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TRAMADOL – A Drug to be used cautiously

Dr. Anil Batta*

Associate Professor, Department of Medical Biochemistry, Govt. Medical College, Amritsar, India

*Corresponding author: akbattafarid@yahoo.co.in

Abstract

Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of two enantiomers, both of which contribute to analgesic activity *via* different mechanisms. (+)-Tramadol and the metabolite (+)-*O*-desmethyl-tramadol (M1) are agonists of the μ opioid receptor. (+)-Tramadol inhibits serotonin reuptake and (–)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate. As one of the least potent opioid painkillers many people believe tramadol is not addictive. This false sense of security can lead some people to develop an addiction without even realizing it. Tramadol was originally considered to have a much better safety profile than other opioid analgesics like morphine or hydrocodone. However, due to mounting evidence of abuse among the general public, as well as evidence of withdrawal symptoms upon using tramadol without a prescription or taking it in higher doses, more often or for longer than prescribed are all considered abuse of this drug. Combining tramadol with other substances to increase its effects is also abuse. It's important to recognize the signs of tramadol abuse as early as possible to prevent an addiction from developing. External signs of tramadol abuse include: Even when the drug is used properly and under the supervision of a doctor, tramadol users can experience adverse reactions to it, such as nausea and dizziness. Abuse of tramadol makes the drug more dangerous and puts the user at risk for severe side effects or overdose. Taking tramadol in combination with other substances, called polydrug abuse, also increases the risk of serious and sometimes fatal side effects. More severe symptoms of tramadol abuse typically occur when higher doses of the drug are taken or when tramadol is taken in combination with another substance. Severe symptoms of tramadol abuse can include seizures and CNS depression. Another potentially dangerous symptom of tramadol abuse is serotonin syndrome, which can be life-threatening if left untreated. It occurs when too much serotonin, a chemical that relays signals in the brain, is produced or remains in the brain. Serotonin syndrome most commonly occurs in patients who take tramadol and antidepressants at the same time. Symptoms of serotonin syndrome include: Pinpoint (very small) pupils, Changes in appetite, Nausea or vomiting, Drowsiness, Seizures (without a history of epilepsy), Slurred speech, Headaches, Impaired coordination. Tramadol is an opioid analgesic (painkiller). It is prescribed to treat moderate to moderately severe pain and is considered a safer alternative to other narcotic analgesics like hydrocodone (Vicodin, Lortab) and methadone. Additional medications containing tramadol include, an extended release formulation for round-the-clock pain relief, and, a combination of tramadol and acetaminophen.

Keywords: Tramadol, CNS depression, hydrocodone, painkiller.

Introduction

Tramadol is mainly metabolized by *O*- and *N*-demethylation and by conjugation reactions

forming glucuronides and sulfates. Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours. The *O*- demethylation of tramadol to M1,

the main analgesic effective metabolite, is catalyzed by cytochrome P450 (CYP) 2D6, whereas *N*-demethylation to M2 is catalyzed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. *O*- and *N*-demethylation of tramadol as well as renal elimination are stereoselective. Pharmacokinetic-pharmacodynamic characterization of tramadol is difficult because of differences between tramadol concentrations in plasma and at the site of action, and because of pharmacodynamic interactions between the two enantiomers of tramadol and its active metabolites. The analgesic potency of tramadol is about 10% of that of morphine following parenteral administration. Tramadol provides postoperative pain relief comparable with that of pethidine, and the analgesic efficacy of tramadol can further be improved by combination with a non-opioid analgesic. Tramadol may prove particularly useful in patients with a risk of poor cardiopulmonary function, after surgery of the thorax or upper abdomen and when non-opioid analgesics are contraindicated. Tramadol is an effective and well tolerated agent to reduce pain resulting from trauma, renal or biliary colic and labor, and also for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain. Tramadol appears to produce less constipation and dependence than equianalgesic doses of strong opioids. In India, because of the laxity in drug regulation implementation, opioids are often available over-the-counter; increasing the risk of opioid misuse. However, we could trace only one case report of tramadol-dependence from India. We looked for cases seeking treatment at our centre for tramadol-dependence. Tramadol is a novel, central-acting synthetic opioid with weak μ -opioid activity, and is approved for treatment of moderate to moderately severe pain in adults. Anecdotally, some clinicians have assumed this popular analgesic's nonscheduled status under the Controlled Substance Act (CSA) means tramadol has no substance abuse potential. (The term "abuse" herein denotes substance abuse or dependence.)

