Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

EDITORIAL

Tapentadol: a new option for the treatment of cancer and noncancer pains

This article was published in the following Dove Press journal:
Journal of Pain Research

Anthony H Dickenson[1]
Hans G Kress[2]

[1]Neuroscience, Physiology and Pharmacology, University College London, London WC1E6BT, UK; [2]Department of Special Anaesthesia and Pain Medicine, Medical University, AKH of Vienna, Vienna, Austria

The last years have witnessed major advances in the knowledge of the basic mechanisms underlying the onset and the chronification of pain. In particular, it has emerged that pain signaling and modulatory mechanisms change following physiopathological events, such as the two major types of pain, neuropathic and inflammatory pains. Very different chemical events and ion channel changes, respectively, underlie these pains at peripheral levels, so treatments have to differ. Low back pain and cancer pain can be one or the other or a combination of these different mechanisms, so-called mixed pains. The final pain experience is a combination of all these peripheral and central events, but within the central nervous system, the pain controlling systems are more common so that therapies acting on central modulation can span a range of pain conditions. Descending controls link the brain back to the spinal cord, where noradrenaline (NRI) is a key inhibitory transmitter in pain control in these pathways. Descending controls run from the brain to the spinal cord and can be gaged in patients – the balance between excitations and facilitations' shift to the latter in persistent pain states, reinforcing pain transmission.[1]

Understanding the mechanisms for pain enhancement and modulation can help to explain these altered pain states in patients and will lead to better treatments.

What if there was a single drug with more than one mechanism that had the efficacy of a strong opioid, yet, with a reduced opioid load? Tapentadol is the only member of the new mu opioid receptor (MOR)–NRI class of analgesic agents. Indeed, it presents an MOR activity, although much less than that of morphine, but with a simultaneous ability to inhibit the reuptake of NA (NRI), a key inhibitory transmitter in pain control.[2]

The extensive preclinical data on tapentadol reveal an efficacy equal to that of morphine but with a major noradrenergic component in behavioral and neuronal measures in models of nerve injury, arthritis, and cancer-induced bone pain.[3,4]

There is a positive synergy between the MOR and NRI actions and an ability to control central sensitization. The MOR action inhibits pain messages at the spinal cord levels and in the brain, and the NRI provides a powerful inhibitory action on spinal events. The prediction from the animal data that tapentadol should be effective in pain from tissue and nerve damage, and so also mixed pain, has translated excellently to the patient.[5]

Indeed, in rats and humans, tapentadol restores the failed NA inhibitions as measured directly in patients through conditioned pain modulation.[6] These actions

Correspondence: AH Dickenson
Neuroscience, Physiology and Pharmacology, University College London, London WC1E6BT, UK
Tel +44 20 7679 3742
Email ucklahd@ucl.ac.uk

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S190171

occur with reduced opioid load and so there are fewer MOR side effects. A failure of descending inhibitions and the presence of central sensitization are predictors of chronic pain in patients. The ability of a drug to restore normal modulation in the central nervous system restores normal transmission, although it does not remove the cause of the pain.

Of note, the pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one molecule, appears to be unique and it seems reasonable to propose for tapentadol, a new class of centrally acting analgesics, designated MOR-NRI.[7] Experimental evidence showing that NRI is a key mechanism that can be predominant in chronic/neuropathic pain reinforces the concept that tapentadol is different to classical opioids and may therefore be an a priori choice for the treatment of chronic, neuropathic, and mixed pains.[5] Moreover, this concept has been strengthened and expanded to other drugs (tramadol, buprenorphine, loperamide, and cebranopadol), suggesting that inclusion of all analgesics that have any component of opioid mechanism of action into the same class is misleading. On the other hand, the recognition of subclasses of opioids seems warranted scientifically and beneficial to health care providers, payers, and regulators. To date, some definitions have been proposed such as atypical and multigesic.[8,9]

Indeed, the umbrella terms "chronic noncancer pain" and "cancer pain" do not tell much about their different underlying pathologies and pain mechanisms. The assessment of individual nature, site, and mechanisms of pain is essential for effective multimodal treatment with invasive and/or noninvasive and, often, pharmacological options. Whereas the WHO analgesic ladder using nonopioids, opioids, and adjuvant analgesics has remained the mainstay of pain management in cancer patients,[10] no such universal guideline for the pharmacological management of chronic noncancer pain exists.

Besides morphine, other MOR agonists, such as fentanyl and buprenorphine, including their transdermal delivery systems, hydromorphone and oxycodone, have been developed for improved efficacy and safety. However, truly innovative analgesics that utilize combined mechanisms of action are required for generating better response rates, fewer side effects, and improved tolerability, particularly in elderly patients. As comprehensively reviewed by the expert authors of this supplement, the innovative centrally acting analgesic tapentadol (Palexia®) represents such a new class of analgesic[7] with two synergistic mechanisms of action in one molecule, MOR agonism and NRI.[11,12]

Registration studies in thousands of nononcological patients have shown tapentadol being effective and well tolerated for the management of moderate-to-severe chronic noncancer pain with comparable efficacy but significantly superior gastrointestinal tolerability to oxycodone controlled release (CR).[13–15] Two clinical trials in patients with painful diabetic polyneuropathy have proven the efficacy of tapentadol prolonged release (PR) even in typical neuropathic pain conditions, and preliminary evidence also exists for its effectiveness in chronic low back pain and other mixed pain conditions characterized by a concomitant neuropathic pain component.[16]

