GUIDELINES FOR THE USE OF KETAMINE AS AN ANALGESIC IN PALLIATIVE CARE

1. GENERAL PRINCIPLES

- Ketamine is an anaesthetic agent used for the induction and maintenance of general anaesthesia. Ketamine also has a role in the treatment of pain unresponsive to standard treatments.\(^1,2,3\)

- The NMDA receptor channel is involved with sensitisation of the dorsal horn neurones which transmit pain signals. Prolonged stimulation by pain causes hyper excitability and reduced opioid responsiveness, hyperalgesia and allodynia.\(^4\)

- Ketamine is a potent NMDA receptor channel blocker as well as acting on other channels including calcium, sodium, dopamine, cholinergic, noradrenergic and serotonergic reuptake channels. It also has some opioid like and anti-inflammatory effects.\(^5,6\)

- Ketamine has been used as an analgesic in many clinical settings including post-surgery, chronic non-cancer pain, cancer pain, procedural pain and painful mucositis. In the management of cancer pain ketamine is mainly used via the oral or subcutaneous route.\(^7,8\)

- Side effects of ketamine include urinary tract problems, tachycardia, hypertension, intracranial hypertension and psychomimetic effects including vivid dreams, hallucinations, disturbed body image and altered mood. These psychomimetic side effects can be managed by the co-administration of midazolam or haloperidol.\(^9,10\)

- Ketamine undergoes extensive first pass metabolism, mainly to norketamine which is renally excreted. Long term ketamine use leads to hepatic enzyme induction and enhanced ketamine metabolism.\(^10\)

- Ketamine is contraindicated in acute intermittent porphyria or any situation where a rise in blood pressure or intracranial pressure would be hazardous. It is contraindicated in epilepsy and should be used with caution in those patients with cerebral metastasis.\(^10\)

- Ketamine is a schedule 2 controlled drug and all prescriptions must satisfy Controlled Drug prescription requirements. Table 1 details available formulations of ketamine.

<table>
<thead>
<tr>
<th>Table 1 Formulations of Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
</tr>
<tr>
<td>Made to order</td>
</tr>
<tr>
<td>Sugar free solution</td>
</tr>
<tr>
<td>Various strengths available</td>
</tr>
<tr>
<td>Unlicensed</td>
</tr>
</tbody>
</table>
2. GUIDELINES

2.1 Administration and Doses

- Ketamine for pain control should be initiated by a Palliative Medicine physician experienced in the use of ketamine.\textsuperscript{13} [Level 4]

- Specialist Palliative Care Units should have a policy for the use of ketamine as an analgesic.\textsuperscript{13} [Level 4]

- The majority of the evidence for ketamine as an analgesic supports the use of ‘burst’ ketamine. This is therefore suggested as first line treatment. Concerns about the association between long term ketamine use and urinary toxicity mean that long term use is only recommended if burst ketamine has been ineffective.\textsuperscript{11} [Level 4]

- Suggested doses and regimens for ketamine use are described in Table 2.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Starting dose</th>
<th>Titration</th>
<th>Duration/ withdrawal recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst Ketamine</td>
<td>100mg over 24 hrs. subcutaneously via a syringe pump</td>
<td>If effective continue for 3 days then stop. If not effective after 24hrs increase to 300mg over 24hrs via syringe pump. If effective continue for 3 days then stop. If not effective after 24hrs increase to 500mg over 24hrs via syringe pump. Continue for 3 days and then stop.</td>
<td>5 days total duration then stop. No need to reduce slowly. Can be repeated as needed although it is recommended to have a break between treatments. Slower titration regimens may be required in some patients. Consider co prescription of haloperidol.</td>
</tr>
<tr>
<td>Via Continuous Subcutaneous Infusion (CSCI)</td>
<td>1mg-2.5mg/kg over 24hrs (in practice 100mg-200mg over 24hrs)</td>
<td>Increase by 50mg-100mg every 24hrs. Usual dose range 100mg-400mg over 24hrs. Maximum reported dose 3.6g/24hrs.</td>
<td>Consider gradual dose reduction or conversion to oral ketamine once pain control stable. Consider co prescription of haloperidol</td>
</tr>
<tr>
<td>Oral</td>
<td>10mg-25mg tds- qds and as required</td>
<td>Increase by 10mg-25mg qds daily Maximum recommended dose 100mg qds</td>
<td>After pain relief is achieved ketamine can be reduced slowly over several weeks. Consider co prescription of haloperidol.</td>
</tr>
<tr>
<td>Mouthwash</td>
<td>20mg in 10ml of artificial saliva gel</td>
<td>Use qds</td>
<td>Evidence for efficacy is limited</td>
</tr>
<tr>
<td>Sublingual</td>
<td>10-25mg sublingually as required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>2.5mg-5mg for cancer pain 0.5mg-1mg/kg for procedural related pain</td>
<td></td>
<td>NOT RECOMMENDED UNLESS UNDER SPECIALIST SUPERVISION</td>
</tr>
</tbody>
</table>
2.2 Compatibility of Ketamine [Level 2]