Prospective studies among patients with known abuse, or at high risk of abuse, reported a

tramadol abuse rate, as well as subjective experiences of tramadol withdrawal. A 3-year post-marketing cohort study measured tramadol's nonmedical misuse rates using urine drug testing for tramadol among 1601 participants in 4 US state monitoring programs for impaired healthcare professionals.⁷ Tramadol exposure occurred in 140 (8.7%) participants. Thirty-nine (28%) were classified as extensive experimentation or abuse of tramadol. Overall, the rate of extensive experimentation or abuse was 18 cases per thousand person years. The Hawthorne effect, where awareness of being monitored alters a subject's behavior, may threaten these measured frequency rates' generalizability. Another prospective study assessed the subjective tramadol withdrawal experience in 219 patients with a diagnosis of "Tramadol misuse" who were attending 6 drug detoxification centers in China.⁸ Validated drug dependence symptom scales found that while the degree of physical dependence reported was uniformly mild, the majority of patients reported the psychic dependence symptom of tramadol craving.

Mode of Action

Dependence and opioid effects

The dual mechanism of action may reduce the risk of opioid-associated adverse reactions and the potential for tolerance, dependence or abuse. However, a risk still remains so caution is recommended when prescribing. Tramadol must not be used for opioid withdrawal treatment as it cannot suppress opioid withdrawal symptoms. In addition, tramadol is contraindicated in patients with acute intoxication due to alcohol, hypnotics, analgesics, opioids or psychotropic drugs.² Tramadol should be administered with caution in patients at risk of respiratory depression and in patients with increased intracranial pressure, head injury, shock or a reduced level of consciousness of uncertain origin.² The μ -opioid receptors are found throughout the CNS and are also found in the intestinal tract. Although less pronounced than with true opiate analgesics, tramadol may also cause constipation due to reduced gut motility.³ Other commonly reported adverse reactions associated with tramadol use include nausea and

vomiting, dizziness, autonomic nervous effects (dry mouth, perspiration/sweating), headache, sedation, asthenia (weakness) and fatigue². Tramadol seizures can be managed with diazepam (Valium).

Seizures

Tramadol, both alone or in combination with other medicines, may lower the threshold for seizures and is contraindicated in patients with uncontrolled epilepsy⁴. The Centre for Adverse Reactions Monitoring (CARM) has received a total of 19 reports of convulsions, grand mal convulsions or convulsions aggravated associated with the use of tramadol since 2000. The convulsions were life-threatening in two cases and 14 patients required hospitalization. The patients recovered in all cases except one where the outcome was unknown. In the majority of cases symptom onset was within 12 hours of the start of tramadol administration.

Serotonin Syndrome/Toxicity

As tramadol inhibits re-uptake of NA and 5-HT, use with other serotonergic agents increases the risk of serotonin syndrome/ toxicity. Tramadol should be used with caution in patients requiring selective serotonin re-uptake inhibitors (SSRIs), serotonin-noradrenalin re-uptake inhibitors (SNRIs) and tricyclic antidepressants. Use of tramadol is contraindicated in patients also taking monoamine oxidase inhibitors (MAOIs) and those who have taken MAOIs within the last 14 days².

