Langford, Richard M. and Knaggs, Roger and Farquhar-Smith, Paul and Dickenson, Anthony H. (2016) Is tapentadol different from classical opioids?: a review of the evidence. British Journal of Pain, 10 (4). pp. 217-221. ISSN 2049-4645

Is tapentadol different from classical opioids? A review of the evidence

Journal:	*British Journal of Pain*
Manuscript ID	BJP-15-0021.R1
Manuscript Type:	Original Manuscript
Keywords:	tapentadol, opioids, pain pharmacology, analgesics, analgesic mechanisms of action
Abstract:	Tapentadol is a single molecule able to deliver analgesia by two distinct mechanisms, a feature which differentiates it from many other analgesics. Pre-clinical data demonstrate two mechanisms of action: mu opioid receptor agonist activity and noradrenaline re-uptake inhibition. From these, one may predict that tapentadol would be applicable across a broad spectrum of pain from nociceptive to neuropathic. The evidence in animal models, suggests that NRI is a key mechanism, and may even predominate over opioid actions in chronic (and especially neuropathic) pain states, reinforcing that tapentadol is different to classical opioids and may therefore be an a priori choice for the treatment of neuropathic and mixed pain. The clinical studies and subsequent practice experience and surveillance support the concept of opioid and non-opioid mechanisms of action. The reduced incidence of some of the typical opioid induced side-effects, compared to equianalgesic doses of classical opioids supports the hypothesis that tapentadol analgesia is only partially mediated by opioid agonist mechanisms. Both the preclinical and clinical profiles appear to be differentiated from those of classical opioids.

Introduction

Tapentadol is synthetic centrally-acting analgesic, with both opioid and non-opioid mechanisms of action: Mu opioid receptor agonist (MOR) and norepinephrine reuptake inhibition (NRI). Being an active compound and not a pro-drug, it is not reliant on enzyme systems , and it is also devoid of active metabolites.

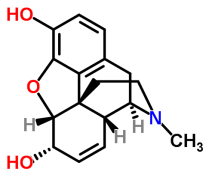
Its development, mechanisms, preclinical and clinical profiles are reviewed below, and compared to those of typical opioids. Aspects are identified which differentiate tapentadol from typical opioids.

Medicinal chemistry and pre-clinical science

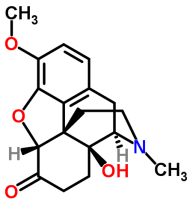
Amongst the most well-known naturally occurring therapeutic substances are alkaloids contained in the poppy *Papaver somniferum*. Of these, morphine, an alkaloid extracted from the poppy, is considered to be the archetypical opioid; other naturally occurring opioids include codeine and thebaine.

Following the identification of these and other pharmacologically active alkaloids contained in the poppy, a vast number of similar molecules have been synthesised with minor modifications to the basic chemical structure. Examples of semi-synthetic opioids in clinical use today include diamorphine (diacetylmorphine), oxycodone and hydromorphone. In addition, a large number of synthetic opioid analogues with diverse chemical structures, including fentanyl, alfentanil, remifentanil, detropropoxyphene and methadone, have been synthesised and evaluated in both pre-clinical models and acute and persistent clinical pain conditions.

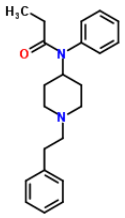
In a clinical context, there are more apparent pharmacokinetic differences between opioids than pharmacodynamic differences.(1) Both pharmacokinetics and pharmacodynamics inform the choice of treatment depending on an individual patient's type of pain and co-morbidities.



(1)

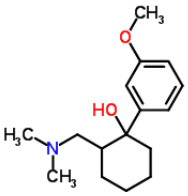


(2)

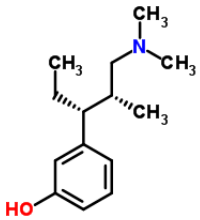


(3)

Tramadol and tapentadol do not fit conveniently in the opioid classes described above. (2) Both are 'atypical' molecules in that they have pro-analgesic effects by variously modulating monoamine concentrations within the central nervous system, in addition to their opioid actions.



