# Tolerability of pimobendan in the ferret (*Mustela putorius furo*)

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## ABSTRACT

**Pimobendan, an inodilator, is often recommended for the treatment of dilated cardiomyopathy (DCM) in dogs. DCM is also quite often seen with ferrets, but little is known about the effects of pimobendan on this animal. In the present tolerability study, three groups of five ferrets were used. Over a period of eight weeks, the first test group received a placebo twice daily, the second group received a dosage of 0.5 mg/kg pimobendan (Vetmedin®, Boehringer Ingelheim, Brussels, Belgium) twice daily, and the third group received a dosage of 1.5 mg/kg twice daily. All the ferrets remained clinically healthy throughout the experiment. Monitoring of the blood values showed a tendency towards increasing gamma glutamyltranspeptidase values. Except for some practical problems due to the taste of the product, no major objections were seen in this study for the use of pimobendan in ferrets. Further research is required to confirm this conclusion.**

## INTRODUCTION

In middle-aged to older pet ferrets, cardiac disease is a commonly occurring problem. Up until now, recommended dosages for cardiac drugs in ferrets have only been published in the literature for classic drugs such as diuretics, Ace inhibitors and digoxin (Petrie, 2004). In canine medicine, pimobendan, an inodilator, is often recommended as a treatment for dilated cardiomyopathy (DCM) (Luis Fuentes *et al.*, 2002). The use of pimobendan as a treatment for DCM in ferrets has only been mentioned anecdotically (Delprat, 2005).

Drugs used in ferrets are generally not registered for use in this animal species and dosages are often determined empirically, based on knowledge of other species (Morrisey and Carpenter, 2004). It may be assumed that pimobendan can be used as an effective drug for the treatment of DCM in ferrets, as it is registered for this indication for use in dogs. However, it is advisable to administer this drug off label to ferrets only after some information concerning the tolerance of the drug in ferrets is available. Therefore, it was the aim of this study to assess the tolerance of pimobendan in this target animal and to identify possible side effects of the use of this drug over the course of long-term administration.

## MATERIALS AND METHODS

The experiment was approved by the Ethical Committee of the Faculty of Veterinary Medicine, Ghent University. Fifteen eight-month old fitch ferrets (*Mustela putorius furo*), seven females and eight males (Triple F Farms Inc., Sayre, PA, USA), were included in this study. The animals were randomly divided into three test groups. They were housed individually and received food (Prestige Duo Ferret®, Versele Laga, Deinze, Belgium) and water ad libitum. Daily food and water uptake was measured. For two hours per day, the ferrets were allowed to play together in a playroom, without access to food or drinking water. Over a period of eight weeks, the first test group received a placebo (cellulose powder) twice daily, the second group received a dosage of 0.5 mg/kg pimobendan (Vetmedin®, Boehringer Ingelheim, Brussels, Belgium) twice daily, and the third group received a dosage of 1.5 mg/kg pimobendan twice daily. These pimobendan dosages were twice and six times the recommended dosages for dogs, respectively. The placebo and the pimobendan powder were suspended in 0.5 ml FerreTone® oil (Eight in One Pet Products, Hauppage, NY, USA), a food supplement for ferrets consisting of different oils and vitamins, and administered orally using a 1 ml disposable syringe. The study was blinded. Weekly, the ferrets were weighed and their dose was adjusted to their actual weight. On day 0 (the day before the first pimobendan administration), day 28 and day 56, the ferrets were anesthetised using isoflurane (Isoflo®, Abbott Laboratories Ltd., Queensborough, UK) and a two-ml blood sample was taken from the *vena cava cranialis*. The following blood parameters were determined: hemoglobin, packed cell volume, number of erythrocytes, reticulocytes and thrombocytes, number and formula of leucocytes, urea, creatinin, total protein, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT or AST), serum glutamic pyruvic transaminase (SGPT or ALT), gamma glutamyltranspeptidase (GGT), alkaline

phosphatase (AP) and glucose. The values obtained were compared with the normal values provided by the analyzing laboratory (AML, Antwerp, Belgium), and with those provided in the literature (Quesenberry and Orcutt, 2004; Gamble and Morrisey, 2005). A statistical comparison was made of the cumulative food and water uptake in the different test groups during the experiment by means of one-way analysis of variance (ANOVA), and pairwise comparisons between groups were performed using the Least Significant Difference (LSD) test (confidence interval 95%, $p < 0.05$). To evaluate the equivalence between the blood parameters of the placebo and the drug treatment groups (0.5 and 1.5 mg/kg) at day 28 and 56, the 95% confidence interval of the difference was derived at these two time points.

