

# Tramadol

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**Background:** Tramadol is a centrally acting synthetic opioid analgesic used orally and parenterally in pain management. The United States Food and Drug Administration (US FDA) has approved Tramadol for the management of moderate to severe pain. Tramadol has minimal sedation and respiratory depression and has less gastrointestinal effect. It produces nausea, vomiting, dizziness, headache, somnolence, vertigo, seizures, etc. Concomitant use of Tramadol with CNS depressants should be avoided because Tramadol may potentiate the respiratory and CNS depressant effects of these drugs. There is an increase risk of convulsions in patient with epilepsy or history of seizures. It is contraindicated in patient receiving warfarin because it prolongs international normalized ration (INR) and prothrombin time and extensive ecchymoses. The concomitant use of Tramadol and serotonergic agents (e.g. Mirtazipine, Selegiline, Venlafaxine etc) is contraindicated because of the risk of serotonin syndrome. It has also got significant drug abuse potential. In Nepal, Tramadol is available as 50 mg capsule and 100 mg controlled release tab. It is also available as 50 mg and 100 mg injection. The safety profile, contraindications, drug interactions and the economic parameters should be considered before prescribing Tramadol.

**Keywords:** Contraindications, Indications, Pain management, Tramadol

## Introduction

Tramadol is a synthetic opioid analgesic and is chemically trans-2 (dimethylaminomethyl)-1-(m-methoxyphenyl)-cyclohexanol hydrochloride. It is a centrally active analgesic, which is used orally and parenterally for the relief of moderate to moderately severe acute or chronic pain, including post-operative, gynecologic and obstetric pain, as well as pain of various other organs, including cancer. Tramadol is available as oral as well as parenteral dosage forms and is one of the commonly prescribed analgesics in the hospital settings. In this article, the authors review the drug profile of Tramadol in order to enhance the rational prescribing of this drug.

**Therapeutic advantages:** It is an analgesic with minimal sedation or respiratory depression, has less gastrointestinal effect and is available as oral and parenteral formulation. In the treatment of mild to moderate pain it is as effective as morphine or pethidine. However for severe pain, Tramadol is less effective. Tramadol is as effective as pethidine in the

treatment of labour pain and may cause less neonatal respiratory depression.<sup>3</sup>

**Pharmacokinetics:**<sup>4,5</sup> Tramadol is readily absorbed following oral administration and the bioavailability is 75% but is subject to first pass metabolism. The rate or extent of Tramadol absorption is not significantly affected by food. It is metabolized by N- and O- methylation and glucuronidation and sulfation in the liver and produce active metabolite O-desmethylTramadol which is pharmacologically active. Production of active metabolite is dependent on the cytochrome P450 isoenzyme CYP2D6, which exhibits genetic polymorphism. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. Tramadol is widely distributed, crosses the placenta and present in small amounts in breast milk.

**Mechanism of action:** Tramadol possesses a weak affinity for the mu-opioid receptor and even less for the kappa and delta receptors. Its affinity is about 1/6000 times that of

morphine and one tenth that of codeine. The (+) enantiomer of Tramadol and its major metabolite bind more strongly to the mu-opioid receptor than the respective (-) enantiomers. The opioid and 5-hydroxy tryptamine (serotonin) reuptake inhibitory effect is about 4 times more potent in the (+) enantiomer, whereas the noradrenaline reuptake inhibitory effect is in the (-) enantiomer. The uptake inhibition in both the non-opioid and opioid systems takes place in the same concentration range (0.5 to 50 micromolar).<sup>6</sup>

**Dosage and administration:**<sup>5</sup> Tramadol can be given orally, intravenously or rectally as a suppository. The intramuscular route has also been used. It may also be given by infusion. Usual oral dose is 50 to 100 mg every 4-6 hours. It may also be given orally as a modified release preparation once or twice daily. The total daily dosage by mouth should not exceed 400 mg. A dose of 50 to 100 mg may be given every 4-6 hours by IV injection over 2 to 3 minutes; or by IV infusion. Rectal dose by suppository is 100 mg up to 4 times daily. The detail dosage regimen of Tramadol for some of the common indications is listed in Table 1.

