Efficacy and safety of the long-term oral administration of carprofen in the treatment of osteoarthritis in dogs

A. AUTEFAGE[1] and J. GOSSELLIN[2]*

[1] *Professor, Head of the Department of Surgery, National Veterinary School of Toulouse, 23 Chemin des Capelles, F-31076 Toulouse Cedex 3, France.*
[2] *Veterinary Medicine Research and Development, Pfizer Ltd., Ramsgate Road, Sandwich Kent, CT13 9NJ, United Kingdom.*

* *Corresponding author: E-mail : jacques.gossellin@pfizer.com*

SUMMARY

The aim of this study conducted in France was to confirm the efficacy and safety of the oral administration of carprofen (Rimadyl®) at 4 mg/kg once a day during four months in the treatment of clinically chronic osteoarthritis in dogs. One hundred and ten dogs with chronic clinical signs of osteoarthritis were enrolled. The overall severity of the osteoarthritis condition and the clinical signs of osteoarthritis were assessed using visual analogue scales (VAS) on days 0, 5, 30, 60, 90 and 120. During the same visits, owners were asked to perform their own efficacy assessment through the grading of seven parameters using categorical scales. Hematological analyses were performed on days 0 and 120. Clinical blood chemistry evaluations were performed on days 0, 5, 60 and 120. The percentage of dogs showing a positive treatment effect increased from 12% on day 5 to 74% on day 120. The mean VAS scores significantly decreased throughout the study ($P \leq 0.05$). Gastrointestinal undesirable effects likely to be related to carprofen but with no harmful consequences were observed in 5% of treated dogs. No detrimental effects of the treatment on haematological, renal and hepatic parameters were observed. These results show that carprofen at 4 mg/kg once daily can be safely used over a 4 month period in the treatment of osteoarthritis in dogs and provides a steadily increasing improvement of the clinical signs.

Key-Words : osteoarthritis, carprofen, efficacy, safety, dog

RÉSUMÉ

Efficacité et innocuité de l'administration orale de carprofène à long terme dans le traitement de l'arthrose chez les chiens.

L'objectif de cette étude menée en France était de confirmer l'efficacité et la sécurité d'emploi du carprofène (Rimadyl®) administré par voie orale à la posologie de 4 mg/kg une fois par jour et pendant quatre mois dans le traitement de l'arthrose accompagnée de signes cliniques chroniques chez les chiens. Cent dix chiens présentant des signes cliniques chroniques d'arthrose ont été inclus dans cette étude. La sévérité globale de l'arthrose ainsi que les signes cliniques d'arthrose ont été évalués en utilisant une échelle analogique visuelle (EAV) aux jours 0, 5, 30, 60, 90 et 120. Aux mêmes visites, les propriétaires ont procédé à leur propre évaluation de l'efficacité en quantifiant sept paramètres sur des échelles qualitatives. Des analyses hématologiques ont été réalisées aux jours 0 et 120. Des analyses biochimiques sanguines ont été réalisées aux jours 0, 5, 60 et 120. Le pourcentage de chiens montrant un effet positif du traitement a augmenté de 12% au jour 5 à 74% au jour 120. Les scores moyens d'EAV ont diminué de manière significative durant l'étude ($P \leq 0.05$). Des effets indésirables gastro-intestinaux probablement liés au carprofène mais sans conséquences dommageables ont été observés chez 5% des chiens traités. Aucun effet préjudiciable du traitement n'a été observé sur les paramètres hématologiques, rénaux et hépatiques. Ces résultats montrent que le carprofène administré quotidiennement à la posologie de 4 mg/kg peut être utilisé sans risque sur une période de quatre mois dans le traitement de l'arthrose chez les chiens tout en améliorant progressivement les signes cliniques.

Mots-Clés : arthrose, carprofène, efficacité, sécurité d'emploi, chien

Introduction

Osteoarthritis is a common concern for owners of old dogs but it has also been estimated that some forms of osteoarthritis affect more than 20% of dogs which are more than one year old [5]. Osteoarthritis is a slowly progressive degenerative disease of synovial joints characterized by pain, disability, destruction of cartilage, and bony remodelling [6]. As it is a chronic disease that cannot be cured, it requires long-term care. The current trend is to promote the continuous use of non steroidal anti-inflammatory drugs (NSAIDs) over long periods because of their ability to reduce joint pain and decrease synovitis [6]. However several NSAIDs used in veterinary medicine have been involved in gastro-intestinal, renal and haematological adverse effects as well as in cartilage destruction in cases of prolonged administration [4].

Carprofen (Rimadyl®; Pfizer) is a member of the group of NSAIDs. It is a carboxylic acid belonging to the subclass of arylpropionic acids which exerts its anti-inflammatory and analgesic effects primarily by inhibiting the cyclooxygenase enzyme and blocking the production of prostaglandins [3]. Carprofen is approved for the long-term treatment of osteoarthritis in dogs in most European countries.