- For subcutaneous regimens ketamine should be diluted with sodium chloride 0.9%.\(^{11}\)

- When administering subcutaneous ketamine via a syringe pump, it is compatible with morphine plus additional drugs when mixed with sodium chloride 0.9%. See Table 3 for compatibility data.\(^{11,12}\)

<table>
<thead>
<tr>
<th>Two Drug compatibility</th>
<th>Three Drug compatibility</th>
<th>Incompatible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Haloperidol or Midazolam</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Clonazepam,</td>
<td>with either</td>
<td>Cyclizine</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Diamorphine or</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>Morphine sulphate</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3 Monitoring

- Ketamine can cause tachycardia and intracranial hypertension. Blood pressure and pulse rate should be checked prior to the commencement of ketamine and twice daily during the dose titration phase or throughout the duration of burst ketamine.\(^{13}\) [Level 4]

- If the pulse rate rises above 20% from baseline or the blood pressure rises by 20% on consecutive readings, a dose reduction should be considered. If the pulse rate or blood pressure does not return to the baseline reading with a dose reduction, then ketamine should be discontinued.\(^{13}\) [Level 4]

- As ketamine has an ‘opioid sparing’ effect, patients should be monitored for signs of opioid toxicity. During the dose titration phase this should include twice daily monitoring of respiratory rate in addition to with measurement of the blood pressure and pulse rate as described above. Conscious level should also be monitored and if there is any concern regarding opioid toxicity the patient should be reviewed by a clinician and a dose reduction of the regular opioid should be considered.\(^{13}\) [Level 4] (see opioid reduction below)

- Liver Function Tests (LFTs) should be checked prior to starting ketamine and further monitoring of LFTs should be considered at regular intervals or at follow up appointments.\(^{13}\) [Level 4]
To assess the effectiveness of ketamine, patients should have pain scores recorded prior to the commencement of ketamine and twice daily during the dose titration phase. This will help to establish whether further incremental increases in the dose of ketamine are required. Pain scores should also be recorded at follow up reviews for patients on long term ketamine or those that have received burst ketamine to establish the on-going effectiveness of pain control.\textsuperscript{13} [Level 4]

For those patients maintained on long term ketamine, reassessment should be carried out by a palliative care specialist at monthly intervals or sooner depending on symptoms or clinical need.\textsuperscript{13} [Level 4]

2.4 Opioid reduction

As ketamine has an opioid sparing effect, a dose reduction of 25% should be considered in those patients commencing parenteral or oral ketamine, or if the patient develops signs of opioid toxicity.\textsuperscript{11} [Level 4]

All units commencing ketamine should ensure that naloxone is available for use in the event of respiratory depression associated with opioid overdose / toxicity.\textsuperscript{13} [Level 4]

The use of ketamine is not generally recommended for patients on transdermal opioids due to the risk of opioid toxicity. An opioid conversion should be considered prior to starting ketamine.\textsuperscript{13} [Level 4]

2.5 Dose conversion

Evidence regarding dose conversion is limited. However, when converting from oral ketamine to subcutaneous ketamine, a conversion of 1:1 is suggested.\textsuperscript{12} [Level 4]

Oral ketamine undergoes extensive first pass hepatic metabolism to norketamine which provides the main analgesic effect. The maximum blood concentration of norketamine is greater after oral administration compared to parenteral administration. When converting from the subcutaneous route to the oral route (SC:PO), a conversion of 3:1 or 2:1 has been suggested.\textsuperscript{12} [Level 4]

When converting between administration routes, there should be the provision for close monitoring and ability to alter the dose of ketamine as necessary.\textsuperscript{12} [Level 4]

2.6 Adjuvant medications

Ketamine can cause undesirable psychomimetic effects such as hallucinations, euphoria and vivid dreams which can be distressing to patients. It is therefore suggested that ketamine is given concurrently with midazolam or haloperidol to control any undesirable effects.\textsuperscript{13} [Level 4]

