Ketamine has been designated a ‘red’ drug in Gwent and is not recommended to be prescribed by non-specialists

All Gwent Palliative Medicine Consultants Group

SPECIALIST GUIDELINES FOR USING KETAMINE

When used to help provide pain relief in palliative care, ketamine can be administered orally, buccally and subcutaneously. Such use of ketamine is not covered by the product licence and should only be initiated by a specialist in palliative medicine. Ketamine is a controlled drug (schedule 4, part 1).

Clinical Use

Ketamine is a short acting anaesthetic that has analgesic properties at subanaesthetic doses. A synergistic effect between ketamine and opioids has been observed in patients who have lost an analgesic response to high doses of morphine.

Ketamine is used in palliative care settings primarily for neuropathic pain which is unresponsive or poorly responsive to first-line analgesics (which may include one or more of opioid drug, NSAID, tricyclic antidepressant, or anticonvulsant). It has also been used for phantom limb and ischaemic pain and for intractable incident pain or prior to procedures such as dressing changes.

Mode of Action

Various mechanisms have been proposed to explain the analgesic effect of ketamine. The effect seems to be mediated in part through inhibition of N-methyl-D-aspartate receptors. Ketamine also interacts with cholinergic and opiate receptors and possibly inhibits the synaptic re-uptake of monoamines. Powerful synergism arises from the combination of morphine with low doses of ketamine.

Supply

Ketamine (Ketalar injection) is available in single use vials – 10mg/mL (20ml vial), 50mg/mL (10ml vial) and 100mg/mL (10mg vial). 50mg/mL vials are normally used.

Ketamine oral solution (usually 50mg/5mls) is available as a ‘special’ and can be used for both oral and buccal administration.

Formulation

Ketamine is administered orally or by subcutaneous infusion in a syringe driver.
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### Indications

Neuropathic pain: Following a trial of strong opioids, anti-convulsants and tricyclic antidepressants +/- trial of high dose dexamethasone.

Other pains: Which may respond to Ketamine:
- Movement related pain.
- Skin pain.
- Mucosal pain.

Patients should be given the appropriate conventional analgesics before Ketamine.

### Preparation for Starting Ketamine

1. Ketamine should only be prescribed by or in conjunction with a doctor experienced in Pain Management or Palliative Care.

2. Adjustment of opioid regime:
   - Consider a switch from long to short acting opioids.
   - Reduce total daily opioid dose by 30%. This may not always be necessary, for example patients on low doses of morphine or patients with incident pain.
   - Prescribe usual opioid rescue medication (ie 1/6th of total daily dose).
   - As a guide the lag time for:
     - MST = 12 hours
     - Oxycodone m/r (Oxycontin) = 12 hours
     - MXL/Morcap = 24 hours
     - Transdermal Fentanyl = 48 hours
     - SR Hydromorphone = 12 hours
   - Note: if ketamine is used with methadone, be alert to the possibility of opioid toxicity developing over several days as a consequence of the long and variable half-life of methadone.
   - Patients should always be observed for opioid toxicity.

3. Relative contraindications (Please document in notes if no contra-indication)

   Ketamine has the potential to increase intra-cranial and intra-ocular pressures.

   Ketamine should be avoided in patients with:
   - Raised intracranial pressure.
   - Severe systemic hypertension.
   - Raised intra-ocular pressure.
   - Recent history of epilepsy.
   - Recent history of psychosis.

4. Ketamine should be used with caution in patients with:
   - Intracranial space occupying lesion.
   - Cardiac arrhythmia.
   - On long-acting opioid.
   - Cardiac failure.
   - Ischaemic heart disease.
   - Previous CVA.
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### Side Effects

Ketamine can cause hallucinations, nightmares and other transient psychotic effects. This is more commonly seen at the higher doses used in anaesthesia. The side effects can be reduced by specialist use of diazepam, midazolam or haloperidol.

Other side effects include tachycardia, hypertension, arrhythmias, hypotension, bradycardia, increased salivation, laryngospasm, anxiety, insomnia, diplopia, nystagmus, raised ICP, rashes and injection site redness.

