Review Article

Tapentadol IR (Immediate Release); A Novel Analgesic for Acute Pain

Sanjeev Kumar[1], *Seema Rani[2], Ram Chander Siwach[1], Prem Verma[2]

1. Department of Orthopaedics, Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan (Sonepat), Haryana, India.
2. Department of Pharmacology, Bhagat Phool Singh Government Medical College for Women, Khanpurkalan (Sonepat), Haryana, India.

ABSTRACT

Acute pain is often undertreated and inadequate management may lead to poor patient outcome and potentially life - threatening complications. Opioids and nonopioid analgesics i.e. non- steroidal anti-inflammatory drugs are the groups of analgesics used to treat acute pain; unfortunately both are associated with potentially serious side effects. Opioids provide relief of moderate to severe acute pain however associated with particularly gastrointestinal side effects. Tapentadol is a FDA approved centrally acting novel analgesic for the treatment of moderate to severe acute pain with a dual mode of action as μ-opioid receptor agonist and as a nor- epinephrine reuptake inhibitor. The drug follows linear pharmacokinetics, absorbed quickly and is excreted primarily by the renal system. The analgesic effects of tapentadol are independent of metabolic activation and tapentadol has no active metabolites so theoretically tapentadol may be associated with a low potential for interindividual variations and drug–drug interactions. In various phase III trials in patients with various types of moderate to severe acute pain have shown that tapentadol immediate release IR 50 to 100 mg every 4 to 6 hours shows analgesic effect comparable to that of oxycodone IR 10 or 15 mg every 4 to 6 hours with a lower incidence of nausea, vomiting, and constipation. So, tapentadol is an important addition to the armamentarium for the management of moderate- to-severe pain.

Keywords: Acute pain, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid, oxycodone tapentadol IR.

Received 31 May 2013 Received in revised form 12 June 2013 Accepted 14 June 2013

***Author for Correspondence:**
Dr. Seema Rani
Associate Professor, Department of Pharmacology, BPS Govt. Medical College for Women, Khanpur Kalan (Sonepat) Haryana, India.
E-mail: seema17march@gmail.com

INTRODUCTION

Low back pain is commonest health problem and is the fifth most common reason among people visiting physician in the United States [1]. The prevalence of low back pain in the adult general population was 22–65% [2]. It puts a lot of personal, community and financial burden globally [3]. For back pain alone, total health care expenditures in year 2005 were estimated at $85 billion to $100 billion [4].

Appropriate management of acute pain remains a considerable challenge for health care providers. Unrelieved acute pain may cause anxiety and sleep disturbances that affect mental status [5]. Acute pain may cause tachycardia, hypertension, suppress immune function and decrease pulmonary function ultimately may lead increased risk of dangerous complications including coronary artery disease, deep vein thrombosis, pulmonary embolism and stroke[6]. Uncontrolled acute pain is also associated with gastrointestinal side effects like nausea, and vomiting [7].

Medications are the most frequently recommended treatment for low back pain [8]. In one of the study, 80% of primary care patients with low back pain were prescribed at least one medication at their initial office visit and more than one third were prescribed two or more drugs [9]. Today we have options for the management

of acute pain include opioid analgesics and nonopioid analgesics. Nonopioid analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs). Conventional NSAIDs have therapeutic ceiling effect and are appropriate for only mild to moderate pain [10] but have potentially serious side effects include gastrointestinal effects. Also NSAIDs are not advised in patients with peptic ulcer disease, renal impairment and bleeding diatheses [11]. Newer NSAIDS i.e. Selective cyclooxygenase-2 (COX-2)-inhibitors do not impair platelet function and cause less gastrointestinal bleeding as compared to other NSAIDs [12]; however, but these are more prone to an increase in the risk of cardiovascular side effects [13].

Opioids are used for the management of moderate to severe acute pain [14]. Opioids exert their analgesic effects primarily through agonistic action on μ-opioid receptors in neurons, which lead to a decrease in neurotransmitter release and there by pain [15]. However, the agonistic action on non-analgesic receptors is responsible for side effects [10]. Their use is restricted because of nausea, vomiting, constipation and sedation because of direct stimulation of receptors at the chemoreceptor trigger zone, vestibular apparatus and in CNS [16]. Tramadol, an opioid analgesic, has genetic polymorphism because it is metabolized by cytochrome P-450 that leads to drug – drug interactions and has a neurotoxic metabolite which may predispose patients to serotonin syndrome [17].

