Paper

Mavacoxib and meloxicam for canine osteoarthritis: a randomised clinical comparator trial

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NSAIDs are the cornerstone of medical management of canine osteoarthritis (OA). Meloxicam is a daily-administered NSAID widely available in a liquid formulation and manufacturer's summary of product characteristics (SPC) advise that it is given at the lowest effective dose. Mavacoxib is a long-acting NSAID given as a monthly tablet. This study compares these drugs in the management of canine OA. In all, 111 dogs with OA of the elbow, hip or stifle were randomly assigned to receive one of these NSAIDs for a 12-week period, and to administer them as per the manufacturer's SPC. Outcomes, including ground reaction forces and three validated clinical metrology instruments, were measured at baseline, 6 and 12 weeks. Improvements were seen in all outcome measures for both groups to a similar degree, and adverse events occurred at a similar rate. There were significant improvements in outcome measures from week 6 to week 12, as well as from baseline. Long-term meloxicam dose was more important than recent dose. Clinical efficacy and adverse event rates are similar for meloxicam and mavacoxib when administered as per their UK SPC. This is relevant information for veterinary surgeons when prescribing NSAID treatment for canine OA.

Introduction

Osteoarthritis (OA) is estimated to affect approximately 20 per cent of dogs over the age of one year (Johnson and others 1994). Clinical signs are largely related to pain, and NSAIDs are considered the medical cornerstone of management (Sanderson and others 2009, Bound and others 2011), with long-term, continuous use being advocated (Innes and others 2010).

Meloxicam is the most commonly prescribed NSAID for canine OA in the UK. Now available as numerous generics, it was originally produced by Boehringer-Ingelheim Vetmedica as the brand Metacam. The UK Metacam Summary of Product Characteristics (SPC) states: *For longer term treatment, once clinical response has been observed (after >4 days), the dose of Metacam can be adjusted to the lowest effective individual dose.* Practically, this frequently results in owners being relied upon to determine the appropriate dose for their animals.

Mavacoxib is a relatively new NSAID, introduced by Pfizer Animal Health (now Zoetis) as Trocoxil in 2009. It is highly protein bound and is released as its active form in equilibrium. It is slowly excreted, giving it a long duration of activity in dogs. It is administered at 2 mg/kg once monthly, after two initial doses 14 days apart.

When examining the clinical effects of treatments, it is important to consider appropriate outcome measures. In terms of limb function, it is widely considered that ground reaction forces (GRF), especially peak vertical force (PVF), as measured with force platforms or pressure sensitive walkways, are the gold standard. PVF, generally of a worst affected 'index' limb, has been used as the primary outcome measure in numerous clinical studies of NSAIDs for canine OA (Budsberg and others 1999, Lipscomb and others 2002, Innes and others 2003, Moreau and others 2003, 2007, Roush and others 2010). However, in studies involving clinical cases this is often confounded by the fact that many dogs will be affected in multiple limbs, and there is variation in how the 'index' limb is identified.

The recent development and validation of several owner-completed 'questionnaires', or clinical metrology instruments (CMIs), have facilitated the repeatable collection of clinical data based on owners' observations (Brown and others 2007, Hercock and others 2009, Hielm-Bjorkman and others 2009, Walton and others 2013). These instruments, to varying degrees, capture aspects of pain, activity levels and mobility (Walton and others 2013).

This study compares the treatment effects of meloxicam (Metacam, Boehringer-Ingelheim Vetmedica) and mavacoxib (Trocoxil, Zoetis) using change in PVF as primary outcome measure, and VI and three validated CMIs as secondary measures. Secondly, the effect of long-term and short-term owner-determined meloxicam dose on PVF was examined. Adverse events (AEs) for both drugs are also reported.

Method

The study protocol was approved by the University of Liverpool Research Ethics Committee. Inclusion and exclusion criteria for the study are detailed in Table 1.

