



Te Kaporeihana Āwhina Hunga Whara

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 20 October 2005

Topic: The effectiveness of tramadol in acute pain management

Background and Purpose: Tramadol is commonly used in pain relief, usually as a second best line of treatment. Tramadol is a synthetic opioid-like drug so therefore has some properties of strong analgesic drugs like morphine and pethidine. Tramadol has been favoured over true opioids due to a belief that it is less addictive and is known to be associated with less adverse effects such as respiratory depression which is commonly caused by morphine. Currently, if tramadol is prescribed then ACC funds it. ACC would like to be able to develop purchasing criteria to guide the purchasing of tramadol by ACC. An evidence-based review of the effectiveness of tramadol in acute pain management has been prepared at the request of Sunita Goyal (Pharmaceutical advisor, Healthwise). Previously, an evidence-based review was prepared on the effectiveness of oral tramadol in chronic, non-malignant pain management. The PGAG were unable to make a purchasing recommendation from this review and recommended that the Evidence Based Healthcare (EBH) team prepare a review on the effectiveness of tramadol in the acute setting, in order to determine if funding should start in the acute setting.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Effectiveness

Sixty two studies looking at the effectiveness of tramadol (+/- paracetamol) in acute pain management that fit the criteria for inclusion in this study. Of these, there were six studies which were appraised as 1++, 28 as 1+, and 28 studies were assigned 1- using the SIGN appraisal system.

The shortest trial was one hour, whereas the longest study trial was seven days. Fifty four trials were carried out in a hospital, four were dental trials, one was set in a university (most likely a university hospital) and one was set in a "research institute." Two trials did not specify where they were set. Fifty nine trials did not mention follow up medication after the study, whereas, three trials did. In one trial [1] tramadol was not prescribed after the trial due to side effects being worse with tramadol compared with codeine. In the trial by Dejonckheere et al; [2] which compared tramadol and paracetamol, morphine was used to treat residual pain after the trial period and in the trial by Thienthong et al; [3] which compared tramadol to placebo, morphine was used if tramadol was not successful.

The main findings were

- 1) Tramadol appears to be more effective than placebo.
- 2) There appears to be no significant difference between the effectiveness of tramadol (+/-paracetamol) vs codeine (+/- Paracetamol).
- 3) Of the 16 trials comparing tramadol to morphine, at least five trials showed morphine to be superior to tramadol in some aspect of improvement in analgesia. In no trial presented in this review was tramadol superior to morphine, suggesting that morphine is superior in some respects, but it cannot be claimed that they are equal in effectiveness. More vomiting and nausea was presented with tramadol compared to morphine, however, morphine was shown to confer greater respiratory depression.
- 4) There is no evidence to suggest that tramadol is more or less effective than pethidine or oxycodone for relieving acute pain. The incidence of adverse reactions was higher for tramadol compared to oxycodone.
- 5) The NSAIDs, bromfenan and lornoxicam proved to be more effective than tramadol in two randomised controlled trials. However, more evidence is required to support these findings. There also, was not enough evidence to show that diclofenac, ketorolac, dipyron and other NSAIDs were more or less effective than tramadol. However, tramadol does not have the potentially hazardous risk of gastric bleeding that affects NSAIDs.
- 6) There was no significant difference in effectiveness and side effects between using bupivacaine and tramadol.
- 7) Meta analysis studies showed that pain relief provided by tramadol/paracetamol (APAP) was superior and more effective than the administration of tramadol or paracetamol alone.
- 8) Tramadol is not associated with clinically relevant respiratory depression or drowsiness and less risk of constipation- unlike morphine, pethidine, or oxycodone. There is also reduced risk of long term addiction with tramadol compared to the opiates.
- 9) Tramadol has serotonergic adverse effects such as diarrhoea, sweating, fever or confusion. You are at a greater risk of developing serotonin syndrome by using tramadol.
- 10) Post abdominal pain was mainly treated with tramadol intravenously, whereas pain relief for post dental pain was administered more via the oral route. Both modes of administration are equally effective.

2. Cost

There appears to be insufficient evidence in the literature to determine whether tramadol is cost-effective compared to other pain relief drugs. The single study found for review has very little relevance to the objectives of this review. The use of nursing time as a cost is not transferable to the likely clinical situation

considered by ACC which is likely to be in outpatients. Also, the legal status of the drugs used is not under consideration.

The current purchase price of 400mg of tramadol (the recommended maximum daily dose) is NZ\$3.19^a for either immediate or slow release (excluding GST). This is much more expensive than 240mg codeine (recommended maximum daily dose) which is NZ\$0.80c^a (excluding GST). The purchase price of 4g of paracetamol (the recommended daily dose for adults) is NZ\$0.15c^a (excluding GST).

At present ACC makes around 1000 payments for tramadol per month, at an average cost of \$96 per payment per month (including GST, mark ups and dispensing fees). This equates to an annual cost to ACC of around \$1million [4].

