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Use of ciprofibrate in dogs with hypertriglyceridemia

Abstract

The objective of this study was to evaluate the effect of ciprofibrate on serum triglyceride concentrations in canine patients. A sample size of 21 canines was study, that had a diagnosis of familial dyslipidemia, and was established with triglyceride levels above 500mg/dl, treatment with ciprofibrate was evaluated at 2 months. The analysis of the variation in triglyceride levels was performed using the non-parametric Wilcoxon matched-pairs signed-rank test. The Wilcoxon test revealed that the triglyceride concentration decreased significantly after two months of treatment with ciprofibrate; from 621 (512 to 1046)mg/dL to 136 (67 to 215)mg/dL ($p < 0.0001$). The difference in medians was -482.0md/dL with a 97.3% confidence interval of -579.0 to -443.0mg/dL. It was concluded that the use of drugs such as ciprofibrate in the treatment of patients with familial hiperlipidemia, had a significant decrease in serum triglyceride concentrations, without generating adverse reactions in this study.

Keywords: dyslipidemia, canine, fibrates, lipemic

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Introduction

Dyslipidemia is a common condition in canines and can be primary or more commonly secondary to other diseases,[1] it is defined as an altered level of one or more types of blood lipid particles: high-density lipoprotein (HDL), low-density lipoprotein (LDL), intermediate density lipoprotein (IDL), very low density lipoprotein (VLDL), triglycerides or cholesterol, generated by a disorder in lipoprotein metabolism.[2]

Primary origin dyslipidemias are rare in canines, appear to have a genetic basis, and are generally, but not always, associated with certain specific breeds such as Miniature Schnauzers, known as the breed with the most common primary lipid disorder among dogs. canines,[1] Shetland Sheepdogs,[3] Beagle, Doberman, Rottweiler, Great Pyrenees, Brie Shepherds and UK Longhaired Collies.[4]

Secondary dyslipidemias are generally associated with endocrine diseases such as: hypothyroidism, diabetes mellitus and hyperadrenocorticism[1], and among the other possible causes reported we find: obesity, high-fat diets, lymphoma, protein-losing nephropathies, cholestasis, Leishmania infantum infections, congestive heart failure associated with dilated cardiomyopathy, parvovirus enteritis, and the use of some drugs such as glucocorticoids, estrogens, phenobarbital, and potassium bromide.[1,4]

Hyperlipidemias generate different complications, in humans the main one is cardiovascular disease such as sudden cardiac death, myocardial infarction or cerebrovascular accidents, but it has been seen that appropriate treatment of this alteration reduces the risk of mortality from all causes.[5]

It has also been associated with different complications in canines, such as pancreatitis, insulin resistance, liver disorders, biliary mucocele, seizures, behavioral disorders, neuropathies, ocular disorders, development of endothelial lesions that can cause cardiovascular dysfunction and affect organs such as brain and kidneys and atherosclerosis, although atherosclerosis in canines is described less frequently than in humans since in this species the HDL/LDL ratio is inverse.

In addition, it has been seen that the severity of the associated complications is closely related to the levels of circulating lipids,[6] which is why it is necessary to implement an effective therapy to normalize the concentrations of lipid particles early.[7]

The first step to be able to carry out effective therapy is to detect whether the dyslipidemia is primary or secondary, and if it is secondary, it is necessary to detect and manage the concomitant disease appropriately. After that, traditionally the first line of treatment is the use of a a low-fat diet and if this does not regulate lipid concentrations, the use of lipid lowering agents must be considered.[1]

There are several lipid-lowering drugs and due to the association in humans between hyperlipidemia and cardiovascular disorders, many new therapeutic compounds are being developed. The oldest are statins, fibrates, bile acid sequestrants and niacins but there are newer compounds such as drugs that act on lipoprotein synthesis: squalene synthase inhibitors, microsomal transfer protein (MTP) inhibitors, or those that act on the intestinal absorption of lipids.[8]

In veterinary medicine, the use of: statins, bile acid sequestrants, niacins, fibrates and inhibitors of intestinal lipid absorption such as dirlotapide has been described in canines.[9]

Fibrates include chlorofibrate, gemfibrozil, gemfibrate, ciprofibrate, bezafibrate, and fenofibrate.[10] These drugs act by stimulating the induction of lipoprotein lipase, increasing hepatic uptake of fatty acids, reducing hepatic production of triglycerides, increasing the elimination of low-density lipoproteins, and increasing the production of high-density lipoproteins.[11]

There are few data on the use of fibrates in veterinary medicine, but recent studies have shown that fenofibrate is a safe and effective compound for the management of severe hyperlipidemia characterized by hypertriglyceridemia, regardless of its cause, and that the combination of fenofibrate and a low fat diet can also reduce cholesterol levels, without generating significant side effects.[12]