Recruitment, screening and randomisation

Suitable cases underwent a screening visit (Day [-14]) that included collection of full general and orthopaedic clinical histories; general, orthopaedic and neurological examinations; and force platform analysis. A blood sample was collected for routine health screening and orthogonal view radiographs of the index joint were examined. Owners completed three CMIs: the Liverpool Osteoarthritis in Dogs (LOAD) (Hercock and others 2009, Walton and others 2013), the

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TABLE 1: Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
▶ Mobility impairment according to the owner, plus painful elbow, hip or stifle ▶ Bodyweight ≥10 kg ▶ Age ≥1 year ▶ Radiographic evidence of OA in the affected joint ▶ Reduced PVF in the index limb compared with the contra-lateral limb (symmetry index >6) (Fanchon and Grandjean 2007) ▶ Not be on nutritional supplements or therapeutic diets, or, have been on them for six weeks or more ▶ Owner agreement to evaluate their dog for a continuous 14-week period and to administer the medication according to instructions	▶ Suspected or diagnosed neurological/musculoskeletal disorder other than OA ▶ Documented or suspected presence of concomitant disease ▶ Pregnancy ▶ Receiving antibiotic drugs with neuromuscular blocking properties ▶ Receiving corticosteroids ▶ Receiving other drugs considered analgesic ▶ OA too severe to allow two-week washout period ▶ Concomitant pathology that is, or may be, altering quality of life ▶ Concomitant pathology that is, or may be, impairing mobility ▶ Skin disease ▶ Results of routine blood testing outside limits defined in the study protocol

OA, osteoarthritis; PVF, peak vertical force

Canine Brief Pain Inventory (CBPI) (Brown and others 2007) and the Helsinki Chronic Pain Index (HCPI) (Hielm-Bjorkman and others 2009).

Dogs then underwent a 14-day 'washout' period when NSAIDs were withheld. Rescue analgesia was provided in the form of paracetamol/codeine tablets (Pardale V, Dechra Veterinary Products, Shrewsbury, UK) for use if required.

At visit 1 (V1) (day 0), dogs were allocated to one of two treatment groups using a computer generated randomisation table, stratified by index joint, on a 1:1 basis in blocks of 6.

Treatments were prescribed as per their UK SPC. Treatment group 'T' received four doses of 2 mg/kg mavacoxib on days 0, 14, 42 and 70. Dogs in treatment group 'M' received 0.2 mg/kg meloxicam, on day 0 and 0.1 mg/kg on days 1, 2 and 3. Thereafter, owners were instructed to 'monitor clinical response and to reduce the dose to the lowest they felt to be effective'. Owners were advised to dose between 0 and 0.1 mg/kg, unless they did not dose for 48 consecutive hours or more, when they should repeat a single dose at 0.2 mg/kg. Owners kept a contemporaneous diary of doses. Used meloxicam bottles were weighed to validate the dosing diaries.

Assessment visits and outcome measures

There were three assessment visits. V1, was performed at day 0, before treatment administration and after the 14-day 'washout' period. Data from this visit were considered baseline. Visit 2 (V2) was performed at day 42 (±5 days) and visit 3 (V3) at day 84 (±5 days).

At each visit, force platform analysis was performed and CMIs were completed.

Force platform analysis

A force platform (Kistler, Winterthur, Switzerland) was set halfway along a 10 metre firm foam runway, both covered with identical non-slip surfaces. Four motion-capture cameras (ProReflex, Qualisys, Sweden) were arranged to create a calibrated arena including the force platform. A digital video camera (Sony, Tokyo, Japan) recorded footfalls on the platform. Synchronised video, motion-capture and GRF data were recorded.

Dogs were familiarised with the environment, including trial runs, before data capture commenced. Motion data for reflective markers on the dogs' trunks were analysed to validate acceptable limits for velocity and acceleration (ranges of 0.5 m/s and 0.05 m/s^2, respectively). A trial was valid if there was an even gait, correct foot placement, and velocity and acceleration were within the predefined ranges. At least five valid trials for each limb were collected, and mean PVF and vertical impulse (VI) were recorded using software (Qualisys Track Manager, Qualisys, Gothenburg, Sweden, and Bioware, Kistler, Winterthur, Switzerland).

Clinical metrology instruments

CMIs were completed by the same owner at all visits, and owners were directed to base their answers on their observations of the preceding seven days. LOAD and HCPI are 13- and 11-item instruments, respectively; all items are reported on a 5-point Likert-type scale. Each item is scored 0–4, and the item scores are summed to give an overall instrument score. The CBPI is a two-part instrument. The Pain Severity Score (CBPI PSS) is the arithmetic mean of four items scored on an 11-point (0–10) numerical scale, and the Pain Interference Score (CBPI PIS) is the mean of six items similarly scored. Only complete CMIs were considered valid.

Adverse events

AEs were defined by the level of suspicion that they were related to the study medication ('probable', 'possible', 'unlikely' or 'unclassifiable') and as 'serious' (fatal, life-threatening or resulting in persistent disability) or 'non-serious'.