Suggested doses are as follows: \textsuperscript{13} [Level 4]
- Haloperidol 2mg-5mg orally at night
- Haloperidol 2mg-5mg via CSCI over 24 hours
- Midazolam 5mg-10mg via CSCI/24 hours

2.7 Urinary tract toxicity

Ketamine has been linked to urinary tract toxicity including interstitial cystitis, papillary necrosis and renal impairment.\textsuperscript{9} [Level 3]
If a patient develops symptoms of a urinary tract infection and there is NO evidence of bacterial infection, consider discontinuing the ketamine. The patient may require a urology review.11 [Level 4]

Screening for urinary tract symptoms should be considered at each follow up appointment for all patients on long term ketamine. This may include urinalysis.13 [Level 4]

2.8 Discharge

Patients discharged on ketamine should be followed up by a specialist palliative care clinician within 4 weeks to review their pain control.13 [Level 4]

Dose alterations of ketamine should be undertaken in a specialist inpatient unit or after specialist palliative care outpatient review.13 [Level 4]

When a patient is discharged on ketamine, standardised information should be given to the patients, GP and community pharmacist.13 This may include a patient information leaflet. [Level 4]

The discharge letter should include a named contact and telephone number for further advice.13 [Level 4]

Units should liaise with the GP and community pharmacist prior to discharge to confirm future supplies of ketamine.13 [Level 4]

Patients on oral ketamine should be aware that they need to request a repeat prescription at least 7 days in advance of their own supply running out.13 [Level 4]

Units should consider the use of a ketamine card to be given to patients on discharge to inform other health professionals that they are on ketamine.13 [Level 4]

3. STANDARDS

1. The decision to commence ketamine, indication and regimen to be used should all be clearly documented in the case notes.13 [Grade D]

2. Prior to commencing ketamine, heart rate, blood pressure, respiratory rate and pain score should be recorded. These should be rechecked twice daily until ketamine is discontinued or the titration is complete.13 [Grade D]

3. If administering ketamine via a subcutaneous infusion, then sodium chloride 0.9% should be used for dilution.11 [Grade D]

4. Ketamine should always be prescribed in milligrams(mg).12 [Grade D]

5. If a patient is discharged on ketamine, the discharge letter should include a named contact and telephone number for further advice.13 [Grade D]

6. For patients who are discharged on ketamine, units should have standardised information to give to the patient, the GP and community pharmacist.13 [Grade D]

7. Patients discharged on ketamine (oral or subcutaneous) should have at least monthly follow-up with a specialist palliative care clinician experienced in the use of ketamine.13 [Grade D]

8. Specialist Palliative Care units should have a policy for the use of ketamine as an analgesic.13 [Grade D]

4. REFERENCES

Cheshire and Merseyside Palliative and End of Life Care Network Audit Group
Standards and Guidelines for the Use of Ketamine as an Analgesic in Palliative Care
September 2012


5. Meller ST. Ketamine: relief from chronic pain through actions at the NMDA receptor? *Pain*, 1996; **68:**435-436.


**GUIDELINE DEVELOPMENT GROUP**

**Lead Contributor**

**Dr Anthony Thompson**, Assistant Medical Director, Willowbrook Hospice, St Helens, Merseyside.

**Contributors**

**Dr Sarah Fradsham**, Specialty Registrar in Palliative Medicine, Marie Curie Hospice Liverpool.

**Dr A Coackley**, Consultant in Palliative Medicine, The Clatterbridge Cancer Centre and Willowbrook Hospice, St Helens, Merseyside.

**Dr A Scott**, Specialty Registrar in Palliative Medicine, Willowbrook Hospice, Merseyside.

**Dr H Bonwick**, Associate Specialist in Palliative Medicine, Marie Curie Hospice, Liverpool and Liverpool Heart and Chest Hospital NHS Trust, Liverpool.

*Cheshire and Merseyside Palliative and End of Life Care Network Audit Group*

*Standards and Guidelines for the Use of Ketamine as an Analgesic in Palliative Care*

*September 2012*
Ms R Clark, Palliative Care and Clinical Trials Pharmacist, Marie Curie Hospice Liverpool. Dr G Whyte, Macmillan Consultant in Palliative Medicine, Aintree University Hospitals NHS Foundation Trust, Liverpool. Mr A Dickman, Consultant Pharmacist in Palliative Care, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool.

Invited Expert
Dr K Levshankov, Consultant Anaesthetist, St Helens and Knowsley Teaching Hospitals NHS Trust, Merseyside.

| Date of Guideline Production | September 2012-September 2013 |
| Date of Guideline Review     | 2018                          |
| Date Posted on Network Website | June 2017                    |