Opioid analgesics, in particular morphine, have an established role in the management of moderate-to-severe cancer pain.[17–19] International, multicenter, placebo- or active-controlled, double-blind, Phase III studies[20,21] and several open-label or observational trials demonstrated at least comparable efficacy, safety, and better tolerability of the MOR–NRI tapentadol PR or extended release (ER) (PR in Europe = ER in USA) for the management of moderate-to-severe chronic cancer pain.[22]

For physicians treating elderly patients with various comorbidities, it is important that tapentadol is characterized by a predictable and reliable pharmacokinetic profile that makes pharmacokinetic drug–drug interactions unlikely to occur. No pharmacologically active metabolites are generated, and no inhibition or induction potential on CYP/CYP450 enzymes has been demonstrated. Explicitly, there was a lack of clinically undesired interactions with paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole, or metoclopramide.

The present supplement summarizes current clinical evidence on tapentadol in the treatment of different types of pain and provides a robust practical guidance for the beneficial use of this innovative centrally acting analgesic in chronic cancer and noncancer pain patients.

Acknowledgments

Editorial assistance was provided by Luca Giacomelli, PhD, and Aashni Shah. This assistance and fees for publications were supported by Grünenthal GmbH.

Disclosure

AHD has received fees from Grünenthal GmbH, Allergan, Janssen, Johnson & Johnson, Teva, and Regeneron. HGK has received speaker's and/or consultancy fees from Bionorica SE, Grunenthal GmbH, Mundipharma Int., TEVA Ratiopharm, Mylan, and Pfizer outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Bannister K, Kucharczyk M, Dickenson AH. Hopes for the future of pain control. *Pain Ther*. 2017;6(2):117–128.
2. Zajączkowska R, Przewłocka B, Kocot-Kępska M, Mika J, Leppert W, Wordliczek J. Tapentadol – A representative of a new class of MOR-NRI analgesics. *Pharmacol Rep*. 2018;70(4):812–820.
3. Tzschentke TM, Christoph T, Kögel BY. The mu-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: the case of tapentadol. *CNS Drugs*. 2014;28(4):319–329.
4. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323(1):265–276.
5. Langford RM, Knaggs R, Farquhar-Smith P, Dickenson AH. Is tapentadol different from classical opioids? A review of the evidence. *Br J Pain*. 2016;10(4):217–221.
6. Bannister K, Patel R, Goncalves L, Townson L, Dickenson AH. Diffuse noxious inhibitory controls and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. *Pain*. 2015;156(9):1803–1811.
7. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? *Eur J Pain*. 2010;14(8):781–783.
8. Raffa RB, Elling C, Tzschentke TM. Does 'Strong Analgesic' Equal 'Strong Opioid'? Tapentadol and the Concept of 'μ-Load'. *Adv Ther*. 2018:1471–1484.
9. Pergolizzi JV Jr, Lequang JA, Taylor R, Ossipov MH, Colucci D, Raffa RB. Designing safer analgesics: a focus on μ-opioid receptor pathways. *Expert Opin Drug Discov*. 2018;13(10):965–972.
10. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;56(6):514–515.
11. Tzschentke TM, De Vry J, Terlinden R. Tapentadol hydrochloride. Analgesic, mu-opioid receptor agonist, noradrenaline reuptake inhibitor. *Drugs Future*. 2006;31:1053–1061.
12. Tzschentke TM, Jahnel U, Kogel B, et al. Tapentadol hydrochloride: a next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. *Drugs Today*. 2009;45(7):483–496.
13. Rinonapoli G, Coaccioli S, Panella L. Tapentadol in the treatment of osteoarthritis: pharmacological rationale and clinical evidence. *J Pain Res*. In press 2019.
14. Polati E, Del Balzo G, Martini A, Matteo T, Schweiger V, Collino M. Tapentadol: an overview of the safety profile. *J Pain Res*. In press 2019.
15. Coluzzi F, Polati E, Freo U, Grilli M. Tapentadol: an effective option for the treatment of back pain. *J Pain Res*. In press 2019.
16. Romualdi P, Kress HG, Freo U. Tapentadol prolonged release for neuropathic pain: a review clinical studies. *J Pain Res*. In press 2019.
17. Mandalà M, Moro C, Labianca R, Cremonesi M, Barni S. Optimizing use of opiates in the management of cancer pain. *Ther Clin Risk Manag*. 2006;2(4):447–453.
18. Droney J, Riley J. Recent advances in the use of opioids for cancer pain. *J Pain Res*. 2009;2:135–155.
19. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2):e58–e68.
20. Kress HG, Koch ED, Kosturski H, et al. Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain. *Pain Physician*. 2014;17(4):329–343.
21. Imanaka K, Tominaga Y, Etropolski M, et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. *Curr Med Res Opin*. 2013;29(10):1399–1409.
22. Kress HG and Coluzzi F. Tapentadol in the management of cancer pain: current evidence and future perspectives. *J Pain Res*. In press 2019.