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POISONING OF DOGS BY HUMAN ANALGESICS, ANTIPYRETICS AND ANTIPHLOGISTICS

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ABSTRACT

Paracetamol, ibuprofen and aspirin are among the most commonly used human analgesics, and antipyretics and ibuprofen and aspirin have antiphlogistic effect. They are found in every household all over the world. People use them every day to treat their pain or fever, and ibuprofen and aspirin to reduce inflammation. Dog owners often use these effective drugs to treat their pets, mostly dogs. They are not aware of their harmful effect on the health of their dogs and have no idea about the risks of poisoning. Intoxication of a dog with these human medicines can end in its death. The article provides a summary of basic information about the clinical symptoms of toxicosis caused by ibuprofen, aspirin and paracetamol in dogs and about their treatment.

Key words: aspirin; dog; ibuprofen; paracetamol; poison

INTRODUCTION

Dog owners often try to treat their pets without consulting a veterinarian. They treat their dogs at home, using humane medicines. Among the "most used" are antiphlogistics and analgesics intended for humans, because they are easily available and every home medicine cabinet contains them. Dog owners do not know about the dosage, possible side effects and poisoning, which is why in some cases dogs are poisoned by these human medicines. Up to 19.6 % of all reported poisonings of dogs with human drugs were NSAIDs during 6 years in the Poison Control Centre of Milan [3].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are substances with analgesic, antipyretic and anti-inflammatory effects – they reduce pain, fever and inflammation NSAIDs work by inhibiting the enzyme cyclooxygenase, which catalyses the synthesis of prostaglandins – mediators of inflammation synthesized from arachidonic acid. Arachidonic acid is part of the cell wall and is formed from membrane phospholipids by the enzyme phospholipase A2. NSAIDs also inhibit the synthesis of cytokines

and leukotrienes, the release of lysosomal enzymes and suppress the activity of polymorphonuclear cells and superoxide radicals. Three cyclooxygenases are known in medicine [11].

Cyclooxygenase-1 (COX-1) occurs in most tissues, e.g. in endothelial cells, kidney and stomach smooth muscle cells and platelets. It is necessary for defensive physiological processes in the body. COX-1 ensures the synthesis of prostaglandins responsible for the blood supply of the gastric mucosa, the production of mucus and bicarbonates, and the secretion of hydrochloric acid into the stomach. NSAIDs reduce mucin production by more than 50 % [21].

Cyclooxygenase-2 (COX-2) is produced in macrophages, synoviocytes, fibroblasts, endothelial cells and mast cells in damaged tissues, e.g. in inflammatory processes. By blocking COX-2, NSAIDs reduce the production of prostaglandins, which are used in the pathogenesis of inflammation and in the occurrence of painful sensations, thereby achieving an anti-oedematous and anti-inflammatory effect. In the central nervous system, inhibition of activated COX-2 reduces central sensitization. However, NSAIDs also act on COX-1, which reduces the level of the necessary prostaglandins, which have protective properties, and this can lead to stomach ulcers, duodenal ulcers and internal [10, 22, 23].

The first knowledge about cyclooxygenase 3 was reported in medicine roughly over 20 years ago. Paracetamol is sometimes classified as NSAIDs because of its inhibitory effects on cyclooxygenase. However, its effects are analgesic and antipyretic and it does not have significant antiphlogistic effects. It influences cyclooxygenase within the central nervous system, which is connected with the discovery of COX 3. The cyclooxygenase 3 isoform was discovered only recently, and its inhibition probably represents the basis of the analgesic effect of NSAIDs and paracetamol [10, 22, 23].

The most common poisonings caused by antiphlogistics, analgesics and antipyretics occur during home treatment with ibuprofen, paracetamol and aspirin [3, 9, 15, 24].