Statistical methods

Groups were compared for age and bodyweight using unpaired *t* tests when normally distributed, and Mann-Whitney U tests when not normally distributed. Groups were compared for gender, index joint, randomisation block and breed using χ^2 tests.

The primary outcome variable was change in PVF in the index limb from V1 to V3. Secondary outcome variables were:

- Change in PVF from V1 to V2 and from V2 to V3
- Change in VI from V1 to V3, from V1 to V2 and from V2 to V3
- Change in CMIs from V1 to V3, from V1 to V2 and from V2 to V3.

For all variables, linear mixed models with repeated measures were used to test if change from baseline was dependent on treatment group. Analyses were performed in IBM SPSS V.20.

A stepwise approach was used for model selection, beginning with fixed effects of group, joint, age, visit, randomisation block, gender, and the interactions group×visit, joint×visit, and group×joint×visit, and random effects of visit and age. Covariance structure was compound symmetry.

To minimise the risk of postrandomisation bias, analyses were performed on an intent-to-treat (ITT) basis, meaning that all cases for which baseline data were collected are included, regardless of protocol deviations or drop-out. For cases with protocol deviations but measured data, these data were included in the analyses. For cases that dropped out of the study due to AEs, a last observation carried forward approach was used. Unobserved data were otherwise treated as missing.

Significance was set as $P \leq 0.05$ for all analyses.

Meloxicam dosing

The following parameters were calculated from dosing diaries, for periods V1 to V3, V1 to V2 and V2 to V3:

- *Average dose for the period (ADP)*–the mean daily dose, as a percentage of the licensed maximum of 0.1 mg/kg/day, for study day 5 to the last day before the final visit for the analysed period.
- *Average dose for the last week (ADLW)*–the mean dose for the seven days preceding the final visit for the analysed period.
- *Last dose (LD)*–the dose given during the 24 hours preceding the final visit for the analysed period.

Linear mixed models were performed to test the effect of these values on change in PVF from V1 to V3.

Results

Out of 525 enquiries received, 121 cases were recruited. Table 2 summarises the reasons for exclusion. Ten dogs were withdrawn, excluded or died before the collection of baseline data; therefore, 111 cases constitute the reported ITT data set.

Table 3 summarises the demographic data. Groups were not different for bodyweight (P=0.61), age (P=0.06), breed (P=0.40) or joint (P=0.93), but were for gender (P=0.04). There were fewer entire females in group M.

TABLE 2: Details of, and reasons for, candidate exclusion

Screening stage	Pretelephone	Telephone	Examination
Number performed	525	508	362
Number passed	508	362	121
Number failed	17	146	241
Previous SAE to NSAID	2	14	0
Concomitant disease	1	20	12
Not elbow, hip or stifle	1	28	17
Owner refusal	3	29 (includes refusal to travel, refusal to allow sedation, refusal to allow washout)	31 (includes problems with travel, refusal to allow sedation, changes in circumstances)
Recent joint surgery	1	4	1
Failed to reply or to arrive	9		7
Too young		2	1
Too small		6	5
Disease too severe for washout			7
Skin or ear disease		11	4
Disease too mild		3	8
Blood/urine test results not appropriate			31
Radiographs not conclusive			6
No PVF asymmetry			44
Unstable CCL failure			17
Spinal disease			18
Other (including lost to follow-up)		29	32

CCL, cranial cruciate ligament; PVF, peak vertical force; SAE, suspected adverse event

Ninety-one cases completed the trial. Nineteen of the 20 drop-outs were due to AEs, and one was due to change of ownership. In all, 82 cases finished the trial per protocol for GRFs and 80 for CMIs. CBPI PIS data were missing for one dog at V1, one dog at V2 and one dog at V3, and HCPI data were missing for one dog at V2.

It was originally intended that VI values would be extracted from raw force data using custom script written for proprietary commercial software (MATLAB, Mathsworks, Cambridge, UK). However, after technical issues, this script was deemed unreliable and VI was subsequently calculated using Bioware software (Kistler, Winterthur, Switzerland). This resulted in missing VI data for 39 cases at V1, 31 cases at V2 and 24 cases at V3.

All outcome data are summarised in Table 4 and Fig 1.

