Use of Meloxicam for the Long-term Treatment of Musculoskeletal Disorders in Cats

FIELD OF THE INVENTION

The present invention is directed to the long-term use of meloxicam to treat musculoskeletal disorders in cats with and without pre-existing renal disease without any negative effects on renal function.

BACKGROUND OF THE INVENTION

Meloxicam is the only molecule licensed for treatment of chronic musculoskeletal disorders in cats. These conditions affect the quality of life of cats and often require treatment. Impaired renal function is currently listed as a contraindication on NSAID data sheets. However, chronic renal disease and chronic musculoskeletal disorders, such as osteoarthritis (OA) are common in elderly cats and often coexist. Osteoarthritis affects synovial joints, associated with loss of cartilage, inflammation, bone remodelling and formation of osteophytes. It is usually idiopathic and primarily affects elbow joints and hips. Clinical signs include for example difficulty in jumping, lameness, stiffness as well as behavioural changes such as demeanour, reduced grooming and resentment of handling.

Meloxicam was licensed for long-term use in cats in 2007 at an oral dose of 0.1 mg/ kg on day 1 followed by 0.05 mg/ kg. However, there is no prior art that demonstrates that the use of meloxicam is appropriate for long-term treatment of feline. It is reported by Gunew that feline suffering from osteoarthritis can be treated with meloxicam in a concentration range between 0.01 – 0.03 mg/ kg. (Gunew et al., Long-term safety, efficacy and palatability of oral meloxicam at 0.01 – 0.03 mg/ kg for treatment of osteoarthritic pain in cats. Journal of Feline

Medicine and Surgery 2008, 10, 235-241) The trials were completed after a mean treatment duration of 5.8 months. However, since this study does not include any comparable placebo product and uses subjectivemeasurements only, its conclusions are questionable. A short-term (23 days) concept study performed by Clarke & Bennett has also shown that a daily meloxicam dosage of 0.05 mg/ cat can be used to treat osteoarthritis. (Clarke & Bennett, Feline osterarthritis: a prospective study of 28 cases. Journal of Small Animal Practice 2006, 47, 439-445) This study does not include any thorough investigation and assessment of meloxicam treatment over a longer period of time.

Therefore, it is an object of the present invention to develop a long-term treatment of musculoskeletal disorders in cats, especially aged cats, with and without pre-existing renal disease and without accelerating the progression of renal diseases in cats.

DESCRIPTION OF THE INVENTION

Surprisingly, it has been found that meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base thereof may be used for the long-term treatment of musculoskeletal disorders in cats, especially aged cats, with or without pre-existing renal disease, without having any negative effect on renal functions in cats during a treatment from 10 to 40 months or more.

Thus, the invention related to the use of meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base thereof for the preparation of a veterinary medical composition having analgesic efficacy for the long-term treatment of musculoskeletal disorders such as but not limiting to osteoarthritis in cats, particularly in older cats, without having any negative effects on renal functions during a treatment from 10 to 40 months or more. Treatment with such a formulation will not accelerate already existing renal diseases in older cats, nor initiate any renal disease. According to the invention the pharmacologically acceptable meloxicam salt comprises the meglumine,

potassium or ammonium salt, preferably the meloxicam meglumine salt.

The present invention provides a formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base, one or more vehicles, and optionally one or more suitable additives, for the long term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more. Further the invention relates to the use of a formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more vehicles for preparing a veterinary medical composition having analgesic efficacy for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more. Said formulation contains or essentially consists of meloxicam or a pharmacologically acceptable salt thereof, water, optionally one or more additives selected from group of consisting of buffers, solubilisers, preservatives and optionally thickeners.

Meloxicam or a pharmacologically acceptable salt thereof for the long-term treatment of musculoskeletal disorders in cats having a pre-existing renal disease or having no pre-existing renal disease. Further, the invention relates to meloxicam or a pharmacologically acceptable salt thereof for the long-term treatment of musculoskeletal disorders in cats with chronic kidney disease. The musculoskeletal disease comprises but not limited to osteoarthritis.

