

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: 14 October 2014

Topic: Ketamine infusion for persistent non-cancer pain

Background and Purpose:

Ketamine produces general anaesthesia in large doses and is a potent analgesic in small doses; low dose ketamine infusion is therefore sometimes used to treat persistent pain such as neuropathic pain. The drug is delivered, mixed in a volume of saline, via a drip or infusion pump through an intravenous cannula over variable time periods.

ACC has prepared two previous reports as part of the Interventional Pain Management (IPM) Guideline in 2005 and 2010, respectively. The 2010 IPM update suggested that:

- The general use of intravenous infusion of ketamine is not recommended in the treatment of adults with persistent non-cancer pain.
- Carefully titrated ketamine infusion delivered in a hospital setting with concomitant medication to control or moderate psychomimetic adverse effects may be appropriate for cases of persistent pain arising from complex regional pain syndrome (CRPS) in patients where other treatments have failed.

The current purchasing recommendation is that intravenous infusion of ketamine should not be purchased for the general treatment of adults with persistent pain of non-cancer origin. However, in rare circumstances where conventional treatment has failed, it may be considered on a case by case basis for the treatment of patients with CRPS.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency / Clinical impact	
<p><i>Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, <input type="checkbox"/> any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence. Comment on <input type="checkbox"/> the relative benefit over other management options, resource implications, balance of risk and benefit.</i></p>	Evidence level (SIGN)
<p>EFFECTIVENESS: Systematic reviews (SR)</p> <p>One low quality SR (Azari et al., 2012) evaluated the efficacy of ketamine in CRPS treatment by reviewing three randomized, placebo-controlled trials, seven observational studies, and nine case studies. This comprehensive SR covered the majority of the studies that were included in ACC's 2010 IPM review on ketamine infusion. The data reveal ketamine as a promising treatment for CRPS (low-moderate quality evidence) at short term. However, there was insufficient evidence to recommend routine use of ketamine in CRPS.</p>	1-

<p>EFFECTIVENESS: Randomised controlled trials (RCTs)</p> <p>One randomised, placebo-controlled trial (Schilder et al., 2013) reported the results of ketamine infusion on pain relief in 29 patients with CRPS. This is a follow-up secondary analysis of time-dependent data on pain and motor function originally reported by Sigtermans et al. (2009) (included in ACC's 2010 IPM review). Consistent with the original study, this report found that pain scores were lower in the ketamine group over a 12-week period with the lowest pain scores seen 1 week after ketamine treatment completion. Although the original study did not initially find functional improvement in the ketamine group, this secondary analysis reported that pain intensity was significantly inversely related to motor function, irrespective of whether patients had received ketamine or placebo.</p> <p>SAFETY</p> <p>The side effects of ketamine were well reported in the 2005 and 2011 IPM evidence reviews. Additionally, one case study (Noppers et al., 2011), one small retrospective study (Patil & Anitescu, 2012) and one case control study (Olofsen et al., 2012) reporting adverse events associated with ketamine infusion were identified in this update. Reported side effects included:</p> <ul style="list-style-type: none"> • hypertension • sedation • vomiting • agitation • confused state • hallucination • restlessness • tachycardia <p>A case study (Noppers et al., 2011) observed that repeated administrations of S(+)-ketamine just 3 weeks following a 100- hour treatment in patients with CRPS caused elevated liver enzymes, resulting in the study being terminated early. The authors suggested that there is an increased risk for development of ketamine-induced liver injury when the infusion is prolonged and repeated within a short time period.</p> <p>Overall, the side effects were minimal in all cases.</p>	1+
<p>2. Cost</p> <p><i>Comment on any economic costs associated with this service, product or procedure</i></p>	
<p>The unit cost of this procedure is around \$500.</p> <p>Anticipated volume for the year 2013-2014 is 6 procedures with a total cost of \$3,148.</p>	
<p>3. Equity, Maori Health, Pacific Health, Acceptability</p> <p><i>Comment on the extent to which the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome), is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and is consistent with values and expectations of New Zealanders.</i></p>	
<p>No equity issues were identified.</p>	
<p>4. Consistency with the intent of the IPRC Act</p> <p><i>Purchasing decisions made by ACC must be consistent with and reflect consideration of factors described in the IPRC Act, Schedule 1, clause 2(1 and 2) and these decisions must be defensible against this statutory requirement in respect of individual claimants.</i></p>	

5. Possible Purchasing Options

List the possible purchasing options.

