Pharmacology and Clinical Experience with Tramadol in Osteoarthritis

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Summary

Tramadol is a centrally acting analgesic that has been shown to be effective in a variety of acute and chronic pain states. Unlike other centrally acting analgesics, it exerts a dual action by binding to the opioid receptor site in the central nervous system and by weakly inhibiting the reuptake of biogenic amines. Tramadol is rapidly and almost completely absorbed, with an onset of action occurring within 1 hour of oral administration. The recommended dosage is 50 to 100mg every 4 to 6 hours; however, regular administration is an alternative, particularly for chronic pain states such as osteoarthritis, where the use of the recently developed sustained release formulation may represent an important advantage. Published studies specifically evaluating the use of tramadol in this disease support its effectiveness. Nausea, drowsiness, constipation, dizziness, and sweating have been reported in association with tramadol use. Nausea occurs early in the course of administration, and may be reduced by slowly titrating the dose of tramadol against response. Tramadol would appear to be particularly useful in the elderly population affected by osteoarthritis because, unlike nonsteroidal anti-inflammatory drugs, it does not aggravate hypertension or congestive heart failure, nor does it have the potential to cause peptic ulcer disease. Compared with narcotics, tramadol does not induce significant respiratory depression, constipation, or have significant abuse potential.

The management of painful osteoarthritis calls for a comprehensive approach that may consist of pharmacological agents, physical medicine and rehabilitation, surgical intervention, minimally invasive techniques, patient education, and psychological support. Pain is the common denominator for the majority of the estimated 18 million patients in the United States with this disease and is responsible for much of the associated disability. What percentage of patients with painful osteoarthritis seek medical care is not known, but a recent Harris poll indicated that 17% of the adult population in the US suffered from chronic pain. Many (46%) had arthritis – osteoarthritis being the most common type of arthritis. Yet, the poll showed that approximately one-third of these felt that their pain caused work disability, and one-fifth were dissatisfied with pain medication.

Although optimal pain management is multidisciplinary, medications are the cornerstone of the therapeutic armamentarium in many patients. Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic or local corticosteroids, muscle relaxants, antidepressant drugs, anticonvulsants, and antihistamines are frequently used categories of drugs. Most acute and chronic musculoskeletal
pain is managed with analgesic agents ranging from weaker compounds containing aspirin or paracetamol to the reluctant use of strong narcotics such as codeine, morphine and pethidine, which is fraught with more common complications such as nausea, lightheadedness, sedation, and constipation. Addiction, dependence, tolerance and respiratory depression are less common but often adversely affect a physician’s willingness to prescribe these drugs. Many physicians recommend paracetamol for mild pain because of its favourable benefit/risk ratio. A study by Bradley et al.\[3\] showed that the efficacy of paracetamol was equal to that of the NSAID, ibuprofen, in the treatment of osteoarthritis of the hip. Unquestionably, stronger narcotics are beneficial for relieving pain, but few physicians are willing to prescribe such drugs for chronic pain because of their adverse reactions. NSAIDs may be effective for mild to moderate musculoskeletal pain; yet, few pharmaceutical manufacturers have pursued indications other than osteoarthritis and rheumatoid arthritis for NSAIDs. Furthermore, there is growing concern about the high incidence of peptic ulcer disease caused by some NSAIDs, particularly when administered to the elderly.\[4\]

The availability of tramadol as an analgesic for the management of painful osteoarthritis represents a desirable therapeutic option.

1. Background

Grüenenthal first introduced tramadol to the German market as a weak opioid in 1977,\[5\] and claimed that respiratory depression or other adverse effects associated with opioids were less pronounced with tramadol. Once released into the marketplace, the drug failed to become popular as an abuse agent.\[6\] Indeed, Keup\[7\] reported no significant abuse with tramadol, making it clearly different from other \(\mu\) opioid receptor agonists. Tramadol has since been marketed in more than 70 countries, and over 40 million patients worldwide have used it. The drug has recently been marketed in the United States as Ultram\(^\text{®}\), for the management of moderate to moderately severe pain.

2. Mechanism of Action

Tramadol is a single-entity, centrally acting analgesic. Unlike other centrally acting analgesics such as codeine, hydrocodone, oxycodone, and morphine, tramadol has a dual mechanism of action at therapeutic doses. Like narcotics, tramadol binds to the \(\mu\) opioid receptor site in the central nervous system, with a binding affinity 6000 times less than that of morphine. However, tramadol-mediated analgesia is only partially reduced by the opioid antagonist, naloxone, thus suggesting an important nonopioid mechanism of action.\[8\] It was subsequently appreciated that the known reuptake inhibitory effects on the monoamines noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) contributed to the analgesic effects of tramadol by inhibiting pain transmission in the spinal cord.\[9\]

The drug is a racemic mixture; the (+) enantiomer has a weakly preferential effect at \(\mu\) opioid receptors and in inhibiting the reuptake of serotonin, whereas the (−) enantiomer preferentially inhibits the reuptake of noradrenaline. These enantiomers act in a complementary and synergistic fashion to produce analgesia.\[10\] Mono-O-desmethyltramadol (M1), the one active metabolite of tramadol, has a greater opioid receptor affinity than the parent compound, but the contribution of the metabolite to the analgesic effect in humans appears minimal after a single oral dose. There are no studies that address the analgesic effect of multiple doses of M1, although there is no build-up of the compound with repeated doses (R.B. Raffa, personal communication).\[11\]

As noted above, tramadol has definite selectivity for the \(\mu\) opioid receptor compared with the \(\delta\) and \(\kappa\) opioid receptors. Codeine has 10 times greater affinity for the \(\mu\) opioid receptor than tramadol. The reuptake inhibitory effects of tramadol on noradrenaline and serotonin are 100 to 1000 times weaker than those of imipramine.