In human medicine, the effectiveness of ciprofibrate in controlling triglycerides and total cholesterol is well known,[13] and it has also been seen that this drug has the ability to reduce fibrinogen levels, a risk factor for vascular events, C-reactive protein, transaminases such as Gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP); probably associated with the decrease in fat deposits in the liver observed with the use of the drug.[14] It is important to consider that, as with the use of other agonist fibrates of the PPAR-α nuclear receptor, such as bezafibrate and fenofibrate, in humans it has been seen that the use of ciprofibrate can cause an increase in plasma creatinine levels, however the increase is mild, reversible and not

develop kidney failure.[14,15] Gemfibrozil is the only fibrate that does not appear to have this side effect and should be preferred in these types of patients.[15]

The effect of Ciprofibrate on HDL particle concentrations has also been studied due to its well-known atheroprotective effect obtained from "reverse cholesterol transport", a process in which cholesterol is removed from peripheral tissues to the liver to be excreted through the bile. In rodents, an increase in bile flow and therefore cholesterol secretion has been seen by this means associated with the use of Ciprofibrate, but contrary to what is observed in humans, fibrates decrease HDL cholesterol concentrations in this species, generating an increase in the size of the particles, this is generated by the reduction in the expression of the apolipoprotein components apoA-I and apo A-II28, which demonstrates a species-specific regulation of the apolipoprotein given by these drugs, and the increase in size is has been associated with a decrease in the expression of the HDL scavenger class B type I receptor (SR-BI) in the liver, which decreases hepatic cholesterol uptake.[15] While in humans, treatment with ciprofibrate combined with an isocaloric diet has shown an effect significant beneficial in the lipid profile, decreasing the concentrations of triglycerides and cholesterol, increasing HDL cholesterol and lowering cholesterol levels no HDL,[1] without generating significant alterations in laboratory tests or incidents of myopathies. Although it is important to consider that the response to treatment varies between individuals, with excessive body weight being an important determinant, especially in the regulation of HDL cholesterol.[16]

In humans, treatment with ciprofibrate combined with an isocaloric diet has shown a constant significant beneficial effect on the lipid profile, decreasing triglyceride and cholesterol concentrations, increasing HDL cholesterol, and lowering non-HDL cholesterol levels; without generating significant changes in the tests, laboratory tests or incidents of myopathies. Although it is important to consider that the response to treatment varies between individuals, with excessive body weight being an important determinant, especially in the regulation of HDL cholesterol.[17]

The objective of this study was to evaluate the effect of ciprofibrate on serum triglyceride concentrations in canine patients.

Materials and methods

For the evaluation of treatment with ciprofibrate, a sample size of 21 canines (n=21) that had a diagnosis of familial dyslipidemia, and was established with triglyceride levels above 500mg/dl. Patients with hyperlipidemia secondary to other pathologies were used as exclusion criteria. Treatment with ciprofibrate was evaluated at 2 months using the "Wilcoxon matched-pairs signed-rank" test.

Experimental design

As inclusion criteria, patients with suspicion or diagnosis will be evaluated and all cases presenting hyperlipidemia secondary to another pathology will be excluded. The study established a maximum sample size of 21 individuals (n=21), based on national incidence data; using a 95% 1-α confidence level, an expected loss ratio of 15%, and a precision of 3%.

Blood samples were collected by venipuncture of the cephalic vein, and then placed in a tube without anticoagulant to measure lipids, which was measured immediately in Mindray BS480 - Valtek.

Animals

The patients studied were eleven (11) females and ten (10) males. With an age range between 4 and 15 years, with a mean age of 10.4 years, all females in the study were neutered at the time of sample collection; When evaluating the analyzed breeds, there were 15 mixed race patients, 2 of the Poodle race, 1 Beagle, and 3 Schnauzers.

Body condition was assessed on a 9 point morphometric body condition index, with dogs considered having an ideal body condition with a score of 5 out of 9, establishing a condition 5, dogs with palpable ribs, waist presence, and abdomen tucked up when viewed from the side.[18]

As inclusion criteria, all dogs presented blood count and serum biochemistry tests, evaluating liver transaminases, creatinine, BUN, calcium, phosphorus, cholesterol, and albumin within range; as well as a normal clinical examination, that evaluated the anamnesis, evaluation of mucous membranes, lymph nodes, auscultation of the thoracic and abdominal, temperature, pressure, and evaluation of the skin.[19] Normoglycemic dogs were considered with glycemia between 80-110mg/dl, glucose measurement was performed by enzymatic method with Mindray BS480 Valtek.

The procedures were authorized by the Bioethics Committee of the Faculty of Life Sciences (FCV) of the University Andres Bello.

Statistical analysis

The analysis of the variation in triglyceride levels was performed using the non-parametric Wilcoxon matched-pairs signed-rank test. All confidence intervals are 95% level, statistical significance of 5% was used and data were processed in the statistical program STATA 16.0.

Results

The Wilcoxon test revealed that the triglyceride concentration decreased significantly after two months of treatment with ciprofibrate; from 621 (512 to 1046)mg/dL to 136 (67 to 215)mg/dL ($p < 0.0001$). The difference in medians was -482.0md/dL with a 97.3% confidence interval of -579.0 to -443.0mg/dL (Figure 1).

