Side-effects of non-steroidal anti-inflammatory drugs on the liver in dogs and hepatoprotective effect of plant remedies

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Abstract

Hepatoprotective effect of plant drugs against hepatic tissue injury induced by non-steroidal anti-inflammatory drugs (NSAIDs) was assessed on Beagle dogs. The adverse effects of carprofen and robenacoxib on the hepatic tissue were evaluated on the basis of histopathological examination of liver sections. It was demonstrated that the use of NSAIDs with liquorice and composed plant remedy Pectosol® caused a reduction of hepatic adverse effects induced by the administration of NSAIDs. This fact indicates a hepatoprotective effect of the tested plant remedies during the treatment with NSAIDs. However, the results require further studies on a larger group of animals. Liquorice and Pectosol® reduce the hepatic side effects, which develop after the treatment with carprofen and, to a lesser extent, robenacoxib in young Beagles. Such studies allow to investigate the negative and positive effects of using robenacoxib and carprofen in dogs and, therefore, help to limit the NSAID-induced side effects on the liver in these animals.

Keywords: dog, liver, non-steroidal anti-inflammatory drugs, liquorice, Pectosol®.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely-used in the long-term treatment of pain associated with arthritis in dogs. They are also used in the prevention and therapy of postoperative pain in these animals (20, 23). This study was prompted by the increasingly common use of NSAIDs and a lack of interest in the use of medicines, that may eliminate the side effects of the therapy on the liver (3). The majority of papers related to this subject discuss only damage to the mucosa of the digestive tract (4, 9, 30). Even though, these lesions are seen as the foreground effect of NSAID treatment, and potential damage to the liver should not be overlooked (28).

A review of literature demonstrates that for many years clinicians have been supporting treatment protocols with human drugs, which often indicate a hepatoprotective action in dogs (5, 32, 33). However, it is not known whether their efficacy is reliable or whether it results only from a reduction in the absorption of NSAIDs used in the combined therapy. A further investigation of the problem is needed.

Carprofen is a poorly-selective cyclooxygenase inhibitor (COX) and robenacoxib is a selective COX-2 inhibitor. Due to the degree of COX inhibition, carprofen administration is more frequently associated with damage of the mucosa of the digestive tract than the treatment with robenacoxib (13, 18, 21). It is unknown whether this relation concerns the hepatic injury. As reported in the studies on the safety of carprofen treatment conducted by McPhail et al. (22), the liver is also susceptible to damage induced by NSAIDs in dogs. Even though, this exemption from the rule is not associated with the basic mechanism of NSAID action; it probably occurs due to the metabolic transformations of the drug in the liver. It is unknown whether the hepatic toxicity induced by NSAIDs seen in some cases is an individual reaction or whether it develops depending on the drug dose (6).

Carprofen is in 99% bound by plasma proteins. Its metabolism involves the liver and the drug is excreted...
with faeces (70% – 80%) and urine (10% – 20%) (13, 21). In dogs, it is predominantly metabolised in the liver. The robenacoxib is mainly excreted with bile (65%) (18).

The data on alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase activities and results of histopathological examination allow to investigate the impact of NSAIDs on the liver in dogs (26). However, the cited authors emphasise that the harmful effects on the liver associated with NSAIDs were probably only an exacerbation of pre-existing organ damage, which was detected in 1.6% of dogs with degenerative joint disease treated with robenacoxib or carprofen in the field studies (6, 22, 23, 26, 29).

It was decided to use liquorice in the experiment, which is considered to be effective in preventing hepatotoxicity on the liver in co-thrapy with NSAIDs (5, 16, 32, 33). However, the protective action on the liver of a liquorice preparation has not been examined in dogs. Huo et al. (16) and Yin et al. (36) demonstrated the anti-oxidative action of liquorice extract and its hepatoprotective effect on the liver in rats and carps. It has also been shown that liquorice exhibits anti-inflammatory properties due to the presence of glycyrrhizic acid and its metabolite glycyrrhetinic acid (1, 19, 25).

