Introduction

As a slowly progressive, degenerative and incapacitating disease, osteoarthritis is a common cause of morbidity in dogs. Currently available treatments are mostly symptomatic ones largely relying on anti-inflammatory / analgesic drugs. Over the past decade, veterinary medicine has seen a number of effective non-steroidal anti-inflammatory drugs (NSAIDs) introduced into practice with different modes of action, therapeutic targets, and with wide ranging efficacies, cyclooxygenase (COX)-2 selectivities, and adverse reaction profiles.

Nimesulide is a member of NSAIDs and has a COX2-selectivity of 5-20 on human as well as canine COX-1 and -2 isozymes [2, 7, 9, 12, 14-16]. COX2 is known to be involved in the production of prostaglandins (PGs), especially PGE2, the key mediator of pain, vasodilatation and oedema. In contrast, COX1 induces PGs and thromboxanes that play an important role in platelet aggregation and cytoprotection of stomach mucosa. COX1 inhibitory drugs have thus been implicated in the frequently observed adverse reactions such as gastrointestinal mucous bleeding and renal dysfunction, whereas COX2-selective NSAIDs are considered to have highly effective and yet relatively safe analgesic, anti-inflammatory and antipyretic effects. Among the COX2-selective NSAIDs, carprofen and meloxicam have been extensively studied and their therapeutic efficacies in canine osteoarthritis have been evaluated [1, 3, 4, 8]. In the present synovitis model study in dogs, we aimed to evaluate the analgesic, anti-inflammatory potential and tolerability of nimesulide in comparison with carprofen and meloxicam.

Materials and methods

ANIMALS

Eight beagle dogs (4 males, 4 females) aged 1 - 5 years and weighing 9.8 - 13.6 kg were employed for the study. The dogs were kept in a controlled animal housing (18°C, 55% humidity, and 12h light/dark cycle), fed once a day with a diet, Vet Complex Adult (Virbac Nutrition, Carros, France), and given free access to water. The dogs had not received medication during the 2 weeks preceding the study, had no known history of lameness, and were considered clinically normal based on complete physical examination.

PRODUCTS

Nimesulide (Zolan® or Sulidene®, 50 mg tablets), carprofen (Rimady®, 20 mg tablets) and meloxicam (Metacam®,...
1.5 mg/ml suspension) were obtained from Virbac S.A. (Carros, France), Pfizer S.A. (Orsay, France), and Boehringer Ingelheim (Reims, France), respectively. Sodium urate crystals (U2875) were purchased from Sigma Chemicals (St. Louis, MO, USA) and propofol (Rapinovet®) was obtained from Schering Plough Veterinary (Levallois-Perret, France).

SYNOVITIS INDUCTION

Acute synovitis was induced by intrasynovial injection of sodium urate crystals [5, 6, 13]. Briefly, urate crystals were dispersed in a physiologic saline at 17 mg/ml, sonicated, and the suspension sterilized by autoclave (20 min at 120°C). One ml of the suspension was injected under strict aseptic conditions into the left and right stifle joints alternately once a week. Prior to the injection, dogs were briefly anesthetized by intravenous administration of propofol at a dose of 6.5 mg/kg. All experiments, including animal handling, were carried out strictly abiding by the protocols approved by the Ethics committee (Virbac S.A.).

TREATMENT AND FOLLOW-UP

The study followed a 4-period crossover design composed of four treatment groups: an unmedicated control, nimesulide (NM), carprofen (CP) and meloxicam (MC).

In this study design, each dog received the four treatments separated by a one-week washout period. The sequence of treatments was randomly allocated to dogs according to a Latin square model.

The treatment consisted of a single dose of NM (5 mg/kg), CP (4 mg/kg), or MC (0.2 mg/kg or 0.13 ml/kg), which was given orally during the meal 15 minutes after synovitis induction.

CLINICAL EXAMINATION AND SCORING

Lameness was evaluated at four time points, i.e., 1.5 h, 2.5 h, 3.5 h and 4.5 h after sodium urate injection, by two investigators in a blinded and independent manner. The scoring was based on 5 parameters with graded severity from 0 to 3 (table I): (i) general behavior (mood), (ii) standing lameness, (iii) trotting lameness, (iv) response to contralateral limb lift, and (v) response to limb flexion/extension. A clinical score was defined as the sum of the 5-parameter values.

STATISTICAL ANALYSIS

Data were analyzed using an ANOVA on such variables as treatment sequence, test drug, time and animal as well as their interactions. In case of a significant difference, further analyses were performed by use of the Newman-Keuls multiple-comparison test. Statistical significance was set at P < 0.05.

Results

In this model of induced synovitis, the arthritic condition reached peak intensity at around 3 h post-injection and then decreased steadily from 4 to 8 h. Dogs recovered normal status generally within 24 h and occasionally in 36 h after the synovitis induction.

Compared with the control, all test drugs demonstrated significant treatment effects (P < 0.0001) and time effects (P < 0.0001) between the 0 and 4.5 h time period (figure 1). CP and MC presented similar profiles of moderate but statistically significant analgesic activity. In contrast, NM displayed a prompt, significantly stronger analgesic activity than the other two drugs.

At the 2.5 h time point, NM demonstrated a maximal difference (4.7-fold) in analgesic activity from CP and MC. The analgesic potency calculated from the data (area-under-curve in figure 1) ranks in the order of NM (6.02) > CP (1.58) > MC (1.39) compared with the control.

Throughout the study period, no adverse reactions (diarhoea or vomiting) were observed with any of the test drugs.

Discussion

In this study, acute synovitis was induced by intrasynovial injection of urate crystals, reproducing the characteristic and consistent clinical signs of lameness, which was reversible in 24 h - 36 h after induction [5, 10, 11, 13]. Our scoring system (table I) used for the evaluation of clinical signs was a subjective one based on variables related to locomotion as well.
as behaviour/demeanour. The locomotion variables were identical to those described by CROSS et al. [3] and shown to have strong correlations with the ground-reaction-force variables measured by means of a biomechanical force plate. The blinded assessments by two independent investigators in our study were meant to render the evaluations as bias-free as possible, which turned out to be fairly coherent. Within the experimental design and especially under the conditions where the 3 drugs (carprofen, meloxicam and nimesulide) were used according to the doses and routes recommended by the suppliers, the therapeutic potentials of the analgesic / anti-inflammatory drugs can be reasonably compared. Under these circumstances, our data suggest in a statistically significant manner that nimesulide had a roughly 4-fold higher therapeutic potency than carprofen or meloxicam.

Perhaps important to be mentioned here is the fact that, as a fundamental feature of the synovitis model, the therapeutic effects observed here are relevant only to the acute phase of the symptoms. Thus the present data do not address the properties related to long-term efficacy or tolerability of any of the drugs tested. Nonetheless, we would like to note that, according to our unpublished observations, the therapeutic profiles of the 3 drugs (figure 1) could generally be extended in a continuous manner to up to 8 h post-synovitis induction. Regarding nimesulide in particular, TOUTAIN et al. [13] have observed under a similar treatment regimen a maximal analgesic activity (measured by lameness reduction) up to 12 h in dogs with Freund adjuvant-induced chronic arthritis.

Within the frame of this study, therefore, our data confirm the utility of nimesulide as a highly effective analgesic / anti-inflammatory drug for managing the acute pain associated with canine osteoarthritis.

References


FIGURE 1. — Time courses of clinical scores (Mean ± SEM) of four measurements after the synovitis induction, where Cont (●) : unmedicated controls, NM (■) : nimesulide, CP (▲) : carprofen and MC (X) : meloxicam.