Tramadol Vs Tapentadol: Anew Horizon in Pain Treatment?

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Abstract: Problem statement: Acute and chronic pain is a common presenting sign in animal species and human beings. **Approach:** Classical opioids provide very effective pain relief, although they may be less effective in the treatment of chronic pain due to their limited therapeutic windows and the induced opioid receptor down regulation. Atypical opioids, such as tramadol and tapentadol, have a dual mechanism of action and have been designed to overcome these issues through an opiate-sparing effect. **Results:** Tramadol activates mu opioid receptors and in addition, inhibits serotonin and noradrenalin reuptake. These actions are the result of the different enantiomers and tend to be reliant on their metabolism. Indeed, the O-desmethyltramadol phase I metabolite, is 200-300 times more potent for mu opioid receptor activation than the parental compound. For these reasons, the drug's effectiveness can vary among subjects. In veterinary medicine its effectiveness, especially after oral administration, is still uncertain and controversial. Tapentadol is a novel, atypical opioid with a unique mechanism of action. It was launched on the European drug market at the end of 2011. It has been proposed as the first representative of a new pharmacological class of centrally acting analgesics, namely, the mu opioid receptor agonist, noradrenalin reuptake inhibitors. The first human studies describe this molecule as safe and effective (equianalgesic to morphine). The drug has great potential for veterinary use because it exists as a single enantiomer only, it does not require metabolic activation to be effective and adverse effects triggered by the serotonin reuptake inhibition action are negligible. **Conclusion/Recommendations:** For these reasons, TAP is a promising compound however at this stage, more investigation is required before it can be recommended for regular use in veterinary medicine, the possibility of undesirable effects is yet to be entirely excluded.

Key words: Non Steroidal Anti Inflammatory Drugs (NSAIDs), Mu Opioid Receptor (MOR), Minimum Effective Concentrations (MEC), Noradrenalin (NA)

INTRODUCTION

Acute and chronic pain is a common presenting condition in animal species and human beings and many pain relief options are available. Non Steroidal Anti Inflammatory Drugs (NSAIDs) and opioid receptor agonists are used most commonly. Unfortunately, the drugs in these classes range widely in both their therapeutic and side effects.

Compounds that activate opioid receptors, in particular the Mu Opioid Receptor (MOR) subtype have been used for decades in the treatment of moderate to severe pain (Meldrum, 2003). Extensive clinical experience with the prototypical MOR agonist morphine indicates that, although this compound is very effective against acute pain, it may be less effective for conditions precipitating chronic pain, especially neuropathic pain or pain of inflammatory origin. This reduced effectiveness for chronic pain is due to the MOR down regulation with long-term therapies; a substantial increase in dosing is required in order to maintain a clinically satisfactory analgesic effect (Dickenson and Suzuki, 2005). Furthermore, morphine has a limited therapeutic window, its analgesic effect generally coincides with several side effects (nausea, emesis, constipation and respiratory depression) which limit its usefulness especially in cases of chronic pain. Given these shortcomings, there is a need for more tolerable opioids that have a better efficacy and safety for chronic pain therapy.

Attempts have been made to synthesize diverse morphine derivatives with the aim of producing a compound with a higher efficacy than morphine however; elimination of undesirable side effects is yet to be achieved (Buschmann, 2002). It is now well established that MOR stimulation accounts for both the analgesic effectiveness and the side effects (Kieffer, 1999).

Another approach has been to combine the MOR activation with an additional compound that provides

analgesia via a different mechanism of action, resulting in an opiate-sparing effect. Activation of the noradrenergic descending pain inhibitory pathway could be considered a candidate for such an additional mechanism (Wang *et al.*, 2008). Active ingredients that inhibit the reuptake of Noradrenalin (NA) are effective analgesics, particularly in chronic pain conditions.