Interactions

Tramadol is metabolized to its principal active metabolite M1, through *O*-demethylation by cytochrome p450 (CYP) isoenzyme 2D6 (CYP2D6). Poor metabolites of medicines via CYP2D6 may therefore get less benefit from tramadol use due to reduced formation of the active metabolite^{3,5}. The isoenzymes CYP3A4 and CYP2B6 are involved in the metabolism of tramadol via *N*-demethylation to a secondary metabolite M2¹. The addition of a CYP3A4 inhibitor may also inhibit the metabolism of tramadol and reduce the therapeutic response (eg, erythromycin, itraconazole). Six reports of an

interaction between oral tramadol and warfarin have been submitted to CARM since 2000. An elevated international normalized ratio (INR) was described in four reports, with onset occurring up to seven days after tramadol was commenced in patients stabilised on warfarin. In five cases, the patients developed haemorrhage-related symptoms, such as melaena, anemia and purpura. The mechanism for this interaction has not been fully elucidated, but may be due to CYP2D6 polymorphism, which subsequently increases competition for CYP3A4 metabolism (involved in metabolism of R-warfarin)⁶. Caution should be exercised if tramadol and warfarin are used concurrently². CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines and sedative hypnotics may potentiate the sedating effects of tramadol, and should therefore be used with caution and in reduced doses².

Overdose

Although some evidence suggests there is less risk of respiratory depression with tramadol, the symptoms of tramadol overdose are similar to other centrally acting analgesics and include coma, convulsion, respiratory depression, respiratory arrest and cardiovascular collapse¹. Seizures may also occur with overdose. Healthcare professionals are encouraged to report any adverse events, including events associated with tramadol, to CARM. Reports may be submitted on paper or electronically.

Review of Literature

Tramadol has been in clinical use in Germany since the late 1970s and has proven effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. Moreover, the negligible abuse potential of tramadol has meant that it has never been a restricted drug, and it therefore very quickly became the most popular analgesic of its class in Germany. Although tramadol has been used in myocardial emergencies, in trauma and obstetric pain, or to supplement balanced anesthesia, most studies have investigated postoperative patients. The focus of this article is to review clinical experience with tramadol in the treatment of acute postoperative pain. Tramadol, a synthetic opioid

of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties, and effects on noradrenergic and serotonergic neurotransmission. In addition, these opioid and nonopioid modes of action appear to act synergistically. Tramadol has been shown to provide effective analgesia after both intramuscular and intravenous administration for the treatment of postoperative pain. The drug is available in formulations suitable for oral, rectal and parenteral administration. Clinically effective analgesic doses of tramadol were comparable to those of pethidine (meperidine) and about 10 times higher than those of morphine. While it is not recommended as a supplement to general anesthesia because of its insufficient sedative activity, tramadol has been successful in the treatment of postoperative pain. A randomized double-blind study reported acceptable analgesia with postoperative intravenous tramadol 50mg, repeated once if required after 30 minutes. It produced an effect similar to that of morphine 5mg or the alpha 2 agonist, clonidine 150 micrograms. In another study, it was shown that the 50mg dose of tramadol fulfilled the requirements of an analgesic for the treatment of moderate postoperative pain, whereas for severe pain a higher dose was recommended. Tramadol is generally well tolerated, the most common adverse events being nausea and vomiting. In contrast to agents such as morphine and pethidine, clinically relevant respiratory depression is rarely observed during tramadol administration at equipotent doses and consequently it can be recommended for first-line management of postoperative pain instead of morphine. It is also associated with a low incidence of cardiac depression and significantly less dizziness and drowsiness than morphine. Finally, the dependence and abuse potential with tramadol is negligible. Comparative studies have generally shown that tramadol is more effective than NSAIDs for controlling post operative pain. Use of a combination of tramadol and NSAIDs allows the tramadol dose to be reduced and results in a lower incidence of adverse effects. Patient controlled analgesia (PCA) with tramadol has been frequently used and is well accepted by patients. Wide individual variations exist with regard to analgesic requirements and, nowadays, it is generally accepted that adequate pain

management implies systematic individualization of the therapy, i.e. titration of the analgesic effect to individual needs. Demand and loading doses play a decisive role in the success of PCA. Analgesic failures requiring rescue medication are rare, but it should be stressed that these can always occur with weak opioids. In conclusion, tramadol can be recommended as a basic analgesic for the treatment of moderate to severe pain. In the event of analgesic failure with tramadol, there is no reason not to switch to more potent opioids. Although no studies are available regarding its use in the management of postoperative pain after day case surgery, tramadol is frequently administered with good results in such patients. The most important side effects of tramadol are nausea and emesis, which can often be prevented by slow injection and administration of a prophylactic antiemetic such as metoclopramid.