Note: In the post operative setting tramadol is funded by DHBs. ACC funds outside of this setting if tramadol is prescribed. The majority of cases in this review are post-operative.

3. Clinical impact

Tramadol is a safe and effective analgesic for the management of acute pain; however, it has not been shown to be more or less effective than codeine (prescribed with or without paracetamol) and has not been shown to be more effective than morphine. This suggests the analgesic properties of tramadol are similar to that of codeine but less than morphine.

Tramadol appears effective to use if the patient was opioid dependent or where there is a clinical rationale as to why tramadol maybe a more suitable agent compared with another analgesic, for example, the patient maybe more prone to constipation and constipation tends to feature more prominently with opioids other than tramadol. This current practice is already being practiced by three DHB's.

Tramadol has an adverse event profile which is similar to other analgesics and commonly includes nausea, vomiting, drowsiness, dizziness, headache and dry mouth. There was reasonable evidence to suggest that nausea and vomiting are greater with tramadol than morphine. Tramadol is not associated with clinically relevant respiratory depression or constipation unlike morphine, pethidine, or oxycodone.

4. Equity, Maori Health, Other Ethnic Group Health Issues, Acceptability

Pharmac does not currently fund Tramadol. Equivalent acting drugs Codeine and Oxycodone are currently funded.

The purchasing recommendation should be applied equally across Maori, Pacific and ethnic populations.

5. Possible Purchasing Options

Option 1: Don't purchase

Option 2: Purchase if other analgesics cannot be prescribed and tramadol is the second best line of treatment. Suggested prescribing criteria are set out below.

Option 3: Purchase if prescribed

6. Evidence Statement

The available studies show that tramadol appears to be as effective as codeine (prescribed with or without paracetamol). Tramadol is not associated with respiratory depression or constipation and the risk of long term addiction is reduced compared to opiates. Common side effects include nausea, vomiting, drowsiness, dizziness, headache and dry mouth.

There is good evidence that tramadol is no more effective than codeine, has a significantly higher rate of side effects than codeine and is significantly more costly.

^a New Ethicals Catalogue May 2005

Tramadol is less effective than morphine but has the advantage of not causing respiratory depression unlike morphine. Nausea and vomiting are commonly associated with both analgesics, and some of the evidence suggests that this is greater with Tramadol compared to morphine.

7. Purchasing Recommendations

Purchase as a second line treatment according to the following prescribing criteria:

Prescribing Criteria:

- An adequate trial to have sufficient analgesia of codeine & paracetamol (e.g at least 3 days) has been tried (at maximum daily adult dose 240mg/1g respectively).
- If sufficient analgesia is not obtained consideration should be given to patient compliance and the possibility of using an increased dose of codeine (to the recommended daily adult dose)
- Prescribing tramadol depends on the status of the individual; it should be prescribed if it is equally effective to an alternative medication, but safer for the patient. (Second best line of treatment). Tramadol should only be prescribed when there are specific reasons to do so:

Tramadol should be used as a second line agent when:

- An opioid dependent patient needs stronger pain relief than paracetamol
- NSAIDS are contraindicated
- Patient has respiratory depression
- An alternative adequate dose of paracetamol/codeine has been tried

Tramadol should not be used when:

- In conjunction with SSRIs or other serotonergic drugs
 - Any drug contraindicated with tramadol that may cause harmful drug interactions.
 - Paediatric use
 - If pulse and blood pressure are not in the normal range
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- Depending on the severity of pain and situation, tramadol is usually replaced with paracetamol or codeine once pain severity has decreased.
 - Caution should also be taken if the patient is over 65 years of age.

Acute injuries get better. Funding of tramadol prescriptions should be limited to 7 days supply (at maximum dosage where applicable) after which time the patient should be reviewed along with their analgesic requirements. A trial of codeine and paracetamol (e.g at least 3 days) (at maximum daily adult dose 240mg/1g respectively) should then occur before Tramadol is re-prescribed, unless it is contraindicated.

References

- [1] Jeffrey, H.M., et al., ***Analgesia after intracranial surgery: a double-blind, prospective comparison of codeine and tramadol.*** British Journal of Anaesthesia., 1999. **83**(2): p. 245-9
- [2] Dejonckheere, M., et al., ***Intravenous tramadol compared to propacetamol for postoperative analgesia following thyroidectomy.*** Acta Anaesthesiologica Belgica., 2001. **52**(1): p. 29-33
- [3] Thienthong, S., et al., ***Two doses of oral sustained-release tramadol do not reduce pain or morphine consumption after modified radical mastectomy: a randomized, double blind, placebo-controlled trial.*** Journal of the Medical Association of Thailand., 2004. **87**(1): p. 24-32

[4] ACC evidence based review. The effectiveness of oral tramadol in chronic non-malignant pain management. 2004. (www.acc.org.nz.)