Tramadol: The first molecule showing this dual mechanism of action was Tramadol (T). It produces MOR activation as well as inhibition of serotonin (5HT) and NA reuptake. T is a racemate (Fig. 1) with active enantiomers; each of these has a different profile of activity. NA and 5-HT reuptake inhibition are predominantly the actions of the (-) and (+) enantiomers of the parent compound, respectively, while MOR activation resides in the (+) enantiomer of O-desmethyl tramadol (the active metabolite is called M1) and to a lesser extent, in (+) T itself (Grond and Sablotzki, 2004). It has been demonstrated that systemic administration of either (+) or (-) T induces analgesia, this finding suggests that a noradrenergic mechanism may contribute to the analgesic profile of the racemic T (Hui-Chen *et al.*, 2004). The relative contributions of the different mechanisms to the overall analgesic effect vary over time. As the parent compound is metabolized, the contribution of NA and 5-HT reuptake inhibition falls while the contribution of MOR agonism rises, resulting in a complex time- and metabolism-dependent pattern of pharmacological activities (Grond and Sablotzki, 2004). In addition, it has been demonstrated that the analgesic efficacy of T is less pronounced in "poor metaboliser" subjects (who showed a reduced capability to form the M1 metabolite) as compared to "normal metaboliser" subjects who produced relatively high levels of the metabolite. This finding indicated that the MOR active metabolite, M1 contributes significantly to the analgesic profile of T (Stamer *et al.*, 2007).

It can be argued, however, that inhibition of 5-HT reuptake contributes less to the analgesic profile of T than MOR and NA reuptake inhibition. First, it is highly likely that the analgesic efficacy of (+) T is mediated by the (+) M1 metabolites (200-300 times more potent on MOR activation than the parental compound). Secondly, it was shown that, while T induced analgesia is partially blocked by co-administration with either the MOR antagonist naloxone or the NA antagonist yohimbine; it was completely abolished by combined administration of both antagonists (Enggaard *et al.*, 2006).
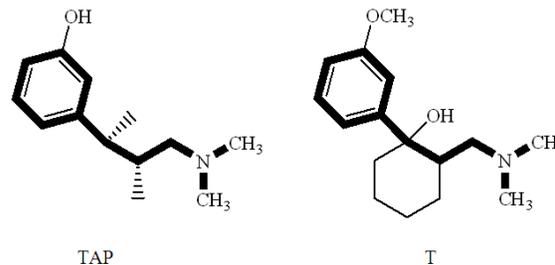

Fig. 1: Molecular structures of tapentadol (TAP) and tramadol (T). The common structure is highlighted in bold

Clinical and preclinical trials with selective 5-HT inhibitors, selective NA reuptake inhibitors and mixed 5-HT/NA reuptake inhibitors showed that analgesia is mostly due to NA reuptake inhibition rather than to 5-HT reuptake inhibition (Staiger *et al.*, 2003; Briley, 2004). Additionally, it has been reported that 5-HT reuptake inhibitor drugs (i.e., selective serotonin reuptake inhibitors) are largely ineffective in the treatment of chronic pain because they indirectly produce concomitant activation of inhibitory as well excitatory 5-HT receptors (Suzuki *et al.*, 2004).

The Minimum Effective Concentrations (MEC) reported for T and M1 in humans have been identified as 0.3 ± 0.2 mg mL^{-1} (Lehmann *et al.*, 1990) and 0.08 ± 0.06 mg mL^{-1} (Grond *et al.*, 1999), respectively. The analgesic potency of T is about 10% of that of morphine following parenteral administration.

T has a low abuse potential, possesses 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 (Grond and Sablotzki, 2004).

The lack of side effects, characteristic of opioid derivatives, shown by this drug and the absence of typical side effects caused by NSAIDs, recommend T as a molecule for long-term treatment of chronic pain in animals. To date, T has been studied in several animal species however these experiments have usually drawn on several assumptions extrapolated from human data. The activity of the diverse enantiomers has never been tested, nor has the activation of MOR by the M1 metabolite. Although many Pharmacokinetic (PK) studies have been carried out in the last 5 years, only a small number of these have investigated Pharmacodynamic (PD) properties.