The safety margin of carprofen was found to be relatively wide compared with other NSAIDs in toxicological studies [4]. In addition, daily administrations of carprofen at 4 mg/kg did not have any deleterious effect on the cartilage structure in several *in vitro* and *in vivo* studies. Instead, the latter studies showed a potential beneficial effect [1, 11, 2]. At therapeutic concentrations in dogs, carprofen increases the synthesis of proteoglycans in the osteoarthitic cartilage [1, 11, 2]. In experimentally induced osteoarthritis in dogs,

carprofen at 4 mg/kg once daily for two months reduces the progression of morphologic changes of the joint in comparison with non-treated dogs [8]. The purpose of the present multi-centre study, which took place in France and involved 16 veterinary clinics, was to confirm the efficacy and safety of the continuous use of Rimadyl® tablets over a four month period in the treatment of clinically chronic cases of osteoarthritis in dogs.

Materials and methods

ANIMALS

One hundred and ten household dogs of 47 different breeds (Labrador retriever (19), German shepherd (18), Brittany (8), Poodle (5), Collie (5), Beauceron (4), Beagle (3) and other breeds represented by one or two dogs) were selected from the clinic population presented to each investigator. Their mean age was 9.3 years, and their mean body weight 30.3 kg. The study population consisted of 49% entire males, 5% neutered males, 32% entire females and 15% spayed females.

All enrolled animals displayed chronic clinical signs of osteoarthritis including but not limited to: lameness (unilateral or bilateral), stiffness when standing up or lying down, muscle atrophy linked to the decreased use of the limb, decreased range of motion of the affected joint, pain on manipulation of the joint, crepitus on movement of the joint or signs more pronounced with cold and wet climatic conditions. These signs had been continuously observed for more than two weeks or recurrently for more than three months.

In dogs presenting with multiple joints affected with osteoarthritis, only the one displaying the most severe clinical signs was selected and considered for the different assessments required by the study. Joints selected for the assessments were as follows: hip (40%), knee (24%), elbow (18%), scapulo-humeral joint (6%), carpus (6%) and tarsus (6%). For 73% of the selected joints, osteoarthritis was secondary to another cause. Dysplasia was the most frequent origin (45% of the cases), followed by the rupture of the cruciate ligament (20% of the cases). All other origins were less frequent and below 8%.

For each dog, the diagnosis of osteoarthritis was confirmed by a radiographic evaluation of the selected joint, showing amongst others the presence of new bone proliferation, decreased joint space (joint degeneration) and increased density of subchondral bone.

The dogs with lameness related to a neoplasic condition, a primary neurologic disorder, an immunologic disorder or an infection were not enrolled in the study. At enrolment, the selected animals hadn't had any surgery on the affected joint within the last month prior to inclusion. They had not received intra-articular injections of any type within the last month prior to inclusion, systemic anti-inflammatory drugs (i.e. NSAID's or short acting corticoids) within the last 7 days prior to inclusion or repository anti-inflammatory drugs within the last 30 days prior to inclusion. They did not suffer from any condition that would have required surgical intervention in the next 4 months following inclusion, or any concurrent disease or medication that could interfere with the carprofen treatment. The dogs presenting with contra-indications to carprofen administration were not included in the study either.

TREATMENT

Two commercial formulations of carprofen were used in this study (Rimadyl® Tablets 20 mg and Rimadyl® Tablets 50 mg; Pfizer). The day treatment commenced was defined as day 0. Treatment was administered once a day until the last scheduled visit on day 120. Rimadyl® tablets were broken to the nearest half tablet (score of the tablet) to achieve the desired dose of approximately 4 mg/kg. Actual dosing was recorded by the animal's owner on a daily basis.

CLINICAL FOLLOW-UP

Apart from a few exceptions, study animals were examined on day 0, on day 5 ± 2 days and on days 30, 60, 90 and 120 ± 4 days and, when relevant, on the day of withdrawal from the study.

At each visit, a physical examination was performed including the assessment of rectal temperature, pulse, respiratory rate and body weight. The severity of the osteoarthritis condition of the selected joint was scored by the investigator and based on the assessment of four clinical parameters using Visual Analogue Scales (VAS) of 100 mm. The investigator drew a vertical bar on the scale, between 0 mm (minimum severity) and 100 mm (maximum severity) according to his/her own judgement of the severity of each of the three following clinical parameters: lameness, limitation of joint movement, pain on movement. Then, the investigator assessed the overall severity of the condition summarising the three above parameters (Table 1). A correspondence between scale zones and clinical descriptions for every parameter enabled consistency of scoring between investigators and the transformation of scores into grades, in order to describe the dog in a qualitative way (frequency by clinical grade for each parameter). The dogs' condition was also assessed by the owner at each observation point. The owner assessment was based on the grading of seven parameters including the dog's ability for standing up or lying down, walking, running, jumping (up and down), going upstairs or downstairs, playing or taking exercise as well as the influence of climatic condition (Table 2).