The options are:

1. Purchase,
2. Don't purchase, or
3. Purchase on a case by case basis on the decision of the Corporate Medical Advisor (or equivalent).

6. Evidence Statements

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

The 2005 the IPM evidence based guidance (a) highlighted a lack of evidence of "long term" effectiveness for ketamine in the treatment of persistent pain of non-malignant origin, (b) questioned the clinical relevance of the very short term relief reported in the studies reviewed, and (c) identified a high incidence of psychomimetic adverse effects in the studies reported. The guidance also noted that use of S+ isomer ketamine may provide additional clinical benefits with fewer side effects.

The 2010 evidence update reported two RCTs of good quality (NHMRC¹ evidence level II) and suggested that ketamine in sub-anaesthetic doses can provide relief for up to 3 months in some patients with CRPS.

The current (2014) evidence update also focuses on studies that report the use of ketamine in patients with CRPS published between 2010 and 2014. Evidence from one poor quality SR and one good quality RCT is consistent with ACC's 2010 evidence update and reveals ketamine as a promising treatment for CRPS in the short term.

7. Purchasing Recommendations

What recommendation(s) does the advisory group draw from this evidence?

'Strong' recommendations should be made where there is confidence that, for the vast majority of people, the intervention/action will do more good than harm (or more harm than good). The recommendation should be clearly directive and include 'should/should not' in the wording.

'Conditional' recommendations, should be made where the intervention/action will do more good than harm, for most patients, but may include caveats e.g. on the quality or size of the evidence base, or patient preferences. Conditional recommendations should include 'should be considered' in the wording.

Suggested purchasing recommendation:

Do not purchase intravenous infusion of ketamine for the general treatment of adults with persistent pain of non-cancer origin.

Strong

ACC should continue to purchase ketamine infusion on a case by case basis for treating neuropathic pain related to CRPS based on the attached funding algorithm.

Conditional

Briefly justify the strength of the recommendation

There is no evidence that challenges ACC's 2005 and 2010 IPM evidence based guidance on ketamine infusion.

¹ National Health and Medical Research Council

PGAG discussions:

SIGN Levels of evidence:

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

References

- Azari, P., Lindsay, D. R., Briones, D., Clarke, C., Buchheit, T., & Pyati, S. (2012). Efficacy and safety of ketamine in patients with complex regional pain syndrome: A systematic review. [Review]. *CNS Drugs*, 26 (3), 215-228.
- Noppers, I. M., Niesters, M., Aarts, L. P. H. J., Bauer, M. C. R., Drewes, A. M., Dahan, A., & Sarton, E. Y. (2011). Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: A report of 3 cases. *Pain*, 152(9), 2173-2178.
- Olofsen, E., Sigtermans, M., Noppers, I., Niesters, M., Mooren, R., Bauer, M., . . . Dahan, A. (2012). The dose-dependent effect of S(+)-ketamine on cardiac output in healthy volunteers and complex regional pain syndrome type 1 chronic pain patients. *Anesthesia and Analgesia*, 115(3), 536-546.
- Patil, S., & Anitescu, M. (2012). Efficacy of Outpatient Ketamine Infusions in Refractory Chronic Pain Syndromes: A 5-Year Retrospective Analysis. *Pain Medicine*, 13(2), 263-269.
- Schilder, J., Sigtermans, M. J., Schouten, A. C., Putter, H., Dahan, A., Noldus, L. P., . . . van Hilten, J. J. (2013). Pain relief is associated with improvement in motor function in complex regional pain syndrome type 1: secondary analysis of a placebo-controlled study on the effects of ketamine. *The Journal of Pain*, 14(11), 1514-1521.
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