Nowadays, T is widely used in veterinary clinical practice. Although it has been used for some time now,

our understanding and ability to predict the time course of its pharmacological effects in animals are still hampered by the presence of active metabolites and the coexistence of opioid and non-opioid mechanisms. Recently, T has been reported to be metabolized faster to inactive metabolites N-desmethyl tramadol (M2) and O,N-didesmethyl tramadol (M5), in goats (Sousa *et al*., 2008), dogs (McMillan *et al*., 2008; Giorgi *et al*., 2009a; 2009b; 2009c; 2009d; 2010a; Kukanich and Papich, 2011), horses (Giorgi *et al*., 2007; Shilo *et al*., 2008; Cox *et al*., 2010; Giorgi *et al*., 2010b), llamas (Cox *et al*., 2011), alpacas (Giorgi *et al*., 2010c), peafowl (Black *et al*., 2010), hawks (Souza *et al*., 2011) than in cats (Pypendop and Ilkiw, 2008). The use of T has also been suggested for zoo animals (Souza and Cox, 2011).

The clinical effectiveness of T is uncertain for some animals, particularly in species that metabolize the molecule to inactive metabolites. It is possible therefore that this drug may not provide as effective and safe treatment for pain as in humans (Giorgi *et al*., 2007; 2009a; 2009b; 2009c; 2009d; 2010a; 2010c; Sousa *et al*., 2008; Kukanich and Papich, 2011). No stereoselective pharmacokinetic studies on T and its metabolite have been reported in animals to date. Although T has been reported as effective in a small number of clinical studies (Vettorato *et al*., 2010, Pypendop *et al*., 2009), its efficacy in veterinary medicine is still controversial.

Tapentadol: At the end of 2011, a novel opioid drug, Tapentadol (TAP), was launched on the European market for human use. This drug has a structure similar to T (Fig. 1). Based on its unique mechanism of action, it has been proposed as the first representative of a new pharmacological class of centrally acting analgesics: the MOR agonist, NA Reuptake Inhibitor (MORNRI) (Kress, 2010).

Interestingly, even though it's MOR affinity is 50-fold lower than that of morphine, this reduces to a 2-3-fold difference after systemic administration. This finding, consistent across different pain relief evaluation models, may be due to a better brain penetration of TAP, but also suggests that the NA reuptake-inhibitory property, contributes to a more potent analgesia that would be expected solely from its MOR agonism (Tzschentke *et al*., 2006). Given the moderate affinity of TAP at the MOR and the opioid-sparing effect of TAP's NRI component, it seems logical that TAP would produce fewer opioid-related side effects than classical MOR agonists, such as morphine. Indeed, compared to morphine, TAP produces much less nausea and vomiting in ferrets, the duration of these side effects was also shorter

(Tzschentke *et al*., 2009). Furthermore, the threshold dose for these effects was 100 times higher for TAP than for morphine. Also aligning with these findings, TAP had a weaker inhibitory effect than morphine at equianalgesic intraperitoneal doses on both (i) gastrointestinal motility assessed from charcoal transit and (ii) prostaglandin-induced diarrhoea (Tzschentke *et al*., 2006). Several comparative human preclinical studies involving other analogue opioids confirm these experimental findings (Afilalo *et al*., 2010; Etropolski *et al*., 2011; Wilhorn and Kraus, 2011).

In vivo and in vitro preclinical pharmacological studies demonstrated that TAP displays weak anticholinercic activity and a negligible 5HT reuptake inhibition but a pronounced NA reuptake inhibition (Tzschentke *et al*., 2006). Following chronic administration of TAP, tolerance development took much longer compared with morphine (Ahlbeck, 2011).

The PK features of TAP have been tested in rodents and humans. In summary, the drug is almost completely absorbed after oral administration but undergoes high levels of phase II metabolism glucuronidation, limiting oral bioavailability at 8 and 32% in rats and humans, respectively. Phase I biotransformation is negligible and does not produce active metabolites. TAP has shown no potential for CYP450 induction or inhibition (Terlinden *et al*., 2007).

