Pharmacokinetic differences of tramadol in several animal species and human beings

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Tramadol (T), (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrocloride, is a centrally acting analgesic structurally related to codeine and morphine. It consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. This drug has been used in the two last decades to trait pain in humans. T has only a weak affinity for the μ opioid receptors and no affinity for δ or κ opioid receptors (Raffa et al., 1992). The affinity of T for μ opioid receptors is approximately 10-fold less than that of codeine and 6000-fold less than that of morphine, an affinity that by itself does not seem sufficient to contribute to the analgesic action of T. The metabolite *O*-desmethyl-T (M1) binds with approximately 300-fold higher affinity than the parent compound, but still with much lower affinity than morphine (Frink et al., 1996; Kögel et al., 1999). The increase in subjective and objective pain thresholds induced by T is, in contrast to that of other opioids, only partially blocked by the opioid antagonist naloxone (Desmeules et al., 1996). Therefore, the activation of μ opioid receptors appears to be only one of the components of the mechanism of action of T. Other indications that it is a non-opioid drug are: (i) the lack of naloxone reversibility; (ii) the lack of significant naloxone-induced withdrawal; (iii) the production of mydriasis (rather than miosis); and (iv) the attenuation of its antinociceptive or analgesic effect by non-opioid (i.e. serotonin or adrenergic) antagonists (Raffa and Friderichs, 1996). T inhibits the neuronal reuptake of norepinephrine and serotonin (5-hydroxytryptamine, 5-HT) (Raffa et al., 1992). These monoamine neurotransmitters are involved in the antinociceptive effects of descending inhibitory pathways in the central nervous system. The α2 adrenoceptor antagonist yohimbine and the serotonin antagonist ritanserin, block the antinociceptive effects of T, (Desmeules et al., 1996) but not those of morphine (Raffa et al., 1992). The reuptake inhibition of the non-opioid system requires the same range of concentrations as the inhibition of the opioid system, suggesting that both mechanisms are active *in vivo*. (+)-T and the metabolite (+)-M1 are agonists of the μ opioid receptors. (+)-T inhibits serotonin reuptake and (–)-T inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate.

T is available, in human medicine, as drops, capsules and sustained-release formulations for oral use, suppositories for rectal use and solution for intramuscular, intravenous and subcutaneous injection. After oral administration, T is rapidly and almost completely absorbed. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours and have a bioavailability of 87–95% compared with capsules. T is rapidly distributed in the body; plasma protein binding is about 20%. The main metabolic pathways of T, *N* and *O*-demethylation (phase I reactions) and conjugation of *O*-demethylated compounds (phase II re actions), were already described over 20 years ago (Lintz et al., 1981). Eleven metabolites were known, five arising by phase I reactions (M1 to M5) and six by phase II reactions (glucuronides and sulfates of M1, M4 and M5). T is metabolised much more rapidly in animals than in humans: 1% and 25–30% of an oral dose, respectively, and it is excreted unchanged in the urine (Lintz et al., 1981). In all species, M1 and M1 conjugates, M5 and M5 conjugates, and M2 are the main metabolites, whereas M3, M4 and M4 conjugates are only formed in minor quantities (Lintz et al., 1981). These metabolites were formed via the following six metabolic pathways: *O*-demethylation, *N*-

