Guidance for the Prescribing of Ketamine injection or oral solution (Amber-G)

Introduction

This document sets out the guidance for the assessment and treatment of complex severe pain (and pain not fully responsive to opioids) by ketamine. The drug is initially prescribed by Consultants in Palliative Medicine and, where shared care is agreed, transferred to primary care for continuation.

This document should provide clear guidance to the GP and hospital prescriber, regarding procedures to be adopted when clinical (and therefore treatment and financial) responsibility for a patient on ketamine is shared between primary and secondary care.

The decision to start a patient on ketamine with complex severe pain or opioid side effects should be taken by a Consultant in Palliative Medicine with prescribing transferred to GPs only when the patient is on a stable regime.

Recommendation is Amber with Guidance

Background Information

Ketamine is a short acting anaesthetic with analgesic properties at low doses. Ketamine may be given orally, subcutaneously or by continuous subcutaneous infusion either as a sole agent or in combination with other agents. Ketamine is **unlicensed** for these indications and should only be initiated by a Consultant in Palliative Medicine.

Indications

Pain unresponsive to standard therapies (postoperative, neuropathic, inflammatory, ischaemic limb, myofascial and procedure-related). It is used particularly for neuropathic pain, ischaemic limb pain and refractory cancer pain and as an adjunct to opioid therapy.

Prescribing Information

Pharmacology

Ketamine has a variety of pharmacological actions, including interaction with N-methyl-D-aspartate (NMDA) receptors, opioid receptors, muscarinic receptors and Na ion channels. The analgesic effect of ketamine that is seen at sub-anaesthetic doses is due to non-competitive antagonism of the NMDA receptor. Ketamine interacts with specific binding site on the NMDA receptor, blocking the influx of Na and Ca. Binding of ketamine will only occur when the ion channel has been opened though neuronal excitation. The analgesic activity is believed to be due to attenuation of the ‘wind-up’ phenomenon by reducing the excitability of the neurons (2).

Ketamine is a schedule 2 controlled drug
As such it is exempt from controlled drug prescription requirements and is not subject to safe custody requirements. However Accountable Officer arrangements mean that prescribing is monitored.

Adult dosage and administration:
Dose recommendation varies depending on oral or subcutaneous use and clinical response**.**

Oral Ketamine:
Doses start at 10-25mg three to four times daily. The dose and frequency can normally be increased in steps of 10-25mg up to a dose of 100mg four times daily.

Ketamine (via continuous subcutaneous infusion):
Start with 50-100mg over 24hours using a syringe driver and increase by 50-100mg increments every 24hours until benefit is achieved, at which point the infusion is slowly titrated down and stopped. It is unusual to require doses greater than 600mg per day.

When given via a syringe driver it can be irritant to the subcutaneous tissue. Dilute with sodium chloride 0.9% to the largest possible volume.

The dose of any concurrently prescribed opioid may need to be reduced when the ketamine is initiated.

Suitability in a Syringe Driver:
At usual shared care doses ketamine is compatible with alfentanil, diamorphine, morphine, oxycodone, haloperidol, metoclopramide, levomepromazine, midazolam in a syringe driver.
Ketamine is incompatible with cyclizine.
Ketamine is generally incompatible with dexamethasone but doses of (0.5-1mg) dexamethasone or less may be added to syringe driver to prevent site irritation.

If more than two drugs are to be mixed in the same syringe, please refer to the current Palliative Care Formulary or www.palliativedrugs.com or seek further specialist advice from the consultants in palliative medicine.

Preparations available:
Subcutaneous Ketamine:

Prescribe only 50mg/ml, 10ml vials – rationale for choice:

Nursing staff who will be administering the sc or syringe driver ketamine must have a clear understanding that a 10ml vial of 50mg/ml is being used. This is based on best practice agreed within Doncaster Barnsley and Rotherham Palliative care services following previous instances of drug administration errors in those areas.

Supply via community pharmacy may take up to three working days after a prescription has been issued, so planning for care at home at the end of life needs to be as well coordinated as possible.

Oral Ketamine Solution

Prescribe only the 50mg/5ml oral solution

This is available as a pack size of 300ml.

It is anticipated that a quantity of 300ml per month is adequate quantity for most patients. This is an unlicensed "special" and will not routinely be stocked by community pharmacy; hence a delay may occur with the initial supply and repeated prescriptions.

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Note this preparation contains preservative and expires 28 days from opening.