Recently, evaluation of new pharmaceutical ingredients approved for use in human medicine and of potential interest for veterinary medicine, included assessment of TAP (Emmerich, 2011). There is great potential for use of this drug in veterinary species. Theoretically, it might overcome a number of the disadvantages of T such as: (i) TAP exists only as a single enantiomer; (ii) only the parent compound is involved in its pharmacological activity (i.e., no metabolic activation is necessary); (iii) the time dependent changes in the dynamic of opioid and monoaminergic analgesia occur in parallel; (iv) no CYP450 induction/inhibition exists which could negatively affect analgesia; (v) the 5HT reuptake inhibition triggering adverse effects is negligible. However, TAP still has some disadvantages, namely: (i) it has antimuscarinic activity, albeit weak, which produces a well known cadre of adverse effects; (ii) it is a weak blocker of 5-HT$_3$ receptor (e.g., as mirtazapine, metaclopramide, ondasteron,…), as yet it has not been determined whether this property is helpful or harmful; iii) it has very low oral bioavailability (although a prodrug with amino acids or short peptides increasing the bioavailability by a factor of 10 has been patented (US Patent Application 20100227921); (iv) the bioavailability in cats and in other animal species deficient of glucuronic acid, might be much higher.

TAP is a promising compound but much more data, especially PK/PD, is required before its regular use in veterinary medicine can be recommended.

REFERENCES

Afilalo, M., M.S. Etropolski, B. Kuperwasser, K. Kelly and A. Okamoto *et al*., 2010. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: A randomized, double-blind, placebo- and active-controlled phase III Study. Clin. Drug Invest., 30: 489-505. DOI: 10.2165/11533440-000000000-00000

Ahlbeck, K., 2011. Opioids: A two-faced Janus. Curr. Med. Res. Opin., 27: 439-448. PMID: 21194392

Black, P.A., S.K. Cox, M. Macek, A. Tieber and R.E. Junge, 2010. Pharmacokinetics of tramadol hydrochloride and its metabolite O-desmethyltramadol in peafowl (Pavo cristatus). J. Zoo Wildl. Med., 41: 671-676. PMID: 21370649

Briley, M., 2004. Clinical experience with dual action antidepressants in different chronic pain syndromes. Hum. Psychopharmacol., Suppl, 1: S21-25. PMID: 15378667

Buschmann, H., 2002. Analgesics: From Chemistry and Pharmacology to Clinical Application. 1st Edn., Wiley-VCH, Weinheim, Germany, ISBN: 3527304037, pp: 604.

Cox, S., N. Villarino and T. Doherty, 2010. Determination of oral tramadol pharmacokinetics in horses. Res. Vet. Sci., 89: 236-241. PMID: 20223494

Cox, S., T. Martin-Jimenez, S.V. Amstel and T. Doherty, 2011. Pharmacokinetics of intravenous and intramuscular tramadol in llamas. J. Vet. Pharmacol. Ther., 34: 259-264. DOI: 10.1111/j.1365-2885.2010.01219.x

Dickenson, A.H. and R. Suzuki, 2005. Opioids in neuropathic pain: Clues from animal studies. Eur. J. Pain, 9: 113-116. PMID: 15737797

Emmerich, I.U., 2011. New drugs for small animals in 2010. Tierarztl. Prax. Ausg. K. Kleintiere Heimtiere, 39: 429-435. PMID: 22167169

Enggaard, T.P., L. Poulsen, L. Arendt-Nielsen, K. Brøsen and J. Ossig *et al*., 2006. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. Anesth. Analg., 102: 146-150. PMID: 16368820

Etropolski, M., K. Kelly, A. Okamoto and C. Rauschkolb, 2011. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv. Ther., 28: 401-417. PMID: 21494892