demethylation, cyclohexyl oxidation, oxidative *N*-dealkylation, dehydration and conjugation (Wu et al., 2002). The previously known metabolites (M1 to M5) (Lintz et al., 1981) are confirmed as major metabolic products. Six additional phase I metabolites (M6 to M11) result from newly identified pathways and have recently been reported (Wu et al., 2002). M12 to M18 are identified as glucuronides and M19 to M23 as sulfates, of which M13 to M15 and M20 to M23 have previously been reported as M1, M4 and M5 conjugates (Lintz et al., 1981). Additional phase I metabolites (M25 to M29) and phase II metabolites (M24 and M30) have been identified in rats or dogs, but not in humans (Wu et al., 2002; 2001). T and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours. The *O*-demethylation of T to M1, the main analgesic effective metabolite, is catalysed by cytochrome P450 (CYP) 2D6, whereas *N*-demethylation to M2 is catalysed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of T can partly be ascribed to CYP polymorphism. Phenotypically, 90–95% of Caucasians are 'extensive metabolisers' and the remainder are 'poor metabolisers' of CYP2D6 (Paar et al., 1997). *O*- and *N*-demethylation of T as well as renal elimination are stereoselective. Pharmacokinetic-pharmacodynamic characterisation of T is difficult because of differences between T concentrations in plasma and at the site of action, and because of pharmacodynamic interactions between the two enantiomers of T and its active metabolites. The minimum effective concentrations (MEC) reported for T and M1 in humans are 0.3±0.2 μg/ml (Lehmann et al., 1990), and 0.08±0.06 μg/ml (Grond et al., 1999), respectively. The analgesic potency of T is about 10% of that of morphine following parenteral administration. T provides postoperative pain relief comparable with that of pethidine, and the analgesic efficacy of T can further be improved by combination with a non-opioid analgesic. T may prove particularly useful in patients with a risk of poor cardiopulmonary function, after surgery of the thorax or upper abdomen and when non-opioid analgesics are contraindicated. T is an effective and well tolerated agent to reduce pain resulting from trauma, renal or biliary colic and labour, and also for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain. T appears to produce less constipation and dependence than equianalgesic doses of strong opioids.

Interest in providing analgesia to veterinary patients has increased substantially over the past 20 years. Currently, several nonsteroidal anti-inflammatory drugs (NSAIDs) are used around the world for analgesic use in different animal species. Despite the recent advances in the development and availability of NSAIDs, their effectiveness only includes mild to moderately painful conditions and the occurrence of adverse effects can limit their use. T has a low abuse potential, possess no clinically relevant respiratory or cardiovascular effects, lacks pharmacodynamic tolerance, has little effect on gastrointestinal motility, and is well tolerated with a low incidence of adverse effects in humans (Raffa et al., 1993). Hence the lack of side effects, characteristic of opioid derivatives, shown by this drug, and the absence of typical side effects due to non steroidal anti-inflammatory drugs, suggest T as a potential molecule for long term therapy in chronic pain in animals. Despite its long-term use, the understanding and prediction of the time course of its pharmacological effects in animals are still hampered by the presence of active metabolites and coexistence of opioid and non-opioid mechanisms. Recently, T has been reported to be metabolized faster to inactive metabolites, in goats (de Sousa et al., 2008), dogs (KuKanich & Papich, 2004; Giorgi et al., 2008) and horses (Giorgi et al., 2007; Shilo et al., 2008) rather than cats (Pypendop & Ilkiw, 2008). Clinical effectiveness of T has been questioned in species that mainly metabolize this molecule to inactive metabolites, suggesting that this drug could be not suitable as effective and safe treatment for pain as in humans (Giorgi et al., 2006; de Sousa et al., 2008; Giorgi et al, 2008).

No stereoselective pharmacokinetic studies on T and its metabolite are reported in animals at the present.

Horses

Several formulations have been tested in this animal species: intravenous and intramuscular injection, immediate release (IR) capsules (fast/feed), sustained release (SR) tablets (Giorgi et al., 2007; Shilo et al., 2008). Injective formulations can lead to adverse effects due to abrupt peaks in plasma concentrations, and they should be injected slowly, whereas oral formulations have poor bioavailability and are not easily administered (an oral cream should be more suitable than tablets/capsules). Moreover, although fasting/feeding seems do not influence oral absorption, the bioavailabilities of the oral formulations (IR 60%, SR 10%) are reported to be variable among the subjects and lower than in humans (Giorgi et al., 2007).