(4)



(5)

Traditional methods of drug discovery rely on the synthesis and testing of a large number of chemical substances on cultured cells or animal models. This process can be extremely time consuming, resource intensive and costly. Rational drug design begins with the hypothesis that modulation of a known, specific biological target may have therapeutic benefit. In order to achieve this, one must assimilate detailed knowledge of the three dimensional structure of the target or other molecules that bind to the biological target of interest, thereby defining the pharmacophore', this being the minimum necessary structural characteristics, a molecule must possess in order to bind to the target.(3) It is now clear that the different interactions between a drug molecule and its biological target strongly depend on the three dimensional spatial arrangement the drug functional groups within the target molecule.

For opioids, the quantitative structural activity relationships, depend on basic physicochemical properties of the molecules (such as lipophilicity, hydrogen bond donor and acceptor properties), however these were previously estimated using a two dimensional

chemical representation of the molecule. The recent elucidation of the crystal structure of the MOR (mu-opioid receptor) may herald a new era in opioid drug discovery.(4)

Understanding the analgesic benefit of multimodal mechanisms of action of the racemic cyclohexyl entities, such as tramadol, led to the development of tapentadol. The latter was the conclusion of a rational drug discovery programme to design a new class of analgesics that retained MOR agonism and inhibition of noradrenaline (norepinephrine) reuptake, but with minimal serotonergic activity. In addition, it was desired that both activities would come from a single molecule, and in order to minimise the interpatient variability observed with tramadol and codeine, activation by the hepatic cytochrome P450 enzyme system should not be required. That tapentadol itself is the active entity, devoid of reliance on enzymatic activity, is in contrast to the situation with the inactive pro-drug codeine, whose analgesic effect is entirely reliant on the CYP2D6 enzyme for conversion to morphine. CYP2D6 enzyme activity depends on the genotype, ranging from no analgesic benefit with complete absence, to elevated expression in 'fast metabolisers', leading to increased side effects and potentially serious complications. The latter led to codeine's absolute contraindication in paediatric practice.

Tapentadol: analgesic mechanisms

Studies in animals, using a number of behavioural, pharmacological, neurochemical and neural measures have validated the MOR and NRI components of tapentadol's mechanism of action.(2)

Central hyperexcitability plays important roles in determining the level of pain perceived. Rightly, much emphasis has been put on spinal cord mechanisms in central excitability, but it is now accepted that the spinal cord can also be regulated by descending pathways from the brain, both excitatory and inhibitory. These pathways act through monoamine systems, mediated by noradrenaline and 5-HT, with the former being inhibitory. Not only do these descending pathways interact with opioid controls at spinal and brainstem levels, but they are the rationale for the use of TCAs and SNRIs.(5) Thus the drug tapentadol is of interest in terms of combining two inhibitory actions in one molecule: mu opioid receptor (MOR) agonism and noradrenaline re-uptake inhibition (NRI). Data with this drug suggests this combination seems to produce a synergistic anti-nociceptive action in animal models of tissue and nerve damage pains.(6) The drug is effective in models of acute pain, osteoarthritic, neuropathic and the mixed pain state of cancer-induced bone pain and in all

cases both the MOR and NRI contributions can be observed.

Interestingly, with persistent neuropathic pain models the NRI component becomes predominant, as demonstrated by selective blockade of NRI or opioid based actions using yohimbine or naloxone, respectively.(7)

That tapentadol is differentiated from classical, single mechanism pure opioids, is further demonstrated most convincingly in 'knock-out' animals with a genetic deletion of the MOR, with the drug retaining efficacy in both acute and persistent neuropathic pain models.(8).

Thus, the ability of tapentadol to retain activity in the absence of MOR activity means it is not sufficient to label it just 'an opioid' without acknowledging the major noradrenergic component to its actions. Recently, Diffuse Noxious Inhibitory Controls (DNIC), an endogenous inhibitory system mediated by descending controls has been shown to be noradrenergic and is lost after nerve injury. DNIC are restored by tapentadol (9) corroborating the concept that the mechanism of restoring NA modulation can alleviate pain. (10)

Together, the lack of potentially meaningful 5-HT effect and the relatively weak MOR affinity may explain the better tolerability than with a pure opioid at equianalgesic doses. Typical opioid effects on gastrointestinal motility and vomiting are reduced with tapentadol compared to classical opioids in animal models. By contrast, sweating, potentially attributable to NRI, is more common in humans with tapentadol than pure opioids.

