Kansas State University Research Foundation
TECHNOLOGY LICENSING PROFILE

New Oral Analgesic Formulation for Control of Pain in Dogs

REF. NO. (2018-017)

INVENTOR: BUTCH KUKANICH, KATE KUKANICH, DAVID RANKIN, CHARLES LOCUSON

Description: Researchers within the College of Veterinary Medicine at Kansas State University have discovered that the repurposing of two human approved drugs if administered orally to dogs provides a long acting opioid effect that can be used for the control of mild to severe acute and chronic pain.

The options for treating moderate to severe pain in dogs on an outpatient basis are very limited. Nonsteroidal anti-inflammatory drugs have limited effect and can cause gastrointestinal ulcerations and perforations, renal failure and death. Injectable opioids are frequently used for inpatients, but are short acting (2-6 hours duration) and are not practical for most outpatients. Opioids administered orally to dogs are poorly effective due to rapid metabolism in the dog's body before analgesia can take effect.

Through several studies analyzing different drug combinations, Dr. KuKanich and his team discovered that combining oral methadone with a frequently used antifungal drug, fluconazole (at a very low dose), the oral opioid bioavailability and duration in dogs are increased. Fluconazole acts as a drug inhibitor of a specific liver enzyme allowing methadone to remain active in the body longer. Methadone plus fluconazole administered orally produced clinical opioid effects for at least 12 hours in dogs and twice daily dosing will allow for excellent dosing compliance for both inpatients and outpatients. Previously approved combinations using this theory (a drug and drug metabolism inhibitor) have been FDA approved in humans (Nuedexta© and Prezcobix®), so an approval precedent has been set.

These two drugs are inexpensive and can be formulated together into a tablet, capsule or an oral suspension for ease of use. **Naltrexone, an inexpensive opioid antagonist could be included in the formulation to avoid intentional misuse and diversion by pet owners, veterinarians and staff (Figure 2).** *A clinical trial in postoperative dogs (43 total) demonstrated no significant difference between the oral methadone / fluconazole / naltrexone formulations every 12 hours and injectable methadone every 4 hours (Figure 3).* This new technology could provide veterinarians and dog owners with a new option for in-house treatment of postoperative or trauma pain or in selected cases chronic pain or hospice care at home. It could also provide clinics with a new option when pain relief for 12 hours is desirable, such as overnight or prior to patient discharge.

Advantages:

- Long-acting oral pain relief
- Inexpensive
- Easy to administer for dog owners and can include a deterrent to human abuse

Applications: New oral analgesic product for pain relief in dogs. A potential additional use includes high efficacy long lasting antitussive effects for chronic poorly controlled cough in dogs.

Patent Status: Patent Pending

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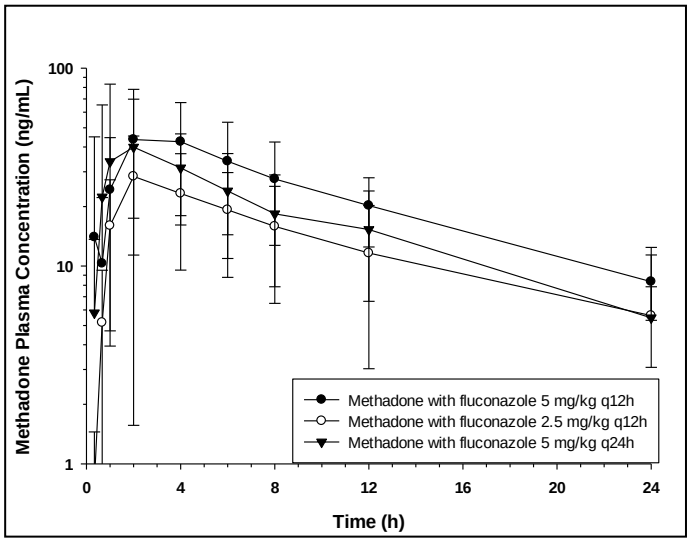

Figure 1. Plasma methadone concentrations (mean ± SD) in 6 dogs/treatment administered fluconazole 2.5 or 5 mg/kg PO q 12h with methadone 1 mg/kg administered 24 hours after fluconazole or fluconazole 5 mg/kg PO q24h with methadone 1 mg/kg administered 12 hours after fluconazole.