Since liquorice increases potassium excretion and the concentration of sodium in the serum, it cannot be used in dogs with confirmed hypernatraemia or hypokaliemia (1). Long-term administration of liquorice preparations causes sodium chloride retention in the body and elevates the water content in tissues, which results in oedema and hypertension (1, 19, 25). As is clear from our clinical experience, liquorice products can be used in dogs for a short period of 1 to 4 weeks, without any impact on the ion profile, at 50 mg for dogs of 10 kg b.w. per day.

Pectosol® (composition: saponariae root, herb hyssop, icelandic lichen, thyme herb, extraction solvent 70% etanole and 10 g glycerol) has been used successfully in human medicine to protect the liver during NSAID therapy (14, 19). This remedy contains many bioactive compounds with potentially hepatoprotective effects. It exhibits anti-inflammatory and antibacterial properties and protectively normalises the function of the hepatocytes (19, 24, 27, 31). Pectosol® is used in dogs at a standard dose of 0.1 mL/kg, PO, once every 24 hours, diluted with warm water 1:5 (unpublished data).

The objective of the study was to compare the potential hepatic toxicity of carprofen and robenacoxib in dogs and to evaluate the hepatoprotective effects of liquorice and Pectosol®.

Material and Methods

All procedures were carried out in accordance with the recommendations of the International Council for Laboratory Animal Science (ICLAS) and the Council of Europe (7). The studies were conducted in accordance with the Animal Ethics Committee for animal testing issued by the Dean of the Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn.

Animals. Twenty-five healthy Beagle dogs (thirteen males and twelve females, aged 13 - 14 weeks, weighing 4.3 – 5.5 kg at the beginning of the trial) were used in the experiment. Before the study, a complete blood count (CBC) and serum biochemical analyses were performed to ensure that the Beagle dogs were healthy. Clinical examinations were performed daily during the experiment. The dogs were placed in rooms prepared for animal experiments at the temperature between 17 and 21°C. They were kept for 51 days in five boxes with five individuals in each. The boxes were tiled and the rooms were air-conditioned. The animals were fed a balanced complete Puppy Junior Diet with fish (FORZA 10, Italy). The animals had an unrestricted access to water. No mortality occurred in the trial.

Experimental protocol and drug administration. The biochemical and haematological analyses, as well as the clinical examination confirmed the good health status of all dogs during a 30-day acclimatisation period. The crossover study comprised 21 d of drug administration. All medicines were applied by the same investigator between 1:00 - 2:00 pm. The dogs were randomly assigned to five treatment groups (n = 5). Each group received different drugs. The dogs in the group I received carprofen (Rimadyl®; Zoetis, Poland) in a dose of 2 mg/kg, PO, q 24 h, while dogs in group II received carprofen at 2 mg/kg, PO, q 24 h, and 50 mg/dog of a liquorice extract (Lukrecja, Herbapol Kraków, Poland) and a herbal drug (Pectosol®; Herbapol Pruszków, Poland) in the dose of 0.1 mL/kg, PO, q 24 h, diluted 1:5 with water. The dogs in group III received robenacoxib (Onsior™ Novartis, United Kingdom) in the dose of 2 mg/kg, PO, q 24 h. The dogs in group IV received robenacoxib 2 mg/kg, PO, q 24 h with liquorice extract in a dose of 50 mg/dog, PO, q 24 h and Pectosol® in a dose of 0.1 mL/kg, PO, q 24 h, diluted 1:5 with water. The dogs in a control group V received an empty gelatine capsule.