Discussion

Tramadol influences 2 primary brain systems: The opioid system - by binding with u-opioid receptors. The monoamine system - by inhibiting the reuptake of serotonin and nor epinephrine. Tramadol is partially metabolized in the liver by the enzymes CYP2D6 and CYP3A4. The tramadol metabolized by CYP2D6 becomes a substance called O-Desmethyltramadol. Both the original tramadol compound and O-Desmethyltramadol stimulate u-opioid receptors in the brain, though the O-Desmethyltramadol has 6 times the affinity for these receptors than the original compound. For analgesia (and intoxication) both the opioid and serotonin/nor epinephrine systems are important. We know this because blocking opioid receptor activation with naloxone does not completely eliminate analgesia or abuse potential. If tramadol is taken chronically it will develop a physical dependence and will experience withdrawal symptoms develop taking the drug too suddenly. Risk of addiction, which is distinct from physical dependence - especially if taken more tramadol than prescribed for pain management or if taken just to feel good. Loss of control over tramadol use (for example, being unable to manage supply of medication to last between prescriptions). Continuing to use tramadol despite being aware that it does harm or

risks. Harm (examples could include excessive financial harms, risks of overdose, a failure to meet responsibilities, legal problems, etc.). Tramadol was originally touted as a drug with significantly less abuse and addiction potential than comparable full-agonist opioid. While it's still considered less addictive than full-opioids, the FDA now acknowledges tramadol's abuse risk and advises against prescribing this drug to people considered addiction prone or those who use alcohol to excess. Study Comparing tramadol's Abuse Risk to Oxycodone's was conducted. In this study of abuse potential, researchers at the University of Kentucky College of Medicine compared tramadol, codeine, oxycodone and a placebo to see how much drug abusers liked each substance (they didn't know what they were taking) and to see how hard they would work for further doses. All subjects were non opiate-dependent recreational opiate abusers. To test the 3 different drugs, all subjects came in for 7 times for 2-day experimental procedures. On each day 1, researchers gave each subject one of the 4 substances; the subjects then rated this drug for recreational likeability and learned they'd be working the next day to earn doses of this substance. On each day 2, subjects came back in and worked (through button clicking exercises) to earn small doses of the same drug. Subjects did not like the placebo and would not work for it. On a scale to 100, when rating how much they liked the pleasurable high, subjects gave 40 mg of oxycodone a score of a little more than 62, 200 mg of codeine a score of 49 and 400 mg of tramadol a score of 47. Though subjects reported liking the oxycodone high more than the tramadol high, subjects were willing to work harder to get more tramadol than they were to get more oxycodone or codeine.³ It has Respiratory depression (less common), Nausea and vomiting, Anxiety and agitation. Overdose Treatment Since tramadol overdose is potentially lethal, it's obviously a medical emergency that demands immediate hospital attention. Some possible tramadol overdose treatments include: Activated charcoal (but only after recent tramadol ingestion).¹⁰, Benzodiazepines - for seizures. Naloxone for respiratory depression or coma - though this is tricky, since naloxone increases seizure risk. Assisted breathing and the

symptomatic treatment of serotonin syndrome symptoms, such as cooling the body, maintaining hydration, sedating muscles and mind are salient features.