**Table 1:** Indications and dosage regimen of Tramadol<sup>1,7</sup>

| Indications                 | Dosage regimen  |
|-----------------------------|---|
| Pain (moderate to severe) * | Titration schedule, 25 mg/day orally every morning, titrated in 25 mg increments as separate doses every 3 days to reach 25 mg 4 times daily; then, may increase total daily dose by 50 mg as tolerated to reach 50 mg 4 times daily. After titration, 50-100 mg orally every 4-6 hr; max 400 mg/day. |
| Lower back pain             | Immediate-release 50 to 100 mg orally, up to 4 times daily as necessary. For pain persisting for more than 5 days sustained-release 100 to 150 mg orally, twice daily   |
| Post operative pain         | 100 mg initially then 50 mg every 10-20 minutes if necessary during first hour to total maximum 250 mg (including initial dose) in first hour, then 50-100 mg every 4-6 hours; max 600 mg daily.  |
| Rotator cuff disease        | Immediate-release 50 to 100 mg orally, as necessary up to 4 times daily For pain persisting for more than 5 days <u>Tramadol</u> sustained-release 100 mg to 150 mg orally, twice daily   |

\*= Approved indication for tramadol by the US FDA

**Fixed dose combination of Tramadol:** The fixed dose combination (FDC) of Tramadol/paracetamol is available as tablets containing 37.5/ 325 milligrams (mg). For relief of acute pain, the manufacturer recommends a dose of two tablets every 4 to 6 hours. Duration of treatment of 5 days or less, and maximum daily dose of 8 tablets is suggested.<sup>8</sup> In a randomized, double-blind, placebo- and active-controlled, single-dose study in patients with, at least moderate pain following dental extraction, 2 Tramadol/Acetaminophen tablets were as effective as 1 hydrocodiene/Acetaminophen tablet in relieving pain.<sup>9</sup> In another placebo-controlled study of the FDC, a single dose of two tablets was superior to placebo in treating pain following oral surgical procedures; the combination was at least as effective as Tramadol and Acetaminophen given alone in the same doses.<sup>8</sup>

**Comparative studies with other analgesics:** Tramadol has been compared with many other drugs for its analgesic effects. Some of these comparisons are summarized below.

In one study rectal Tramadol provided equivalent analgesic efficacy to rectal Acetaminophen with Codeine. However, rectal Tramadol is not as well-tolerated as rectal Acetaminophen with Codeine.<sup>10</sup>

A prospective, double-blind study compared Codeine and Tramadol for postoperative analgesia in 75 patients after elective intracranial surgery. The study found that patients receiving codeine had significantly lower pain scores over the first 48 h after operation ( $P < 0.0001$ ). The Tramadol 75 mg group also had significantly higher scores for both sedation and nausea and vomiting ( $P < 0.0001$  for both scores). The authors concluded that codeine 60 mg IM provided better postoperative analgesia than Tramadol after craniotomy and that Tramadol 75 mg should be avoided because of its side effects of increased sedation and nausea and vomiting.<sup>11</sup>

In another randomized, 3-day study, the analgesic efficacy and tolerability of intramuscular ketorolac and Tramadol were comparable in 66 women with post-operative pain following gynecologic surgery. No significant differences between the study drugs was observed for pain relief on days 2 and 3, frequency of night pain and quality of sleep, number of injections required daily and overall judgment of efficacy by both investigators and patients. Three Ketorolac patients and one in the Tramadol group required drug discontinuation and rescue analgesics due to inefficacy. Tolerability was comparable; one patient in each group was withdrawn due to an adverse event.<sup>12</sup>

Tramadol 50 mg, Tramadol 100 mg, and Meperidine 75 mg were compared in 90 primigravida females for relief of labor

## Tramadol

**Table 2:** Drug interactions with Tramadol <sup>4</sup>

| Interacting drugs | Outcomes  | Management  |
|-------------------|---|---|
| Carbamazepine     | Decreased Tramadol efficacy due to the induction of metabolism of Tramadol by Carbamazepine | Monitor patients for Tramadol efficacy. Doses may need to be increased, even doubled, in patients who are receiving chronic carbamazepine therapy.  |
| Warfarin          | Increased risk of bleeding due to an unknown mechanism.                                     | Closely monitor international normalized ratio (INR) and adjust warfarin doses accordingly. Also monitor for signs and symptoms of bleeding and bruising.   |
| Amitriptyline     | Increased risk of seizures due to an unknown mechanism                                      | Use with caution if Tramadol is to be administered to patients receiving concomitant tricyclic antidepressant (TCA) therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures |
| Promethazine      | Increased risk of seizures due to an unknown mechanism                                      | Caution should be used if Tramadol is to be administered to patients receiving Promethazine therapy. If possible, this combination should be avoided especially in patients with underlying conditions that might predispose to seizures.             |