Animals showing a greater "overall severity of the condition" score than on day 0 after a minimum of 5 days of therapy were considered to show worsening of the osteoarthritis condition, and were therefore removed from the study. In case of suspected adverse reactions to carprofen, the treatment was either suspended for a few days or stopped, at the investigator's discretion. Removal from the study due to any of the reasons above, was considered a treatment failure.

At each visit, the treatment effect was assessed (Table 3). At the end of the 4-month study, the overall treatment efficacy compared with day 0 was assessed by both the investi-

Scale zone	Grade	Clinical parameters
		Lameness
0-20	0	Walks normally
21-40	1	Slight lameness
41-60	2	Serious lameness
61-80	3	Severe lameness
81-100	4	Walks on 3 limbs
		Limitation of Joint Movement
0-20	0	No limitation of joint movement (0 %)
21-40	1	Mild limitation of joint movement (10-20 %)
41-60	2	Moderate limitation of joint movement (20-30%)
61-80	3	Serious limitation of joint movement (30-50 %)
81-100	4	Severe limitation of joint movement (>50 %)
		Pain on movement
0-20	0	No pain on motion of affected joint
21-40	1	Slight pain on motion of affected joint (slightly pulls limb away)
41-60	2	Moderate pain on motion of affected joint (pulls limb away)
61-80	3	Severe pain on motion of affected joint (becomes aggressive)
81-100	4	Refuses to be approached
		Overall Severity of the Condition
0-20	0	Normal Condition
21-40	1	Mild Condition
41-60	2	Moderate Condition
61-80	3	Serious Condition
81-100	4	Severe Condition

TABLE 1. Scoring and grading scale for the assessment of osteoarthritis by investigators

gator and the owner according to the following scale: clinically cured (0), substantially improved (1), moderately improved (2), slightly improved (3), equal (4) or worse (5).

SAMPLINGS

Blood samples were taken on the day of inclusion and on days 5, 60, 120 and before any withdrawal from the study.

Hematology (haemoglobin, hematocrit, RBC, WBC (including WBC differential count), platelet count) was performed on the day of inclusion, day 120 and before any removal. Clinical chemistry (total proteins, albumin, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum bile acids) was performed on the day of inclusion, days 5, 60 and 120 and before any withdrawal.

Blood samples were collected, either on a dry tube with a serum separating gel for clinical chemistry or on an EDTA tube for haematology, from dogs which had been fasted for at least 6 hours and at most 12 hours. Tubes were kept for a maximum of 3 days between +4 and +8˚C and then sent by mail to the laboratory at ambient temperature. All analyses were performed by the same laboratory. The blood cell counts were done using a COULTER T540 model counter in veterinary mode. The white blood cell differential count was carried out by counting the various cell types (from 100 cells) on a smear after colouring. The total protein concentrations were read on an ATAGO SPR-T2 refractometer. The analyses of the other biochemical parameters were carried out in liquid chemistry by optical reading of density on a LABSYSTEM FP9 spectrophotometer.

DATA ANALYSIS

The efficacy and safety of the carprofen long-term treatment were primarily assessed on basis of:

Evolution over time of the treatment effect through the percentage of patients in the different possible categories of treatment effect (Table 3).

Evolution over time of the four clinical parameters assessed by the investigators.

Evolution over time of RBC, WBC, platelets, urea, creatinine, ALT and serum bile acids.

All other parameters were considered secondary.

The four clinical parameters assessed by the investigators and the blood parameters were analyzed using a general linear repeated measure mixed model analysis of variance, including the fixed effect of time and the random effects of block and animal within block where the investigators were considered as blocks. Fisher's protected LSD for pairwise comparisons were performed between every on-treatment time point (day 5, 30, 60, 90 or 120 visits) and the pre-treatment (day 0 visit) means.

