FERGUS COUTTS
VETERINARY PAIN MANAGEMENT

Broadleys Veterinary Hospital
Stirling
FK7 7LE
Appointments: 01786 445665

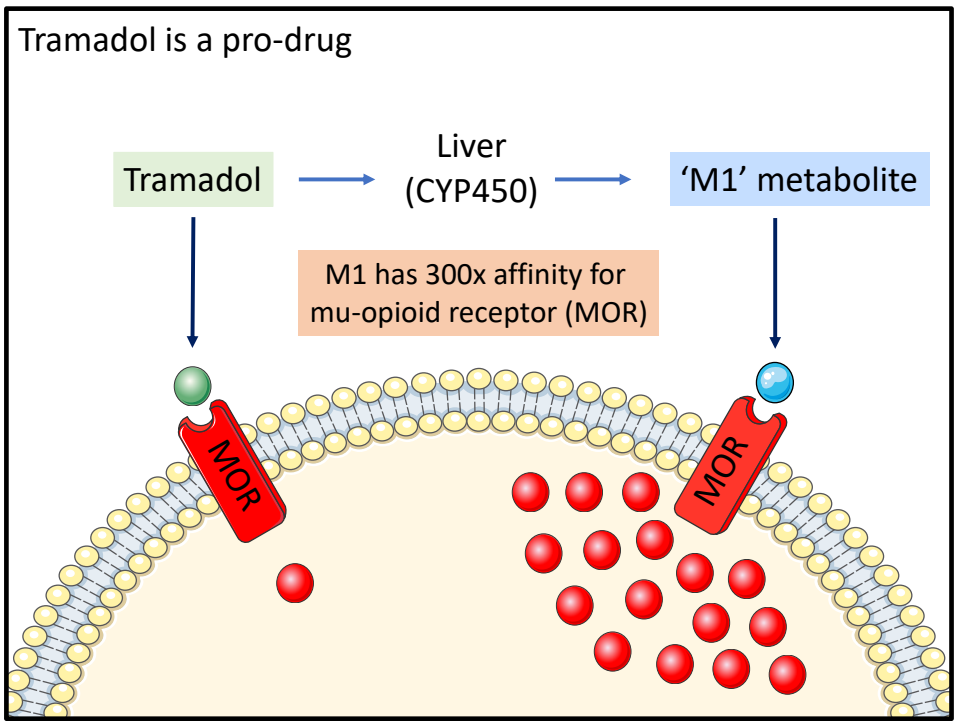
Pharmacology of pain: tramadol

Key points:

1. Tramadol is a weak opioid and acts as a pro-drug; its metabolite 'M1' has 300x greater affinity for mu-opioid receptors.
2. Dogs produce little M1 from tramadol and a short t/2 limits its opioid efficacy. This may vary within and between breeds. Bioavailability in dogs decreased by ~65% after oral dosing for eight days.
3. Cats produce higher amounts of M1 from tramadol, providing an opioid analgesic effect.
4. There is also an analgesic effect following inhibiting of the re-uptake of noradrenalin and serotonin.
5. Co-administration of tramadol with NSAID may increase the risk of GI bleed.
6. Tramadol should not be combined with other drugs affecting serotonin mechanisms, to avoid causing Serotonin Syndrome.

1. Modes of action

- **Mu-opioid receptors (MOR).**
  - Tramadol, a codeine analogue, is a centrally acting analgesic drug with weak affinity for MOR [31].
  - Tramadol is a pro-drug as one metabolite, *O-desmethyltramadol* (M1), shows a 300-fold greater affinity for MOR than the parent molecule [12]. M1 is muscarinic receptor antagonist [20].
- **Central neurotransmitters.** Tramadol also has analgesic efficacy through:
  - **Noradrenergic pathways:** Tramadol inhibits noradrenaline (NA) re-uptake [8]. Tramadol also downregulates central α-2- & upregulates α-1 adrenoreceptors [9, 10]. Faron-Gorecka et al (2004) proposed these noradrenergic mechanisms are responsible for the antidepressant-like effect of tramadol in mice [9]. There is no evidence to support an antidepressant-like activity in dogs or cats.
  - **Dopamine:** Inhibits dopamine reuptake [8] and upregulates dopamine receptors [9]
  - **Serotoninergic pathways:** Tramadol inhibits 5-HT re-uptake, a 10x greater than M1 [7].
- Inhibiting NA re-uptake may provide greater analgesia than inhibiting 5-HT uptake [13].