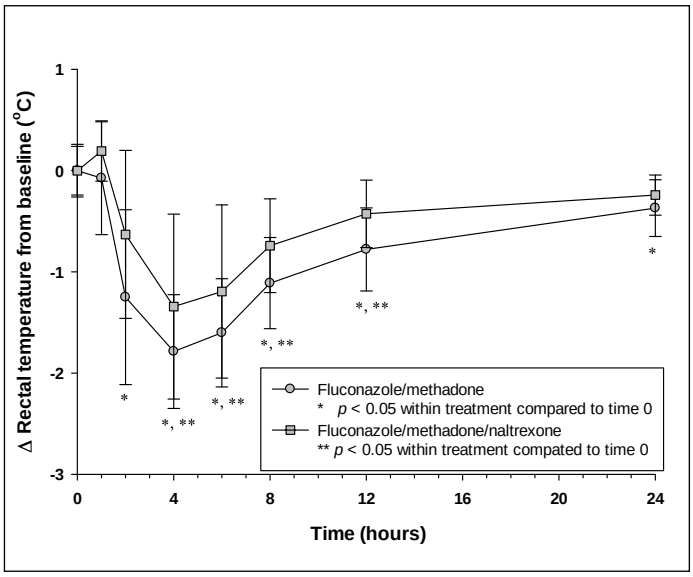

Figure 2. Changes in rectal temperature (a central opioid effect) in 6 dogs/treatment after administration of oral methadone (1 mg/kg) with fluconazole (5 mg/kg) or oral methadone (1 mg/kg) with fluconazole (5 mg/kg) and naltrexone (0.25 mg/kg). Both treatments had significantly decreased rectal temperature compared to baseline until at least 12 hours and the treatments were not different. These data indicate incorporation of the human abuse deterrent naltrexone does not interfere with central mediated opioid effects in dogs.

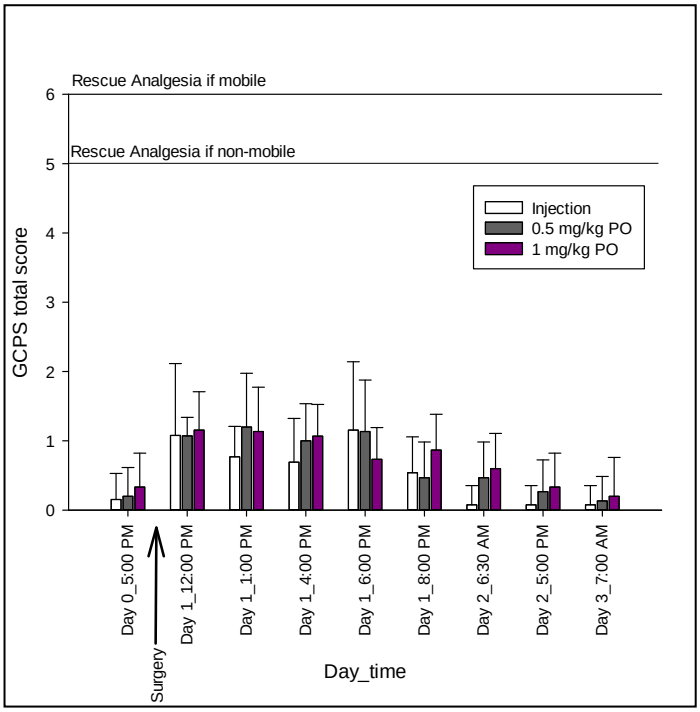

Figure 3. Glasgow Composite Pain Scores (GCPS), short form, in postoperative ovariohysterectomy 43 dogs after: 1) methadone injection 0.5 mg/kg subcutaneously every 4 hours (positive control), 2) oral administration of methadone 0.5 mg/kg with fluconazole 2.5 mg/kg and naltrexone 0.125 mg/kg every 12 hours, and 3) oral administration of methadone 1 mg/kg with fluconazole 5 mg/kg naltrexone 0.25 mg/kg every 12 hours. There were no significant differences between the treatments and no dogs required rescue analgesia.

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