## RESULTS

Clinically, all the ferrets remained healthy during the experiment. Vomiting was seen in one ferret of the third group immediately after the administration of 1.5 mg/kg pimobendan, on day 5 and on day 7 of the experiment. Although the study was blinded, after a few days it became clear which ferrets belonged to the placebo group and which ferrets were receiving the pimobendan. The placebo group was very docile when the oil was administered, while the ferrets of the two other test groups struggled and were unwilling to ingest their medication. No significant differences were found between the cumulative food and water uptake of the three test groups ($p > 0.05$). Table 1 shows the mean value of the different blood parameters at day 56 for the placebo and the 1.5 mg/kg group. The difference and the confidence intervals on the difference are also shown. All the observed differences between the placebo group and the treatment group were small. The 95% confidence intervals were sometimes rather wide (due to the restricted sample size), but nevertheless they were sufficiently narrow to claim equivalence. The results of these blood parameters for the individual ferrets were also compared with the normal values for ferrets provided by the analyzing laboratory, and no animals fell out of the normal range except for the number of leucocytes, which varied substantially and was sometimes found to be lower and sometimes higher than expected from the normal values. This was seen in all three groups and in animals of both sexes. GGT increased in three out of five ferrets of the 1.5 mg/kg dose, both on the second and the third blood sampling occasions, with one animal slightly exceeding the normal value as provided by the laboratory (16 IU/l).

## DISCUSSION

From this study, it appears that pimobendan has no negative effect on the general health of ferrets. The biggest disadvantage noted in this study was the fact that the ferrets were reluctant to ingest the pimobendan.

**Table 1. Mean (± standard deviation) value of the different blood parameters at day 56 for the 1.5 mg/kg group and the placebo group. The difference between these groups and the 95% confidence interval on the difference is also shown.**

| | Normal values | | | Mean (1.5 mg/kg) | Mean (placebo) | Difference | Confidence interval | |
|---|---|---|---|---|---|---|---|---|
| | a | b | c | (± SD) | (± SD) | | lower | upper |
| Blood urea nitrogen (mg/dl) | (12-43) | 28 (12-43) | (8-90) | 52.6 (± 9.6) | 62.4 (± 10.8) | -9.8 | -24.2 | 4.8 |
| Creatinine (mg/dl) | (0.2-0.6) | 0.4 (0.2-0.6) | (0.16-0.84) | 0.308 (± 0.033) | 0.37 (± 0.046) | -0.062 | -0.132 | 0.008 |
| Total protein (g/dl) | (5.3-7.2) | 5.9 (5.3-7.2) | (4.4-7.3) | 6.18 (± 0.29) | 6.38 (± 0.63) | -0.2 | -0.888 | 0.488 |
| Total Bilirubin (mg/dl) | (0-0.1) | - | (0.1-0.5) | 0.13 (± 0.04) | 0.156 (± 0.05) | -0.026 | -0.092 | 0.040 |
| AST (IU/l) | (57-248) | - | (23-99) | 114.4 (± 37.2) | 147.6 (± 19.8) | -33.2 | -75.9 | 9.5 |
| ALT (IU/l) | (82-289) | 170 (82-289) | (13-176) | 103.6 (± 32.8) | 108.6 (± 22.5) | -5 | -46 | 36 |
| GGT (IU/l) | - | 5 | (1-13) | 7.4 (± 5.41) | 4.2 (± 1.79) | 3.2 | -2.7 | 9.1 |
| AP (IU/l) | (30-120) | 53 (30-120) | (6-30) | 17.2 (± 6.53) | 29.6 (± 40.61) | -12.4 | -51.1 | 26.3 |
| Glucose (mg/dl) | (62.5-134) | 101 (63-134) | (65-164) | 95 (± 6.0) | 100 (± 14.7) | -5 | -20 | 10 |
| Hemoglobin (g/dl) | (15.2-17.7)* | (12.0-17.4)* | (13.0-18.0) | 14.82 (± 0.94) | 14.6 (± 0.75) | 0.22 | -1.01 | 1.45 |
| Hematocrit (%) | (46-57)* | (36-51)* | (38-54) | 51.08 (± 3.16) | 50.36 (± 2.28) | 0.72 | -3.33 | 4.77 |
| Red blood cells ($10^6$/ul) | - | - | (7.0-11.0) | 9.10 (± 0.49) | 9.14 (± 0.41) | -0.034 | -0.960 | 0.892 |
| White blood cells ($10^3$/ul) | (2.5-10.8)* | (2.5-15.4)* | (2.8-8.0) | 7.37 (± 2.18) | 9.71 (± 1.87) | -2.34 | -5.68 | 1.00 |
| Neutrophils (%) | - | (12-78)* | (39-85) | 41.2 (± 13.54) | 53.84 (± 8.45) | -12.64 | -28.61 | 3.33 |
| Lymfocytes (%) | - | (25-95)* | (11-55) | 49.6 (± 13.43) | 39.06 (± 8.45) | 10.54 | -5.04 | 26.12 |
| Monocytes (%) | - | (1.7-8.2)* | (0.8-4.4) | 2.26 (± 0.29) | 2.08 (± 0.83) | 0.18 | -0.83 | 1.19 |
| Eosinophils (%) | - | (0-9)* | (1.0-8.0) | 6.60 (± 1.98) | 4.56 (± 1.11) | 2.04 | -0.43 | 4.51 |
| Basophils (%) | - | (0-2.9)* | - | 0.30 (± 0.19) | 0.44 (± 0.13) | -0.14 | -0.38 | 0.10 |
| Platelets ($10^3$/ul) | - | - | (350-600) | 453 (± 181) | 443 (± 43) | 10.2 | -170.7 | 191.1 |
| Reticulocytes (%) | (1-14)*/** | - | - | 0.64 (± 0.38) | 0.76 (± 0.29) | -0.12 | -0.58 | 0.34 |