2. **Comparative pharmacokinetics**

- **Humans** show marked pharmacogenetic variation in the production of M1 [32], with a corresponding effect on the opioid analgesic effect. The M1 metabolite has $t_{1/2}$ ~6hrs in people. The serotoninergic effects of tramadol are believed to be responsible for the adverse effects reported in people, e.g. nausea, hallucinations, headaches [28]. Tramadol does not cause opioid-induced constipation in people [33].

Table 1. Comparative aspects of M1 production

Species	M1 produced?	$t_{1/2}$ M1 (hrs)
Human	+ to +++++ *	6hrs
Dog	+ *?	1.5hrs
Cat	++++	4.5hrs
***: Pharmacogenetic effect**		

- **Dogs** Oral bioavailability decreased by ~65% after oral dosing for eight days [24]. Dogs produce at least 24 metabolites from tramadol [34]. Studies showed healthy Beagles and Greyhounds metabolise tramadol to produce low levels of M1 and it has $t_{1/2}$ ~1.5hrs [14]. Older Beagles showed slower tramadol clearance [19] . Tramadol demonstrated analgesic efficacy in greyhounds, despite low levels of M1 production, due to the effects on NA and 5-HT re-uptake enhancing descending pain-inhibitory pathways[21]. Tramadol has a $t_{1/2}$ ~1.4hrs in dogs.
  Dose: the BSAVA Formulary recommends 2-5mg/kg TID [5].
- **Cats** metabolise tramadol to produce significant amounts of M1 [29] and tramadol showed antinociceptive efficacy in preclinical tests [30]. Tramadol has $t_{1/2}$ ~6hrs in cats.
  Dose: the BSAVA Formulary recommends a dose of 2-4mg/kg TID [5].

3. **Clinical evidence**

- **Dogs:** Prescribing tramadol as an adjunctive drug to manage acute or chronic pain in dogs remains controversial [2].
  - Malek et al (2012) demonstrated moderate efficacy of tramadol in dogs with hip OA, assessed with the Canine Brief Pain Inventory (cBPI) [23].
  - Budsberg et al (2018) recruited dogs with elbow or stifle OA to a 'randomised, blinded placebo- and positive-controlled cross-over study'. All dogs were treated, in a random order, with each of carprofen, tramadol & placebo. In this study tramadol was no better than placebo (force-plate & cBPI assessment) [6]. (*Note: It would have been interesting had the study included a fourth arm, where dogs were treated with both carprofen and tramadol*).
  - Anecdotally some dogs do seem to benefit from tramadol and a pharmacogenetic effect has been proposed in dogs, with M1 production varying within and between breeds [15, 27].
- **Cats:** Tramadol has demonstrated efficacy in cats for managing post-surgical pain [3 2, 4] and OA-related pain [1, 16, 25, 26].

4. **Precautions – see Kukanich[20]**

- Co-administration of tramadol with NSAID may increase the risk of GI ulceration [22].
- Tramadol reduces seizure thresholds in people, owners of animals with epilepsy should be warned treating them with tramadol may increase their pets' risk of seizures [20].
- Co-administration of tramadol and other drugs with serotoninergic activity may cause 'Serotonin Syndrome', characterised by neuromuscular and autonomic hyperactivity. Serotonin Syndrome has been described in dogs and cats [11, 17, 18].

5. **Tralieve ™**, a veterinary licensed formulation of tramadol, is soon to be released to the UK market.

Reference list available on request **Rev. October 2018**