Blood biochemistry. The following blood chemistry parameters were analysed: activity of alanine aminotransferase (ALAT), aspartate aminotransferase (ASPAT), alkaline phosphatase (ALP), γ-glutamyltransferase (GGTP), as well as concentrations of glucose (GLU), urea (UREA), Na⁺, and K⁺. Blood biochemistry analysis was done three times: on the day preceding the beginning of drugs administration (day “0”) and on days 11 and 21 of the trial. Blood was collected from the cephalic vein. Blood for testing (2 mL) was collected into a tube with a coagulation activator (Serum Separation – Eurotubo, DETALAB, Spain). All samples were tested within one
hour after collecting. The biochemical parameters were determined with an automatic biochemical analyser and reagents manufactured by the same company (ACCENT-200; Cormay, China). The ion profile was performed on a Rapilab-348 analyser with ion-selective electrodes (Rapilab-348 analyser; Simens, Poland).

Anaesthesia. The anaesthetic was administered with 0.05 mg/kg atropine sulfate (Atropinum sulfuricum, Polfa, Poland) and 0.4 mg/kg acepromazine maleate (Calmivet, Vétoquinol, France) given subcutaneously. In all cases, a 24-gauge catheter was inserted in the cephalic vein. The induction of general anaesthesia was performed using a combination of 4 mg/kg of ketamine (Bioketan, Biovet, Poland) and 1 mg/kg of xylazine (Rometar, SPOFA, Czech Republic) in the same syringe, given into the cephalic vein. All animals were intubated after the abolition of laryngeal reflexes. The anaesthesia was deepened by administration of isoflurane (Isoflurane, Abbott, United Kingdom) at a concentration of 1.8% - 2%. During the endoscopic procedure, a 0.9% sodium chloride solution was administered at 5 mL/kg/h intravenously. Pain therapy was continued for 24 h after endoscopy with tramadol hydrochloride (Tramal 50, Polpharma SA, Poland) 2 - 3 mg/kg, administered in the hind limb.

Liver biopsy. A laparoscopic biopsy of the liver was performed on day “0” and day 21 of the trial. It was done with a laparoscopy set composed of the following devices: a source of cold light Power Led 175 (Storz, Germany), a camera header with a HDTV driver Image 1 (Storz, Germany), a CO₂ thermoflator insufflator with a SCB module with gas heating (Storz, Germany), a Hamou Endomat wash and suction pump (Storz, Germany), and 10 mm Hopkins II 0° optics (Storz, Germany). The laparoscopy procedure was protected with a set of tools for a classic celiotomy.

The dogs were positioned in dorsal recumbency for the procedure. Pneumoperitoneum was set at 10 – 14 mmHg with the use of carbon dioxide heated to the body temperature. An optical port (11 mm in diameter) was placed in the medial line approx. 1 cm cranially to the navel. The optics were directed to the subcostal area where, with direct visual guidance, a Bard Monopony (Bard, USA) biopsy needle was introduced laterally to the linea alba into the peritoneum. Due to the small dimensions of the examined organs, 150 mm needles of 18 G in size were used and the biopsy plates were 7 mm long. In each case, the left lateral liver lobe was biopsied, which resulted in minor interstitial bleeding.

Preparation of histopathological specimens and lesion scoring. The needle with liver tissue was removed and the sample was then put in a container with a 10% buffered formalin solution. The specimens were saturated with "intermediate" solutions and embedded in paraffin blocks. The sections were stained with haematoxylin and eosin (HE). A NIKON ECLIPSE 80i optical microscope equipped with a NIKON PS – Fi1 digital camera (ECLIPSE 80i; NIKON, Japan) was used for the evaluation of the preparations.

The microscopic lesions were evaluated with a scale, where 0 represented a lack of evident changes in relation to the normal tissue; 1 – minor lesions (up to 30% of the tissue were affected); 2 – moderate lesions (between 31% and 60% of the tissue were affected); 3 – severe lesions (the most advanced lesions; from 61% to 100% of the tissue were affected).

In order to perform the Q Cochran test, the microscopic lesions were encoded as follows: when no histopathological lesion was seen before or after the treatment, the lesion was marked as “0”, but if a lesion was found at the beginning of the trial or at the end, it was encoded as “1”. If at the beginning of the trial a lesion was assessed as 1 and on day 21, it was encoded as 2, then the code “2” was assigned.