Urinary toxicity can occur. The causal agent has not been determined, but direct irritation is a possibility. Symptoms (especially in doses over 400mg/24 hours) can include frequency, urgency, urge incontinence, dysuria and haematuria, as well as supra-pubic pain, requeal interstitial cystitis, detrusor overactivity, reduced bladder capacity, vesico-ureteric reflux, hydro-nephrosis, papillary necrosis and renal impairment. Irreversible damage has occurred leading to long term catheterisation and even cystectomy in some patients. The Palliative Care Formulary 4 recommends that if patients on ketamine experience urinary symptoms with no evidence of bacterial infection consider discontinuing and seeking the advice of an urologist. Symptoms usually settle several weeks after stopping ketamine (Ideally wean the patient off gradually) Unfortunately some symptoms may persist despite stopping the drug.

Hepatotoxicity is also described in the pain literature. Rash, fever ALT> ALK PHOS suggests allergic hepatitis. Latency can be 1-6 weeks. Acute liver failure can occur. Other features to be aware of are jaundice, abdominal pain, nausea and vomiting. The management of drug induced liver injury is to discontinue the drug and provide supportive/symptomatic treatment, including possibly corticosteroids when there is failure to improve. With long term use abdominal pain may be reported and in some dilatation or strictures of the common bile duct may occur. The cause is unknown and with discontinuation of ketamine, LFTs, abdominal pain and biliary duct dilatation generally improve.

Any suspected side effects to ketamine should be reported urgently to the specialist palliative care team.

For a full list of side effects, see the BNF or manufacturers SPC

### Drug Interactions

- Ketamine interacts with theophylline (tachycardia and seizures) and levothyroxine (monitor for hypertension and tachycardia).
- Diazepam increases the plasma concentration of ketamine.

### Prescribing Ketamine

- Ketamine may ordinarily be given by the oral or subcutaneous route.
- Ideally treatment with Ketamine should be commenced before 2:00 pm so that patients can be monitored for side effects particularly opioid toxicity before bedtime.
- Do baseline bloods, particularly to assess renal + hepatic function.
- Dose titration and alteration of doses is complex and should only be undertaken by specialists in palliative care.
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<table>
<thead>
<tr>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score, pulse and BP should be recorded at 0 mins, 30 min, 1 hour and 4 hours on day 1 for all patients.</td>
</tr>
<tr>
<td>Thereafter patients with the following should have 4 hourly observations until dose titration is complete.</td>
</tr>
<tr>
<td>a) patients with a relative contra-indication to ketamine</td>
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<tr>
<td>b) where ketamine is started while patient is on long acting opioid</td>
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<tr>
<td>c) patients where rapid dose titration of ketamine is needed</td>
</tr>
<tr>
<td>For all other patients daily Pain Score, pulse and BP is recommended during titration and monthly thereafter.</td>
</tr>
</tbody>
</table>

See Ketamine monitoring chart
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## Oral Route

### Starting Dose – Oral route:

10- 25 mg every 6-8 hrs and prn

- If the patient is already taking an opioid a dose reduction should be considered e.g. up to 30-50% dose reduction. Occasionally it may be necessary to change patients from controlled release morphine to an immediate release formulation. Reduce the opioid dose if excessive drowsiness or psychotomimetic side-effects occur.
- Consider the use of oral haloperidol 1.5mg – 3mg nocte or oral diazepam 5mg for neuropsychiatric side effects.

### Rate of Increase – Oral route:

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>Daily Percentage Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-45 mg QDS</td>
<td>50-100% daily</td>
</tr>
<tr>
<td>45-100 mg QDS</td>
<td>25-33% daily</td>
</tr>
<tr>
<td>&gt; 100 mg QDS</td>
<td>20-25% daily</td>
</tr>
</tbody>
</table>

**Example.**

- Day 1. 10mg qds
- Day 2. 20mg qds
- Day 3. 40mg qds
- Day 4. 60mg qds
- Day 5. 80mg qds
- Day 6. 100mg qds

- Analgesia may be achieved at low doses and higher doses may not be needed.
- Delay dose increases if side effects are a problem
  - Titrate the opioid dose down further if possible
  - If pain is returning before the next dose is due the dosing interval can be shortened to every 4-6 hours
  - Use a smaller dose more frequently if psychotomimetic phenomena or drowsiness occurs which does not respond to a reduction in opioid dose.
- Dose increases should be stopped at 100mg qds and response assessed over the next few days as the active metabolite norketamine will start to contribute to analgesia.
- Doses above 100mg qds are only occasionally required.