a: Quesenberry and Orcutt, 2004; references for fitch ferrets
b: Gamble and Morrisey, 2005; references for fitch ferrets
c: AML laboratory
* the full range is given (taking into account both the male and the female values)
** reference for albino ferrets

This can probably be attributed to the palatability of the product. The FerreTone® oil, which is being marketed as a tasty food supplement, was not able to mask the unpleasant taste of pimobendan. Therefore in practice it would be advisable to prepare capsules with the correct dose for administration, to prevent the pimobendan from coming into contact with the ferret's mouth. In dogs, as well, the product is administered in the form of capsules. However, the administration of capsules or pills to ferrets is not easy (Quesenberry and Orcutt, 2004) and there is a risk that the capsules will be bitten open or dissolve in the oral cavity. Very recently in Germany an alternative formulation of pimobendan was registered for use in dogs, consisting of a chewable tablet with an artificial meat flavor. This could also be an alternative for the administration of the product to ferrets. The development of a palatable solution or suspension would be even more beneficial for simplifying the product's administration.

Vomiting was seen twice in one ferret immediately after the administration of 1.5 mg/kg pimobendan. Vomiting is a side effect that has also been noticed in dogs, where it appeared to be dose-dependent and disappeared with lowering of the dose (Lombard, 2000). However, it is not sure whether the vomiting in this ferret should not be attributed to the taste of the product or to stress provoked by the handling of the animal.

The normal upper value of GGT provided by the laboratory (1 – 13 IU/l) was slightly exceeded in one ferret out of five receiving 1.5 mg/kg pimobendan twice daily. An increase of GGT was additionally seen in three out of five ferrets for the duration of the experiment when compared to their GGT value before the first pimobendan administration. It must be noted, however, that in another ferret of this test group, after an initial increase to 6 IU/l with the second blood sampling, the GGT value lowered again to less than 3 IU/l with the third blood sampling. Not much literature is available concerning the significance of GGT in ferrets, but the serum enzymes of the ferret are similar in many ways to those of the cat (Jenkins, 2000). In the cat, GGT is analyzed for indicating liver disease (Willard, 1989; Meyer and Harvey, 1998). Other liver enzymes and metabolites examined in this study, including SGPT, SGOT, AP and total bilirubin, remained within the normal range, however. Furthermore, in ferrets receiving the lower dose of 0.5 mg/kg pimobendan twice daily, which is double the dose recommended for dogs, this increase in GGT level was not clear. Therefore, it cannot be concluded from this study whether the long-term administration of pimobendan does or does not have a negative effect on the liver of ferrets. If this drug is to be used for the long-term treatment of ferrets in practice, it might possibly be advisable to monitor the liver enzymes of the patient with regular blood samplings. In view of these preliminary results, it would be wise to conduct a larger tolerance study including more animals, which would also have to be sacrificed for histopathological analysis of their organs, such as the liver, after long-term pimobendan administration. Furthermore, in view of the fact that the oral bioavailability in humans is only moderate (about 53%) (Chu *et al.*, 1995), the pharmacokinetics and bioavailability after administration of different pharmaceutical preparations should be included in further studies of pimobendan in ferrets.

In conclusion, it can be stated that, except for some practical problems due to the taste of the product, no major objections were seen in this study to the use of pimobendan in ferrets, though further research is required to confirm this conclusion.

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