Preclinical studies suggest that this combined and synergistic MOR and NRI activity might translate to an ability to be effective in a wide range of painful conditions with reduced opioid related side effects. Thus, tapentadol is effective in models of nerve injury and inflammation as well as predictably, in cancer induced bone pain, a mixed pain state with elements of both nociceptive and neuropathic pain.

Clinical aspects

Tapentadol has been investigated in a many acute and chronic pain conditions including post-surgical, musculoskeletal and neuropathic pains.

In a pooled analysis of three randomised controlled trials in chronic pain, nearly 3000 patients with predominantly severe osteoarthritis (OA) pain or low back pain, prolonged release tapentadol was compared to placebo and an active comparator, oxycodone CR (Controlled Release).(11) Both of the active comparators were significantly superior to placebo, and tapentadol demonstrated analgesic efficacy which was 'non-inferior' to oxycodone CR. Recently, a further planned analysis of this data set has shown superiority for tapentadol over oxycodone.(12) Furthermore, patients taking tapentadol PR experienced improved tolerability

with fewer side effects particularly during the titration phase compared to patients taking oxycodone CR. In contrast, patients taking oxycodone CR exhibited higher rates of early treatment discontinuation, attributed to gastrointestinal side effects classically associated with opioids (constipation, nausea and vomiting). The tapentadol group patients had a similar discontinuation rate (36.8 %) to patients taking placebo (35.0 %), both of which were markedly lower than for patients taking oxycodone (55.4 %).(11) This improved tolerability profile would seem to be compatible with the preclinical study evidence that tapentadol's efficacy is only partially derived from opioid mediated mechanisms, and hence has a clinical profile different to a pure mu opioid agonist. Tapentadol's non-opioid NRI mechanism of action may contribute to its demonstrated analgesic efficacy in patients with painful diabetic neuropathy.(13)

The concept of 'mixed pain' (for example in low back pain) is increasingly recognised and accepted and may comprise inflammatory, musculoskeletal and neuropathic pain mechanisms, for which a multimodal analgesic approach would be appropriate. Tapentadol was shown to be effective in an open label trial of patients with chronic low back pain, in which the 'pain DETECT' neuropathic pain screening tool was used to characterise each patient's pain.(14) Patients with a detectable neuropathic pain component required lower doses of tapentadol (than patients without neuropathic pain features), which in turn was associated with a reduction in opioid-related side-effects, again potentially also attributable to the NRI mechanism and relatively less opioid activity.(15) Tapentadol's NRI based mechanism may contribute to enhanced management of neuropathic pain and is also supported by a recent randomised, controlled, open-label 12 week study of patients with severe chronic low back pain with a neuropathic component. Change from baseline in pain intensity with tapentadol PR was found to be superior to oxycodone/naloxone PR (P=0.003).

Androgen deficiency (OPiAd) is a recognised effect of long-term opioid (MOR) agonists use in males, which may result in erectile dysfunction, decreased sperm counts, small testes, and loss of body hair. That tapentadol analgesia may only be partially mediated via the MOR, provided the rationale for a twelve week study of serum testosterone levels in male patients (≤64 years of age), conducted in a subset of the patients (described above) with severe low back pain with a neuropathic pain component, randomised to receive twice-daily tapentadol PR or oxycodone/naloxone PR.(15,16) The baseline testosterone levels were normal in all subjects, but by the final evaluation at week 12 (or early study termination), 45.5% (5/11) of

the oxycodone/naloxone PR groups had low (below normal) testosterone levels compared to only 10.5% (2/19) of the patients receiving tapentadol PR. There was a significant decrease from baseline to final evaluation in least-squares mean (SD) testosterone levels in the oxycodone/naloxone PR group (–4.23 [1.232] nMol/L; P = 0.004), but not in the tapentadol PR group (–1.50 [0.946] nMol/L; P = 0.134) (16) These results further support the premise that tapentadol may exert a relatively smaller magnitude of opioid mediated effect.

