

TRAMADOL: WHAT DO WE REALLY KNOW?

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Key Points:

- Tramadol is a centrally acting analgesic with low affinity for the mu opioid receptor and with an analgesic action that may be primarily related to inhibition of norepinephrine and serotonin reuptake
- The M1 metabolite is the only one shown to be clinically active but has recently been shown to be a relatively minor metabolite in dogs, with plasma levels being lower than those associated with analgesic effects
- Pharmacokinetic studies have raised questions regarding appropriate dose and dosing intervals for tramadol and more studies proving efficacy are needed

Opioids are frequently used for pain control in veterinary patients. However, the poor oral bioavailability and high abuse potential of opioids such as morphine and methadone have led to an increased interest in and use of tramadol. Tramadol is a centrally acting analgesic with complex pharmacokinetics and mechanism of action. Tramadol, a synthetic analogue of codeine, binds with low affinity to the mu- and delta- opioid receptors and inhibits norepinephrine (NE) and serotonin (5-HT) reuptake. The primary antinociceptive activity of the parent compound is presumed to be relatively independent of the opioid receptor and may be primarily related to inhibition of NE and 5-HT reuptake in descending inhibitory pathways within the central nervous system.

After oral administration in dogs, tramadol is rapidly and extensively metabolized by cytochrome P450 enzymes (CYP) to several metabolites, only one of which, O-desmethyltramadol (M1), has been shown to be clinically active. O-desmethyltramadol has a much higher affinity (200X) for the mu opioid receptor than the parent compound although the affinity is still only 10% that of morphine. It was previously suggested that rapid metabolism to the more potent M1 metabolite was responsible for the majority of tramadol's analgesic effect. However, that assumption has been recently called into question. Giorgi et al (2009) found that tramadol was rapidly absorbed after oral administration of an immediate release capsule (4 mg/kg), but then rapidly metabolized to two other main metabolites the M5 (N,O-desmethyltramadol) and M2 (N-desmethyltramadol) metabolite, rather than the M1 metabolite. KuKanich and Papich (2011) similarly found M1 to be a minor metabolite after a dose of 10mg/kg tramadol in Greyhounds. The half-lives of both tramadol and all three metabolites were relatively short (tramadol: 1.1hr vs M1: 1.4 hr). Differences in pharmacologic formulations can have a large effect on both the bioavailability and the pattern of metabolites formed. For example, tramadol administered orally in dogs as an immediate release tablet is 65% bioavailable with a short half-life of 1.5 - 2 hours while both a sustained release formulation and a rectal suppository were only 10% bioavailable.

Tramadol has become popular in veterinary medicine due to a relatively low incidence of gastrointestinal and cardiovascular side effects with chronic use. However, as our understanding of tramadol's metabolism in the dog grows, questions regarding its efficacy and appropriate dosing interval have also grown. In greyhounds, an increase in pain pressure threshold was found at 5-6 hours after a dose of 10 mg/kg, but at no other time point in a 12 hour study. Plasma concentrations of the M1 metabolite were below levels previously found to be analgesic,

suggesting M1 may not be the source of analgesia. Simulated dosing of tramadol suggested that 5 mg/kg q 6 hours or 2.5 mg/kg q 4 hours was required for adequate analgesic levels. This is in contrast to the 2 – 4 mg/kg bid/tid generally recommended. In human patients, oral tramadol has been shown to be effective in some patients with moderate cancer pain, although efficacy is dependent upon the source of pain, with 83% efficacy in patients with bone pain, but only 33% efficacy in patients with neuropathic pain. Another study comparing the efficacy of celecoxib vs. tramadol in treatment of patients with chronic low-back pain found celecoxib to be more effective than tramadol, with fewer adverse events. Most adverse events in humans are related to gastrointestinal side effects including nausea and vomiting. One study looking at mortality in human patients hospitalized for perforated peptic ulcers, found that tramadol increased mortality at a level comparable to NSAIDs.

Further studies are needed to look at other potential side effects with chronic tramadol use in veterinary patients, including those on concurrent medication. For example, chronic inhibition of norepinephrine reuptake can lead to hypertension in humans while inhibition of serotonin reuptake has a potential effect on platelet function. Tramadol should not be combined with other psychotropic drugs (e.g. amitriptyline) due to the possibility of serotonin syndrome. Seizures have been reported with tramadol use in man.

References

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