Grade	Parameters
	Standing up or lying down
0	My dog stands up or lies down without difficulty
1	My dog sometimes shows some difficulty to stand up or to lie down especially after prolonged rest
2	My dog often shows some difficulty to stand up or to lie down
3	My dog permanently shows great difficulty to stand up or to lie down
4	My dog refuses to stand up or to lie down
	Walking
0	My dog walks normally
1	My dog shows stiffness when walking ; this vanishes after some paces
2	My dog shows permanent stiffness when walking and/or slight lameness
3	My dog permanently shows slight lameness
4	My dog permanently shows severe lameness
	Running
0	My dog runs without difficulty
1	My dog shows slight lameness after rest, disappearing after a few paces
2	My dogs shows lameness after prolonged physical exercise
3	My dog shows permanent lameness, when running
4	My dog refuses to run or runs on 3 limbs
	Jumping up and down (into or from a car, for example)
0	My dog jumps enthusiastically
1	My dog sometimes shows some difficulty to jump
2	My dog permanently shows some difficulty to jump
3	My dog permanently shows a lot of difficulty to jump
4	My dog refuses to jump
	Going upstairs or downstairs
0	My dog easily goes upstairs or downstairs
1	My dog sometimes shows some difficulty to go upstairs or downstairs
2	My dog often shows some difficulty to go upstairs or downstairs
3	My dog permanently shows a lot of difficulty to go upstairs or downstairs
4	My dog refuses to go upstairs or downstairs
	Playing or doing physical exercise
0	My dog is able to play or do physical exercise for a long time without showing exaggerated tiredness
1	My dog is able to play or do physical exercise for a long time but sometimes shows some pain or great tiredness
2	My dog plays or does physical exercise only for a short period of time, after which he seems not to take further interest in playing or doing exercise
3	My dog is reluctant to play or to do physical exercise; he gets rapidly tired and/or shows evident pain
4	My dog refuses to play or to do exercise
	Influence of climatic conditions
0	Climatic conditions have no influence on clinical condition of my dog
1	My dog seems to have difficulty to move when it is cold and wet

TABLE 2. Grading scale for the assessment of osteoarthritis by owners

Results

At each scheduled visit, treatment compliance was assessed by counting the number of days the treatment had been taken correctly. A patient was considered as treatment compliant if the percentage of days with correct dosing (from day 0) was more than 80% and if there were no more than 2 days of incorrect dosing for every seven-day sequence from the previous to the current scheduled visit. Following this definition, more than 88% of the dogs were treatment compliant throughout the study.

EFFICACY

From the 110 dogs enrolled into the study, 97 completed the study, three were considered treatment failures (two due to suspected adverse reactions (gastro-enteritis) on days 5 and 57 and one due to worsening of the osteoarthritis condition on day 93) and were therefore withdrawn from the study and ten were withdrawn for other reasons than treatment failure.

A continuous and steady improvement of clinical signs associated with the osteoarthritis condition, as the carprofen

Categories	
Treatment in Progress : Any animal that is still in the study at the time of observation	**Positive Treatment Effect :** Any animal with an "Overall Severity of the Condition" score reduction > 20 mm to that observed at Day 0 visit. **Neutral Treatment Effect :** Any animal with an "Overall Severity of the Condition" score reduction ≤ 20 mm to that observed at Day 0 visit. **Unknown :** No information available to estimate the treatment effect.
Treatment Failure	**Due to worsening of the osteoarthritis condition :** Any animal that has been removed from the study by the investigator due to an "Overall Severity of the Condition" score greater than that observed at Day 0 visit. **Due to suspected adverse reaction related to carprofen :** Any animal that has been removed from the study by the investigator due to a side effect/suspected adverse reaction related to carprofen, independently of its score in the 'Overall Severity of the Condition'.
Removal for any other reason than Treatment Failure	Animal removed from the study due to concurrent disease, death, absence of follow up, etc ...

TABLE 3. Categories of treatment effect

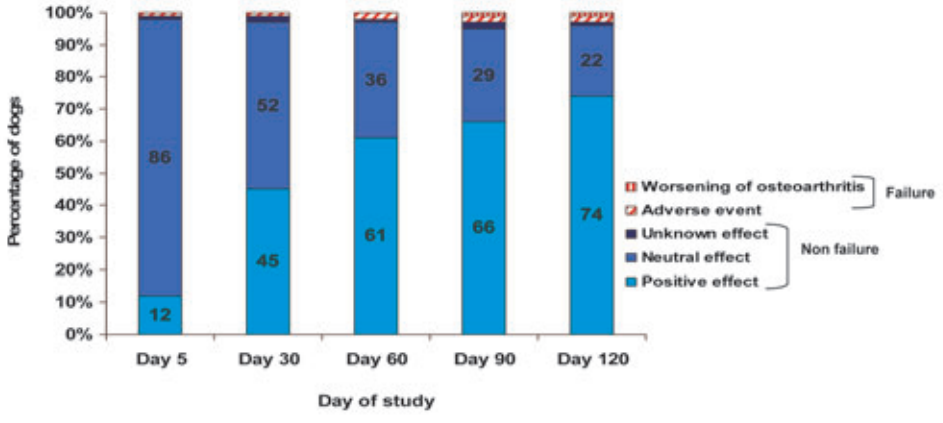
treatment continued, was seen. Thus, the percentage of dogs with a positive treatment effect increased steadily from 12% on day 5 to 74% on day 120. Similarly, the percentage of dogs with a neutral treatment effect steadily decreased from 86% on day 5 to 22% on day 120 (Figure 1).

As a result of the prolonged use of carprofen, the mean overall VAS scores of the four clinical parameters assessed by the investigators continuously and significantly decreased between day 0 and days 5, 30, 60, 90 and 120 ($P \leq 0.05$) (Figure 2). VAS scores of individual dogs showed the same trend.

