Loperamide can be very dangerous for the animals with MDR1 gene mutation for P-glycoprotein in which it crosses blood brain barrier and causes central nervous system toxicity [38, 79]. Moreover, due to its influence on P-glycoprotein and cytochromes P450, loperamide exhibits many drug interactions and has many contraindications - in patients with hypothyroidism, renal and adrenocortical insufficiency, in intoxications, increased cranial pressure, acute abdominal conditions, respiratory dysfunction, hepatopathic encephalopathy. Dogs can develop sedation, paralytic ileus, toxic megacolon, pancreatitis. In cats, possible excitatory behaviour due to the opioid structure of the drug should be taken into consideration [74]. Its administration in humans might be associated with a prolonged urinary retention [29].

Zolpidem belongs to the group of hypnotic drugs used for the treatment of insomnia in humans. It has also sedative and anxiolytic properties. As its half-life is very short in humans, it is believed this substance has a low potential for abuse. Zolpidem becomes prescribed with increasing frequency and increasing are also reports on animals poisoned with it. The substance is pharmacologically similar to benzodiazepines. Clinical signs of poisoning involve ataxia, lethargy, weakness, but sometimes paradoxical reactions can be seen - CNS stimulation, hyperactivity, tremors. Also vomiting, hypersalivation, hyperthermia, dyspnoea and paresis have been noted. Fortunately no fatal cases were described [21, 77].

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