TABLE 3: Group summary data

	Group M N=53	Group T N=58	All N=111
Gender			
M	9	9	18
MN	20	22	42
F	1	10	11
FN	23	17	40
Age (years)			
Mean (range)	7.89 (2–13)	6.72 (1–14)	7.28 (1–14)
Bodyweight at V1 (kg)			
Mean (range)	33.9 (11.1–84.6)	33.9 (12.8–66)	33.9 (11.1–84.6)
Breed			
Labrador	14	23	37
Crossbreed	11	12	23
Border collie	6	2	8
Golden retriever	3	2	5
German shepherd	3	1	4
Springer spaniel	3	1	4
Staffordshire bull terrier	2	4	4
Other	13	13	26
Index joint			
Elbow	29	30	59
Hip	11	12	23
Stifle	13	16	29

F, female entire; FN, female neutered; M, male entire; MN, male neutered

Change in PVF

'Visit' (P<0.01) and 'Joint' (P<0.01) were the only significant effects, PVF being lower at V1 and higher for 'elbow' cases.

Increases in PVF from V1 to V3 and from V1 to V2 were significant for both groups. Increase in PVF from V2 to V3 was significant for Group M and the cohort as a whole.

Change in VI

'Visit' (P<0.01) and 'Joint' (P<0.01) were the only significant effects, VI being lower at V1 and higher for 'elbow' cases.

For the cohort as a whole, there were significant increases in VI from V1 to V3, from V1 to V2 and from V2 to V3. For group M, there was a significant increase from V1 to V3, but not from V1 to V2 or from V2 to V3. For group T, there were significant increases from V1 to V3 and from V2 to V3, but not from V1 to V2.

Change in LOAD

'Visit' (P<0.01) and 'Age' (P<0.01) were the only significant effects, LOAD being greater at V1 and generally increasing with age.

For both groups and the cohort as whole, there were significant decreases in LOAD from V1 to V3, from V1 to V2 but not from V2 to V3.

Change in HCPI

'Visit' (P<0.01) was the only significant effect, HCPI being greater at V1.

For both groups and the cohort as a whole, there were significant decreases from V1 to V3 and from V1 to V2. For Group M and the cohort as a whole, there was a significant decrease from V2 to V3.

Change in CBPI PSS

'Visit' (P<0.01) was the only significant effect, CBPI PSS being greater at V1.

For both groups and the cohort as a whole, there were significant decreases from V1 to V3 and from V1 to V2.

Change in CBPI PIS

'Visit' (P<0.01) was the only significant effect, CBPI PIS being greater at V1.

For both groups and the cohort as a whole, there were significant decreases from V1 to V3 and from V1 to V2.

Adverse events

Twenty-four dogs suffered AEs; these are summarised in Table 5.

The frequency of AEs of all causality assessments was not different between groups. All AEs with 'probable' or 'possible' causality assessments were associated with gastrointestinal clinical signs.

Five dogs died or were euthanatised; four of these had causality assessments of 'unlikely'. One dog, in group T, died in relation to an AE with a 'possible' causality assessment. Clinical signs for this dog included anorexia, depression, abdominal pain and peritoneal effusion. Clinical biochemistry included abnormal canine pancreatic lipase immunoreactivity. Postmortem examination was inconclusive and autolysis confounded examination of intestinal mucosa.

Meloxicam dosing

Meloxicam dosing values are summarised in Table 6.

For the period V1 to V3, 'Joint' (P<0.01) and 'Visit×ADP' (P<0.01) had effects on PVF, with change in PVF increasing with ADP.

Discussion

Recruitment

There was a ratio of 4.7:1 (525:111) of enquiries received to cases randomised. For any trial, this ratio is dependent on the inclusion criteria,