With the four clinical parameters transformed into grades, the positive effect of the carprofen treatment was also obvious, when the distribution of dogs in the different grades was compared between day 0 and day 120 (Figure 3).Even the condition of the most severely affected animals (grade 4) quickly improved with the carprofen treatment.

The owners also observed a continuous and steady improvement of the parameters, as the carprofen treatment went on (Figure 4).Overall, this improvement was comparable to that observed by the investigators. The effect of carprofen on the sensitivity to climatic conditions was not as noticeable as on other parameters. The percentage of animals in grade 0 (no influence of climatic conditions) only increased from 44% on day 0 to 59% on day 120.

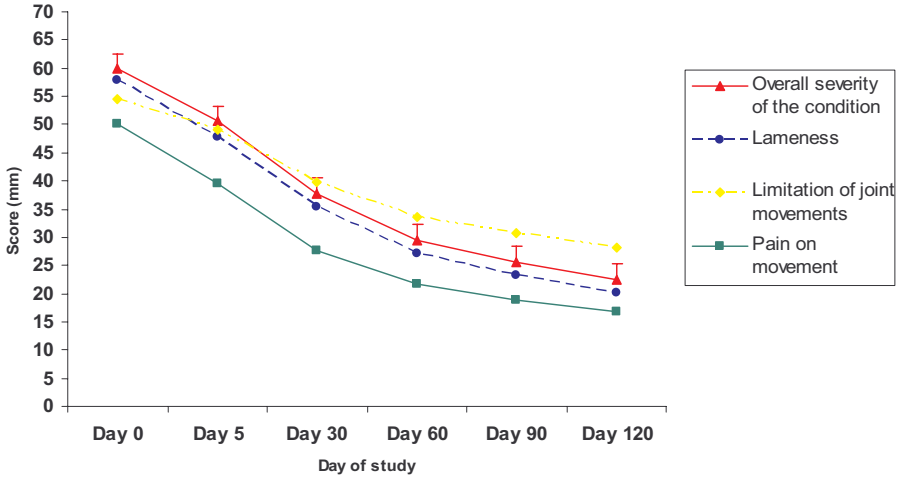
