

Pharmacological and Cross Validation of a Translational Pain Questionnaire Assessing Behavioral Quality of Life Measures Across Acute Urate-Induced Pain in dogs and a Naturalistic Canine Model of Osteoarthritic Pain

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INTRODUCTION

Evaluation of pain in animal models typically relies on responsive measures, such as withdrawal reflexes from noxious stimuli. Because affective pain measures relevant to quality of life often are not included or not available, the translational value of animal models of pain is limited. In the current study, a questionnaire assessing pain during performance of standard daily functions, which potentially improves translational predictability, was validated using approved NSAID pain therapeutics in both naturalistic and induced canine models of pain.

METHODS

The naturalistic canine model employed aged dogs (>6 years of age) with radiographic evidence of osteoarthritis scored by a veterinary radiologist. The induced model employed injection of sodium urate into the stifle of radiographically normal dogs. Both models were used to evaluate the utility of the pain questionnaire under control conditions compared to treatment with meloxicam, which is approved for human and veterinary use. For the urate model, circumference of the stifle was also measured.

The quality of life questionnaire evaluated functional ability and observable pain of dogs performing standard behaviors such as walking, trotting, galloping, stepping over obstacles, climbing and descending stairs, rearing for food and jumping down from a perch. Pain and function behaviors were scored by a trained technician using a scale ranging from 0-3 where higher scores reflected pain and functional deficits.

SODIUM URATE INJECTION MODEL

Study Design: Eight Beagle dogs were injected twice with 1 ml sodium urate (20 mg) in the stifle joint following a 7-day wash-out between the two injections. No treatment was provided at the time of the first injection and meloxicam was administered (0.2 mg/kg PO as per label) at the time of the second injection. Function scores, pain scores and stifle circumference were collected before injection and at 4.5, 8.5, 24.5 and 30.5 hours after the injection.

RESULTS

Meloxicam reduced measures of pain and improved function measured using the questionnaire as well as reduced joint circumference (Fig 1).

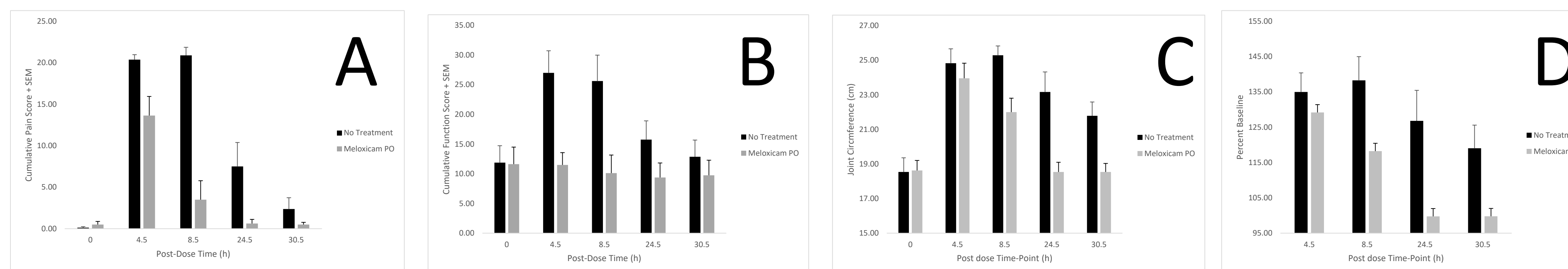


Fig 1. Mean (A) pain and (B) functional scores were significantly reduced by meloxicam compared to control across the study. Similarly, joint circumference, as a measure of inflammation, was reduced by meloxicam compared to control across the study when looking at (C) absolute and (D) percent baseline measures.

NATURALISTIC OSTEOARTHRITIS MODEL

Study Designs: In the first study, 17 Beagle dogs were tested in a balanced crossover design in which all dogs received meloxicam (0.4 mg/kg SC) or saline control injection. Dogs were treated and tested on the questionnaire daily over 14 days for each treatment condition. The second study employed a parallel group design including 6 dogs per group. Dogs were treated with meloxicam (0.2 mg/kg PO) or control for 4 days and tested daily on the questionnaire.

RESULTS

Meloxicam reduced measures of pain in both studies (Fig 2).

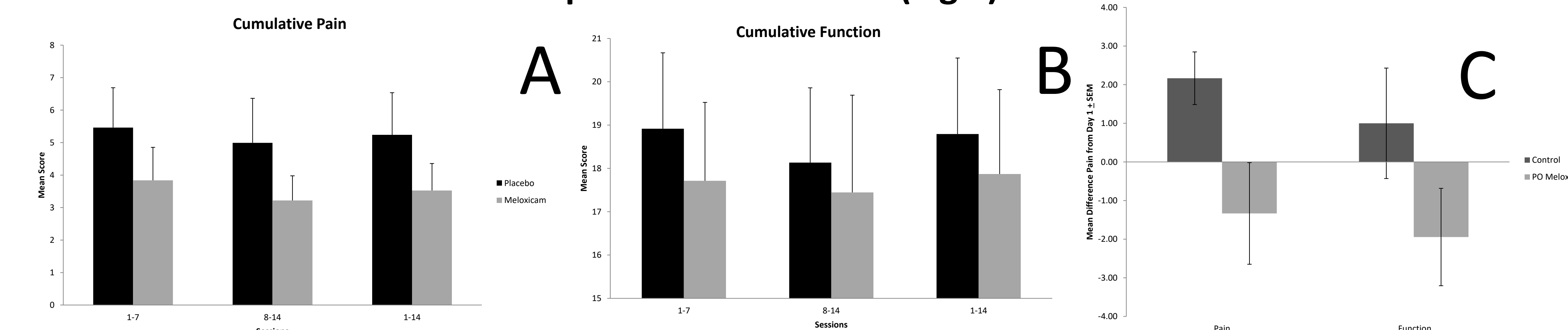


Fig 2. Mean (A) pain and (B) functional scores were significantly reduced by meloxicam (0.4 mg/kg PO) compared to control across the study. Following treatment with meloxicam (0.2 mg/kg PO) pain, but not functional deficits, was significantly reduced following treatment (C).

DISCUSSION AND CONCLUSIONS

- 1) The questionnaire used to assess pain is sensitive in the acute pain and OA models.
- 2) The sodium urate model provides the ability to assess the acute time course of drug effects.
- 3) Meloxicam significantly improved quality of life questionnaire measures of both pain and function, and reduced joint inflammation in the sodium urate model at the clinical dose for dogs.
- 4) Meloxicam significantly improved measures of pain, but not function, in both within- and between-subject designs at dose levels used in veterinary medicine.
- 5) The naturalistic model can be used to assess long-term effects of treatment including time of onset and time to peak effects.
- 6) Given Meloxicam improves pain in both humans and dogs, this study pharmacologically validates the model for translational assessment of therapeutics for osteoarthritis.

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