A Risk-Benefit Assessment of Tramadol in the Management of Pain

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Summary

Tramadol is a cyclohexanol derivative with μ-agonist activity. It has been used as an analgesic for postoperative or chronic pain since the late 1970s, and became one of the most popular analgesics of its class in Germany. International interest has been renewed during the past few years, when it was discovered that tramadol not only acts on opioid receptors, but also inhibits serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine) reuptake. This review aims to provide a risk-benefit assessment of tramadol in the management of acute and chronic pain syndromes.

Tramadol has been used intraoperatively as part of balanced anaesthesia. Such use is under discussion, however, as it was associated with a high incidence of
intraoperative recall and dreaming, and postoperative respiratory depression has been described after intraoperative administration of high doses.

Postoperatively, intravenous and intramuscular tramadol has been used with good efficacy. Analgesic doses were comparable with pethidine (meperidine) and 10 times higher than morphine. Nausea and vomiting were the most frequently reported adverse effects. In controlled studies, haemodynamic and respiratory parameters were only minimally impaired. The risk of severe respiratory depression in typical dosages is negligible in comparison with other opioids used for postoperative pain management.

Tramadol has been used with good results for the management of labour pain without respiratory depression of the neonate. It was also effective for the treatment of pain from myocardial ischaemia, ureteric colic and acute trauma.

Good results have been published for cancer pain management with tramadol in several studies. The potential for abuse or addiction seems to be minimal, and serious complications have not been reported. For patients with severe pain, the efficacy of morphine is superior, and most patients with adequate analgesia from tramadol had to be changed to a more potent opioid after a few weeks due to increased nociceptive input during tumour progression. Tramadol can be recommended as a safe and efficient drug for step II according to the World Health Organization guidelines for cancer pain management.

Tramadol is a weak opioid analgesic, the potency of which is comparable with that of pethidine (meperidine). It has been available for clinical use in Germany since 1978[11] and is now available in a number of other major markets including the US, UK, France and China. Because of its low abuse potential,[2] tramadol has never been a restricted drug, which has made prescription easy in comparison with other opioids. A variety of formulations for oral, rectal and parenteral administration is available. These features have made tramadol very popular in Germany for postoperative and chronic pain syndromes.

In the past few years, the analgesic activity of tramadol was found to be mediated not only by opioid mechanisms but also by inhibition of monoamine reuptake, which led to increased international interest. The low incidence of adverse effects, minimal respiratory depression and negligible abuse or addiction potential has been confirmed in several recent studies. The aim of this review is to provide a clinical risk-benefit assessment of tramadol in acute and chronic pain situations.

1. Pharmacology

Tramadol is an aminocyclohexanole derivative with opioid agonist activity. Its affinity for opioid receptors is low (dissociation constant values 2.1-57.5 µmol/L[3]) with marginal preference for µ-receptors.[4] It also inhibits noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5HT) uptake.[4-6]

The activity of this agent seems to be stereospecific, as the (−) enantiomer is about 5 to 10 times more potent than the (+) enantiomer for inhibition of noradrenaline uptake, whereas the (+) enantiomer is about 4-fold more potent for inhibition of serotonin uptake.[3,7-9] Tramadol does not have any significant binding even at high concentrations to α2 adrenoceptor, serotonin, N-methyl-D-aspartate (NMDA) or benzodiazepine receptors.[4,10]

The combination of opioid and nonopioid mechanisms is believed to result in synergistic potentiation of analgesia.[11] The affinity for µ-opioid receptors, 6000-fold less than that of morphine, does not appear to be sufficient by itself to account for the antinociceptive potency. In animal models, even