According to the assessment of the overall efficacy made by the investigators, 98% of the dogs completing the study were deemed improved (Figure 5) whilst no improvement was reported in only 2% of them. It should be reminded that only one and two dogs did not complete the study because of worsening of the osteoarthritis condition or Suspected Adverse Reactions before study end, respectively. The assessment of overall efficacy made by the owners was very close to the investigators' assessment.



Patients removed from the study for reasons other than treatment failure were omitted from scheduled visits following removal onwards; patients removed from the study for treatment failure were carried over following scheduled visits until study end, i.e. Day 120 visit (Number and percentage of Treatment Failure are therefore cumulative).

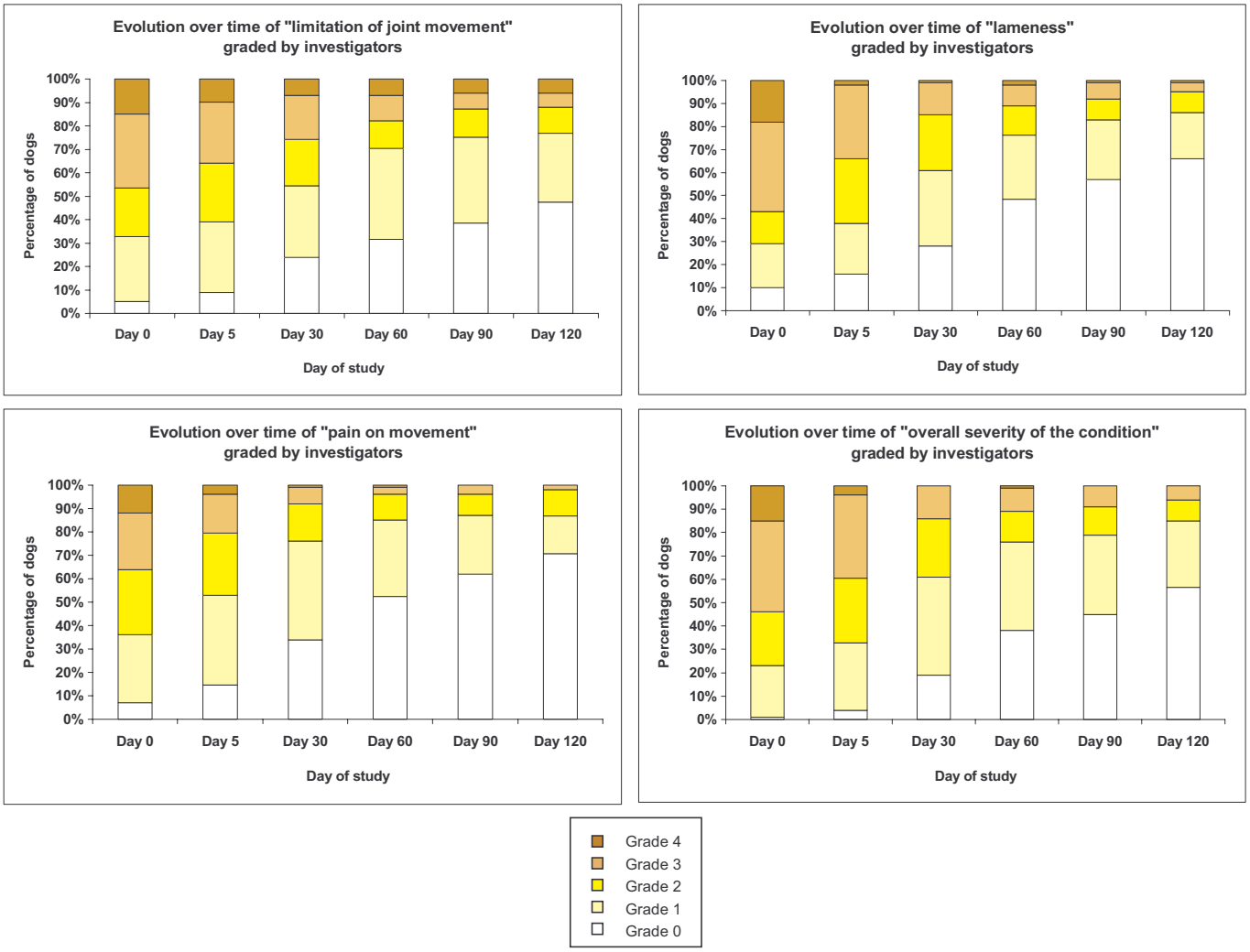
Number of dogs still involved in the study: 110 on Day 5; 109 on Day 30; 106 on Day 60; 104 on Day 90 and 100 on Day 120