Consultant in Palliative Medicine Responsibilities

- Assess patient's pain with regard to appropriateness of ketamine use, considering any contraindications.
- Determine baseline BP, LFTs
- Initiate and titrate the dosage regimen for ketamine, either as an inpatient in the hospital or hospice, or on an outpatient/home visit assessment.
- Assess response and side effects.
- Arrange shared care with GP when patient is managed on a stable regimen.
- Retain prescribing responsibility for patients on ketamine doses > 200mg/mg
- Provide clear instructions, with a copy of this prescribing advice, in a letter to the GP, community specialist palliative care nurses and the local hospitals. The patient will have a copy of this letter and advice.
- Provide a copy of this information to Out of Hours services in case of deterioration or if the patient requires additional medications. The consultant on call for palliative medicine can be contacted through Doncaster Royal Infirmary switchboard for these patients and advice on both symptoms and issuing scripts out of hours.
- Provide patient/carer with relevant written information on use, side effects and need for monitoring of medication.
- Ensure the prescription written for the patient is for a 28 day supply for the oral preparation, or an appropriate quantity of vials for subcutaneous use to ensure continuity of supply in the community.
- **Strength of vial must be 50mg/ml, 10ml vial.**
- **Strength of oral solution must be 50mg/5ml.**
- Review the patient's response and continuing appropriateness of ketamine at specified intervals, sending a written summary to the GP. This may be facilitated by community specialist palliative care team.
- Provide any other advice or information for the GP and district nursing, hospital teams or hospice teams if required.
- Provide clear advice for the pre-emptive prescribing of ketamine and any syringe driver use.
- Stop the treatment when no longer considered to be appropriate.

GP can undertake:-

- Once stable, prescribe ketamine and arrange ongoing monitoring as advised by and agreed with the specialist to a maximum dose of 200mg/day. Using
    - **Strength of vial must be 50mg/ml, 10ml vial (max 2 week duration).**
    - **Strength of oral solution must be 50mg/5ml in 250 or 500ml units**
- Refer to specialist when symptoms fail to respond to the management of analgesia or when a change of administration route may be indicated.
- Review the patient at regular agreed intervals to monitor control of symptoms.
- Identify adverse drug reactions and report to Specialist and CSM.
- Liaise with community and specialist nurses regarding ongoing patient care.

District nursing team/community specialist palliative care nurses/ward nursing teams/hospital specialist palliative care nurses' responsibilities

- Should ensure that they have this advice and an understanding of the formulations and route (oral and subcutaneous route) of the Ketamine medication when admitting the patient/completing a care plan or first assessment and reviews.
- Understand that the subcutaneous route will have vials of 50mg/ml 10ml vials prescribed.
- Understand the time that it may take to obtain different formulations in the community and work with the team and the patient to plan that the medication does not run out.
- Be aware of the potential side effects and beneficial effects of ketamine from this advice.
- Have the contact details for the GP and consultants in palliative medicine in the patient's care plan and understand who to contact if problems.
- Follow the usual policies for syringe drivers, 'Instruction to Administer' and care plans as for any syringe driver or subcutaneous medications prescribed as per policy within the organization in which the nursing staff are employed.

Adverse Effects, Precautions and Contraindications

Contraindications:
Intracranial hypertension and seizures are absolute contraindications.
Hypertension, cardiac failure, previous cardiovascular events and CVA are relative contraindications.

Precautions:
Concurrent use of aminophylline/theophylline may reduce seizure threshold.
Avoid grapefruit juice with oral ketamine.
Ketamine may cause drowsiness and dizziness and dizziness. Patients should be advised not to drive (or operate machinery) if affected.
Concurrent doses of opioids may need to be reduced.
Dose adjustment may be necessary in the elderly and patients with liver impairment.

Adverse effects:
Vivid dreams, hallucinations, excessive salivation/secretions, and sedation are the most commonly reported problems. Hypertension and tachycardia can also occur. Occasionally, pain and inflammation can occur around the injection site.
Rarely the patient can develop psychotomimetic phenomenon involving euphoria, dysphasia, blunted affect, psychomotor retardation and altered body image (particularly with CSCI).

If the patient experiences dysphoria or hallucinations, contact the consultant. If necessary midazolam or haloperidol should be prescribed as an interim measure e.g. 2.5-5mg midazolam subcutaneously or 1.5-5mg haloperidol orally or subcutaneously.

The Consultant in Palliative Medicine should then be contacted to agree dose reductions and to arrange review

Common Drug Interactions
Plasma concentrations of ketamine may be increased by diazepam. Ketamine may affect hepatic metabolism of warfarin, carbamazepine, phenytoin and theophylline.

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the full prescribing data SPC, the BNF and the current Palliative Care Formulary. Information is also available at www.palliativedrugs.com

The Consultants in Palliative Medicine are available during working hours through their secretaries and out of hours there is a consultant in Palliative medicine available through DRI switchboard.

Guidance Development

Reference

1. Palliative Care Formulary third edition (PCF7) A Wilcock; P Howard; S Charlesworth 2020. www.palliativedrugs.com

2. Drugs in Palliative Care, A Dickman; Oxford University Press 2010

Written By:

Dr L. McTague, Consultant in Palliative Care
Dr A. Carey, Consultant in Palliative Care
Dr M Fernando, Consultant in palliative Care

Reviewed by:
NHS Doncaster and Bassetlaw APC
Jan 2012

Reviewed by:
NHS Doncaster and Bassetlaw APC
March 2016

Reviewed by:
Lee Wilson, Consultant Pharmacist (with input from specialist team)
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