

Prescribing information

KETAMINE use in chronic pain

This information is intended to support hospital doctors prescribing ketamine for chronic pain under the supervision of the Palliative Care Team. Ketamine is unlicensed for use in pain and the patient's GP would not normally be asked to take on prescribing. This document may however also serve as a useful GP reference if one of their patients is maintained on ketamine by the Palliative Care Team

Clinical Use

Ketamine is a short acting anaesthetic agent that has analgesic properties at sub-anaesthetic 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 usually used in pain that has failed to respond fully to opioids despite escalating doses and combination with appropriate adjuvants. It may be particularly helpful in neuropathic pain.

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.

Formulation

Ketamine is usually administered orally, or occasionally by subcutaneous infusion in a syringe driver.

Starting oral ketamine

1.	If the patient is already taking an opioid a dose reduction should be considered e.g. up to 30 to 50% dose reduction. Occasionally it may be necessary to change patients from controlled release morphine to an immediate release formulation.
2.	A typical starting dose of oral ketamine is 10 to 25mg every 6-8 hours and prn
3.	Consider the use of oral haloperidol 1.5mg to 3mg at night or oral diazepam 5mg for neuropsychiatric side effects.
4.	Doses are usually increased in steps of 10 to 25 mg per dose every 3-4 days until the desired dose is reached up to a usual maximum of 50mg every 6 hours (maximum reported dose 200mg every 6 hours).
5.	Titrate the opioid dose down further if possible
6.	If pain is returning before the next dose is due the dosing interval can be shortened to every 4-6 hours.

Notes on availability

- The only licensed commercially available formulation of ketamine is an injection (50mg/mL and 100mg/mL multidose vials). The injection may be given orally using a syringe to measure the dose, it does however have a bitter taste that may be disguised with flavourings such as orange juice and cola drinks. The 50mg/mL is less bitter than 100mg/mL and should be used in preference. For convenience the pharmacist supplying the ketamine *may* be prepared to draw the injection out of the vials and supply it in a bottle with an oral syringe. This however is an unlicensed transaction
- An **unlicensed** oral solution is available from Martindale in various strengths.

Starting ketamine s/c infusion

1.	If the patient is already taking an opioid a dose reduction should be considered e.g. up to 30 to 50% dose reduction. Occasionally it may be necessary to change patients from a controlled release morphine to an immediate release formulation.
2.	Give a loading dose of 10mg ketamine subcutaneously (diluted in 1mL sodium chloride)
3.	Commence a subcutaneous syringe driver containing 50-150mg ketamine over 24 hours.
4.	Consider the use of haloperidol 1.5mg to 3mg (s/c in syringe driver over 24hrs or orally) or midazolam 5-10mg (s/c in syringe driver over 24hrs) for neuropsychiatric side effects.
5.	Doses are usually increased by 50mg every 24 hours until the desired dose is reached up to a usual maximum dose of 700mg over 24 hours.
6.	Titrate the opioid dose down further if possible

Note

- Subcutaneous ketamine can be irritant and if used alone is probably best diluted with sodium chloride 0.9%. If mixing with other drugs use water for injection for dilution.
- Use a dilute solution i.e use of a 20mL or 30mL syringe
- Ketamine is compatible with diamorphine, metoclopramide, haloperidol, midazolam, metoclopramide, levomepromazine
- Ketamine may be incompatible with cyclizine and some doses of dexamethasone

Changing patients from subcutaneous to oral ketamine

1.	The dose of ketamine orally is approximately half of that given subcutaneously
2.	Prescribe the appropriate oral dose in 3 divided doses.
3.	For the first 24 hours continue the subcutaneous route but at 50% of the original dose
4.	Increase the oral dose by 10-25mg daily every 3-4 days
5.	If pain is returning before the next dose is due the dosing interval can be shortened to every 4-6 hours.

Notes on availability of oral ketamine

See previous page (starting oral ketamine)

Monitoring of patients

Consider monitoring respiration rate, blood pressure, heart rate, sedation and pain every 4 hours for the first 24 hours and for 24 hours following any dose change.

Pharmacokinetics

The onset of action of ketamine is 15-30 minutes after subcutaneous administration and 30 minutes 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 P450 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 interactions with concurrently administered drugs that are metabolised by the same enzymes. The main metabolite norketamine does however also have analgesic properties and is produced in greater quantities than ketamine resulting in an oral:subcutaneous dosing ratio of between 2:1 and 4:1. Tolerance has been reported.

Less than 10% of the drug is excreted unchanged, 5% in the faeces and 5% by the kidneys. The biologically active metabolite, norketamine, is subject to hydroxylation and conjugation before being excreted by the kidneys. Impaired renal function does not prolong the effect of the drug.

Drug interactions

Ketamine may potentially interact with other drugs metabolised by cytochrome P450. CYP3A4 has been shown to be the major enzyme responsible and CYP2B6 and CYP2C9 play a minor role. The plasma concentration of ketamine may be increased by diazepam.

Side effects

Neuropsychiatric side effects such as dysphoria, hallucinations and nightmares may occur early in therapy, but tolerance usually occurs rapidly. If necessary these can be reduced by concurrent treatment with haloperidol or a benzodiazepine. Care must however be taken as benzodiazepines can increase the amount of available ketamine and may also enhance the respiratory depressant effects.

Other side effects includes sedation, confusion, increased muscle tone, disorientation, delirium and dizziness, and if encountered require patients reassurance.

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

Contra-indications

Absolute : Intracranial hypertension, seizures, neurological impairment

Relative : Hypertension, cardiac failure, previous CVA

Patient information

Patients should be issued with a Trust patient information leaflet (Ketamine in pain)

Prescribing responsibility

As the use of ketamine in pain is unlicensed, treatment will normally continue to be supplied by the Consultant initiating treatment.

Cost (Mims Aug 2007)

Ketamine injection 50mg/mL (10mL multidose vial) £ 8.77

Ketamine injection 100mg/mL (10mL multidose vial) £16.10

Ketamine solution (unlicensed from Martindale) 50mg/5mL 500mL £112 (inc VAT)

References

1. Mercadante S. Ketamine in cancer pain, an update. Palliative Medicine 1996;10:225-230
2. Broadley KE et al. Ketamine injection used orally. Palliative Medicine 1996;10:247-250
3. Luczak J et al. The role of ketamine an NMDA receptor antagonist in the management of pain. Progress in Palliative Care 1995;3:127-134
4. Dickman A et al..The Syringe Driver. Oxford University press 2002
5. The Palliative care Formulary PCF 2
6. Bell RF et al. Ketamine as adjuvant to opioids for cancer pain. A qualitative systematic review. Journal of Pain and Symptom Management 2003; 26(3): 867-875.

Prepared by : Palliative care pharmacy team - available from Jane Crewe (Pharmacy)

Approved by : York Interface D&T Committee 10/05

Date of preparation : 10/05 Reviewed: 08/07

Date of review : Version 3 Review date: 8/2010