Giorgi, M., G. Soldani, C. Manera, P. Ferrarini and M. Sgorbini *et al*., 2007. Pharmacokinetics of tramadol and its metabolites M1, M2 and M5 in horses following intravenous, immediate release (fasted/fed) and sustained release single dose administration. J. Equine Vet. Sci., 27: 481-488. DOI: 10.1016/j.jevs.2007.10.004

Giorgi, M., S.D. Carlo, G. Saccomanni, B. Lebkowska-Wieruszewska and V. Turini *et al*., 2009a. Biopharmaceutical profile of tramadol in the dog. Vet. Res. Commun., 33: S189-S192. PMID: 19585256

Giorgi, M., S.D. Carlo, G. Saccomanni, B. Lebkowska-Wieruszewska and C.J. Kowalski, 2009b. Pharmacokinetic and urine profile of tramadol and its major metabolites following oral immediate release capsules administration in dogs. Vet. Res. Commun., 33: 875-885. PMID: 19533402

Giorgi, M., S. Del Carlo, G. Saccomanni, B. Lebkowska-Wieruszewska and C.J. Kowalski, 2009c. Pharmacokinetics of tramadol and its major metabolites following rectal and intravenous administration in dogs. N Z Vet. J., 57: 146-52. PMID: 19521463

Giorgi, M., G. Saccomanni, B. Lebkowska-Wieruszewska and C. Kowalski, 2009d. Pharmacokinetic evaluation of tramadol and its major metabolites after single oral sustained tablet administration in the dog: A pilot study. Vet. J., 180: 253-255. PMID: 18313955

Giorgi, M., S.D. Carlo, B. Lebkowska-Wieruszewska, C.J. Kowalski and G. Saccomanni, 2010a. Pharmacokinetics of tramadol and metabolites after injective administrations in dogs. Pol. J. Vet. Sci., 13: 639-644. PMID: 2137074

Giorgi, M., G. Saccomanni and V. Andreoni, 2010b. Pharmacokinetics of tramadol after epidural administration in horses. J. Equine Vet. Sci., 30: 44-46. DOI: 10.1016/j.jevs.2009.11.004

Giorgi, M., G. Saccomanni, S. Del Carlo and V. Andreoni, 2010c. Pharmacokinetic of tramadol and its major metabolites after intravenous and intramuscular injections in alpacas (Vicugna pacos). J. Camel Pract. Res., 17: 123-126.

Grond, S. and A. Sablotzki, 2004. Clinical pharmacology of tramadol. Clin. Pharmacokinet., 43: 879-923. PMID: 15509185

Grond, S., T. Meuser, H. Uragg, H.J. Stahlberg and K.A. Lehmann, 1999. Serum concentrations of tramadol enantiomers during patient-controlled analgesia. Br. J. Clin. Pharmacol., 48: 254-257. PMID: 10417506

Hui-Chen, L., Y. Yang, W. Na, D. Ming and L. Jian-Fang *et al*., 2004. Pharmacokinetics of the enantiomers of trans-tramadol and its active metabolite, trans-O-demethyltramadol, in healthy male and female chinese volunteers. Chirality, 16: 112-118. PMID: 14712474

Kieffer, B.L., 1999. Opioids: First lessons from knockout mice. Trends Pharmacol. Sci., 20: 19-26. PMID: 10101958

Kress, H.G., 2010. Tapentadol and its two mechanisms of action: Is there a new pharmacological class of centrally-acting analgesics on the horizon. Eur. J. Pain, 14: 781-783. PMID: 20659810

Kukanich, B. and M.G. Papich, 2011. Pharmacokinetics and antinociceptive effects of oral tramadol hydrochloride administration in Greyhounds. Am. J. Vet. Res., 72: 256-262. PMID: 21281202

Lehmann, K.A., U. Kratzenberg, B. Schroeder-Bark and G. Horrichs-Haermeyer, 1990. Postoperative patient-controlled analgesia with tramadol: Analgesic efficacy and minimum effective concentrations. Clin. J. Pain, 6: 212-220. PMID: 2135015

McMillan, C.J., A. Livingston, C.R. Clark, P.M. Dowling and S.M. Taylor *et al*., 2008. Pharmacokinetics of intravenous tramadol in dogs. Can. J. Vet. Res., 72: 325-331. PMID: 18783021

Meldrum, M., 2003. Opioids and Pain Relief: A Historical Perspective. 1st Edn., IASP Press, Seattle, USA., ISBN: 0931092477, pp: 222.