Opioid loads and issues

In routine clinical practice, it is common to switch or rotate between different opioids. In order to do this safely and successfully it is essential to have knowledge of the relative potency or equivalences of the opioids being used, and a range of reference sources and decision tools are available to support the conversion. Most clinical studies have suggested that tapentadol 50 mg has a similar efficacy to oxycodone 10 mg.(17,18) However, for drugs such as tramadol and tapentadol that have other mechanisms that contribute to their analgesic effect, it is essential to consider analgesic equivalence rather than opioid equivalence. Analgesic equivalence with tapentadol may be achieved with lower opioid receptor activity than a drug that only acts on opioid receptors, which may have implications for tolerability and switching.

Evidence of the lesser contribution of opioid action in tapentadol-mediated analgesia is also supported by the observation that switching a patient from a high dose of conventional opioid to an equianalgesic dose of tapentadol may lead to features of acute opioid withdrawal.(19)

A further benefit of these mixed mechanism agents appears to be reflected in their reduced potential for abuse and diversion compared to other opioids. The Researched Abuse, Diversion and Addiction-Related Surveillance ('RADARS') system during the first 24 months following the initial release and marketing of tapentadol IR in the USA, found rates of abuse and diversion were much lower than for oxycodone or hydrocodone.(20) Similarly, the rate of non-medical use of tapentadol (Immediate Release) by college students was lower than other opioids and common drugs of abuse.(21)

Summary

Tapentadol is a single molecule able to deliver analgesia by two distinct mechanisms, a feature which differentiates it from many other analgesics. Pre-clinical data demonstrate the MOR and NRI mechanisms and predict that tapentadol would be applicable across a broad

spectrum of pain from nociceptive to neuropathic. The evidence in animal models, suggests that NRI is a key mechanism, and may even predominate over opioid actions in chronic (and especially neuropathic) pain states, reinforcing that tapentadol is different to classical opioids and may therefore be an a priori choice for the treatment of neuropathic and mixed pain. The clinical studies and subsequent practice experience and surveillance support the concept of opioid and non-opioid mechanisms of action. The reduced incidence of some of the typical opioid induced side-effects, compared to equianalgesic doses of classical opioids supports the hypothesis that tapentadol analgesia is only partially mediated by opioid agonist mechanisms. Both the preclinical and clinical profiles appear to be differentiated from those of classical opioids.

References

(1) Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, Riley J, Dahan A. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. Br J Clin Pharmacol 2013; 75(1):60-78.

(2) Raffa RB, Buschmann H, Christoph T, Eichenbaum G, Englberger W, Flores CM, Hertrampf T, Kogel B, Schiene K, Strassburger W, Terlinden R, Tzschentke TM. Mechanistic and functional differentiation of tapentadol and tramadol. Expert Opin Pharmacother 2012; 13(10):1437-1449.

(3) Hahn M. Three-Dimensional Shape-Based Searching of Conformationally Flexible Compounds. J Chem Inf Comput Sci 1997; 37:80-86.

(4) Manglik A1, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature. 2012. 485(7398):321-6

(5) Bannister K, Bee LA, Dickenson AH. Preclinical and early clinical investigations related to

monoaminergic pain modulation. Neurotherapeutics 2009; 6(4):703-712.

(6) Christoph T, Schroder W, Tallarida RJ, De VJ, Tzschentke TM. Spinal-supraspinal and intrinsic mu-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI) synergy of tapentadol in diabetic heat hyperalgesia in mice. J Pharmacol Exp Ther 2013; 347(3):794-801

(7) Tzschentke TM, Christoph T, Schröder W, et al. Tapentadol: with two mechanisms of action in one molecule effective against nociceptive and neuropathic pain : Preclinical overview. Schmerz. 2011;25:19-25

(8) Kogel B, De VJ, Tzschentke TM, Christoph T. The antinociceptive and antihyperalgesic effect of tapentadol is partially retained in OPRM1 (mu-opioid receptor) knockout mice. Neurosci Lett 2011; 491(2):104-107.