Even though the large numbers of drugs are available in the market for the treatment of acute pain, a potent analgesic drug with a low side-effect profile is a today's need. Tapentadol immediate release (IR), a centrally acting synthetic oral analgesic was approved by the FDA on November 20, 2008 for the relief of moderate- to-severe acute pain [18].

Pharmacology and pharmacokinetics of tapentadol

Tapentadol is a novel centrally opioid analgesic with dual mechanism of action. It is μ-opioid receptor agonist and epinephrine reuptake inhibitor [19]. It is a pure enantiomer with chemical formula C14H23NO.HCL. After oral administration, it does not require metabolic activation and is rapidly and completely absorbed with peak serum levels reached within 1.25 hours. Mean absolute bioavailability is nearly 32% after a fasting single-dose administration [20]. Plasma protein binding is approximately 20% and the protein binding is independent of substance concentration [21]. The half-life elimination is 4 hours for the immediate release formulation. Tapentadol undergoes extensive metabolism and is metabolized primarily via phase II glucuronidation to tapentadol-O-glucuronide (70%), to a lesser degree by CYP2C9 and CYP2C19 to desmethyl tapentadol (13%), and CYP2D6 to hydroxytapentadol (2%) [20, 22]. In-vitro studies did not show a potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. All the metabolites are pharmacologically inactive and the parent molecule is only responsible for analgesic activity [17]. This profile reduces the probability of large individual variations in the pharmacological effects of tapentadol. Tapentadol is excreted 99% in the urine; 70% as conjugated metabolites and 3% unchanged substance. The apparent half-life of tapentadol following oral administration is 3.93 hours and more than 95% of the drug is excreted within 24 hours of dosing [20]. There is no clinically relevant difference in the pharmacokinetics of tapentadol in men and women, young adult and elderly subjects. Exposure and peak serum concentrations of tapentadol were increased in subjects with mild or moderate hepatic impairment, whereas the maximum concentrations of the metabolite, tapentadol-O-glucuronide, were decreased in subjects with moderate liver impairment. In subjects with mild, moderate and severe renal impairment, the AUC∞ of tapentadol-O-glucuronide was 1.5-fold, 2.5-fold and 5.5-fold higher as compared to subjects with normal renal function, respectively. The population pharmacokinetic model predicted that the clearance of tapentadol in Black, Hispanic-Latinos and other combined non-Caucasian racial groups was approximately 17%, 11% and 15% lower, respectively, compared to that predicted in Caucasian subjects. Therefore, the effect of

race on tapentadol pharmacokinetics is of little clinical relevance [19].

Efficacy and Safety of tapentadol IR prepration:

Phase III trial:

Daniels SE and his colleague[23] conducted a randomized , double, blind , phase III study to evaluate the efficacy and safety of multiple doses of tapentadol IR (50 or 75 or 100 mg), oxycodone HCl IR (10 mg), and placebo in postoperative bunionectomy patients. 603 patients were randomized to received tapentadol IR 50 or 75 or 100 mg, oxycodone HCl IR 10 mg, or placebo orally every 4 to 6 hours over a 72 hour period following for bunionectomy. The primary endpoint was sum of the pain intensity difference (SPID) over the first 48hours (SPID48). Secondary efficacy endpoint include SPID over 12,24 and 72 hours ; total pain relief, use of rescue medication; patient global impression change; and perceived onset of action of medication.

Results showed that all tapentadol IR treatment group significant reduction in pain based on primary efficacy measure i.e. $SPID_{48}$ compared to placebo ($p< 0.001$) Increasing levels of pain relief were associated with higher doses of tapenadol IR. A similar decrease in pain intensity was noted in $SPID_{12}$, $SPID_{24}$ and $SPID_{72.}$ The proportion of patients achieving pain reduction of at least 30% to50% was significantly higher in the active –treatment patients compared with patients assigned to receive placebo patients. A reduction in pain intensity of 50% or greater was noted in 30% of the placebo group, 56.7% to 70.3% of patients assigned to tapentadol and in 72.8% of patients receiving oxycodone ($p< 0.001$ vs placebo). The percentage of patients using rescue medication was 49% in the placebo group, 10% to 19% in the tapentadol groups, and 9% in the oxycodone group. Patients receiving tapentadol also attained pain relief more quickly than those receiving placebo ($P < 0.005$).

The incidence of adverse effects reported were 70% with tapentadol 50 mg; 75% with tapentadol 75 mg; 85% with tapentadol 100 mg; 87% with oxycodone IR 15 mg; and 41% with placebo. The incidence of GI effects was lower with tapentadol compared with oxycodone. The difference in AEs between the tapentadol and oxycodone groups were statistically significant.