**Note:** The risk of seizure is increased if Tramadol is administered concomitantly with other drugs that have the potential to lower the seizure threshold.

pain. Pain relief was assessed at 10, 20, 30, 45, and 60 minutes after intramuscular administration. Pain relief was satisfactory in 18 of the 30 patients receiving Tramadol 100 mg and 19 of 30 receiving Meperidine 75 mg. Tramadol 100 mg IM appears to offer comparable analgesia with slightly lesser side effects and a higher neonatal respiratory rate than Meperidine 75 mg IM. <sup>13</sup>

**Adverse effects:** <sup>1,3</sup> Tramadol can produce common as well as serious adverse effects. Some of the common side effects include pruritus, constipation, diarrhea, nausea, vomiting, dizziness, headache, somnolence, vertigo. The serious side effects are postural hypotension (rare), syncope (rare), tachyarrhythmia (rare) anaphylactoid reaction, impaired cognition, seizure (at therapeutic dose range), hallucinations and dyspnea (rare).

It is also known to cause difficulty in concentration, paresthesia, suicidal tendencies, symptoms of serotonin syndrome (e.g. hyperreflex, fever, shivering, agitation, diaphoresis etc). These adverse effects are reported in less than 1% of patients receiving the drugs.

**Drug interactions:** Tramadol is known to have drug interactions with many commonly used drugs. Some of them are mentioned in Table 2.

**Precautions:** Tramadol should be used with caution in patients with renal or liver impairment and should be avoided if renal impairment is severe. Abrupt discontinuation may

induce withdrawal symptoms (i.e. anxiety, sweating, nausea, diarrhea, tremors, and insomnia). It should not be used in opioid dependent patients or in patients with tendency to opioid abuse or opioid dependence and in elderly or debilitated patients. Concomitant use with CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics should be avoided because Tramadol may potentiate the respiratory and CNS depressant effects of these drugs.

Tramadol should be used with caution in patient with increased intracranial pressure or head injury because of its respiratory depressant effects which includes CO<sub>2</sub> retention and secondary elevation of cerebrospinal fluid pressure. There is an increased risk of convulsions in patient with epilepsy or history of seizures.

**Contraindications:** It is contraindicated in patients hypersensitive to Tramadol, intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. Contraindicated in patient receiving warfarin because it prolongs international normalized ration (INR) and prothrombin time and extensive ecchymoses. The concomitant use of Tramadol and serotonergic agents (e.g. Mirtazipine, Selegiline, Venlafaxine etc) is contraindicated because of the risk of serotonin syndrome.

**Use in special population:** The use of Tramadol in special population needs attention. The details are listed in Table 3.

**Table 3:** Use of Tramadol in special populations

| Population                | Comments  |
|---------------------------|---|
| Pediatric patients        | Safety and efficacy in patients under 16 years of age has not been established  |
| Renally impaired patients | Creatinine clearance less than 30 ml/min, increase dosing interval to 12 hours; maximum dose 200 mg/day. Tramadol should not be given to patient with more severe renal impairment (creatinine clearance less than 10 ml/min) |
| Liver disease             | A dose interval of 12 hours is recommended in severe hepatic impairment. For patients with cirrhosis, 50 mg orally every 12 hours   |
| Geriatric patients        | Patients over 75 years, maximum dose 300 mg/day   |
| Pregnant women            | US FDA pregnancy category C *   |
| Breast feeding mothers    | Infant risk cannot be ruled out.  |

\*= Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

**Drug abuse:** Withdrawal symptoms, including anxiety, insomnia, sweating, rigors, pain, tremors, nausea, diarrhea, upper respiratory symptoms, piloerection, and hallucinations may occur if Tramadol is abruptly discontinued. Other symptoms such as panic attacks, severe anxiety, and paresthesias have been less frequently associated with discontinuation. It is recommended that the dosage of Tramadol be gradually tapered when treatment is going to be discontinued.<sup>14</sup>

A proactive United States post-marketing surveillance program under the leadership of an independent steering committee reported 283 cases of Tramadol abuse/dependence during the first 3 years of marketing (April 1995 through June 1998). Sources included spontaneous reporting to the manufacturer and/or MedWatch program as well as a key informant network and Internet surveillance. Almost all such cases (97%) occurred in individuals with a history of substance abuse. The estimated rate of Tramadol abuse/dependence decreased from 2 to 3 cases per 100,000 patients exposed (mid-1996) to 1 case per 100,000 patients exposed (mid-1998).<sup>15</sup>

