

**National Essential Medicine List Medication Review Process**  
**Adult Hospital Level**  
**Component: Pain**

---

**Date:** July 2015

**Medicine:** Tramadol, IV

**Indication:** Analgesia in the post-operative setting.

**Introduction**

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is an intermediate acting analgesic with dual properties. It has limited action at the  $\mu$ -opioid receptors but has a secondary action at the spinal cord level where it results in an increase in noradrenaline and serotonin levels.<sup>1, 2,4, 8</sup> There are no similar acting analogs available. The time to onset of analgesia is approximately 90 - 300s and duration of action is approximately 6 hours.<sup>9, 10</sup> The conversion factor for dosing of tramadol is 10:1 when compared to morphine.

Tramadol is indicated for rapid onset analgesia in the peri-operative period, in the trauma or emergency unit, as well as in the intensive care and ward settings.

Tramadol has been in clinical use for over three decades and has a good safety record comparable to the other intravenous analgesic agents.

**Reasons for inclusion in Essential Medicines List**

Tramadol is used for analgesia for the following reasons:

1. It causes less respiratory depression than conventional intravenous opioid therapy<sup>11</sup>
2. It is a good analgesic alternative for use in patients who are opioid dependent or opioid addicts.<sup>6, 7, 8,</sup>
3. Tramadol causes less constipation than morphine.<sup>3,4</sup>
4. The oral form of the drug is available to allow for continuity of analgesic therapy without the need for an intravenous line.
5. The agent is a Schedule 5 drug and provides a good analgesic alternative to the Schedule 6 opioids.

Tramadol is beneficial in the peri-operative period for the following reasons:

1. It is a useful agent in treating post-operative shivering.<sup>12,13</sup>
2. It is an analgesic adjunct, for example, when used for local skin infiltration and intra-articular injection perioperatively.<sup>14,15</sup>
3. It can be used for pre-emptive analgesia and post-operative analgesia, which would promote earlier patient mobilization and reduced morbidity.<sup>16-20</sup>
4. It can be used as an alternative agent to pethidine for labour analgesia.<sup>12,13</sup>

**Current Essential Medicines List Alternatives**

The other opioids currently on the EML are morphine and fentanyl.

The duration of action of fentanyl is over 45 minutes and this can be problematic for short surgical procedures, particularly if respiratory depression must be avoided. Morphine has a longer duration of action and respiratory depression is a well-documented side effect.

## **TRAMADOL FOR ANALGESIA**

### **1. Opioid respiratory depression**

It is a well-documented fact that opioids cause respiratory depression. The degree of respiratory depression varies depending on the agent.

The analgesic properties of tramadol are attributed to a dual mechanism of action the molecule does have some activity at the  $\mu$ -opioid receptors but this is 1/6000 of the activity exhibited by morphine at these receptors. Its main activity is exhibited at the serotonergic and noradrenergic receptors at the spinal cord level. Tramadol acts by re-uptake inhibition of serotonin and noradrenaline thereby increasing the level of these two molecules thereby enhancing analgesia.<sup>1, 2, 4</sup> Because of the reduced  $\mu$ -opioid activity it does not cause the same degree of respiratory depression as other opioids that act at the  $\mu$ -receptors.

The lower rate of respiratory depression and sedation compared with other opioids (eg. morphine), make tramadol a useful alternative to the treatment of pain in the emergency or trauma setting.<sup>11</sup>

### **2. Analgesic alternative for opioid dependent or opioid addicted patients**

Tramadol has been found to have a very low potential for misuse, abuse, and dependency. There are cases described where dependence on tramadol does develop but these cases indicate long-term oral usage in very high doses.<sup>6</sup> Short-term use of the injectable formulation does not appear to be problematic. Even with oral formulation the incidence of dependence was low with tramadol.<sup>7, 8</sup>

### **3. Tramadol causes less constipation than morphine.**

This fact is attributable to its reduced activity at the opioid m-receptors.<sup>3, 4</sup> The mucosa of the large intestine exhibits  $\mu$ -receptor activity and agonists such as morphine will attach to these receptors with resultant constipation. This is true for other opioids including codeine. As tramadol has weak m-receptor activity it follows that tramadol induced constipation will be less than with the pure  $\mu$ -opioid agonists.