Ibuprofen poisoning

Ibuprofen with its antiphlogistic, antipyretic and analgesic properties is a classic representative of drugs from the group of NSAIDs. From a chemical point of view, it is a substituted phenylalkanoic acid with the exact name 2-p-isobutylphenyl propionic acid [4, 17]. In human medicine, it is used as an over-the-counter, relatively safe NSAID drug in the treatment of various painful (e.g. muscle, bone, tooth, ear pain), inflammatory conditions (e.g. arthritis, bone inflammation) and fever. Ibuprofen is not recommended for treatment in dogs, mainly because of the possible risk of stomach ulcers and perforation of the stomach wall. The determined possible therapeutic dose for a dog is 5 $mg.kg^{-1}$ [15]. Intoxication occurs very easily, e.g. when the owner gives a small dog weighing 8 kg one tablet containing 400 mg of ibuprofen. In such a small dog, nausea, diarrhoea, vomiting, loss of appetite, pain in the abdominal area and stomach ulcers were recorded after application. These adverse effects of overdose are described at 50–125 $mg.kg^{-1}$. Renal damage occurs at a dose of 175 $mg.kg^{-1}$ and adverse CNS effects (seizures, ataxia, coma) occur at 400 $mg.kg^{-1}$ [23].

The main clinical symptoms of ibuprofen intoxication include anorexia, nausea, vomitus, lethargy, diarrhoea, melena, ataxia, polyuria and polydipsia. In more severe cases, cardiac arrhythmias, hypotension, acute renal failure, severe CNS depression, hyperkalaemia, respiratory depression, and metabolic acidosis are added [9]. Post mortem, erosions, ulcerations and perforations are recorded in the stomach, duodenum, but also in the large intestine of poisoned dogs. The diagnosis of intoxication is based on a detailed anamnesis, which depends on the ability of the owner to correctly and truthfully inform the veterinarian about the administration of drugs, but also on the development of clinical symptoms. The blood level of ibuprofen cannot be routinely determined, but gas chromatography or mass spectrophotometry can be used for analysis from serum, urine or liver tissue [17, 19].

The basic principle of therapy is the prevention and treatment of stomach ulcers, kidney failure, effects on the CNS and liver. The prognosis is good if the animal is treated in the early stages of intoxication. According to the animal's current condition, the veterinarian determines the appropriate therapy. In milder cases, the first step is the administration of activated charcoal, which must be repeated because of the enterohepatic recirculation of ibuprofen [9, 19].

A very important step is the protection of the gastric mucosa, the most commonly used is misoprostol. Misoprostol is a synthetic prostaglandin that reduces the secretion of gastric acids and has a cytoprotective effect on the gas-

tric mucosa. The dosage is 1–5 μg.kg^{-1} 3–4 times a day per person. It should be served for at least a week. For ulcers, sucralfate (0.5–1 g.kg^{-1} *per os* every 8–12 h) is used, which binds to the proteins of the necrotic tissue at the site of the ulcer. Sucralfate creates a protective layer that prevents the digestive activity of pepsin, stomach acid and bile salts. It prevents pepsin activity by approximately 30 % [16]. To reduce the secretion of gastric acid, H2 blockers are administered, which also inhibit histamine. Ranitidine is 3–13 times more potent than cimetidine and is administered at a dose of 2 mg.kg^{-1} orally or intravenously every 8 hours. Moreover, it was found that cimetidine was found to increase the rate and extent of ibuprofen absorption in rats [12, 14]. Metoclopramide (0.2–0.4 mg.kg^{-1} every 6–8 hours orally or subcutaneously) is administered to control vomiting. Mild stomach irritation in a milder case can be solved by administering antacids, e.g. magnesium or aluminium hydroxide [16]. A case was described in which an intoxicated dog (200 mg.kg^{-1}) underwent therapeutic plasma exchange in addition to general procedures. A cycle of therapeutic plasma exchange was performed over 180 minutes, achieving 1.5 plasma volume exchanges. An 85 % reduction in plasma ibuprofen concentration occurred and the authors recommend considering therapeutic plasma exchange in acute ibuprofen intoxication due to the rapid and effective nature of the treatment [24].

If the condition is serious and convulsions are also present, diazepam is administered in a dose of 0.5–1.0 mg.kg^{-1} intravenously, the application must be gradual in a dose of 5–10 mg. In case of bleeding conditions, hypotension and to maintain renal functions, infusions with electrolytes, possibly with dopamine and blood substitutes are applied. In metabolic acidosis, sodium bicarbonate is given slowly intravenously. Serious states of intoxication end in coma and death of the animal [9, 16, 25].

