

Short Communications

Preferential accumulation of meloxicam in inflamed synovial joints of dogs

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MELOXICAM is a NSAID classified as a derivative of enolic acid, licensed to treat acute and chronic musculoskeletal disorders in the dog. Meloxicam achieves maximal plasma concentration 4.5 hours after oral administration, has a low volume of distribution (0.3 l/kg), is highly plasma protein bound (97 per cent) and has an elimination half-life of 24 hours in dogs (EMA 2011). Steady state pharmacokinetics are achieved within one day using the licensed dose rate in the dog (EMA 2011).

Preferential accumulation and persistence of meloxicam in inflamed joints of both the rat and the human being have previously been documented (Busch and Engelhardt 1990, Lopicque and others 2000).

The objective of this study was to investigate the concentration of meloxicam in the synovial fluid of inflamed joints versus non-inflamed joints in dogs at the lowest plasma concentration (ie, trough level), 24 hours postdosing.

Materials and methods

Eight healthy male dogs (mean age 17.8 ± 3.5 -months-old, mean bodyweight 12.59 ± 0.83 kg) were treated with 0.2 mg/kg of meloxicam (Metacam oral suspension) on Day 1 and 0.1 mg/kg of meloxicam on Day 2. All treatments were administered orally. On Day 3, inflammation was experimentally generated using a reversible, induced synovitis model. The eight animals were randomly allocated into two groups containing four dogs. In four dogs, synovitis was induced in the left stifle and in four dogs the same procedure was used in the right stifle.

Uric acid sodium salt (Rg U2875, Sigma-Aldrich) in a sterile solution of NaCl 0.9 per cent was used to prepare a 10 mg/ml suspension, using a previously described method (Toutain and others 2001). Synovitis was induced under general anaesthesia in one stifle by aseptic, intra-articular administration of 1 ml of the sodium urate crystal suspension. A 30 mm length and 1 mm diameter sterile needle and a 2.5 ml syringe were used, with synovial aspiration to check that the joint puncture was successful. The anaesthetic protocol used was intravenous propofol at a dose of 6.5 mg/kg, without premedication (Rapinovet, 1 g/100 ml, MSD). The duration of the induced inflammatory process was approximately 16 to 24 hours (Toutain and others 2001).

A single synovial fluid sample was collected from both the right and left stifle of each dog. Sample collection occurred eight hours after the administration of sodium urate which was equal in time to 24 hours after the last administration of meloxicam. In each dog, the stifle without induction of synovitis served as the control sample, representing the 'normal' joint.

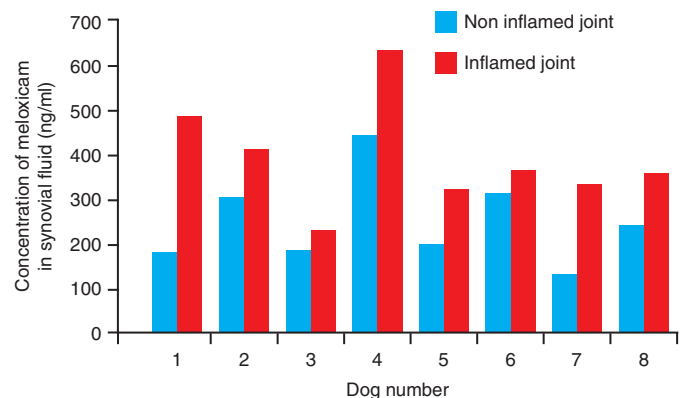


FIG 1: Meloxicam concentration in individual joints

TABLE 1: Mean meloxicam concentration in normal versus inflamed joints

Mean meloxicam concentration in normal joint (ng/ml)	246 (SEM 35.3)
Mean meloxicam concentration in inflamed joint (ng/ml)	391 (SEM 43.4)
P Value	P=0.002

Synovial meloxicam concentration was analysed using high performance liquid chromatography-mass spectrometry. The 10 μ l aliquot samples were extracted by protein precipitation using ethanol (100 μ l). These were then run down an API 4000 LC-MS/MS using an Ace C4 column (20 x 2.1 mm internal diameter 3 μ m). Mobile phase A was acetonitrile and mobile phase B was water/acetic acid (100/0.1, v/v). This was performed using a gradient method. The lower limit of detection was 0.5 ng/ml.

The concentration of meloxicam in the inflamed versus non-inflamed joint in each dog was compared using the paired *t* test ($P < 0.05$).

Results

Fig 1 shows that the meloxicam concentration (ng/ml) in the inflamed joint was greater than that of the control joint in each individual animal. The mean meloxicam concentrations (ng/ml) in the inflamed joints versus those of the control joints are shown in Table 1. The results indicate that the mean concentration of meloxicam was significantly higher in uric acid treated joints than in control joints.

Discussion

Drugs with a low volume of distribution, such as acidic NSAIDs, do not distribute equally throughout the body, and often achieve a higher concentration in one compartment. The physicochemical properties of acidic NSAID molecules, such as meloxicam, combine with the acidic environment of inflammatory sites to result in higher concentrations in those body compartments. Acidic NSAIDs are amphiphilic, that is, both water soluble and fat soluble, and are highly plasma protein-bound, mainly to albumin (Day and others 1999, Brune and Hinz 2004), at neutral pH such as in blood. Blood vessels supplying inflammatory sites become porous ('leaky') and allow both protein-bound and unbound drug to escape into surrounding tissue. Inflamed tissue has mildly acidic extracellular fluid (Williams and Morley 1974) which reduces plasma protein binding at the site, increasing the free fraction of drug which can then penetrate the cell wall (Brune and others 1981, Rainsford and others 1981). This increased concentration of intracellular molecule can then bind to the COX (cyclooxygenase) receptors, decreasing prostaglandin production and therefore inflammation.

Busch and Engelhardt (1990) used (14 C) meloxicam given orally to rats to demonstrate preferential distribution of meloxicam. Autoradiography showed that radio-labelled meloxicam preferentially localised in the inflamed connective tissue of arthritic joints, and

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negligible radioactivity was found in non-inflamed areas. Lapique and others (2000) investigated the distribution of meloxicam into the human knee joint after a single therapeutic dose given orally. The ratio of meloxicam concentration between synovial fluid and plasma was calculated. The ratio was higher in the synovial fluid of patients with inflammation versus those with no inflammation.

Intra-articular injection of sodium urate creates acute reversible inflammatory synovitis. This model is often used experimentally to predict the efficacy of anti-inflammatory drugs in animals with osteoarthritis. The study confirms that the concentration of meloxicam is statistically significantly higher in joints with experimentally induced inflammation than in non-inflamed joints. This indicates that in common with other species studied, meloxicam also preferentially accumulates in the inflamed joints of dogs.

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