Constipation prolongs post-operative recovery and by implication increases the length of stay in hospital with subsequent increase in hospital costs.

### **4. Tramadol is available in oral and injectable form**

The intravenous form of tramadol is a useful analgesic for intra-operative pain relief. This form of therapy can be continued into the post-operative phase until the patient can be placed on enteral drug formulations. It is thus possible to continue the same drug through the entire peri-operative period without seeking alternative analgesic agents for pain relief.

## **TRAMADOL IN THE PERI-OPERATIVE PERIOD**

### **1. Tramadol reduces postoperative shivering**

Postoperative shivering is a common complication that occurs in up to 60% of patients recovering from general anaesthesia, and up to 70% of patients undergoing regional anaesthesia. Postoperative shivering can range from a spectrum of mild shivering to severe shivering that requires pharmacological therapy for resolution. Shivering results in patient discomfort and may result in physiological responses of increased oxygen consumption and stress on the cardiovascular and respiratory systems, which may result in increased patient morbidity<sup>12, 13</sup>

Pethidine is the most widely used agent to treat shivering; however, it has many disadvantages including increased patient sedation and respiratory depression. Tramadol has been shown to be equally as effective, if not more than Pethidine, with fewer sedative side effects.<sup>12,13</sup>

### **2. Tramadol as an Analgesic Adjunct**

Tramadol is useful adjunct to the multimodal peri-operative analgesic regime, when used in alternative ways:

- There is evidence that tramadol, in combination with bupivacaine (local anaesthetic), injected intra-articularly, prolongs the duration of postoperative analgesia after arthroscopic knee surgery.<sup>14</sup>
- Local skin infiltration of tramadol at the trocar sites following laparoscopic surgery has been shown to improve early postoperative pain.<sup>15</sup>

### **3. Tramadol for Pre-emptive and Postoperative Analgesia**

Pre-emptive analgesia is defined as an analgesic intervention provided before surgery to prevent or reduce subsequent pain. It has been suggested that tramadol administration prior to, or soon after induction of anaesthesia, offers better postoperative pain relief, similar or better recovery times and reduced postoperative morphine PCA (patient controlled analgesia) use.<sup>16,17,18</sup>

The benefits of adequate postoperative analgesia are well documented, and include a decreased physiological stress response, improved patient comfort and earlier mobilization, reduction in morbidity, reduced length of hospital stay and overall decrease in cost.

Tramadol, either as a sole analgesic agent, or in combination with other opioids and non-opioid analgesics is used as part of a multimodal analgesic regime with good effect.<sup>20</sup>

It has also been shown that the administration of tramadol may be as effective as epidural analgesia, and may avoid the need of placement of epidural catheters, thereby avoiding complications (epidural haematoma, infection).<sup>19</sup>

### **4. Tramadol for Labour Analgesia**

Tramadol does not exhibit a depressive effect on ventilatory activity in the mother and the newborn; it can be used in the obstetrical analgesia, at most in the form of an intramuscular

injection. It offers the advantage of having a less sedative effect as well as less pruritis than pethidine.<sup>12,13</sup>

## Summary

Tramadol is an injectable opioid with dual action resulting in less of the opioid side effects than the conventional opioids such as morphine and pethidine. It has a longer duration of action than fentanyl but a shorter duration of action than morphine. The agent may be used as an alternative form of therapy for acute pain especially when there are concerns regarding respiratory depression, addiction, and opioid induced constipation.