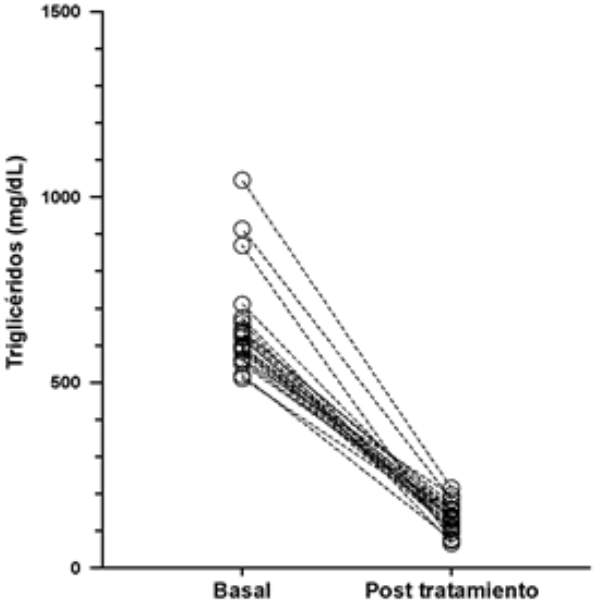

Figure 1 Baseline and two months triglyceride levels after treatment with Ciprofibrate.

Discussion

The evaluation of primary or secondary dyslipidemia is essential to evaluate the best therapy for patients with dyslipidemia. In the

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secondary dyslipidemia, management must be comprehensive, managing the concomitant disease, in conjunction with low-fat diets, and in some cases implementing pharmacological therapy.[1] Especially in those patients in which triglycerides are above 500mg/dl.[9]

Currently there are several options for lipid-lowering drugs for canine patients, HMG CoA reductase inhibitors or statins, bile acid sequestrants such as nicotinic acid, and fibric acid derivatives. Recently, dirlotapide began to be used in veterinary medicine.[8]

In the study carried out, the efficacy of ciprofibrate in canines with hyperlipidemia was demonstrated for the first time, administering the drug in a period of two months, where the values of hypertriglyceridemia presented by the patients before treatment with ciprofibrate were between 512mg/dL and 1046mg/dL, and after the administration of ciprofibrate, significantly lower levels of triglycerides were obtained, with a mean of 134.9mg/dL.

In a study conducted in humans, successful results were also obtained with the use of ciprofibrate in dyslipidemic patients, where a decrease in total cholesterol of 15%, LDL of 10% and triglycerides of 52% was observed. In addition, an effect was also found on apoprotein levels, generating an increase in apoprotein A and a decrease in apoprotein B and E.[14] In another study in humans, in which 437 patients were studied, successful results were also obtained, observing a 44% decrease in triglyceride levels and a 10% increase in HDL cholesterol concentrations after receiving 100 mg/day of ciprofibrate for 4 months. In humans, these alterations receive particular importance since they represent a risk factor for the development of cardiovascular diseases.[17]

The impact of fibrates on HDL cholesterol metabolism and the functionality of high-density lipoproteins in the species has been evaluated in rodents. For this, they were fed with a diet supplemented with 0.2% ciprofibrate for 7 days. Ciprofibrate significantly decreased plasma triglyceride levels (15.6±3.97mg/dL vs. 0.98±0.63mg/dL, p=0.0286) and hepatic expression of the HDL SR-BI receptor, which was correlated with an increase in the size of HDL particles, without generating an improvement in HDL cholesterol levels.[16]

Based on previous studies, it can be seen that ciprofibrate is an efficient drug to reduce hypertriglyceridemia concentrations in canines, rodents, and humans; however, one of the limitations of our study, was that side effects were not analyzed in Depth, and neither is its effectiveness in managing HDL cholesterol after the 2-month study.

In humans, its effect on the kidneys is well known, since in several studies, it is described that serum creatinine levels increase, albeit slightly, without generating significant changes in urea and uric acid.[14,15] In rodents, treatment with ciprofibrate generates hepatomegaly, evidenced by an increase in their absolute weight, as a consequence of hepatocyte hypertrophy,[16] while in humans the activity of GGT and ALP transamines decreased afterwards. The use of ciprofibrate, independent of triglyceride levels.[14]

Finally, the side effects of long-term use of ciprofibrate in canines were not studied in depth with this study design, although no changes were seen in its levels in the short term.

Conclusion

Hyperlipidemia is an important pathology in canine patients, however, there is a predominance by some breeds, such as Miniature Schnauzers. Primary or secondary hyperlipidemia, when it persists over time and worsens, should be treated with drugs like the fibrates.

Based on the data generated previously, it is possible to conclude that the use of drugs such as ciprofibrate in the treatment of patients with familial hyperlipidemia had a significant decrease in serum triglyceride concentrations in the recently analyzed samples, without generating adverse reactions during the time it was administered the drug in the study.

Further studies are needed to evaluate the side effects of fibrates in canines. It is known that in humans the use of ciprofibrate can cause an increase in plasma creatinine, while in rodents it can cause hepatomegaly, changes that should be evaluated in future studies with the use of this drug.

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Conflicts of interest

Author declares there is no conflict of interest in publishing the article.

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