### Sublingual or buccal ketamine.

**Indication.** Movement or procedure related pain. e.g. painful dressing changes or pathological fractures.

**Dose:** 2.5mg- 5mg of ketamine oral solution 50mg/5ml

Sublingual ketamine has a rapid onset peak blood level (similar to parenteral ketamine), therefore it may be useful for rapid analgesic effect. However there is also the potential for dysphoric type side effects.

For buccal administration deliver the solution in a syringe to the space between the teeth and cheek.

Ketamine injection is occasionally used orally in patients who cannot tolerate large volumes of the suspension. However the injection is extremely bitter to taste.
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- As Required Ketamine

  The duration of action of oral ketamine is 4-6 hours. Therefore it would be appropriate to prescribe a PRN dose of oral ketamine equivalent to the current regular dose, especially at night.

  However repeated extra doses will result in a rapid increase in the total daily dose of ketamine and will increase the chances of dysphoric symptoms. Therefore there should be clear instructions regarding PRN ketamine.

### Subcutaneous Route

**Starting Dose – Subcutaneous route:**

- Frail patient: 25-30 mg subcutaneous infusion / 24 hours.
- Fit patient: 50-100 mg subcutaneous infusion / 24 hours.

  Maximum dose in the region of 500 mg/24 hours depending on patient, side effects and response.

  - If the patient is taking an opioid a dose reduction should be considered e.g. up to 30-50% dose reduction. Occasionally it may be necessary to change patients from a controlled release morphine to an immediate release formulation

  - Give a loading dose of 10mg ketamine subcutaneously (diluted in 1ml of sodium chloride)

  - Consider the use of haloperidol 1.5mg – 3mg (s/c in syringe driver over 24hrs) or orally or diazepam 2mg nocte orally or midazolam 5-10mg (s/c in syringe driver over 24 hrs) for neuropsychiatric side effects

**Rate of Increase – Subcutaneous route:**

- Severe uncontrolled pain – 50-100% 8 hourly.
- Other patients – 50-100% daily.

  Titrate opioid dose down further if possible

### Burst Ketamine

Ketamine is prescribed as a burst or pulse course for a maximum of 5 days. The dose is titrated up, in a stepwise fashion and once the lowest effective dose is achieved it is continued for 3 days and then stopped. This method has the advantages of an adequate trial of treatment (with discontinuation if analgesia is ineffective or significant side effects occur) and minimisation of the logistics of longer term ketamine use.
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Burst Ketamine Protocol

- Starting dose 100mg per 24 hours via syringe driver
- If effective continue for 3 days then cease
- If 100mg is ineffective after 24 hours, increase to 300mg
- If 300mg is effective, continue for 3 days then cease
- If 300mg ineffective after a further 24 hours increase to 500mg
- Cease ketamine at day 5 whether effective or not, or earlier if significant side effects occur

‘Burst’ Ketamine Dose Escalation Protocol

Starting dose 100mg per 24 hours via syringe driver
If effective continue 3 days then cease

```
Day  0  1  2  3
100mg 100mg 100mg  Stop
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If 100mg ineffective after 24 hours, increase to 300mg
If 300mg effective, continue three days then cease

```
Day  0  1  2  3  4
100mg 300mg 300mg 300mg  Stop
```

If 300mg ineffective after 24 hours increase to 500mg