## References:

1. Vazzana M, Andreani T et al. Tramadol hydrochloride: pharmacokinetics, pharmacodynamics, adverse side effects, co-administration of drugs and new drug delivery systems. *Biomed Pharmacother.* 2015 Mar;70:234-8. doi: 10.1016/j.biopha.2015.01.022. Epub 2015 Feb 7.
2. Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. *Drugs.* 1997;53 Suppl 2:18-24.
3. Wilder-Smith CH, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci.* 1999 Jun;44(6):1107-16.
4. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923
5. Radbruch L, Glaeske G, Grond S, et al. Topical review on the abuse and misuse potential of tramadol and tilidine in Germany. *Subst Abus.* 2013;34(3):313-20. doi: 10.1080/08897077.2012.735216.
6. Tjäderborn M, Jönsson AK, Ahlner J, Hägg S. Tramadol dependence: a survey of spontaneously reported cases in Sweden. *Pharmacoepidemiol Drug Saf.* 2009 Dec;18(12):1192-8. doi: 10.1002/pds.1838.
7. Daveluy A, Miremont-Salamé G, Kostrzewa A, Couret A, Lacoïn L, Lecomte C, Moore N, Gilleron V, Haramburu F. Identification of abuse and dependence cases through a hospital database. *Pharmacoepidemiol Drug Saf.* 2012 Dec;21(12):1344-9. doi: 10.1002/pds.3369. Epub 2012 Oct 30.
8. Lehmann KA<sup>1</sup>. Tramadol in acute pain. *Drugs.* 1997;53 Suppl 2:25-33.
9. Lintz W<sup>1</sup>, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. *Int J Clin Pharmacol Ther.* 1999 Apr;37(4):175-83.
10. Lintz W, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. *Int J Clin Pharmacol Ther.* 1999 Apr;37(4):175-83.
11. Vergnion M, Degesves S, Garcet L et al. Tramadol, an alternative to Morphine for treating Posttraumatic pain in the Prehospital Situation. *Anaesth Analg.* 2001; 92 : 1543-6
12. Mohta M, Kumari N, Tyagi A et al. Tramadol for prevention of Postanaesthetic Shivering: a randomized double-blind comparison with Pethidine. *Anaesthesia* , 2009; 64 : 141-146

13. Mahesh T, Kaprati L. A Randomised Trial comparing Efficacy, Onset and duration of action of Pethidine and Tramadol in Abolition of Shivering in the IntraOperative Period. Jour of Clinical and Diagnostic Research. 2014; 8(11) : GC07-GC09
14. Zeidan A, Kassem R et al. Intraarticular Tramadol-Bupivacaine Combination Prolongs the Duration of Postoperative Analgesia After Outpatient Arthroscopic Knee Surgery. Anesth Analg 2008; 107: 292-9
15. Matkap E, Bedirli N et al. Preincisional local infiltration of tramadol at the trocar site versus intravenous tramadol for pain control after laparoscopic cholecystectomy. Jour of Clinical Anesthesia 2011; 23 : 197-201
16. Wang F, Shen X et al. Preoperative tramadol combined with postoperative small-dose tramadol infusion after total abdominal hysterectomy: a double-blind, randomized, controlled trial. Pharmacological Reports. 2009; 61 :1198-1205
17. Shen X, Wang F. Comparison of the analgesic efficacy of preemptive and preventive tramadol after lumpectomy. Pharmacological Reports. 2008; 60, 415-421
18. Unlugenc H, Ozalevli M et al. Pre-emptive analgesic efficacy of tramadol compared with morphine after major abdominal surgery. BJA 2003; 91(2) : 209-213
19. Bloch M, Dyer RA, Heijke SA, James M. Tramadol Infusion for Postthoracotomy Pain Relief: A Placebo-Controlled Comparison with Epidural Morphine. Anesth Analg. 2002; 94 : 523 – 528
20. Hadi, MA, Kamaruljan HS et al. A Comparative Study of Intravenous Patient- Controlled Analgesia Morphine and Tramadol in Patients Undergoing Major Operation. Med J Malaysia. 2006; 61(5): 570 -576