Pypendop, B.H. and J.E. Ilkiw, 2008. Pharmacokinetics of tramadol and its metabolite O-desmethyl-tramadol, in cats. J. Vet. Pharmacol. Ther., 31: 52-59. PMID: 18177319

Pypendop, B.H., K.T. Siao and J.E. Ilkiw, 2009. Effects of tramadol hydrochloride on the thermal threshold in cats. Am. J. Vet. Res., 70: 1465-1470. PMID: 19951117

Sousa, A.B.D., A.C. Santos, S.G. Schramm, V. Porta and S.L. Gorniak *et al*., 2008. Pharmacokinetics of tramadol and o-desmethyltramadol in goats after intravenous and oral administration. J. Vet. Pharmacol. Ther., 31: 45-51. PMID: 18177318

Souza, M.J. and S.K. Cox, 2011. Tramadol use in zoologic medicine. Vet. Clin. North Am. Exot. Anim. Pract., 14: 117-130. PMID: 21074707

Souza, M.J., T. Martin-Jimenez, M.P. Jones and S.K. Cox, 2011. Pharmacokinetics of oral tramadol in red-tailed hawks (Buteo jamaicensis). J. Vet. Pharmacol. Ther., 34: 86-88. PMID: 21219350

Staiger, T.O., B. Gaster, M.D. Sullivan and R.A. Deyo, 2003. Systematic review of antidepressants in the treatment of chronic low back pain. Spine, 28: 2540-2545. PMID: 14624092

Stamer, U.M., F. Musshoff, M. Kobilay, B. Madea and A. Hoeft *et al*., 2007. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin. Pharmacol. Ther., 82: 41-47. PMID: 17361124

Suzuki, R., L.J. Rygh and A.H. Dickenson, 2004. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol. Sci., 25: 613-617. PMID: 15530638

Terlinden, R., J. Ossig, F. Fliegert, C. Lange and K. Göhler, 2007. Absorption, metabolism and excretion of 14C-labeled tapentadol HCl in healthy male subjects. Eur. J. Drug Metab. Pharmacokinet., 32: 163-169. PMID: 18062408

Tzschentke, T.M., J. De Vry, R. Terlinden, H.H. Hennies and C. Lange *et al*., 2006. Tapentadol hydrochloride: Analgesic mu-opioid receptor agonist noradrenaline reuptake inhibitor. Drugs Future, 31: 1053-1061. DOI: 10.1358/dof.2006.031.12.1047744

Tzschentke, T.M., U. Jahnel, B. Kogel, T. Christoph and W. Englberger *et al*., 2009. Tapentadol hydrochloride: A next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. Drugs Today, 45: 483-496. PMID: 19834626

Vettorato, E., A. Zonca, M. Isola, R. Villa and M. Gallo *et al*., 2010. Pharmacokinetics and efficacy of intravenous and extradural tramadol in dogs. Vet. J., 183: 310-315. PMID: 19138866

Wang, Y., C. Feng, Z. Wu, A. Wu and Y. Yue, 2008. Activity of the descending noradrenergic pathway after surgery in rats. Acta Anaesthesiol. Scand., 52: 1336-1341. PMID: 19025524

Wilhorn, S. and C. Kraus, 2011. In patients experiencing acute pain, how does the efficacy and gastrointestinal tolerability of tapentadol compare with oxycodone. Evidence-Based Pract., 14: 14-14.