```
Day  0  1  2  3  4  5
100mg 300mg 500mg 500mg 500mg  Stop
```

Cease ketamine at day 5 whether effective or not, earlier if ineffective and/or significant side effects.

Note
- Subcutaneous ketamine can be irritant and if used alone is probably best diluted with sodium chloride.
- It is best used alone in the initial phase, but can be combined with diamorphine, metoclopramide, haloperidol, midazolam, levomepromazine
- Ketamine may be incompatible with cyclizine and some doses of dexamethasone

Rescue Medication: The usual 4 hourly opioid dose.
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Preparation of subcutaneous infusion

- Dilute with sodium chloride 0.9%
- The McKinley T34 syringe pump is calibrated in ml per hour. It is recommended that only 20ml or 30ml luer-lock syringes are used. The maximum volumes, which will fit in the pumps, are about 17mL in a 20mL syringe and 22mL in a 30mL syringe.
- Check syringe driver daily for turbidity. Protect it from light.
- Change the infusion site daily to prevent skin necrosis. Dexamethasone 0.5mg -1mg may be added to the infusion if irritation is a problem.
- It is best used alone in the initial phase.
- Do not mix with other medication except the following:
  - dexamethasone (low dose),
  - diamorphine,
  - haloperidol,
  - metoclopramide,
  - midazolam and
  - levomepromazine (methotrimeprazine),
  - oxycodone
- Ketamine may be incompatible with cyclizine and some doses of dexamethasone.

Once the vials have been opened they must be discarded (single use only).

Clinical review of patient: Should be carried out within 24 hours of starting Ketamine and documented in case notes.
Ketamine has pharmacokinetic and pharmacodynamic peculiarities. The bioavailability of oral ketamine has been reported to be 15%. PO ketamine undergoes extensive first-pass metabolism to norketamine (via CYP3A4). As an anaesthetic, norketamine is about 1/3 as potent as parenteral ketamine. However, as an analgesic, it is equipotent. The maximum blood concentration of norketamine is greater after PO administration than after injection, and in chronic use norketamine may be the main analgesic agent. This explains why, when switching from CSCI to PO after several weeks-months, an equianalgesic PO dose is smaller than the parenteral dose. It can be as little as 25-50% of the previous parenteral dose.1

Ketamine can be started by the subcutaneous route in order to assess response. If there is a good response, conversion to the oral route may be attempted. Some clinicians now start treatment with oral ketamine and avoid the initial subcutaneous titration for those patients able to use the oral route. There are case reports of conversion from subcutaneous to oral ketamine, where good analgesia was achieved at doses of 30-40% of the previous parenteral dose.2 However, other clinicians have used an oral: subcutaneous dose ratio of between 2:1 and 4:1.3 In other practice, a conversion ratio of subcutaneous to oral ketamine can be anything from 1:1 to 1:34.

After weeks-months of use, when switching from CSCI to oral, a smaller total daily dose (25-50% of the parenteral dose) maintains a similar level of analgesia. e.g. CSCI 400mg/day → PO 150mg/day.5

It is difficult to assess the potency ratio in view of the wide dose ranges used and the pharmacokinetic and pharmacodynamic peculiarities of ketamine.

The consensus of this group is to prescribe the oral ketamine in four divided doses, generally at a conversion 1:1 ratio.6 7 8

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3 North Yorkshire and York NHS prescribing Information. Ketamine use in Chronic pain
4 Northern Region Palliative Care Physicians March 1999. Guidelines for using ketamine.
5 Twycross R, Wilcock A (eds) Palliative Care Formulary 3rd edition
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Once Analgesia is achieved

a) The subcutaneous infusion may be stopped abruptly, or tailed off as the PO dose is titrated. Consider reducing regular opioid daily dose by 33% and gradually reduce further if possible.

b) Review need for concurrent analgesics (eg NSAIDS, Paracetamol, anti-convulsants and Tricyclic antidepressants) one week after achieving stable pain control with Ketamine and gradually optimise medications as deemed appropriate. If analgesia is not achieved consider stopping Ketamine.

Review the need for ongoing Ketamine treatment at one month.

Pharmacokinetics

The onset of action of ketamine is 15-30 mins after subcutaneous administration and 30 mins after oral administration.