The treatment occurs over a long-term period of at least 6 months, preferred ranges are selected from the group selected of 10 to 40 months, 10 to 37 months, 10 to 30 months, 10 to 25 months, 10 to 20 months, 10 to 17 months, 11 to 40 months, 11 to 37 months, 11 to 30 months, 11 to 25 months, 11 to 20 months, 11 to 17 months, 12 to 40 months, 12 to 37 months, 12 to 30 months, 12 to 25 months, 12 to 20 months, 12 to 17 months, 13 to 40 months, 13 to 37 months, 13 to 30 months, 13 to 25 months, 13 to 20 months, 13 to 17 months,

14 to 40 months, 14 to 37 months, 14 to 30 months, 14 to 25 months, 14 to 20 months and 14 to 17 months.

Older cats or aged cats are herein defined as being 5 years old or older, preferably from 5 to 20 years, even more preferably from 7 to 17 years, especially preferred from 10 to 13.4 to 15.5 to 16 years. Studies have shown that 53 % of cats over 7 years of age have renal diseases. Renal diseases may include acquired renal diseases such as chronic tubulo-interstitial nephritis, glomerulonephritis, pyelonephritis, amyloidosis, hydronephrosis, renal lymphoma or congenital diseases that cause kidney failure in cats such as polycystic kidney disease, renal aplasia, renal hypoplasia, renal dysplasia, amyloidosis. These may or may not be in a chronic disease state. However, the treatment is also appropriate for cats over 5 years of age without any pre-existing renal diseases.

In another embodiment the treatment of cats may be performed in a formulation useful for cats that are 5 years or older. The daily dose of the formulation is between 0.01 and 0.075 mg/kg daily, preferably 0.05 mg/kg. The lowest effective dose for a median maintenance dose was found to be 0.02 mg/kg. This range can be used to treat musculoskeletal disease such as osteoarthritis. The musculoskeletal disease is a chronic disease. The formulation contains or essentially consists of meloxicam salt, water, optionally one or more additives selected from the group consisting of buffers, solubilisers, preservatives and optionally thickeners.

Example

The medical records of a feline-only practice were searched for cats with OA being treated with meloxicam during a 4 year period. A diagnosis of OA was based upon any two of the following: owner noted mobility changes and/ or physical examination findings or radiographic changes. Cats included were older than 7 years and treated with meloxicam for a duration of more than 6

months. Complete medical records were available for review. Biochemistry, urinalysis and body weight were regularly monitored. The progression of renal disease in the aged non-renal and renal group treated was compared to age matched and IRIS matched untreated controls from the same clinic.

These results prove that a maintenance dose of 0.02 mg/kg meloxicam does not hasten progression of renal disease in aged cats or aged cats with pre-existent stable IRIS stage 1-3 renal disease. Therefore meloxicam can be used as a treatment for aged cats with painful musculoskeletal disorders and concurrent renal disease. The aged cats treated with NSAID therapy shall be carefully monitored.

Materials and Methods

The database of a feline-only practice in suburban Melbourne was searched for cats which had been treated for chronic musculoskeletal disorders with meloxicam (Metacam oral suspension, Boehringer Ingelheim) during a 4 year period. The diagnosis of osteoarthritis or spondylosis deformans had been made based upon any two of the following: owner noted mobility changes, physical examination findings or radiographic changes. The inclusion criteria included cats greater than 7 years old which had been treated continuously with meloxicam for a duration of more than 6 months and which had complete medical records available for review. In addition, cats were only included if serum biochemistry, urine analysis and body weight had been regularly monitored.

Young cats were excluded, as were cats with no pre-treatment renal parameter measurements. In addition cats were also excluded if the owner could not be contacted to check that the cats were still receiving daily treatment with meloxicam.

Age, breed, sex, concomitant diseases and medications as well as date treatment commenced, treatment duration and daily dose of meloxicam were recorded.

The presence or absence of pre-treatment renal disease and staging of the renal disease was carried out using plasma creatinine and urine specific gravity according to the following recognised International Renal Interest Society criteria (IRIS staging 2006):
www.iris-kidney.com

IRIS stage 1: Inadequate concentrating ability, abnormal renal palpation. Creatinine < 140 μmol/l (< 1.6 mg/dL)

IRIS stage 2: Mild or absent clinical signs associated with renal disease. Creatinine 140-250 μmol/l (1.6-2.8 mg/dL)

IRIS stage 3: Many clinical signs present. Creatinine 251-440 μmol/l (2.8-5 mg/dL)

The treated cats were then subdivided into two groups: the renal treated group that belonged to IRIS stage 1-3 and were pre-treated, and the non-renal treated group that has no identifiable renal disease pre-treatment. Urine specific gravity, serum creatinine and bodyweight were used as indicators of renal disease progression. The progression of renal disease was then compared to age and IRIS matched untreated controls were then randomly identified from the database of the same clinic.

