

Is oral tramadol a reasonable PRN analgesic?

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Tramadol is a unique analgesic with multiple mechanisms of action. Reports as early as the late 1970s describe its characteristics and utility for antinociception. Although much research has demonstrated tramadol's efficacy for both acute and chronic pain syndromes, it appears that the more we learn of tramadol's unique neuropharmacologic properties, the less we actually understand about this compound's interaction with inhibitory pain pathways. Furthermore, it appears as more specialties turn to this agent for specific pain syndromes, surgeries, delivery techniques, and specific sites of administration, the more interpatient and interdelivery variability is exhibited by this compound.

Tramadol, when formulated without acetaminophen, is approved by the Food and Drug Administration within the United States for moderate to moderately severe pain in adults. Interestingly, when combined with acetaminophen, tramadol is indicated solely for acute pain for short durations of therapy (less than 5 days). Although the indication for the combination product was solely an artifact of the clinical data supplied to the Food and Drug Administration (primarily dental pain models), this still raises questions as to the appropriate patient population in which to use tramadol and the correct clinical setting. When originally launched in the United States, the drug was marketed as an opioid with similar equianalgesic efficacy to morphine, without the respiratory depression or abuse liability. As clinical experience with tramadol grew, many pain clinicians became disenchanted because of the unrealistic expectations regarding efficacy and the unbenign side effect profile.

To date, clinical studies, with largely unequivocal results, have proven tramadol's place in therapy for acute, acute postoperative, malignant, chronic nonmalignant, and neurogenic pain states.¹⁻⁶ Recently, the American Pain Society, in collaboration with the American College of Physicians, released clinical practice guidelines addressing pharmacotherapy for chronic low back pain, an incredibly difficult condition to palliate.⁷

Although the guidelines panel classified the strength of data to support the chronic dosing of tramadol for chronic low back pain as "fair," this still affirms its place in the

management of this condition. Other evidence-based technical reviews, such as the Cochrane Collaborative, have given tramadol the nod for use in treating numerous neuropathic pain syndromes, including diabetic neuropathic pain, postherpetic neuralgia, and trigeminal neuralgia.^{5,6} Interestingly, similar recommendations are lacking for tramadol's use in more acute situations, including postoperative pain management, perioperative preemptive analgesia, or specific breakthrough pain episodes, especially within the United States where parenteral tramadol is not available.

When discussing parenteral tramadol's efficacy in acute pain scenarios, published reports as early as 1995 confirmed the analgesic potential of this agent when compared with parenterally administered pethidine (meperidine) or morphine.⁸ However, in the first published study of orally administered tramadol for acute musculoskeletal pain, tramadol proved inferior to hydrocodone/acetaminophen in a prospective, single-center, randomized, double-blind, single dose trial.⁹ Similar studies in acute settings support this concern with equivalence or inferiority to such analgesics as acetaminophen, combination codeine/acetaminophen, and traditional and COX-II selective nonsteroidal anti-inflammatory drugs.^{10,11} The disconnect between the plethora of positive data to support parenteral tramadol for acute pain syndromes and the lackluster support for similar efficacy from oral tramadol may lie within the extent of metabolism of this drug to active metabolites when administered via these two distinctly different routes.

To appropriately appreciate the complexity of tramadol, a relatively succinct review of its pharmacology and pharmacokinetics is warranted. Tramadol is largely demethylated via Cytochrome (CYP) 450 2D6 to three metabolites, M1, M3, and M5, with M1 proving to be active. The M1 tramadol metabolite (O-desmethyltramadol) is by far the most clinically significant of the demethylated products of tramadol metabolism. M1 appears to be up to six times the potency of the parent compound for producing analgesic and exhibits greater than 200 times the affinity for the mu opioid receptor (MOR).¹² Pharmacokinetically, both parent and M1 track similarly

with regards to time to detection in plasma and time to maximal plasma concentration.¹² The maximal plasma concentration of both parent and metabolite is approximately 2 hours, which again supports concerns for acute and as-needed dosing for this product. As the M1 metabolite appears to provide much of the analgesia exhibited by tramadol, it seems counterintuitive that intravenously administered tramadol, which would avoid much of the hepatic first pass phenomenon, should prove to be such a valuable ally against acute, postoperative pain.

As mentioned previously, both tramadol and the M1 metabolite are relatively weak agonists of the MOR. Much work has recently focused on further elucidating the contributing pharmacology to tramadol's analgesic effects given its activity at the MOR.^{13,14} Little human data exist to support a significant contribution of MOR agonist activity to tramadol antinociception. Unpublished data provided within the package labeling for tramadol suggest some partial reversal of analgesia when the nonselective opioid antagonist naloxone is administered to patients receiving this agent.¹⁵ Additionally, the addiction medicine literature provides several reports of opioid withdrawal symptom attenuation when tramadol is introduced to volunteers experiencing this syndrome.^{16,17} Animal data are not supportive of this notion. Ide and colleagues¹³ describe their experiences with tramadol and MOR knock-out mice in which tramadol maintains its antinociceptive properties as assessed by the hot-plate and tail-flick experimental animal pain models. However, activity at the MOR may be just the tip of the iceberg.

It is widely recognized that tramadol additionally modulates the monoaminergic neurotransmitters in addition to its weak MOR binding affinity. Interestingly, conflicting data exist that question the actual contribution of tramadol's serotonergic activity to the drug's overall analgesic profile. In animal models, methysergide, a serotonergic antagonist, failed to exhibit an effect on tramadol antinociceptive properties when coadministered with tramadol.¹³ However, numerous studies in humans display a relative pharmacodynamic interaction between ondansetron, a selective 5-HT₃ serotonergic receptor antagonist, and tramadol.^{18,19} Concurrent administration of ondansetron with tramadol postoperatively resulted in significantly higher tramadol dose requirements compared with those receiving saline infusion tramadol. With the concept that the serotonergic modulation of tramadol may indeed play a clinically significant role to tramadol's analgesic properties, receptor effect may not be viable when dosed on a PRN basis.

Other recently reported pharmacologic properties of tramadol additionally question this agent's classification as an opioid versus a "neuromodulator." Several animal studies have revealed that tramadol's unique neuropharmacology may additionally involve α_2 -adrenergic agonist effects, voltage-gated sodium channel antagonistic effects, nicotinic acetylcholine antagonist effects, potassium

channel agonist effects, and nitric oxide modulation effects.^{13,20-22} These proposed contributing mechanisms of action for tramadol begin to model that of currently used anticonvulsants.

In summary, tramadol continues to be a useful and widely used enigma in the pain management armamentarium. Although it is premature to make strong recommendations regarding its appropriate use in various patient populations and pain syndromes, the overwhelming abundance of robust clinical data to support orally administered tramadol comes from clinical studies of chronic pain conditions in which around-the-clock dosing occurs, in many cases in a forced titration design. Although weak MOR agonist action may provide limited analgesia acutely when oral tramadol is administered, the evidence cannot be ignored that this agent's pharmacologic profile may mirror the anticonvulsants typically used in pain practice today. With this concept in mind, tramadol should be dosed similarly to these agents and patients counseled regarding the necessity for around-the-clock dosing with titration to maximally tolerated doses. Additionally, appropriate education should be provided to patients with tramadol naïve pain regarding the adherence and realistic expectations.

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