TABLE 4: Results of outcome measures

		Visit 1		Visit 2				Visit 3					
	N	N Missing	Mean (σ)	N Missing	Mean (σ)	Change from V1	P value v V1	N Missing	Mean (σ)	Change from V1	P value v V1	Change from V2	P value v V2
PVF (N/kg)													
Group M	53	0	6.29 (2.05)	0	6.49 (2.11)	0.2*	0.02	1	6.77 (2.29)	0.48*	<0.01	0.28*	<0.01
Group T	58	0	6.22 (1.96)	0	6.55 (2.07)	0.33*	<0.01	1	6.62 (1.22)	0.4*	0.01	0.07	0.13
All	111	0	6.25 (1.99)	0	6.52 (2.08)	0.27*	<0.01	2	6.69 (2.19)	0.44*	<0.01	0.17*	<0.01
VI (NS/kg)													
Group M	53	18	1.40 (0.61)	14	1.42 (0.59)	0.02	0.13	12	1.51 (0.65)	0.11*	<0.01	0.09	0.06
Group T	58	21	1.33 (0.60)	17	1.35 (0.59)	0.02	0.23	12	1.38 (0.63)	0.05*	<0.01	0.03*	0.03
All	111	39	1.36 (0.60)	31	1.38 (0.59)	0.02*	0.05	24	1.44 (0.64)	0.08*	<0.01	0.06*	<0.01
LOAD													
Group M	53	1	19.3 (6.77)	2	15.5 (7.28)	−3.8*	<0.01	3	14.8 (7.60)	−4.5*	<0.01	−0.7	0.76
Group T	58	0	19.9 (7.29)	0	15.6 (8.64)	−4.3*	<0.01	1	14.3 (8.84)	−5.6*	<0.01	−1.3	0.46
All	111	1	19.6 (7.03)	2	15.6 (8.00)	−4.0*	<0.01	4	14.6 (8.25)	−5.0*	<0.01	−1.0	0.12
HCPI													
Group M	53	1	17.1 (6.26)	3	13.9 (6.53)	−3.2*	<0.01	3	13.0 (6.72)	−4.1*	<0.01	−0.9*	0.05
Group T	58	0	17.4 (6.37)	0	13.6 (8.07)	−3.8*	<0.01	1	12.8 (8.23)	−4.6*	<0.01	−0.8	0.21
All	111	1	17.2 (6.29)	3	13.7 (7.36)	−4.0*	<0.01	4	12.9 (7.54)	−4.3*	<0.01	−0.8*	0.03
CBPI PSS													
Group M	53	1	3.25 (2.07)	2	2.30 (2.06)	−0.95*	<0.01	3	2.09 (2.06)	−1.16*	<0.01	−0.21	0.28
Group T	58	0	3.92 (1.99)	0	2.54 (2.31)	−1.38*	<0.01	1	2.58 (2.37)	−1.34*	<0.01	0.04	0.86
All	111	1	3.61 (2.04)	2	2.43 (2.19)	−1.18*	<0.01	4	2.35 (2.24)	−1.26*	<0.01	−0.08	0.56
CBPI PIS													
Group M	53	2	3.84 (2.18)	3	2.40 (2.32)	−1.44*	<0.01	3	2.20 (2.22)	−1.64*	<0.01	−0.20	0.20
Group T	58	0	4.38 (2.16)	0	2.93 (2.35)	−1.45*	<0.01	2	2.77 (2.47)	−1.61*	<0.01	−0.16	0.72
All	111	2	4.13 (2.18)	3	2.69 (2.34)	−1.44*	<0.01	5	2.50 (2.36)	−1.63*	<0.01	−0.19	0.58

*Highlight significant results
CBPI, Canine Brief Pain Inventory; HCPI, Helsinki Chronic Pain Index; LOAD, Liverpool Osteoarthritis in Dogs; PIS, Pain Interference Score; PSS, Pain Severity Score; PVF, peak vertical force; VI, vertical impulse; σ, sd

which are defined by the nature of the study treatments and, in particular, the outcome measures.

The single most common reason for exclusion in this study (n=44) was lack of asymmetry for PVF. This inclusion criterion influenced our population in a number of ways, for example, a greater proportion of dogs with hip OA were symmetric for PVF than those with stifle or elbow OA, and were hence excluded. Specifically, of the 111 cases, 'hip' was the index joint for a total of 23 (21 per cent), 'stifle' for 29 (26 per cent) and 'elbow' for 59 (53 per cent). This is in contrast to other studies where asymmetry was not an inclusion criterion: in the study by Peterson and Keefe, 'hip' was the index joint for 93 cases out of 217 (43 per cent), 'stifle' for 40 (18 per cent) and 'elbow' for 65 (30 per cent) (Peterson and Keefe 2004); in the study by Wernham and others, only 12/59 cases (20 per cent) were considered 'forelimb' impaired (Wernham and others 2011); and in the study by Doig and others, 28/40 cases (70 per cent) had hip OA (Doig and others 2000).