Aspirin poisoning

Acetylsalicylic acid (a synthetic derivative of salicylic acid) is known as aspirin and is one of the oldest NSAIDs. It was already produced in 1897. It is an analgesic, antiphlogistic, antipyretic and also acts as an anticoagulant [2]. Its greatest use is in human medicine, but it also has its place in veterinary medicine, where it is used in the prevention and treatment of certain diseases of poultry, calves, pigs and horses. Not recommended for therapy in dogs and cats [23].

Acetylsalicylic acid is rapidly absorbed in the stomach of monogastric animals. An acidic environment accelerates its absorption, but also its deacetylation to salicylic acid. Clinically significant concentration in plasma is reached in 30 minutes, maximum concentration in 2 hours. After absorption, it binds to proteins, especially albumin, and passes into tissues affected by inflammation. Acetylsalicylic acid is hydrolysed in the body into salicylic acid and acetic acid. This transformation takes place mainly in the liver, to a lesser extent in the gastrointestinal tract, plasma, red blood cells and synovial fluid. Acetylsalicylic acid is excreted from the body mainly through urine [2].

The analgesic effect caused by the inhibition of cyclooxygenase and subsequently prostaglandins is peripheral (in inflamed tissues), but also central at the level of the hypothalamus. The antiphlogistic effect also consists in inhibiting the production of prostaglandins and other mediators of inflammation. The antipyretic effect of aspirin is central and peripheral. With central, the production of prostaglandins and other mediators of inflammation in the CNS, especially in the hypothalamus, decreases. The peripheral effect consists in the subsequent increase in perfusion (temperature) of the skin, acral parts of the body and the production of sweat. The result of the mentioned processes is a decrease in the central body temperature. The stated effect is not achieved when the body is dehydrated. Acetylsalicylic acid inhibits platelet cyclooxygenase before it is broken down (anti-aggregative action) [2, 23].

Clinical signs of acetylsalicylic acid poisoning are characterized by depression, fever, hyperpnoea, gastritis or gastric ulcers, seizures, metabolic acidosis, renal failure, and coma [5, 23]. Although dogs tolerate acetylsalicylic acid better than cats, therapy with this drug can result in the development of gastric ulcers. The therapeutic dose for dogs, although not recommended, is set at 10 mg.kg^{-1} per person. Administering aspirin at a dose of 25 mg.kg^{-1} 3 times daily *per os* caused 50 % of dogs to develop gastric erosions after 2 days. When aspirin was administered at a dose of 35 mg.kg^{-1} 3 times a day, the development of gastric ulcers was detected after 3 days in 66 % of dogs. Acute intoxication (450–500 mg.kg^{-1}) can result in gastrointestinal disturbances, hyperthermia, dyspnoea, seizures and even coma [8, 23].

Intoxication therapy is symptomatic, similar to ibuprofen intoxication. The first step is the decontamination of the organism, in the form of administration of black

coal, vomiting can be induced immediately after taking the medicine. Similar to the treatment of ibuprofen intoxication, substances are administered to protect the gastric mucosa and i.v. sodium bicarbonate solution to adjust the acid-base balance. In the early stages of overdose or poisoning and in mild cases of intoxication, the prognosis is good [16].

Paracetamol poisoning

Paracetamol, also known under the name acetaminophen (4'-hydroxyacetanilide N-acetyl-p-aminophenol N-(4-Hydroxyphenyl) acetamide), is a synthetic non-opiate derivative of p-aminophenol. It has analgesic and antipyretic activity similar to aspirin, but does not have anti-inflammatory effects and does not act on platelets. The inhibition of paracetamol on individual COXs is the subject of several scientific discussions and opinions are not uniform. In a simplified way, the effect of paracetamol can be summed up in a definition: paracetamol inhibits COX-2 (cyclooxygenase 2) in the hypothalamus (antipyretic effect) and indirectly acts on serotonin 5-HT3 receptors in the spinal cord (analgesic effect) [16, 18, 23].

A therapeutic dose of 10 $mg.kg^{-1}$ is given for the dog, but it is not used to treat canine diseases [6, 16]. In dogs, acetaminophen toxicosis develops after consumption of the drug in ranges from 75 $mg.kg^{-1}$ to 150 to 200 $mg.kg^{-1}$ [20]. The toxicity of paracetamol in dogs manifests itself after a single toxic dose or after several, cumulative doses. Symptoms of toxicity usually appear at doses greater than 100 $mg.kg^{-1}$. Paracetamol is rapidly absorbed in the stomach and small intestine. The maximum plasma concentration is reached in 30–60 min. after ingestion. It penetrates the tissues by simple diffusion [7].