Ketamine is poorly absorbed after oral administration and is also subject to first pass metabolism. Oral bioavailability is therefore only 20%. Ketamine is metabolised in the liver by the cytochrome P45 enzyme system. CYP3A4 has been shown to be the major enzyme responsible and CYP2B6 and CYP2C9 play a minor role. Chronic ketamine administration increases the activity of the enzymes involved in its own metabolism, and this may modify the response with repeated administration and may be responsible for drug interaction with concurrently administered drugs that are metabolised by the same enzymes. The main metabolite norketamine does however also have analgesic properties (one third as potent as ketamine) and is produced in greater quantities than ketamine which may result in an oral:subcutaneous dosing ratio of between 2:1 and 4:1. Tolerance has been reported following chronic administration.

Common Drug Interactions

Plasma concentrations of ketamine may be increased by diazepam. Ketamine may affect metabolism of warfarin, carbazepine, phenytoin and theophylline (tachycardia and seizures) levothyroxine (monitor for hypertension, tachycardia)

Side Effects

Neuropsychiatric side effects such as dysphoria, hallucinations and nightmares may occur early in therapy, but tolerance usually appears rapidly. Their occurrence can be minimised by concurrent treatment with haloperidol or a benzodiazepine. Care must be taken, as benzodiazepines can increase the amount of available ketamine and may also enhance the respiratory depressant effects. Central side effects are less common with oral Ketamine usage and slow upward dosage titration.

Other side effects include sedation, confusion, increased muscle tone, delirium, dizziness, excessive salivation and secretions and if encountered require reassurance.

Side effects associated with higher doses and may warrant a dose reduction include tachycardia, hypertension, diplopia and nystagmus.

Erythema and pain at injection site may occur. Dilute with normal saline in 20-30ml syringe. Addition of 0.5-1mg of dexamethasone may reduce site inflammation.
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The undesirable effect of ketamine when added to high doses of morphine can be explained by blocking the ‘wind up’ in the dorsal horn neurones, which dramatically reduces the tolerance to the analgesic and respiratory effects of morphine.

If the patient experiences dysphoria or hallucinations, the dose of ketamine or opioid should be reduced. If patient is not drowsy, it is more likely to be ketamine effect. If necessary midazolam or haloperidol should be prescribed as an interim measure. It can be stopped when the patient is stable. The Palliative Medicine Consultant should be contacted to agree dose reductions and to arrange review.

**Preparations available**

**Subcutaneous Ketamine:**
Ketamine vials are available as Ketalar® 10mg/ml (20ml vial), 50mg/ml (10ml vial) and 100mg/ml (10ml vial). The nominated community pharmacist needs to register with Pfizer as an “approved pharmacy”. Tel 013 0464 5262 fax 013 0465 5885. Orders should be made by contacting customer services at Pfizer or through Unichem once registered with Pfizer. The pharmacy order should contain the following information: patient's name, prescribing doctor, pharmacist's name, strength and quantity of ketamine vials and details of account with wholesaler. Supply is usually 1-2 working days after request, but ketamine injection is commonly used 'off label' for prn S/C and continuous subcutaneous infusion via the syringe driver in palliative care.

**Oral Ketamine Solution:**
Community pharmacists can obtain supplies of ketamine oral solution from the various specials manufacturers. It is available in many strengths and flavours from 'Specials' manufacturers e.g.

- Cardinal Health (Martindale Pharmaceuticals Ltd) - Tel 0800 137627
- The Specials Laboratory in Prudoe – Tel 0800 0828 4925
- Pfizer – contact customer services
- Unichem – contact local Unichem customer services
- IDIS – contact IDIS telephone number in BNF

These companies usually keep limited stocks of some strengths, pack sizes and flavours, which are generally cheaper and have longer shelf-lives (e.g. up to 12 months vs. 3 months) than products that are made to order.

Ketamine oral solution can usually be supplied within a period of about 3-4 working days. However to ensure continuity of supply in the event of any delay, the patient should be advised to obtain repeat prescriptions and take them to the community pharmacy that he/she uses 10 to 14 days before the next supply is needed.

An oral syringe and adaptor bung should accompany the prescription.

The suspension may contain un-dissolved clumps of flavouring agent. This is normal and has no untoward effect on the product or patient.

Once the vials have been opened they must be discarded (single use only).

**Patient information**

Patients should be issued with patient information leaflets ‘Ketamine for Pain Management’ and 'Strong Pain Killers and Driving'.
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References


Guidelines for Ketamine Use :St Joseph’s Mercy Hospice Auckland NZ


Ketamine use in Chronic Pain Prescribing Information: North Yorkshire and York Primary Care Trust


WHO www.whocancerpain.wisc.edu/eng/15_2/adjuvants.html