It was concluded that multiple doses of tapentadol significantly reduced acute postsurgical pain when compared with placebo. Also tapentadol 100mg efficacy is comparable and potentially superior GI tolerability to that of oxycodone IR 15 mg.

Hartrick and colleagues [25] conducted a randomized, double-blind study to evaluate the efficacy and tolerability of 10 days of treatment with tapentadol IR 50 mg, 75 mg, oxycodone 10 mg and placebo for patients with poorly controlled pain associated with osteoarthritis of the hip or knee. The numeric rating scale (NRS) and patient Global Impression of Change (PGI–C) are used as primary efficacy outcomes. The results showed statistically significant decrease in pain intensity compared with placebo at days 2, 5 and 10. Mostly GI and neurological effects were the primary reason for discontinuing the study drug in 13% of the tapentadol 50-mg group, 18% of the tapentadol 75 mg group, 30% of the oxycodone group, and 4% of the placebo group. The number of adverse events was lower for both doses of tapentadol as compared with oxycodone.

Dosage and administration

Recommended dose of tapentadol immediate release tablets - 50mg- 100mg orally every 4-6 hrs depending upon pain intensity. If adequate pain control is not achieved, the second dose may be administered one hour following first dose, with titration up to maximum total daily dose of 700 mg on first day and subsequent maximum daily dose is .Dose adjustments are not needed in mild to moderate patients with renal impairment but use in severe renal impairment is nor studied neither recommended. No dose adjustment is needed in mild hepatic impairment but in patients with moderate hepatic impairment, tapentadol is recommended as initial dose of 50 mg every 8 hours. Tapentadol has not been studied and not recommended in patients with severe liver impairment [23].

Adverse effects, contraindications and precautions

The most common adverse effects reported with tapentadol IR are nausea, vomiting, constipation, pruritus, dizziness and somnolence. The adverse effects are more pronounced on higher doses [23].

Tapentadol should not be given in patients with paralytic ileus and decreased pulmonary function. It should be used with caution in asthma, chronic obstructive pulmonary disease, corpulmonale, kyphoscoliosis, sleep apnea, myxedema, severe obesity, central nervous system depression, seizures, or coma. It should not be used in along with monoamine oxidase inhibitors or within 14 days of discontinuation of monoamine oxidase inhibitors [24].

Tapentadol Overcomes Some of the Drawbacks of Tramadol

Tramadol is a racemic mixture of negative and positive enantiomers while tapentadol is a nonracemic compound. .Tapentadol does not have active metabolites while tramadol is a prodrug and its analgesic activity relies on metabolic activation to the active opioid O-desmethyltramdol, which may lead to variability in pain relief. The absence of active metabolites with tapentadol also avoids potential side effects that may be caused by such metabolites. The nonopioid activity of tapentadol only consists of NE reuptake inhibition. Conversely, the nonopioid activity of tramadol is due to 5-HT and NA reuptake inhibiton, The 5-HT reuptake inhibition by tramadol produces analgesia by enhancing effects of the descendige inhibitory pathways; however, this analgesic effect may partly be offset by simultaneous enhancement of the proalgesic effect of the descending pain- facilitatory pathways, where 5-HTand NA is a main neurotransmitter. On contrary, since tapentadol monoaminergic activity is dominated by NA, it acts selectively on the descending inhibitory pathways but not on the descending faciliatory pathways. Tramadol different mechanisms of action are distributed in a complex manner across its enantiomers and metabolites. NE reuptake inhibition resides mainly in the (-) enantiomer and 5- HT reuptake inhibition in the reuptake inhibition in the (+) enantiomer of the parent compound, whereas MOR agonistic activity resides in the (+) enantiomer of odesmethyl- tramadol itself. So, the relative contribution of different mechanisms of action to overall analgesia with tramadol changes over time following administration, leading to complex time-and metabolism – dependant pattern of pharmacological activities. In contrast, both mechanisms of action of tapentadol reside within the same molecule and do not require metabolism to be pharmacologically active. Also, the relative contribution of these two mechanisms does not change during conversion to (inactive) metabolites. This may explain why its potency is higher that tramadol.

Tramadol is mainly metabolized via cytochrome P450 2D6 (CYP2D6), which is polymorphic in humans, about 5-15% of the white population are 'poor metabolisers' of tramadol and so do not experience satisfactory analgesia with standard doses. Also, drug-to- drug interactions at the level of CYP2D6 can be an additional complicating factor. In contrast, tapentadol is only minimally, so it has a low potential for drug- to-drug interactions and interindividual variability.