Although the effectiveness of the drug epidurally administered has been reported by clinical studies (Natalini and Robinson, 2000), pharmacokinetic studies suggest a less effectiveness in horses than in humans. It seems to be due to both the high metabolic rate of T and its wide biotransformation in inactive substances as M2 and M5 rather than M1. These *in vivo* findings agree with *in vitro* results which did not identify M1 in horse microsomes incubated with T (Giorgi et al., 2006). Following iv/im administration of T 2 and 5 mg/kg, the MEC reported for humans are maintained up to 2 and 4 hours, respectively. Plasma concentration of M1 resulted ever above the target plasma MEC level either in 2 mg/kg iv and im than in 2 and 5 mg/kg IR and SR oral administrations (Giorgi et al., 2007; Shilo et al., 2008).

Goats

Only a single recent study exists on goats, administered with T 2 mg/kg via iv and oral (de Sousa et al., 2008). The pharmacokinetic of T is reported in this animal species to be faster than in humans. Following iv and oral IR administration, the target plasma MEC level of T was maintained up to 1.5 and 0.5 hours after dosing, respectively, whereas the MEC level of M1 was not achieved in both administrations. It was suggested a doubled iv dose at 6 h intervals to obtain an effective analgesia. The pH rumen (6.8) could increase the T absorption (pKa 9.41), compared to humans (pH gastric 1-2), as it is presumed that the medium should generate more non-ionized molecules. In this way the fasting/feeding seems to influence the absorption of T.

Camels

A single study describes pharmacokinetics of T administered via iv and im at 2.33 mg/kg and the metabolites detection in urine (Elghazali et al., 2007). In agreement with human data, these formulations result bioequivalent. The MEC level of T is maintained for 4 hours following both administrations. A new finding which is speculating on the drug's metabolism is the high amount of M1, M5, T and hydroxyl-T (T-OH) coniugated in urines. These results coupled with the well known opiates extra-hepatic glucuronidation, suggest an early phase I and a delayed phase II before excretion in urine. It agrees with the flip/flop effect first suggested in dogs (Kukanich and Papich, 2004). No data is reported on M1 plasma concentrations.

Cats

The formulations tested in cats are iv (2 mg/kg), oral IR (5.2 mg/kg) (Pypendop & Ilkiw, 2008) and oral IR (4mg/kg) (Papich and Bledsoe, 2007). The pharmacokinetics behaviour of T in the cat is closer to humans than other animals. The oral bioavailability is very good (93%), the half life results comparable (3.4 hours) with that reported in humans (5 hours), and double respect to the dog (1.7). The plasma concentration of M1 is very good, maintaining a

T/M1 plasma ratio of about 1. No adverse effects are observed after T administration, despite cats appeared euphoric for several hours. In cats the MEC levels of T and M1 are maintained up to 8 and 10 hours after iv and oral administration, respectively.

Dogs

The formulations tested in dogs are: intravenous injection (4.4 mg/kg), immediate release (IR) tablets (11.2 mg/kg) (KuKanich & Papich, 2004) and sustained release (SR) tablets (5 mg/kg) (Giorgi et al., 2008), but also suppositories and intramuscular injection (4 mg/kg) (author unpublished data). In this animal species the pharmacokinetic of T is fast, suggesting 6 daily drug administrations to maintain the analgesic effect. The oral IR tablets bioavailability results of 65%, but this data should be interpreted with caution due to its wide variability among the animals, whereas SR bioavailability is of 10%. Moreover, plasma level concentration of M1 results ever above the target plasma MEC in SR oral, while in oral IR administration M1 plasma concentration is higher than in humans. These findings imply that SR administration is not suitable in dogs. Intramuscular injection is bioequivalent to intravenous in accordance with camels and humans, while rectal suppository administration has a poor bioavailability (10%) disagreeing with humans (author unpublished data). M1 has been also administered in dogs (iv 1 mg/kg) as pure substance, but it has led to adverse effects as nausea, salivation, increased swallowing and episodes of retching.

In conclusion, in animals (except in cats), T has a rapid metabolism widely directed to the inactive metabolites, while the M1 (active metabolite) is only marginally produced. These findings suggest that this drug could not have the same effectiveness reported for humans.

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