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Therapeutic Review

Tramadol

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Tramadol is a synthetic codeine analog which acts centrally as a μ-opiod agonist and inhibits reuptake of serotonin and norepinephrine.[1] First synthesized in 1962, tramadol has been used in Germany to control pain in humans since 1977 and in 1995 was finally approved by the United States Food and Drug Administration.[2] Currently tramadol is widely used as an oral analgesic for veterinary patients, especially dogs with an ever increasing application for companion exotic animals. However, the pharmacology of tramadol is complex with the drug being a racemic compound composed of both + and – enantiomers.[2] The + enantiomer primarily affects μ-opiod receptors, with 6000 times less affinity than morphine, and inhibits serotonin reuptake. The – enantiomer primarily causes inhibition of norepinephrine reuptake.[3] Inhibition of norepinephrine reuptake leads to activation of the descending pain inhibitory system, causing inhibition of the transmission of painful stimuli through the dorsal horn of the spinal cord via endogenous opiods.

In mammals, tramadol is converted to several metabolites by P450 enzymes in the liver, with 86-100% of the drug and its derivatives being excreted through the renal system.[4] There is one primary active metabolite, O-desmethyltramadol (M1), which has 200 times the affinity of tramadol for μ-opiod receptors. In humans, some individuals are unable to convert tramadol to its metabolites efficiently due to a P450 enzyme deficiency. The inability to produce tramadol metabolites results in decreased serum levels concentrations of M1 and consequently a significantly reduced analgesic effect of the medication.[5] In dogs, this may explain the lack of M1 metabolite production and subsequent analgesic effect in beagles.[6] Additionally, it is possible that induction of P450 liver enzymes may be variable between species.

In humans, reported mean minimum effective concentrations (MEC) of tramadol range from 298 μg/L to 590 μg/L. For the M1 metabolite, the mean minimum effective concentrations were 39.6 μg/L to 84 μg/L with wide variation was noted in individual MEC.[7,8] Most of the tramadol research investigations performed in exotic animal species have attempted to reach serum or plasma concentrations consistent with those known to provide analgesia in humans.