Despite these limitations, we felt it was important that an 'index' limb was clearly identifiable at baseline in order that a clinically important change in PVF could subsequently be measured. Force distribution in experimentally induced lameness (Abdelhadi and others 2012, 2013) and naturally occurring OA (Bockstahler and others 2009) has been reported, but this has not led to practical recommendations for processing force data in cases of multiple limb lameness. Waveform analysis of force curves by Fourier analysis (Katic and others 2009) and generalised indicator function analysis (Al-Nadaf and others 2012) have been reported, but again, validation of these analyses as clinical outcome measures is not available. Measurement of change in force parameters for a single limb remains the most validated kinetic outcome measure, but this requires that an index limb be identified at baseline. Investigators have varied in how they have identified index limb. In 2003, Moreau and others identified the index limb by a combination of veterinary assessment and kinetic data, with kinetic data taking precedent. If subjective assessment and kinetic data were symmetric, the radiographically most severe joint was used (Moreau and others 2003). In 2007, the same primary author used comparison with his own unpublished data from a cohort of dogs with hip OA to identify clinical cases with reduced pelvic limb forces (Moreau and others 2007). Innes and others identified index limb based on veterinary assessment of joint pain and lameness scored on ordinal scales (Innes and others 2003). Roush and others also identified index limb based on subjective veterinary assessment, confirmed by kinetic data (Roush and others 2010). However, subjective veterinary assessments have shown poor agreement with kinetic measures of lameness (Quinn and others 2007, Waxman and others 2008), as has radiographic severity of OA (Gordon and others 2004). The accuracy of symmetry indices in the assessment of lame dogs has been reported (Fanchon & Grandjean 2007), and a symmetry index for PVF of 4 per cent provided sensitivity of 77 per cent and specificity of 86 per cent for the

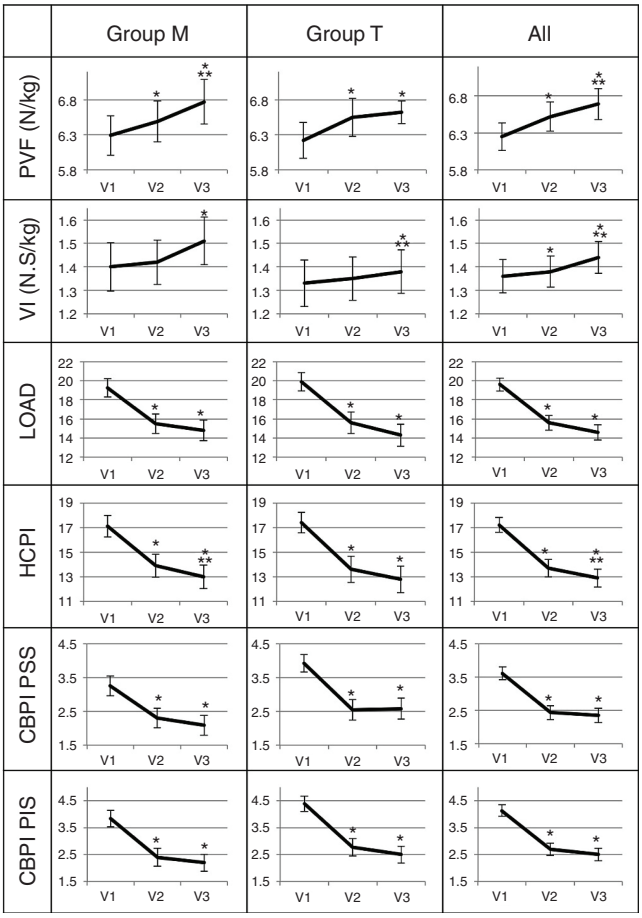

Fig 1: Outcomes Measures Results PVF = peak vertical force, VI = vertical impulse, LOAD = Liverpool Osteoarthritis in Dogs, HCPI = Helsinki Chronic Pain Index, CBPI = Canine Brief Pain Inventory, PSS = Pain Severity Score, PIS = Pain Interference Score, * significant change from V_1, ** significant change from V_2

differentiation of lame dogs from sound ones. We used a slightly higher cut-off to minimise enrolment of non-lame dogs.

A number of dogs were excluded as they were too severely affected to be subjected to the washout period, as judged by the study veterinarian (n=9) or the owner (n not specified). This means that very severely affected animals were not recruited. Eight dogs were excluded because their disease was considered to be too mild by the study veterinarian, or the owner, to justify NSAID treatment. Therefore, some caution should be exercised when extrapolating the findings of this study to the general population.

