Investigation of a Transdermal Delivery System for a Topical NSAID, Meloxicam, in Healthy Canines – A Pilot Study

Miyuki Kumagai, B.Sc.
University of Guelph, Department of Biomedical Sciences

Background

Canine osteoarthritis (OA) is an irreversible chronic condition affecting 1 in every 5 adult dogs. It is characterized by inflammation and the gradual breakdown of joint structures, followed by pain and decreased mobility of the affected area. Treatment strategies aim to slow the progression of disease and decrease the associated pain and inflammation.

The cyclooxygenase (COX) enzyme, specifically the COX-2 isomer, is suggested to be involved in the pathogenesis of OA. Various drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzymes, thereby decreasing inflammation and providing analgesia.

The NSAID meloxicam, a COX-2 selective inhibitor, is commonly used to treat OA cases, and is associated with fewer adverse effects relative to other NSAIDs. Frequently administered as an oral suspension, this mode of delivery poses various challenges including decreased owner compliance and reduced tolerance in some dogs. Recently, transdermal delivery systems have been suggested with advantages such as: better patient compliance, consistent and controllable drug levels, and localized drug delivery with reduced systemic levels of drug.

In 2009, Yuan et al. demonstrated that higher levels of meloxicam were achieved in synovial fluid compared to the plasma of beagles dogs when treated with a gel form of meloxicam that was topically applied to the stifle joint. They also showed that this ratio was higher than that achieved with an oral meloxicam pill.

In this study, meloxicam compounded in delivra® is being investigated for use in veterinary medicine as an alternative to currently available meloxicam dosage forms. Meloxicam is administered to healthy research dogs as a clinically approved oral suspension (Metacam®) or compounded in a transdermal delivery system (delivra®). Levels of meloxicam in plasma and synovial fluid are compared between the two delivery systems. Additionally, any adverse systemic or local effects on the skin tissues are compared.

Objectives

Objective 1: Compare meloxicam levels in the synovial fluid of the stifle joint of healthy research dogs following topically applied delivra® to orally administered Metacam®

Objective 2: Compare meloxicam levels in the plasma of healthy research dogs following topically applied delivra® to orally administered Metacam®

Objective 3: Evaluate systemic and local adverse effects following topical application of delivra® or oral administration with Metacam®

Hypothesis

It is expected that:

i) Topically applied meloxicam using delivra® will achieve equal or higher synovial fluid drug levels in the stifle compared to orally administered Metacam®

ii) Topically applied meloxicam using delivra® will achieve lower plasma drug levels compared to orally administered Metacam®

iii) Topically applied meloxicam using delivra® will result in fewer adverse effects compared to orally administered Metacam®

Methods

Dogs were randomized to either oral or topical meloxicam groups in phase 1, then crossed over in phase 2 after a 21-day washout period, as shown above. Dogs were also randomized to either left or right stifle joint for sample collection in phase 1, with the remaining stifle joint used for sample collection in phase 2.

Metacam® and delivra® were given once daily for 6 days, as shown above. After treatment assignment, dogs were randomized to group 1 or 2. Group 1 dogs began treatment on day 1, Group 2 dogs began treatment on day 2. A loading dose of meloxicam was administered on day 1 in the Metacam® treatment group.

Daily assessments were performed on temperature, weight, respiration rate, pulse and behavior of every dog.

Sample collection

- Plasma
- Biochemical profile
- Complete blood cell count
- Urine
- Weight
- Subjective clinical assessment

Post-treatment samples:

- Plasma
- Meloxicam concentration
- Biochemical profile
- Complete blood cell count
- Synovial fluid
- Cytological slide
- Meloxicam concentration
- 2 stifle skin biopsies
- Histological analysis

Results

Synovial fluid and plasma sample analyses for meloxicam concentration are currently being conducted. In addition, analyses of skin biopsy samples for local adverse effects are currently being conducted.

Biochemical analyses of plasma and urine samples demonstrated no systemic adverse effects with topical or oral administration of meloxicam. Daily assessments of temperature, respiration rate, pulse, weight and behavior for each dog were similar between oral and topical meloxicam treatment groups.

Future Directions

Drug stability study

Investigate the effects of various storage conditions on the shelf life and distribution of meloxicam compounded in the delivra® carrier system.

Conditions include varying:

- Temperatures
- Light sources
- Freeze-thaw cycles

Rel paw edema study

Investigate the effects of topically applied meloxicam in delivra® on the carrageenan-induced paw edema model of inflammation in rats.

References


Acknowledgements

Dr. Ron Johnson (Faculty Advisor)
Dr. Joseph Gabriele (Faculty Advisor)
Dr. Saad Enouri (Faculty Advisor)

The University of Guelph, Ontario Veterinary College

Drugs from U of G Central Animal Facility (Hunter, Janey, Baron, Major, Ruby, Baby)