Figure 1 : Effect of treatment over time



The errors bars represent the standard errors for Overall severity of the condition

Figure 2 : Evolution over time of the four clinical parameters scored by investigators (Least square means)



Grade 0 corresponded to a scale zone of 0-20 mm; Grade 1 corresponded to a scale zone of 21-40 mm; Grade 2 corresponded to a scale zone of 41-60 mm; Grade 3 corresponded to a scale zone of 61-80 mm; Grade 4 corresponded to a scale zone of 81-100 mm.

Figure 3 : Evolution over time of the four clinical parameters graded by investigators

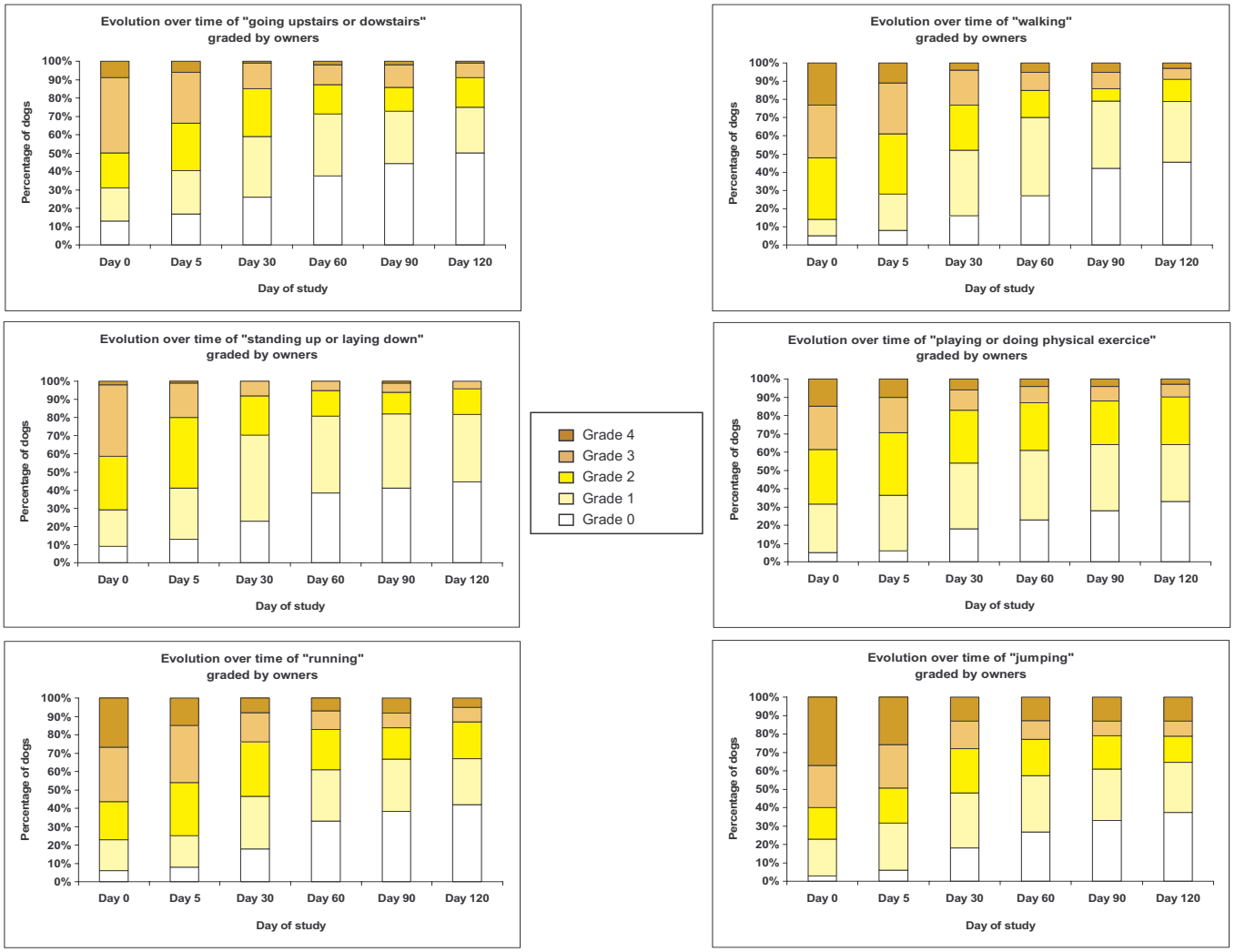


Figure 4 : Evolution over time of six parameters assessed by owners

SAFETY

No suspected adverse reactions were reported from 86 out of the 110 enrolled dogs over the whole study period.

Thirty-four suspected adverse reactions involving 24 dogs were recorded during the study. Only 11 events involving 5 dogs (5% of all dogs), all described as gastro-intestinal cases, were judged by the investigators to be related to carprofen. Only two dogs (2% of all dogs) were withdrawn from the study because of suspected adverse reactions considered by the respective investigators to be related to carprofen. These dogs recovered following normal veterinary care after the carprofen treatment was stopped and no long-term detrimental effects were reported.

No detrimental effects of the prolonged carprofen treatment period on hematological parameters (especially red and white blood cell counts and platelet counts) were seen, as shown by similar means and ranges between study start and study end. Mean and range values of renal and hepatic parameters did not substantially change throughout treatment (Table 4). The few significant differences with concentrations at day 0 were biologically insignificant. Mean levels of secondary biochemical parameters remained also unchanged throughout the study period.

DISCUSSION

The results of the present study are in accordance with those of previous studies. Indeed, several controlled (versus placebo) or uncontrolled studies on long-term use of carprofen in the treatment of osteoarthritis in dogs have been conducted over the past years. In a randomized controlled trial in which carprofen was administered at 2.2 mg/kg twice a day for 14 days to 36 dogs, Vasseur and others [13] noted no difference in the results of clinical blood chemistry, urinalysis or fecal occult blood test between carprofen and placebo-treated animals. In the same study, the force plate evaluation showed that a dog treated with carprofen was 3.3 times more likely to have a positive response than a dog treated with placebo. These proportions were 3.5 and 4.2 for the investigator and owner clinical evaluations, respectively. In another randomized controlled study, Holtsinger and others [3] administered 2.2 mg/kg of carprofen twice a day for 14 days to 97 dogs. The results showed that dogs treated