TABLE 5: Summary of AEs

Causality assessment	Group M (n=53)	Group T (n=58)	P value
Probable/possible			
N (%)	8 (15.1)	4 (7.3)	0.20[FE]
Mean (σ) last dose to onset time: (days)	1 (0)	10.3 (10.7)	0.18[T]
Mean (σ) duration of signs (days)	5.9 (5.5)	9.5 (6.9)	0.40[T]
Withdrawn (n)	6	3	0.31[FE]
Serious AE (n)	0	1 (Fatal)	0.33[FE]
Unlikely			
N	5	7	0.76[FE]
Withdrawn (n)	2	3	1.00[FE]
Serious AE (n)	2 (Fatal)	3 (2 Fatal)	1.00[FE]
Total			
N (%)	13	11	0.50[FE]
Withdrawn (n)	8	6	0.57[FE]
Serious AE (n)	2 (Fatal)	4 (3 Fatal)	0.68[FE]

AE, adverse event; FE, Fisher's Exact; T, Student's *t* test; σ, sd

TABLE 6: Meloxicam dosing values

	V1 to V2	V2 to V3	V1 to V3
ADP			
Mean	0.067	0.071	0.069
Median	0.078	0.082	0.084
ADLW			
Mean	0.070	0.073	
Median	0.081	0.084	
LD			
Mean	0.076	0.082	
Median	0.090	0.092	

All doses are mg/kg/day
ADLW, average (mean) dose for the last week of the period; ADP, average (mean) dose for the period; LD, dose given within 24 hours of assessment visit; V, visit

Of 362 cases examined that the owners believed had OA, 17 (4.7 per cent) actually had undiagnosed failure of a cranial cruciate ligament and 18 (4.9 per cent) had spinal disease.

Ground reaction forces

'Joint' was consistently a significant effect on GRFs in our analyses: this reflects that GRFs are higher in thoracic limbs than in pelvic limbs (Budsberg and others 1987, Rumph and others 1994).

GRFs increased from baseline to both on-treatment assessments, and also from V2 to V3. Increase in PVF from V2 to V3 was observed as a trend and was significant for group M and for the cohort as a whole. One possible reason for this increase in Group M is an increase in meloxicam dosing, especially as ADP was higher for V2 to V3 than for V1 to V2 (albeit by only an average of 0.004 mg/kg/day, 4 per cent of the maximum daily dose). In one study, as measured by percentage of bodyweight distributed to the limb, improvement in limb function of dogs receiving a reducing dose of meloxicam only deviated from those receiving the maximum daily dose when the dose dropped to 40 per cent of maximum (Wernham and others 2011). This, perhaps, makes it unlikely that the 4 per cent (of maximum) average change in dose affected PVF.

There may be genuine clinical benefit of continuous, long-term NSAID treatment. Plasticity of pain transmission pathways and the concept of central sensitisation are described (Kuner 2010), and cyclooxygenase inhibition has reversed aspects of sensitisation in rodents (Telleria-Diaz and others 2010) and experimentally induced hyperalgesia in human beings (Sycha and others 2005). There is moderate evidence that continuous, long-term administration of NSAIDs may have some therapeutic benefits in dogs and people (Luyten and others 2007, Innes and others 2010, Wernham and others 2011). In a multi-centre, 1000-dog study of the safety and effectiveness of firocoxib, veterinarian and owner subjective assessments both improved from baseline to day 10 of treatment, and improved further at day 40 of treatment (Ryan and others 2006); and in another study, more dogs receiving firocoxib improved by 360 days than by day 90 (Autefage and others 2011). A study of the long-term effects of carprofen in 805 dogs with OA showed veterinary-assessed outcome improved from baseline to day 14 of treatment, and improved again at day 84 of treatment (Mansa and others 2007).

Although there was a small increase in PVF from V2 to V3 (0.07 N/kg) for Group T, this was not significant. A greater proportion of the overall increase from baseline (0.4 N/kg) was seen by V2 (0.33 N/kg) in Group T than it was in Group M. This might suggest a difference in the time to maximum effect between mavacoxib and meloxicam. The present data do not strongly support continued improvement beyond six weeks.

Clinical metrology instruments

LOAD, HCPI and CBPI have all been validated as measures of the clinical impact of OA. To greater or lesser degrees, these instruments capture aspects of clinical OA that are not captured by the objective measurement of limb function (Walton and others 2013). They are influenced by caregiver placebo effect (Hercock and others 2009), but have all been demonstrated as responsive to change in clinical status.

Again, the trend for apparent improvement beyond V2 was generally observed, although this was only significant for HCPI in Group M and the cohort as a whole.

