USE OF KETAMINE IN CANCER PAIN

Keywords: Palliative care, palliative pain management, palliative analgesia, cancer pain

AIM

• The appropriate management of pain in palliative care patients.

BACKGROUND

Ketamine is a short acting N-methyl-D-aspartate (NMDA) receptor antagonist. The analgesia role of ketamine (when given in sub anaesthetic doses) appears to be linked to an alteration in opioid sensitivity as part of its clinical effect.\(^1\)

Ketamine is given either orally or subcutaneously by continuous infusion via a syringe driver as a single agent or in combination with other analgesics.

There is an absence of large controlled trials supporting ketamine as an analgesic for cancer or neuropathic pain, but a large body of case reports and uncontrolled trials. Two small randomised controlled trials reported decreased morphine use and reduced neuropathic pain intensity. However a recent systematic review found insufficient evidence that ketamine improves the effectiveness of opioid treatment in cancer pain.\(^2\)

KEY POINTS

1. Ketamine should only be prescribed by or in consultation with a doctor experienced in pain management or Palliative Care.
2. Ketamine potentiates the action of opiates and careful monitoring of opiate requirement is necessary at initiation and on dose increments. Be prepared to reduce the opioid dose significantly as the ketamine takes effect (usually the opioid dose is reduced by 50%).
3. Patients should always be observed for opioid toxicity.
4. Ketamine is a reserve line agent used in the management of neuropathic, ischaemic limb pain and refractory limb pain, and should only be used once the following medications have been tried and tested (usually concurrently):
   - Paracetamol
   - NSAID
   - Opiates
   - Anti depressants
   - Anti epileptic.
5. For subcutaneous administration, ketamine should always be diluted with sodium chloride 0.9%.
6. It is not excreted renally therefore impaired renal function does not prolong the effect of ketamine or increase the side effects.
7. The syringe shall be made up daily.
8. Rotate the infusion site daily to prevent tissue inflammation.
9. The usual opioid rescue medication should be prescribed (i.e. 1/6th of the total daily dose).
CONTRA INDICATIONS

ABSOLUTE
- Intracranial hypertension
- Glaucoma
- Seizures
- Patients receiving MAOIs

RELATIVE
- Hypertension
- Cardiac failure
- Previous cardiovascular events
- Cerebrovascular accidents

SIDE EFFECTS
- Hallucinations, delirium vivid dreams, emergent phenomena (the feeling of detachment from the body).
- Routine administration of either haloperidol or a benzodiazepine can eliminate or minimise these side effects but may not be necessary in all women, particularly when using low doses.
- Hypertension (or hypotension), tachycardia, diplopia, respiratory depression, laryngospasm, raised intracranial pressure, myoclonus, rigidity and nystagmus can all occur.

COMPATIBILITY
- Ketamine may be combined with morphine
- It has been mixed with Midazolam, but not Clonazepam
- No more than two drugs are to be mixed in any infusion (SC or IV)

METHOD OF ADMINISTRATION – CONTINUOUS SUBCUTANEOUS INFUSION
1. An initial ‘test dose’ of subcutaneous ketamine 10mg is recommended to establish that the medication is tolerated with no acute side effects.
2. Ketamine is irritant to tissues, in an infusion it must be diluted with sodium chloride 0.9% to the largest volume possible.
3. A usual starting dose would be 100mg per 24 hours (unless the woman is frail in which case it should be 60mg / 24 hours).
4. A loading dose may be given, e.g. 0.5mg/kg body weight.
5. Titrate up or down by 50mg each day.
6. Usual dose schedule is a 5 to 7 day infusion – it is generally not given long term, but doses can be repeated if they have been successful. Oral formulations are available.
7. If administered via a central venous line (e.g. PICC, Infusaport), flush the line with saline at the same rate as the Ketamine infusion for 24 hours prior to heparin locking the device (or a large IV bolus will be given).
8. Once analgesia is achieved consider reducing the regular daily dose by 33% and gradually reduce further if possible.
9. Review the need for concurrent analgesics (e.g. NSAIDs, Paracetamol, anti convulsants and tricyclic anti-depressants one week after achieving stable pain control with ketamine and gradually optimise the medications as deemed appropriate.
OBSERVATIONS

THE FIRST 12-24 HOURS ARE THE MOST IMPORTANT

Perform and record the following observations at the time of initiation, at 1 hour then 4 hourly for 24 hours

- Pulse, respiratory rate, blood pressure.
- Pain score
- Sedation score.
- If the dose rate is increased revert to 1 hour and then 4 hourly for 24 hours.
- Women with the following should have 4 hourly observations until dose titration is complete
  - Women with relative contraindications to ketamine.
  - Where ketamine is started while the woman is on a long acting opioid.
  - Where a rapid dose titration of ketamine is needed.
- For all other women daily pain score, pulse and blood pressure is recommended during titration.

Note: Be aware for potential opioid toxicity (i.e. respiratory depression, drowsiness, jerking during titration, especially for those women on high dose and long acting opiates, however in most circumstances it is rare).

Modest blood pressure rises need no action; significant rises should prompt medical review.
- Clinical review of the woman should be carried out within 24 hours of starting ketamine and documented in the notes.

OPIATE OVER DOSAGE

- If the respiratory rate is less than 8 per minute and the woman is not cyanosed, no action other than observation is required.
- If life threatening respiratory depression occurs, dilute Naloxone 400micrograms in 10mL saline 0.9% and give intravenously at the rate of 1 mL per minute. Repeat until the woman’s condition improves.
- If there is no response after 3200 micrograms reconsider the diagnosis.
- If relapse occurs (likely after about 20 minutes) give a further 400-800 micrograms intravenously and consider commencing an intravenous infusion of 400 micrograms per 100mL saline 0.9% and titrate the rate according to the woman’s response.

NB: Most opioids used in palliative care have a longer half life than Naloxone and therefore relapse is likely. With sustained release preparations there may be relapses for 24 hours or more.
- Total reversal of opioid action will result in the recurrence of pain. The aim is to reverse respiratory depression to safe levels and not necessarily abolition of opioid effects.
REFERENCES (STANDARDS)


Do not keep printed versions of guidelines as currency of information cannot be guaranteed.
Access the current version from the WNHS website.