

ACC Review

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»» *A distillation of best practice reflecting ACC's current position*

Tramadol in acute and chronic non-malignant pain

- »» Tramadol is a centrally acting analgesic with a unique mechanism of action that involves both weak opioid receptor binding and norepinephrine and serotonin reuptake inhibition
- »» Tramadol is comparable to, but not more effective than, other opioid and non-opioid analgesics in equipotent doses
- »» Qualitatively tramadol's adverse effect profile is similar to the opioids, although tramadol has a lower incidence of constipation and little respiratory depression potential
- »» Drug interactions can occur with concomitant use of CYP3A4 inducers (eg carbamazepine), and serotonin enhancers (eg monoamine oxidase inhibitors). The risk of seizure may also increase if used with tricyclic anti-depressants, selective serotonin reuptake inhibitors and other neuroleptics
- »» The risk of addiction with tramadol is thought to be lower than with other opioids.

Background

Tramadol, a synthetic analogue of codeine, is a centrally acting analgesic with a unique mode of action that is extensively used in pain management.¹ Historically, codeine, a pro-drug of morphine, was regarded as the standard among the 'weak' opioids. Codeine has a similar effect profile as low doses of morphine.²

Tramadol is classed as a 'step 2' analgesic by the World Health Organisation¹⁷ and is not listed on the New Zealand Pharmaceutical Schedule. It is available in Section H for in-hospital access.

Mode of action²

Tramadol is a racemate with both enantiomers and metabolites acting via two separate mechanisms. These involve weak opioid receptor binding and norepinephrine and serotonin reuptake inhibition. The relative contribution of each pathway to tramadol's efficacy is unknown. Tramadol has modest affinity (around 10-fold less than codeine and 6000-fold less than morphine) for the mu opioid receptor and little affinity for kappa and delta receptors.

Pharmacokinetics and drug interactions

Tramadol is well absorbed with an oral bioavailability of 70 to 75% following a single oral dose, rising to 90 to 100% on multiple dosing, which is unaffected by food.³ The immediate release formulation has an onset of action within 1 hour and the effect lasts about 6 hours at normal doses.^{3,4} Peak concentrations are reached within 2 to 3 hours.³ Tramadol is metabolised via cytochromes P450 (CYP) 2D6 and 3A to several metabolites. CYP2D6 produces the only active metabolite, M1.^{2,4} M1 has a higher affinity than tramadol for mu opioid receptors and contributes significantly to the analgesic action.² CYP polymorphism may in part explain inter-individual variability in response. Thirty per cent of the parent drug is excreted unchanged by the kidney⁴ and 10% in the bile.³ The half life is 5 to 6 hours.⁴ Dosing intervals may need to be extended in patients with significant renal or hepatic impairment.

Carbamazepine and other CYP3A4 inducers (eg phenytoin and rifampicin) may increase tramadol metabolism.^{1,3,4} Concurrent use with tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and other neuroleptics may increase seizure risk and serotonin syndrome if used with serotonin enhancers, eg monoamine oxidase inhibitors.¹

Efficacy and potency

Although tramadol's efficacy has been studied in a variety of pain models, meta-analysis is difficult due to differences between individual studies in baseline pain intensity, pain types, efficacy criteria, and doses of active drug controls.² Recent literature reviews,^{2,5} however, indicate that tramadol provides adequate analgesia in moderate/severe acute pain settings, being superior to placebo and, in the majority of studies, as effective as various opioid and non-opioid analgesics.² Likewise, in chronic non-malignant pain, tramadol appears to be as effective as other opioid and non-opioid analgesics.^{5,9} Tramadol has also been found to be effective for neuropathic pain.^{6,10}

In an analysis of single oral dose studies in acute pain, tramadol 50mg was equipotent to codeine 60mg, with 100mg the optimal dose.⁷ Because tramadol has higher oral bioavailability than morphine, an equipotent oral dose ratio of 4:1 respectively may be expected. The equipotent ratio of parenteral tramadol and morphine is estimated to be between 6:1 and 10:1.⁸

Analgesic tolerance has been reported with tramadol.⁶

Adverse drug reactions (ADRs)

The incidence of opioid ADRs is dependent on potency, dose and route of administration.² Although qualitatively tramadol's ADR profile is similar to the opioids, tramadol has a lower incidence of constipation and in therapeutic doses little respiratory depression potential.²

In a review of safety data from clinical and post-marketing surveillance, the most frequent ADRs reported were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness/fatigue (2.3%), sweating (1.9%), vomiting

(1.7%) and dry mouth (1.6%).¹¹ ADRs that occurred in <1% but >0.1% of patients were somnolence, hypotension, flush, stomach upset, constipation, nausea plus vomiting, sedation, circulatory failure, sleep disorder, pruritus, abdominal pain, diarrhoea, tachycardia and local irritation.¹¹ The ADR profile for single-dose or short-term (<24 hours) use was similar to that of longer-term administration. Rare ADRs include respiratory depression, lowered seizure threshold, hallucinations, confusion, motor system weakness, tremor, co-ordination disturbance, and clouded judgement.¹²

It has been estimated that in neuropathic pain one in 7.7 (95% CI: 4.6-20) patients will discontinue treatment due to side effects.⁶

With oral administration for chronic pain, low doses should be given initially to reduce nausea and dizziness.^{4,13} In one study a starting dose of 25mg daily titrated over 2 weeks reduced the incidence of vomiting by 60% and nausea by 38%.¹⁴

Addiction and withdrawal reactions

Dependence has been reported^{6,15} but tramadol is thought to have a lower abuse potential than other opioids.^{1,3,4,6} Opioid-dependent patients or those with a tendency for abuse should only be prescribed tramadol under careful supervision.^{1,3,15}

Gradual withdrawal is recommended after prolonged use as reactions have been reported following sudden cessation.^{3,16}

Summary

Tramadol appears to be comparable to, but not more effective than, other drugs in equipotent doses. Compared to other opioids, tramadol has a lower incidence of constipation and respiratory depression. It may have a lower abuse potential. Care should be taken when co-prescribing with CYP3A4 inducers, TCAs, SSRIs and other neuroleptics. In carefully selected patients (not the majority) tramadol may be an effective alternative to other analgesics.

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