**Advice to patients:** <sup>2</sup> Patient should be advised that Tramadol may impair mental or physical abilities required for the

performance of potentially hazardous tasks such as driving a car or operating machinery. Patient should also be advised against taking Tramadol or Tramadol in combination with Acetaminophen, with alcohol containing beverages and to use caution when taking the drug concomitantly with drugs such as tranquilizers, sedatives and hypnotics or other opiate-containing analgesics that may impair mental abilities. Female patient should be instructed to inform their physician if they are pregnant, think they might become pregnant, or are trying to become pregnant.

**Availability:** In Nepal, Tramadol is available as 50 mg capsule costing NRs 10.00 (Approx) and controlled release tab 100 mg costing NRs 28.00 (approx). It is also available as 50 mg Inj costing NRs 22.00 (approx) and 100 mg costing NRs 40.00 (approx).

## Conclusion

In the recent years Tramadol is being used extensively for pain relief which could have been achieved with other relatively safer, cost effective analgesics. Since Tramadol is a drug associated with several side effects and also belongs to opioid group of drugs, the decision to prescribe Tramadol should be carefully considered. Before choosing Tramadol as the analgesic, one should clearly measure the risk versus benefit and economic consequences. In patients who are at risk of developing seizures and in patients who developed vomiting to Tramadol, alternatives should be sought.

## References

1. Compact disc. Therapeutic Guidelines Limited (eTG18, April 2006)
2. McEvoy GK, Miller J, Litvak K et al editors. *AHFS Drug Information*. United States of America: American Society of Health-System Pharmacists; 2003. ISBN 1-58528-039-9
3. Gustein HB, Akil H. Opioid analgesics. In Goodman and Gilman's The pharmacological basis of therapeutics. Brunton LL, Lazo JS and Parker KL (eds). 11<sup>th</sup> edition, McGrawhill medical publishing division, New York, 2006, 547-90.
4. Klasco RK (Ed): *DRUGDEX® System*. Thomson Micromedex, Greenwood Village, Colorado (Edition expires [6/2006]).
5. Sweetman SC. Editor. *Martindale The Complete Drug Reference*. 33<sup>rd</sup> edition. London, Pharmaceutical Press; 2002. ISBN 0-85369-499-0
6. Shipton EA. Tramadol - present and future. *Anaesth Intensive Care* 2000;**28**:363-74.
7. Mehta DK, Martin J, Costello I, Jordan B et al editors.

## Tramadol

*BNF 50*; London: BMJ publishing group, September 2005.

8. Product Information: Ultracet(TM), Tramadol/paracetamol. Ortho-McNeil Pharmaceutical, Raritan, NJ, 2001.
9. Fricke JR, Rosenthal N, Karim R. Tramadol/Acetaminophen tablets (Ultracet(TM)) vs hydrocodone bitartrate/acetaminophen for dental pain, Presented at the International and American Association of Dental Research Meeting, San Diego, CA, 2002.
10. Pluim MAL, Wegenert JT, Ruprecht J, et al. Tramadol suppositories are less suitable for post-operative pain relief than rectal Acetaminophen/codeine. *Eur Acad Anaesthesiol* 1999; **16**: 473-8.
11. Jeffrey HM, Charlton P, Mellor DJ, Moss E, Vucevic M. Analgesia after intracranial surgery: a double-blind, prospective comparison of codeine and tramadol. *Br J Anaesth* 1999; **83**: 245-9.
12. Mais V, Peiretti R, Melis GB, et al. Intramuscular tramadol in gynaecological postoperative pain: multicentre controlled clinical trial against ketorolac. *It J Gynaecol Obstet* 1997; **4**: 33-9.
13. Viegas OAC, Khaw B, Ratnam SS. Tramadol in labour pain in primiparous patients: a prospective comparative clinical trial. *J Obstet Gynecol Reprod Biol* 1993; **49**:131-5.
14. Product Information: Ultram(R), Tramadol hydrochloride tablets. Ortho-McNeil Pharmaceutical, Inc., Raritan, New Jersey, 2004
15. Cicero TJ, Adams EH, Geller A, et al. A postmarketing surveillance program to monitor Ultram(R) (Tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend* 1999; **57**: 7-32.