Paracetamol is primarily metabolized in the liver and is subsequently eliminated by conjugation into ineffective glucuronide and sulphate metabolites and excreted by the kidneys. A smaller percentage of acetaminophen (5–10 %) is metabolized within the hepatic cytochrome P-450 enzyme system to a highly reactive minor alkylating metabolite (N-acetyl-p-benzo-quinoneimine, abbreviated NAPQI), which represents the main toxic effects of acetaminophen. NAPQI is neutralized in the liver by glucuronidation with glutathione, but when glutathione stores are depleted (below 70 %) and the reaction is saturated, NAPQI binds to liver cell membranes, disrupts lipid layers, and subsequently causes damage and death of hepatocytes. NAPQI has a strong oxidizing effect on red blood cells, which leads to the conversion of haemoglobin into methaemoglobin (incapable of binding oxygen). Haemoglobin oxidation can also lead to the formation of Heinz bodies (denatured haemoglobin clusters) [7, 15].

The main consequences of paracetamol intoxication are methaemoglobinaemia and hepatotoxicity. The clinical presentation is variable from moderate to severe cases. The main findings are depression, weakness, tachypnoea, dyspnoea, cyanosis, icterus, vomitus, hypothermia, facial or paw oedema, etc. Due to methaemoglobinaemia, the mucous membranes are brown, mud-coloured, and tachycardia, tachypnoea, and lethargy are present. Large doses of acetaminophen can cause hepatic necrosis, nephrotoxicity (necrosis of the proximal tubules in the kidney), and death [15]. A veterinarian determines paracetamol intoxication most often on the basis of anamnesis and accompanying clinical symptoms. The level of paracetamol is determined in plasma preferably within 4 hours after exposure. As part of the differential diagnosis, substances damaging the liver and causing methaemoglobinaemia must be excluded: naphthalene, nitrites, chlorates, some mycotoxins, coal tar, plants containing pyrrolizidine alkaloids, etc. [18]. The prognosis is good if treatment is started in the early stages of poisoning. The basic principles of paracetamol intoxication treatment are stabilization of the patient, replenishment of glutathione, the conversion of methaemoglobin back to haemoglobin, prevention and treatment of hepatic necrosis. Hepatotoxicity develops 24–36 hours after ingestion of a toxic dose [7].

If there are no contraindications, emesis should be induced as soon as possible (vomiting also occurs as one of the symptoms of poisoning). In case of contraindications, gastric lavage is possible, but it is less effective. Another procedure involves the administration of black coal at a dose of 1–3 $g.kg^{-1}$, always at 2–3 hourly intervals because of enterohepatic recirculation of acetaminophen [1, 9]. For several reasons, the administration of N-acetylcysteine (NAC) (precursor of glutathione, binding to acetaminophenol metabolites) is recommended in a 5 % solution *per os* at an initial dose of 140 $mg.kg^{-1}$ and then 70 $mg.kg^{-1}$ every 4 hours in 3–5 repetitions. In humans, its administration is described as most effective within 8–10 hours of paracetamol ingestion [1, 7, 16]. For supportive therapy, ascorbic acid is used at a dose of 30 $mg.kg^{-1}$ 4 times a day *per os*, to accelerate the conversion of methaemoglobin

back to haemoglobin [13]. It is also recommended to use cimetidine in a dose of 5–10 mg.kg^{-1} per person, i.m. or i.v. every 8 hours. Blood methaemoglobin values and values of liver and kidney biochemical parameters should be monitored in the patient. The length of treatment depends on the degree of intoxication, on clinical symptoms, while the treatment of hepatic necrosis can take several weeks to months [16, 18].

CONCLUSIONS

Ibuprofen, acetylsalicylic acid and paracetamol are drugs that are not suitable for the treatment of inflammation and fever in dogs. Currently, safer antiphlogistics, analgesics and antipyretics are available in veterinary medicine for clinical practice, such as: ketoprofen, carprofen, meloxicam, flunixin and others. Veterinarians should warn dog owners about the possible risks of self-treatment and the use of human drugs in the treatment of their pets.

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