Statistical analysis. The blood biochemistry results and ion profile were analysed with parametric and non-parametric statistical methods. A multivariate analysis of variance with repeatable measurements (MANOVA) was applied for GLU, ALAT, ASPAT, and UREA. The other biochemical indices were analysed separately with the Kruskal – Wallis non-parametric test. P < 0.05 was assumed as significant for all analysed parameters. This data was presented as the mean and standard deviation (SD).

A Q Cochran test was performed to analyse the impact of the examined drug combinations on the effects seen in the liver. By performing the Chi² statistics, the odds ratio (OR) and the absolute risk increase (ARI) were calculated as the measurement independent of the number of cases.

The statistical analysis was performed with the Statistica 9.1 (StatSoft, Inc. 2010, STATISTICA data analysis software system, version 9.1. www.statsoft.com).

The Chi² statistics were performed and the standardised remainders were calculated to indicate which box in the table differed most from the normal distribution by size. The standardised remainders were fitted to the normal distribution with the mean at 0 and the standard deviation of 1; values higher than 2 were statistically significant.

Results

Blood biochemistry. The results of blood biochemistry, tested on day “0” in the dogs from all experimental groups, did not show any deviation from the physiological reference values.

The results of the analysis showed that the ASPAT concentration increased in the serum and reached the highest value in mid-trial (on day 11) in all examined groups (I – 52.8 U/L; II – 50.8 U/L; III – 50.4 U/L; IV – 48.2 U/L; V – 25.4 U/L). After 21 d of treatment, this value still exceeded the reference values, yet with
a reduced tendency (I – 50.6 U/L; II – 43.0 U/L; III – 49.6 U/L; IV – 46.6 U/L; V – 27.8 U/L). By comparing the groups with each other over time, it was found that the animals that were administered carprofen had the lowest concentration of urea on day 21 and the means for the groups I and II were slightly above the reference (group I – 2.992 mmol/L; III – 3.180 mmol/L). An increase in average ALP concentration was detected in the majority of examined animals on day 11 (I – 234.5 U/L; II – 164.4 U/L; III – 211.2 U/L; IV – 160.1 U/L). On day 21, the average serum concentration of ALP was within the reference values in all examined dogs.

The results of GLU, GGTP, and ALAT concentrations in serum were compatible with the reference values.

The analysis of the results for the animals that were administered the capsules with powdered liquorice root (groups II and IV) did not reveal any long-term changes in the concentration of sodium ions (P = 0.374966) or the concentration of potassium ions over time (P = 0.141038). No statistically significant differences were found in relation to the concentration of sodium (P = 0.601425) and potassium (P = 0.661626) ions, when the data from dogs in groups II and IV were compared with the results of control group.

Macroscopic examination of the liver. Diagnostic laparoscopy allowed for a thorough inspection of the abdominal organs during their biopsy. By using artificially-induced pneumoperitoneum, it was possible to evaluate macroscopically the liver, as well as to control bleeding after biopsy. In all cases, both before and after treatment, the liver did not show any gross lesions.

Microscopic examination of the liver. In order to statistically analyse the impact of the examined drug combinations on the hepatic tissue, a Q Cochran test was performed to compare the changes before and after the treatment. Statistically significant changes (P < 0.013202) were found between the groups. The highest number of changes was found in group I (55%) whereas group II differed least from the control group (25% of changes).

The Chi² statistics was used to estimate the variation in the number of individual microscopic lesions depending on the drug used. This method compared the occurrence and severity of individual lesions between groups. The highest count of lesions was detected in the dogs administered robenacoxib (mild degeneration in three dogs) and carprofen (mild degeneration in two dogs and moderate degeneration in two dogs) (Fig. 1). It is worth mentioning that the results were better in the dogs receiving protective plant remedies: in group I (mild degeneration in one dog and moderate degeneration in one dog) and in group IV (mild degeneration in two dogs). Hepatic parenchymatous degeneration was also seen in one dog from the control group which may suggest congenital liver defect.