Serotonin Syndrome

Tramadol is a mild serotonin reuptake inhibitor, so taking tramadol causes an upswing in neural serotonin levels. If take tramadol together with another drug that also increases serotonin levels, like SSRI/SNRIs, MAOIs, dextromethorphan (a cough syrup ingredient), Demerol and others - or with illicit drugs like MDMA or LSD, risk bumping serotonin to dangerous levels and experiencing a possibly lethal condition known as serotonin syndrome can occur. Agitation, Nausea and vomiting, Rapid heartbeat, high blood pressure and rapid changes in blood pressure, An elevated body temperature are found. Heavy sweating, Overactive reflexes, A loss of coordination and twitching muscles, Hallucinations, Confusion, Headache, Shivering, Diarrhea.¹¹ Symptoms of severe serotonin syndrome include: Seizures, Unconsciousness, Irregular heartbeat, High fever. Symptoms generally appear within minutes to hours after taking one or more serotonin raising medications. Serotonin syndrome is a possibly lethal condition that demands immediate medical attention. With appropriate treatment, symptoms will usually dissipate within 24 hours. Typical treatments include: Benzodiazepines, Serotonin blocking drugs, I.V. fluids, Temporary induced muscle paralysis and assisted ventilation (in severe cases).

Tramadol's Influence on Sleep

Tramadol significantly disrupts sleep quality in non-dependent or tolerant subjects. In a sleep study, healthy volunteers given 100 mg of tramadol experienced increased light stage 2 sleep and significantly decreased slow-wave sleep (stage 4) and REM sleep (stage 5) Chronically reduced deep and REM sleep could impair health and well-being: During slow wave sleep blood flows away from the brain and into muscle tissue, the body builds muscle and bone, the immune system is strengthened and the body repairs damaged tissues, such as those damaged by

ultraviolet rays. Areas of the brain which control emotion, decision making and social functioning go dormant. Sleep scientists think this decreased activation while sleeping helps us maintain maximal social attention and functioning while awake. Deep sleep may also play a role in learning and memory encoding.¹⁴ Of course, everything depends on your individual situation. For example, if tramadol provides analgesia that increases sleep likelihood, it may have a net-positive impact on sleep quality and quantity.

Cancer and Organ Damage

There is no evidence from animal-model studies that chronic tramadol use increases human cancer risk. Because tramadol is not associated with an increased cancer risk, or with gastrointestinal, renal or cardiovascular complications, it is considered an appropriate (safe) medication for chronic pain treatment.¹⁵ It is not, however, totally benign. Researchers who compared the long term use of tramadol to morphine in an animal-model study concluded that though tramadol was far less toxic to the liver and kidneys than morphine, it still did some damage over time.¹⁶

Use during Pregnancy/Nursing: - Tramadol may slightly increase birth defect risks if used during the first 2 months of pregnancy. If used during pregnancy, especially chronically or in high doses close to the expected date of delivery, the baby may be born with neonatal abstinence syndrome (NAS).¹⁷ Tramadol is passed through breast milk to your infant. Talk to your doctor before using tramadol while nursing.¹⁸

Conclusion and Summary

- Tramadol is a centrally-acting synthetic analgesic with a dual mechanism of action - binding at μ -opioid receptors and inhibiting noradrenalin and serotonin re-uptake.
- The most notable side effects of tramadol include serotonin syndrome/toxicity, seizures (including lowered seizure threshold), respiratory depression, and increased intracranial pressure and anaphylactic reactions.

- Common adverse reactions include nausea, vomiting, constipation, dizziness, autonomic nervous effects (mainly dry mouth, perspiration), headache, sedation, asthenia (weakness) and fatigue.
- Tramadol is metabolised primarily by CYP2D6. CYP2D6 polymorphisms may affect the metabolism of tramadol alone as well as form the basis for interactions (e.g., warfarin). Tramadol is a centrally-acting synthetic analgesic used for the relief of moderate to severe pain. Tramadol and its principal metabolite *O*-desmethyltramadol (M1) have opioid-like effects since they bind to μ -opioid receptors distributed throughout the central nervous system (CNS). The binding affinity of tramadol for μ -opioid receptors is approximately 6,000-fold less than morphine and approximately 20-fold less for M1.¹ In addition to its opioid actions, tramadol also inhibits the neuronal re-uptake of nor adrenaline (NA) and serotonin (5-HT). The data sheet provides more information on tramadol.

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