Statistical Analysis

The median age of the renal and non-renal treated cats, median treatment duration and median maintenance dose was calculated.

The progression of renal disease in the non-renal treated group was compared to the age matched untreated controls. The progression of renal disease in the treated renal-diseased group was compared to age matched and IRIS matched untreated controls from the same clinic. Statistical analysis was carried out using a time adjusted area-under-the-curve (AUC) changes from baseline time 0 until the last recorded value (n).

$$\mathrm{AUC}_{(0-n),\,adj} = \frac{\mathrm{AUC}_{(0-n)}}{t_n - t_0} = \frac{\sum_{i=0}^{n} \frac{C_i + C_{i+1}}{2} (t_{i+1} - t_i)}{t_n - t_0}$$

t_0: time point of first measurement (baseline)

t_n: time point of last measurement

C_i: difference of parameter concentration at time point i=0,...,n to baseline

The Wilcoxon rank-sum-test was used to compare the groups. With this nonparametric test the distribution of the adjusted AUC of two groups was compared regarding the location. Under the null hypothesis it is assumed that there is no location shift in the distributions of the two treatment groups. If the resulting p-value is lower than the two-sided significance level of 5 % the null hypothesis is rejected.

Results

Out of a total database of 3016 cats, 214 cats which had been treated with Metacam® oral suspension were identified. Of these, 38 cats met the inclusion criteria for the treated group. 22 cats of these cats (58%) had IRIS stage 1-3 renal disease prior to treatment, whereof 8 cats were categorized to fit IRIS stage 1, 13 cats belonged to stage 2 and 1 cat was classified to belong to stage 3. 16 cats had no identifiable renal disease prior to treatment.

The median age of the renal treated group was 15.5 years and the non-renal treated group was 13.4 years.

The median treatment duration was 527 days in the renal group and 400 days in the non-renal group. After dose titration to the lowest effective dose, the median maintenance dose was 0.02 mg/kg daily in both the renal treated and non-renal treated groups. There were no differences in the progression of renal parameters in the renal group treated with meloxicam versus the age and IRIS matched untreated renal group or the non-renal group treated with meloxicam versus the non- renal group not treated with meloxicam.

Two renal-treated cats were excluded from analysis of creatinine changes from baseline as their pre-treatment sample was not carried out within 3 days of the start of treatment. There were no statistically significant differences in weight loss or the loss of urine concentrating ability in the renal group treated with meloxicam versus the age and IRIS matched untreated renal group or the non-renal group treated with meloxicam versus the non- renal group not treated with meloxicam. Mean serum creatinine concentration increased statistically significantly less over time in the renal group treated with meloxicam than in the renal untreated group.

Example

The following formulation may be used according to the invention but not limited to:

1) Metacam® Suspension Boehringer Ingelheim for Cats

Claims

1. Meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base thereof for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more.

2. Meloxicam or a pharmacologically acceptable salt thereof according to claim 1, characterised in that the cats have a pre-existing renal disease.

3. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 2, characterised in that the cats have no pre-existing renal disease

4. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 3, characterised in that the cats have a chronic kidney disease.

5. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 4, characterised in that the daily dose is from 0.01 and 0.075 mg/kg daily.

6. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 5, characterised in that the daily dose is from 0.02 to 0.06 mg/kg daily.

7. Meloxicam or a pharmacologically acceptable meloxicam salt thereof according to any one of claims 1 to 6, characterised in that the daily dose is 0.05 mg/kg daily.

8. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 7, characterised in that the musculoskeletal disease is osteoarthritis.

9. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 8, characterised in that the musculoskeletal disease is a chronic disease.

10. A formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more vehicles for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more.

11. A formulation according to claim 10, characterised in that it contains or essentially consists of meloxicam salt, water, optionally one or more additives selected from the group consisting of buffers, solubilizers, preservatives and optionally thickeners.