The results of a Chi² test for hepatic necrosis as a variable demonstrated that this lesion was present in the dogs administered carprofen. In three dogs from this group, necrosis was evaluated as “1” (a mild degree) (Fig. 2). Mild necrosis was seen in two dogs from this group. The dogs that were administered robenacoxib alone for 21 d were free of hepatic necrosis. In the animals that received robenacoxib and plant remedies, mild necrosis was observed in two cases.

The results of a Chi² test showed that inflammatory cells infiltrated the liver statistically significantly more often in the dogs administered carprofen separately than would have resulted from
a randomised distribution (a mild lesion in one dog and a moderate lesion in one dog) (Fig. 3). Mild infiltration was detected only in one dog in group II and one individual in group III. No such lesions were found in the animals receiving robenacoxib with plant remedies or in the control group.

![Image of liver biopsy](image_url)

**Fig. 3.** The liver of a dog from group I on day 21 of the trial. Infiltration with inflammatory cells surrounding hepatocytes (black arrow) is observed. A lymphocyte (blue arrow) and an eosinophil (red arrow) are seen. HE, 40x

The results of a Chi² test showed that mild cholestasis was most often reported in the liver bioplates in the dogs administered carprofen (mild cholestasis in two dogs). A mild lesion was observed in only one dog from the group, which received robenacoxib (Fig. 4). No cholestatis was observed in the liver in the groups II and IV treated with plant remedies.

![Image of liver biopsy](image_url)

**Fig. 4.** The liver of a dog from group III on day 21 of the trial. Cholestasis is observed. Vague structure of the hepatic parenchyma; a distended bile tubule filled with bile is seen. HE, 40x

The absolute risk increase (ARI) as the factor that increases the risk of an adverse effect and is a measurement independent of the number of cases, was also calculated for the microscopic lesions in the liver. The highest probability of an adverse microscopic lesion in the liver was determined in the dogs administered carprofen (ARI = - 0.45) whereas the results indicating the lowest severity of lesions were recorded in the group of dogs that received carprofen and plant remedies for 21 d (ARI = - 0.15). In described groups III and IV, ARI was equal to 0.2.

**Discussion**

This is the first study on the protective effect of plant extracts on hepatic tissue in young dogs. However, this protocol has been widely used in clinical practice on young dogs tested with NSAIDs. None of the animals has displayed clinical side effects (Szweda, unpublished observations). This is the first study under laboratory conditions focusing on a detailed investigation of the side-effects of carprofen on the hepatic tissue compared with robenacoxib in dogs. An increase in the activity of transaminases was reported during treatment with NSAIDs. This is a manifestation of hepatic functional disorders, a disruption of hepatocyte integrity or an increase in bilirubin and alkaline phosphatase. This fact reflects damage to the bile tract or bile release mechanism in the hepatocyte (2, 17). The most advanced changes were recorded for ASPAT, as its concentration increased and reached the highest level in the mid-treatment in the group of dogs that received carprofen.

Carprofen is metabolised by P<sub>450</sub> cytochrome in the liver, which is associated with hepatic and bile tract disorders such as an increase in the activity of transaminases, alkaline phosphatase, γ-glutamyltransferase, and in bilirubin concentration (2, 12, 13). Similar to other NSAIDs, the administration of carprofen poses a risk of idiosyncratic reaction in the liver. The hepatotoxic effects of carprofen in dogs have been reported by some authors (13, 23, 25). Nakagawa et al. (26) described a fatal case of carprofen-induced hepatic toxicity in a young Siberian Husky, by blood tests that revealed an increase in ALAT (3489 U/L), ASPAT (2630 U/L), ALP (211 U/L), and TBA (51.2 µmol/L). The use of carprofen, as confirmed in numerous studies (10, 22, 26), resulted in an increase in the ASPAT concentration in the present study.