CONCLUSION

Tapentadol IR is the first new molecule with established efficacy in acute pain. It is a new, centrally- acting oral analgesic with unique dual mechanism of action that resides in a single enantiomer. In acute pain of various aetiologies like postoperative setting and end-stage joint disease, tapentadol has demonstrated comparable analgesia to that of oxycodone and less incidence of adverse effects, so improving patient outcome and recovery and lower treatment discontinuation rate.

Due to the combination of potent analgesia and improved tolerability, tapentadol is an important addition to the armamentarium for the management of moderate –to-severe pain symbolizing considerable improvement over currently practiced acute pain relief strategies.

REFERENCES

1. Hart LG, Deyo RA, Cherkin DC. Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns

from a U.S. national survey. Spine 1995;20:11-9.
2. Walker BF.The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord 2000;13:205-17.
3. Andersson GB. Epidemiology of low back pain. Acta Orthop Scand Suppl 1998;281:28–31.
4. Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10(2):113–130
5. Breivik H. Postoperative pain management: why is it difficult to show that it improves outcome? Eur J Anaesthesiol. 1998; 15(6):748–751.
6. MacIntyre P; on behalf of the Working Party of the Australian and New Zealand College of Anaesthetists. Acute pain management: scientific evidence, 2nd ed. Melbourne, Australia: Australian and New Zealand College of Anaesthetists, 2005. Available from: http://www.nhmrc.gov.au/publications/synopses/cp104syn.htm. Accessed October 30, 2009.
7. Spacek A. Modern concepts of acute and chronic pain management. Biomed Pharmacother. 2006;60(7):329-335.
8. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from U.S. national surveys, 2002. Spine. 2006;31:2724-7.
9. Vogt MT, Kwoh CK, Cope DK, Osial TA, Culyba M, Starz TW. Analgesic usage for low back pain: impact on health care costs and service use. Spine. 2005;30:1075-81
10. Brown AK, Christo PJ, Wu CL. Strategies for postoperative pain management. Best Pract Res Clin Anaesthesiol. 2004;18(4):703–717.
11. Power I, Barratt S. Analgesic agents for the postoperative period nonopioids. Surg Clin North Am. 1999;79(2):275-295.
12. Stephens J, Laskin B, Pashos C, Pena B, Wong J. The burden of acute postoperative pain and the potential role of the COX-2-specific inhibitors. Rheumatology (Oxford). 2003;42(Suppl 3):40-52.
13. Mc Gettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006;296 (13):1633–1644.
14. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs. 2003;63(1):17–32.
15. Chevlen E. Opioids: a review. Curr Pain Headache Rep. 2003;7(1):15–23.
16. Herndon CM, Jackson KC II, Hallin PA. Management of opioid induce gastrointestinal effects in patients receiving palliative care. Pharmacotherapy. 2002;22(2):240–250.
17. Barkin RL, Barkin D. Pharmacologic management of acute and chronic pain: Focus on drug interactions and patientspecific pharmacotherapeutic selection. South Med J 2001;94(8):756–770.
18. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: Consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008;8(4):287–313.
19. Tzschentke TM, De Vry J, Terlinden R, et al. Tapentadol HCl. Drugs Future. 2006;31(12):1053–1061.
20. Terlinden R, Ossig J, Fliegert F, et al. Absorption, metabolism, and excretion of 14C-labeled tapentadol HCl in healthy male subjects. Eur J Drug Metab Pharcontinuedmacokinet 2007; 32(3):163-169.
21. Kneip C, Terlinden R, Beier H, Chen G. Investigations into the drug–drug interaction potential of tapentadol in human liver microsomes and fresh human hepatocytes. Drug Metab Lett 2008; 2(1):67–75.
22. Terlinden R, Kogel BY, Englberger W, Tzschentke TM (2010). In vitro and in vivo characterization of tapentadol metabolites. Methods Find Exp Clin Pharmacol 32(1): 31-38.
23. Stegmann JU, Weber H, Steup A, 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;24(11): 3185–3196.
24. Nucynta (tapentadol HCl) film-coated tablets, prescribing information. Rari - tan, N.J.:PriCara/Ortho-McNeil-Janssen. Available at: www.nucynta.com/ nucynta/index.html. Revised March 2010. Accessed April 19, 2010.
25. Hartrick C, Van Hove I, Stegmann JU, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: A 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. Clin Ther 2009;31(2):260–271.