Pharmacokinetics and Assessment of Meloxicam-Infused Diet Gel in Comparison with Subcutaneously Injected Meloxicam Using an Incisional Pain Model in Mice

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for the treatment of mild to moderate pain, and are commonly used in human, veterinary and laboratory animal practice to control post surgical pain. However, administration requires handling and repeat injections in order to maintain sufficient analgesia, which can be stressful on the animal. Development of a self-administered oral gel could reduce handling stress if it could be proven to deliver an effective dose. Previous studies have shown that rodents will consume adequate amounts of hazelnut paste/Jell-O mixed with analgesics to reduce and relieve pain linked with laboratory procedures[1].

Hypothesis & Aims

We hypothesized that self-administration of MediGel™ oral meloxicam in mice would:

1. Result in a blood PK level associated with an effective dose
2. Provide effective analgesia as assessed by a pressure model of incisional pain (von Frey Filament Assay, VFFA).

Methods

Male C57BL/6NCrl mice, weighing 20 – 30 grams were utilized for this study. Animals were housed in IVC Allentown NextGen caging on corncob bedding with EnviroDri nesting material in a 12:12 light cycle. Animals in the MediGel™ dosing group were provided with meloxicam-infused gel as their sole means of food consumption for the duration of the study period.

Mice were randomly divided into two groups: pharmacokinetics (n = 42), and clinical efficacy (n = 16). In each group, mice were equally divided and randomly assigned to receive either meloxicam 5 mg/kg SQ q24 hours, or meloxicam-infused gel 5 mg/kg PO ad lib.

In the pharmacokinetic (PK) animals, blood was collected from three randomly selected mice at time points 2, 4, 8, 12, 24, 48, and 72 hours post drug administration for analysis of plasma meloxicam concentration. In the clinical efficacy cohort, meloxicam was initiated as described above 24 hours prior to surgery. Mice were anesthetized with isoflurane and the right hind paw was surgically prepared. A 5 mm longitudinal incision was made on the plantar aspect of the paw, and closed with a single suture. Mice were recovered from anesthesia and a standardized VFFA was performed to assess withdrawal reflex at 4, 12, 24, and 48 hours postoperatively. As a control, time-matched assessments of the plantar surface of the left hind paw were performed.

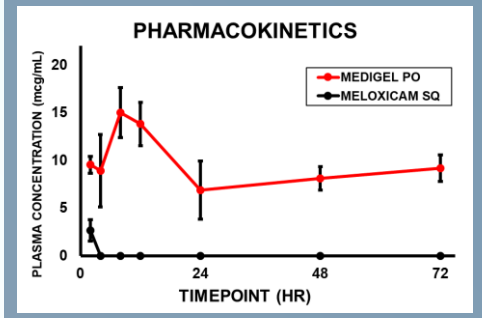
Results

Pharmacokinetics

Meloxicam concentrations were detected in the plasma at 2 hours following the initial administration of both MediGel™ and Meloxicam SQ (MediGel™ 9.55±0.9, Meloxicam SQ 2.69±1.1 mcg/mL). Peak MediGel™ plasma concentration was detected at the 8-hour time point (15.01±3.8 mcg/mL), and relatively stable concentrations were observed at 24, 48, and 72 hours of administration. Meloxicam SQ was not detected following the 2 hour time point on the first day of administration or prior to the repeat dosing at 24, 48, or 72 hours (**Figure 1**).

Clinical Efficacy

MediGel™ animals consistently demonstrated a higher threshold on VFFA at all time points compared to the meloxicam SQ cohort (4 hours post-surgery: VFFA 0.55±0.23 vs 0.02±0.0 g; MediGel™ incision vs. Meloxicam SQ incision). This same pattern was observed in the control paw groups at all time points. In both MediGel™ and meloxicam SQ groups, animals exhibited a significantly higher threshold on the control paw in comparison to the incision paw, however, in MediGel™ animals, this effect was attenuated to achieve insignificance at 48 hours post-surgery (9.1±2.5 vs. 4.85±1.2 g, p>0.05; **Figure 2**)



▲ **Figure 1.**
Meloxicam plasma concentrations at designated post-dose time points in animals receiving self-administered meloxicam infused oral gel (MediGel PO) or meloxicam SQ q24hr. Data expressed as mean±SEM.

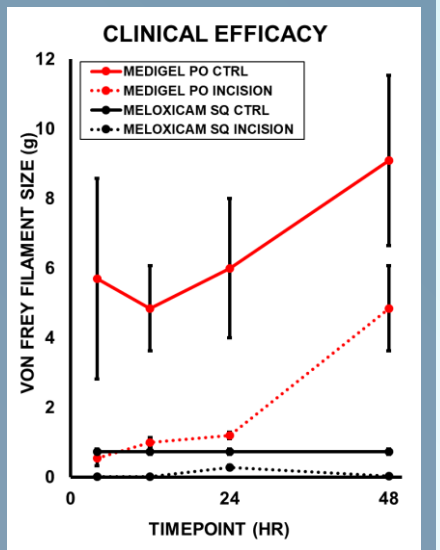


Figure 2. ▶
Clinical efficacy at designated post-operative time points, as assessed by VFFA in points in animals receiving MediGel PO or meloxicam SQ q24hr. Data expressed as mean±SEM.

Conclusions

Taken together, these data indicate that Meloxicam SQ at 5 mg/kg is ineffective in achieving sustained plasma levels at once daily dosing or providing alleviation of pain as assessed by VFFA. These findings are consistent with previous publications[2]. When administered orally according to the manufacturer's directions, MediGel™ achieves sustained plasma levels for the duration of administration. MediGel™ animals achieved peak VFFA threshold at 48 hours post-operatively, therefore, a lag effect on plasma concentration and analgesia may be present and warrants further investigation.

References & Acknowledgements

1. AMB Hovard, et al., 2015 LAB ANIM 10.1177
2. Patricia L Foley, et al., 2019 CM 10.30802

The authors would like to thank Clear H2O for the provision of the product and the animals, and William J. Lindblad, PhD at the Department of Basic Pharmaceutical Sciences at Husson University for the assessment of PK.