Adverse events

There were twice as many AEs with either 'possible' or 'probable' causality assessments in Group M as in Group T, but this difference was not significant. AE (15.1 per cent) and withdrawal (11.3 per cent) rates to meloxicam in this study are somewhat higher than some of those previously reported (see Table 7).

One AE with a 'possible' causality assessment was classed as serious. A dog died in association with diffuse small intestinal disease and acute pancreatitis. Serious and fatal AEs appear to be rarely associated with NSAID treatment. In a review of clinical studies involving long-term NSAID treatment for canine OA, out of a total of 1589 dogs, one suffered a serious AE and no fatalities were reported (Innes and others 2010). However, fatal AEs associated with meloxicam (Wernham and others 2011) and deracoxib (Lascelles and others 2005) have been reported.

Meloxicam dosing

The average dose for the treatment period (ADP) had a significant effect on change in PVF from V1 to V3, whereas the most recent dose (LD) or the average of doses for the preceding week (ADLW) did not. This might be further evidence that long-term dosing has more effect on limb function than recent doses.

Overall, owners elected to give 30 per cent less than the maximum licensed dose of meloxicam. This represents a fairly modest reduction from the maximum and, as previously stated, a median meloxicam dose reduction of 60 per cent can be achieved before owners consider pain control to be insufficient (Wernham and others 2011).

Although reduction from the maximum meloxicam dose can apparently be achieved without loss of clinical effectiveness, there is evidence that some dogs will suffer. When compared with animals on maximum meloxicam dose, dogs subjected to a reducing dosing regimen dropped out because of poor pain control, as perceived by the owners, more quickly (Wernham and others 2011).

Owner-determined dosing in this trial may not represent that of the general practice scenario for several reasons. First, the recruitment process may have selected for certain owner-types. The recruitment process also preferentially excluded animals with very mild or very severe disease. Aspects of study design may have influenced dosing, such as scheduled appointments with vigilant outcome assessments, diary keeping and a constant supply of medication (owners were supplied to ensure they did not run out between visits). Finally, medication in this trial was supplied at no cost to the owner.

Complexity of treatment regimen is cited as having a negative influence on treatment adherence (Vermeire and others 2001), and instructing owners to clinically assess their dog and adjust meloxicam dose accordingly may add a layer of complexity that adversely affects adherence. Conversely, engaging patients as a 'partner' in their own medical management, and placing some clinical decision making in their hands, has been mooted to improve adherence in the treatment of some conditions in human beings (Holm 1993). Owners were more compliant with regard to antibacterial treatment if they felt there had been a thorough veterinary assessment (Grave and Tanem 1999). Cost of treatment is reported to inhibit good adherence in human patients with diabetes (Piette and others 2004) and other conditions (World Health Organisation 2003). Widely spaced visits have been implicated in reduced treatment adherence in psychiatric and asthma patients (Centorrino and others 2001, Bender 2002), and 'forgetfulness' as a cause in numerous conditions requiring long-term therapy (World Health Organisation 2003).

To the authors' knowledge, no data are published on NSAID dosing behaviour of owners in the general population. However, complete compliance with a short course of daily antibacterials was reported to occur in only 44 per cent of owners in one study (Grave and Tanem 1999).

TABLE 7: Reported AE and withdrawal rates for meloxicam

Study	AE n/group n (%)	Withdrawals n/group n (%)
Current	*8/53 (15.1)*	*6/53 (11.3)*
Nell and others (2002)	13/108 (12)	6/108 (5)
Doig and others (2000)	3/38 (10.5)	0/38 (0)
Wernham and others (2011)	5/65 (7.7)	5/65 (7.7)
Sauve and others (2003)	1/14 (7.1)	1/14 (7.1)
Moreau and others (2003)	1/17 (5.8)	1/17 (5.8)
Peterson and Keefe (2004)	1/105 (1)	1/105 (1)

AE, adverse event

Conclusions

Administered on-label, mavacoxib and meloxicam provide similar improvements in limb function and owner-assessed mobility in dogs with OA and have similar safety profiles.

Clinical improvement in meloxicam-treated dogs was dose dependent, and average dose over several weeks was more important than recent doses. Owner-determined dose-titration of meloxicam can be successful, and careful attention should be paid to factors that may affect this behaviour. Treatment compliance with a long-acting NSAID was complete in this study.

Clinical improvement may continue to occur with NSAID use beyond six weeks.

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