In rare cases of robenacoxib administration in dogs ASPAT and ALAT exceed the reference values (18). It is reported by the producer that in up to 10% of
animals, an increase in the hepatic enzyme activity has been observed during a long-term administration of the product. No increase in the hepatic enzymes has been reported during a 2-week treatment in dogs. However, long-term clinical trials have often demonstrated increased activities of hepatic enzymes. In the majority of cases, no clinical symptoms were observed and the level of hepatic enzymes stabilised or decreased despite further administration of the product. An increase in hepatic enzyme activities combined with the clinical symptoms, namely anorexia, apathy, and vomiting, is uncommon (10, 15). The concentrations of ALP, ALAT, and ASPAT, and gross and microscopic examinations of the liver did not demonstrate any hepatic injury during treatment with robenacoxib in dogs (even after six months of therapy at a dose of 10 mg/kg) (18, 29). In our study, an increase in the concentration of ASPAT was detected. This confirms that the administration of robenacoxib in puppies for three weeks may provoke hepatic injury, manifested by an increase in ASPAT.

An increase in the average concentration of ALP observed in the majority of dogs, most probably results from bone growth in these animals in the present study. Increased activity of ALP reported in these dogs also at day 0 may confirm this thesis (27).

Based on the blood biochemistry tests (due to a lack of statistically significant differences), it cannot be decisively concluded how plant remedies impact the changes in the blood biochemistry parameters and, thereby, hepatic functions in the dog. It should be emphasised that an increase in ASPAT and ALP activity was lower when the tested NSAIDs were administered together with plant remedies. However, it should be noted that some studies carried out in Switzerland have demonstrated a hepatoprotective effect of liquorice in laboratory rats as evidenced by blood biochemistry tests (16, 32).

The present study demonstrates that the use of NSAIDs in dogs is associated with microscopic lesions in the liver. Parenchymatous and vacuolar degeneration of the hepatocytes was the predominant lesion in this organ.

A Q-Cochran test was performed in order to analyse statistically the impact of investigated drug combinations on the adverse effects in the liver and to compare the lesions before and after treatment. The test included all analysed morphological lesions (degeneration, necrosis, infiltration with inflammatory cells, and cholestasis). The majority of the lesions were seen in group I treated with carprofen while the dogs in group II, receiving carprofen and plant remedies, differed the least from the control.

The same results were recorded by calculating the odds ratio (OR) and the absolute risk increase (ARI) in the liver.

However, the results were not so unequivocal when the groups were compared for the occurrence and severity of individual lesions in the liver. The analysis of the variable “hepatic degeneration” indicated that the dogs administered carprofen or robenacoxib separately differed from the control group. If the plant remedies were used together with the tested NSAIDs, degenerative lesions were less frequently reported in the liver. Necrosis was most often seen in the dogs, which received carprofen for 21 d, whereas necrosis was not found in the liver biopsies in the dogs administered robenacoxib alone for 21 d. In the group that was administered robenacoxib with plant remedies, hepatic necrosis was detected in two bioplates. The cause of necrosis in these dogs seems to depend on herbal components but this thesis requires additional research. Furthermore, this result is not reflected by the results of blood examination and descriptions of the cited authors (16, 25, 34). Hepatic necrosis was not observed in the dogs that were treated with robenacoxib alone. However, hepatic necrosis was observed in two dogs that were treated with robenacoxib and hepatoprotective plant drugs. As evidenced by own studies, inflammatory cells infiltrated the liver most often in the dogs administered carprofen. This lesion was not found in the animals, which received robenacoxib with plant remedies. Cholestasis was most often reported in the liver biopsies sampled from the dogs that were administered carprofen. Cholestatitis was not observed in the animals that received NSAID with plant medicines.

