Changing Methadone Metabolism to Prolong Analgesia

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In the literature

KuKanich B, KuKanich K, Rankin DC, et al. Perioperative analgesia associated with oral administration of a novel methadone-fluconazole-naltrexone formulation in dogs undergoing routine ovariohysterectomy. *Am J Vet Res*. 2020;81(9):699-707.

FROM THE PAGE ...

Opioids are potent analgesic drugs commonly used to control acute pain (eg, pain caused by surgery or traumatic injury). When administered orally to humans, methadone has a high bioavailability, prolonged elimination time, and results in 6 to 12 hours of analgesia.[1] Opioid effects are terminated via hepatic cytochrome P450 enzymes, which is a species-specific process.[2,3] In a previous study, there was no measurable plasma methadone in a majority of dogs following oral administration[4]; this is unlike pharmacokinetics in humans. Drugs with opioid potency, long duration of action, and efficacy following oral administration are desirable for veterinary patients but are not currently available.

As an alternative to the discovery and development of new drugs, effects of existing drugs can be modified through a variety of mechanisms, including changing the rate and/or extent of drug metabolism via manipulation of hepatic enzymes using pharmacokinetic enhancers (eg, fluconazole, ketoconazole, chloramphenicol). In dogs, enhancers coadministered with oral methadone have been shown to increase the bioavailability and prolong the elimination time of methadone.[4-6] However, the clinical impact of this was previously unknown.

In this clinical study, dogs undergoing ovariohysterectomy were either given methadone (0.5 mg/kg SC every 4 hours) alone or methadone with fluconazole and naltrexone in 2 oral drug combinations (ie, methadone [0.5 mg/kg], fluconazole [2.5 mg/kg], and naltrexone [0.125 mg/kg] or methadone [1 mg/kg], fluconazole [5 mg/kg], and naltrexone [0.25 mg/kg]) PO every 12 hours.[7] Pain scores (using the Glasgow Composite Measure Pain Scale Short Form) were compared among groups every 4 hours, which is the expected analgesic duration following IV administration. A significant difference in scores was identified at only one time point, and no dog required rescue analgesia, indicating adequate analgesia was provided by both protocols. All dogs also received carprofen, which may mask minor methadone insufficiency but does not change the utility of the results, as the drugs would be used together in clinical protocols.

As with all drugs, both efficacy and safety should be considered. A major safety concern of potent opioids is diversion to human use. Naltrexone, an orally administered long-duration opioid antagonist, was added to the methadone/fluconazole combination as an abuse deterrent. Although naltrexone could potentially reverse some of the analgesia provided to the patient, the drug combination was shown to be effective in this study, and opioid-mediated adverse effects (eg, vomiting) were not eliminated.

The results in this study are promising, as they demonstrate that long-duration analgesia can potentially be achieved in dogs using currently available drugs. The authors state that the efficiency of oral twice-daily administration, as compared with injectable administration every 4 hours, is expected to increase the probability patients will receive adequate analgesic treatment.

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… TO YOUR PATIENTS

Key pearls to put into practice:

1. Drug metabolism is often species-specific, and the effects of drugs in humans cannot be extrapolated to veterinary species.
2. Orally administered methadone (2 mg/kg) without an enhancer like fluconazole is not bioavailable in dogs and should not be administered for analgesia.
3. As shown by pain scores in this study and others,[7-9] ovariohysterectomy is painful, and adequate analgesia—along with pain scoring to assess treatment efficacy—should be a standard component of patient care.

References

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Research Note:
Stored Packed RBCs for Blood Transfusion

This study evaluated the impact of storage time on canine packed RBCs over 28 days. Packed cell volume increased from 70% to 78.33%, lactate increased 627%, potassium content increased 183%, hemolysis reached 0.69%, and pH decreased 9% after 28 days. There was no determined negative effect on dogs receiving transfusions. The authors concluded that, despite alterations that occur during storage, packed RBCs stored ≤21 days are effective and safe for transfusion therapy.

Source

Rodrigues RR, Kayano CK, dos Santos VP, Moroz LR, Fantoni DT, Ambrósio AM. Evaluation of hematologic, biochemical, and blood gas variables in stored canine packed red blood cells, and the impact of storage time on blood recipients. *Vet Clin Pathol*. 2020;49(2):198-206.