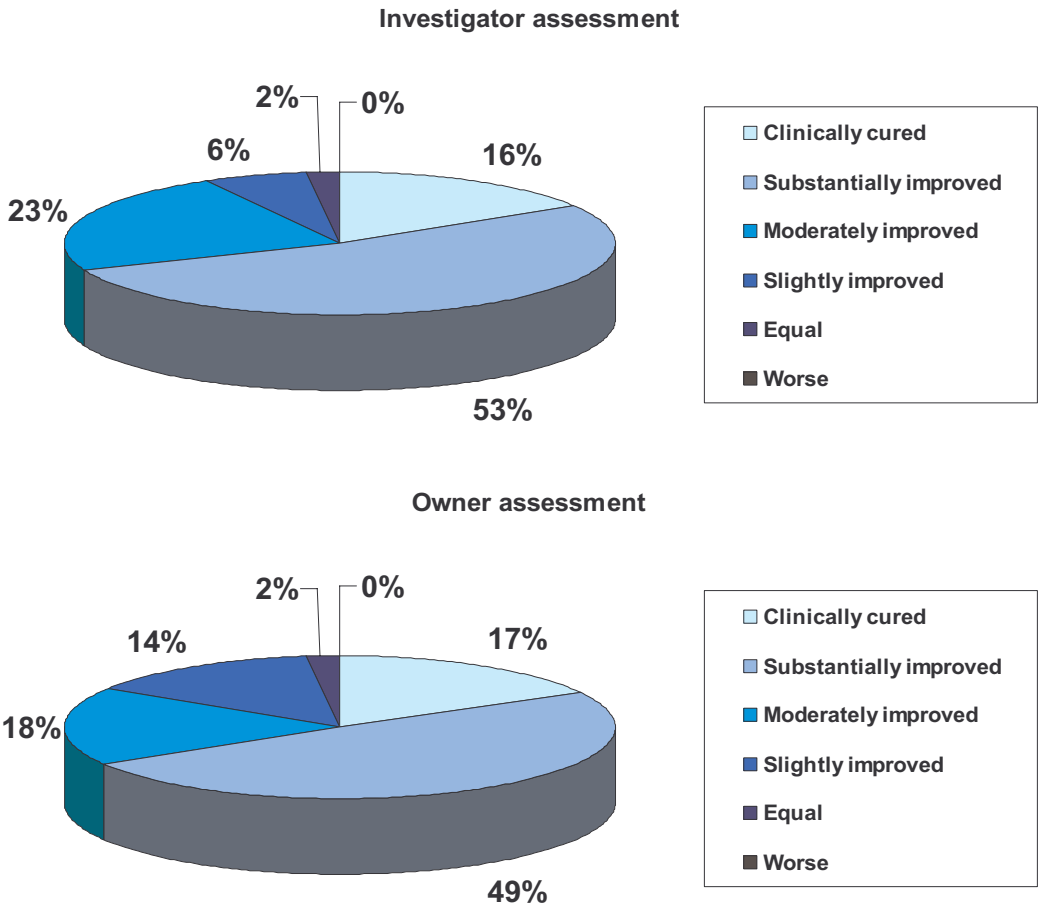


Figure 5 : Assessment of "overall efficacy" at study end (comparison Day 120 vs Day 0)

	Day 0			Day 5			Day 60			Day 120		
PARAMETER	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
Urea (mmol/L)	7	1.7	20	7 ns	1.7	18	7 ns	1.7	18	7 ns	1.7	18
Creatinine (µmol/L)	53	9	141	53 ns	9	132	62*	9	114	62*	18	132
ALT (IU/L)	38	2	283	37 ns	1	272	52*	5	324	43 ns	3	343
Serum Bile Acids (µmol/L)	27	5	144	32 ns	5	200	33 ns	5	217	19*	5	89
Total Proteins (g/L)	73	48	92	73	56	94	72	60	94	74	60	92
Albumin (g/L)	33	24	50	33	26	46	33	22	50	33	21	41
AST (IU/L)	14	1	39	13	1	43	19	2	139	20	3	75

Statistical comparisons were carried out only for Urea, Creatinine, ALT and Serum Bile Acids; ns means not statistically different (P>0.05) from Day 0 visit; * means statistically different (P ≤ 0.05) from Day 0 visit.

TABLE 4 : Summary table of biochemical parameters

with carprofen responded favourably to the drug in 79% of the cases and that they were 24.8 times more likely to receive a positive evaluation by the veterinarian than those treated with a placebo. The suspected adverse reactions in this study were minor, transient and similar in both treatment groups. A third randomized controlled trial conducted by Moreau and others [7] involved 17 dogs, which received 2.2 mg/kg twice a day during 60 days. Ground reaction forces of the arthritic

limbs and clinical signs assessed by the investigators were improved by carprofen; in addition, no changes were seen in blood and faecal analyses. A survey conducted in France [10], showed that the clinical signs of osteoarthritis continuously and steadily improved in 337 dogs treated during more than 2 months with carprofen at 4 mg/kg once a day. A very low incidence of suspected adverse reactions was observed in this survey. The most recent study reported by RAEKALLIO and others [9] concluded that a two-month oral administration of carprofen at 4 mg/kg once daily in osteoarthritic dogs was well tolerated.

NSAIDs are widely used in human medicine where their adverse effects are well known. The assumption that adverse reactions may increase with the length of NSAID administration seems to be logical. However, VALLOT [12] reported studies in humans showing that the relative risk of suspected adverse reaction was almost 2 times higher when NSAIDs were administered for less than 30 days than for longer periods of administration. Therefore, the risk seemed to reach its maximum during the initial days of long-term treatment. The studies on carprofen administration over a period longer than one month are consistent with the observations reported in the present study. Thus, the extension of treatment periods with carprofen is not correlated with a higher incidence of gastro-intestinal suspected adverse reactions compared to shorter treatment lengths.

The results of the present study as well as those of previous studies clearly demonstrate that the long-term administration of carprofen provides a steadily increasing improvement of clinical signs of osteoarthritis in dogs and does not result in an increase of the incidence of suspected adverse reactions. The risk/benefit ratio of long-term carprofen treatment is therefore clearly proven to be positive in dogs.

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