Few studies have focused on identifying histopathological lesions associated with the administration of NSAIDs similar to the studies on the reduction of toxic effects of NSAIDs in dogs. Based on the results of studies on humans and animals, it was agreed that the digestive tract, kidneys, and liver are the organs predisposed to NSAID-induced damage in dogs (3). NSAIDs may cause a toxic injury in the liver. Rey’s syndrome is the extreme example. In dogs, the liver damage associated with NSAID administration seems to be independent of the degree of cyclooxygenase inhibition by the tested drugs (12, 18, 21). The authors, who have discussed the hepatotoxic effect of carprofen in dogs do not agree on whether it results from an idiosyncratic reaction (dose-independent) or depends on the dose (13, 21). An individual reaction seems to be the most probable explanation of the toxic damage in the liver reported in dogs administered carprofen (22). The case of a 4-year-old Siberian Husky has shown that with individual predispositions, carprofen administration at the recommended dose for 14 d may be fatal due to acute necrosis of hepatocytes. The post-mortem gross examination of this animal revealed hepatomegaly and petechiae in the kidney. Histopathologically, multinucleolar hepatocytes, enlarged nuclei and nucleoli, as well as vacuolar degeneration and hepatocyte necrosis were predominant. The accumulation of bile pigments in the bile tubules and in hepatocytes was observed (26). Numerous papers have reported fatal cases of hepatotoxic effects of carprofen...
administration (22). The conducted study allowed for the identification of the toxic effects of this drug in the liver. However, they were not advanced enough to be clinically manifested. The observed microscopic lesions were predominantly of a degenerative nature (parenchymatous or vacuolar), which is probably associated with the pathways of this drug in the body (12, 13). King et al. (18) confirmed that robenacoxib administration (even at a dose five times higher than recommended) does not induce any gross or histological lesions in the liver. Reymond et al. (29) proved that the adverse effects in the liver (reported in 1.6% of dogs with osteoarthritis that were administered robenacoxib and carprofen) were probably caused by hepatic damages before the initiation of the treatment. These results are contradictory with the conclusions of our studies where the microscopic lesions were observed in biopates sampled from dogs, which were administered robenacoxib (alone or in combined treatment), which is probably related to metabolism drug in the liver (18). As shown in the literature, the use of carprofen was more often associated with liver damage than robenacoxib. This explains why the administration of carprofen combined with plant remedies has more beneficial effect on liver protection than robenacoxib.

There are studies confirming beneficial impact of liquorice on the liver in animals. Studies conducted in Switzerland demonstrated hepatoprotective properties of liquorice. In 1985, in Japan, this plant was shown to be effective in the treatment of chronic jaundice and hepatic cirrhosis in humans (8, 11, 16). Our studies also indicated that the microscopic lesions in the liver were less statistically advanced in the dogs administered with plant remedies.

In human medicine, some authors have indicated that liquorice increases potassium excretion from the body and elevates the concentration of sodium in the blood (1, 8, 11, 16, 30, 34). These observations were not confirmed in the present trial and there was no linear tendency over time for these parameters in the dogs.

There are many studies confirming hepatoprotective effect of particular components of Pectosol®. In human medicine herb hyssop and icelandic lichen are indicated for the treatment of cholelithiasis and cholelastis, thyme herb helps digestion of fat and acts relaxant on the bile ducts, while the saponariae root increases the amount of bile secretion by the liver and facilitate its flow into the duodenum (2, 5, 14, 19). Our study for the first time concerns the relationship between components of Pectosol® and liver pathology.

In conclusion, carprofen causes more severe microscopic lesions in the canine liver than robenacoxib. Liquorice and Pectosol®, by showing hepatoprotective properties, reduce the side effects of carprofen and, to a lesser extent, robenacoxib in the liver of young Beagles. The standard blood biochemistry is not a sufficiently sensitive test to demonstrate the toxicity of NSAIDs and to confirm the hepatoprotective properties of the tested plant remedies in dogs. The above results may not necessarily apply to the whole dog population. Further studies, including the pharmacokinetics of Pectosol and Lukrecja in the dogs including the distribution and elimination phases, are needed to confirm the suitability of the protocol used in this experiment.

References