(9) Bannister K, Patel R, Goncalves L, Townson L, Dickenson AH. DNIC and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. Pain. 2015;156(9):1803-11

(10) Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth. 2014;113(1):148-56

(11) Lange B, Kuperwasser B, Okamoto A, Steup A, Haufel T, Ashworth J, Etropolski M. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther* 2010; 27(6):381-399.

(12) Sánchez Del Águila MJ, Schenk M, Kern KU, Drost T, Steigerwald I Practical considerations for the use of tapentadol prolonged release for the management of severe chronic pain. Clin Ther 2015; 37: 94-113

(13) Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin.

2011;27(1):151-62

(14) Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22(10):1911-20.

(15) Baron R, Likar R, Martin-Mola E, Blanco FJ, Kennes L, Müller M, Falke D, Steigerwald I. Effectiveness of Tapentadol Prolonged Release (PR) Compared with Oxycodone/Naloxone PR for the Management of Severe Chronic Low Back Pain with a Neuropathic Component: A Randomized, Controlled, Open-Label, Phase 3b/4 Study. Pain Practice 2015. Published online

(16) Tolerability, Safety, and Quality of Life with Tapentadol Prolonged Release (PR) Compared with Oxycodone/Naloxone PR in Patients with Severe Chronic Low Back Pain with a Neuropathic Component: A Randomized, Controlled, Open-label, Phase 3b/4 Trial Baron R, Jansen J-P, Binder A, Pombo-Suarez M, Kennes L, Muller M, Falke D, Steigerwald I. Pain Pract. 2015. Published online

(17) Daniels SE, Golf M. Clinical efficacy and safety of tapentadol immediate release in the postoperative setting. J Am Podiatr Med Assoc. 2012;102(2):139-48

(18) Stegmann JU, et al The efficacy and tolerability of multiple-dose tapentadol immediate release for the relief of acute pain following orthopedic (bunionectomy) surgery . Curr Med Res Opin. 2008 Nov;24(11):3185-96

(19) Mercadante S, Porzio G and Gebbia V. New Opioids. Journal of Clinical Oncology. 2014; 32(16):1671-6

(20) Dart RC, Cicero TJ, Surratt HL, Rosenblum A, Bartelson BB, Adams EH. Assessment of the abuse of tapentadol immediate release: the first 24 months. J Opioid Manag 2012; 8(6):395-402

(21) Dart RC, Adams E, Bucher Bartelson B, Baker G, Pitner J, Vorsanger G. Trends in the

Non-Medical Use of Tapentadol Immediate Release by College Students. Poster presented at the American Academy of Pain Medicine (AAPM) February 23-26. 2012

Declaration

This article was conceived at an expert advisory board of pain experts, arranged by and paid for by Grünenthal Ltd, with funding of the subsequent writing process. However, the manuscript was produced solely by the four authors, devoid of any editorial input or influence. Grünenthal Ltd has only checked the article for correctness and has not exercised any editorial rights.

Acknowledgements:

Thanks are expressed to the following panel members (additional to the authors):

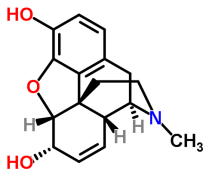
Beverly Collett

Martin Johnson

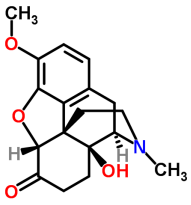
Victor Mendis

Val Conway

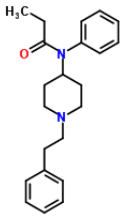
Andrew Nicalaou



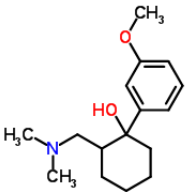
(1)



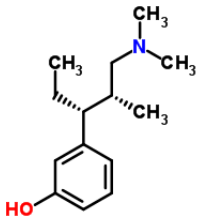
(2)



(3)



(4)



(5)