Ketamine and Methadone Supra-Regional Audit Presentation

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Background to audit

- Methadone re-audit
- New ketamine audit
- Supra- regional
- Two parts:
  - Health care professionals questionnaire,
  - Prospective data collection in individual units
Plan for Presentation

- Methadone:
  - Current Standards, Literature review, Audit results.
- Ketamine:
  - Literature review, Audit results.
  - Standards and Guidelines for methadone and ketamine.
- Comments from external experts
- Discussion
Ketamine literature review

September 2012
Dr Anthony Thompson
Ketamine Revision

• Class – general anaesthetic

• Indications – anaesthesia, pain unresponsive to standard treatments

• Contraindications – any situation where raised Blood Pressure/Intracranial pressure is hazardous. Acute Porphyria
Pharmacology 1

- NMDA receptor channel complex

- Involved in developing central sensitisation of dorsal horn neurones which transmit pain signals

- At rest the channel is blocked by Magnesium ions
Pharmacology 2

• But if prolonged stimulus and excitation the channel unblocks and Calcium moves into the cell

• This causes neuronal hyper excitability and reduction on opioid responsiveness, hyperalgesia and allodynia
Pharmacology 3

• KETAMINE is the most potent NMDA receptor channel blocker available clinically

• Binds to the channel sites when open and activated

• Antagonises the hyper excitation state
Pharmacology 4

- Multiple receptor activities
- Interacts with other calcium, sodium channels
- Dopamine receptors, cholinergic transmission, noradrenergic and serotonergic re-uptake and opioid-like and anti-inflammatory effects
Pharmacology 5

- Commercially available Ketamine is equal enantiomers of S(+) and R(-) forms of the drug
- Bioavailability - parenterally 93%, orally 17%
- Oral Ketamine → Norketamine (equipotent)
Pharmacokinetics

- Bioavailability – 93% intramuscular (im), 45% nasal, 30% sublingual, 30% PR, 20% oral (PO)

- Onset – 5min im, 15-30 min s/c, 30 min PO

- $t\frac{1}{2}$ - 1-3 h im, 3h PO,

- Duration – 30min-2h im, 4-6h PO
Cautions

- Psychiatric disorder, epilepsy, glaucoma, hypertension, cardiac failure, history of strokes
- Plasma concentration raised by diazepam, CYP3A4 inhibitors e.g. clarithromycin, ketoconazole
Undesirable effects

- Dose related
- Psychomimetic – euphoria, dysphasia, blunted affect, vivid dreams and nightmares, inattention, memory, illusions, hallucinations, altered body image
- Delirium, dizziness, diplopia, blurred vision, nystagmus, hearing, HYPERTENSION, tachycardia, hyper salivation, nausea and vomiting, injection site erythema, URINARY TRACT TOXICITY
**Urinary tract toxicity 1**

- Unclear of cause, direct irritation or metabolites
- Frequency, urgency, urge incontinence, dysuria, haematuria
- Interstitial cystitis, detrusor over activity, reduced bladder capacity, vesico-ureteric reflux, hydronephrosis, papillary necrosis, renal impairment
Urinary tract toxicity 2

• If symptoms of urinary tract infection and NO evidence of bacterial infection, consider discontinuing and seeking Urology review

• Symptoms settle in a few weeks, gradual reduction in dose ideally to prevent pain escalation
The Literature Review
Cochrane Collaboration 2009

- Bell, Eccleston and Kalso 2009

- To determine the effectiveness of ketamine as an adjuvant to opioids in the treatment of cancer pain
- Medline, embase, cancerlit, Cochrane library
- **Selection criteria** adult, cancer, on opioid, received ketamine or placebo/active control
Cochrane Collaboration 2009

• **Data** 4 RCTs (2 excluded, poor design) and 32 case studies

• **Results** 2 trials included, small numbers of patients

• **Conclusion** More RCTS needed, current evidence insufficient
Results

• 2 studies
• **Mercandante 2000**, Italy, Placebo, 3 hour trial
• **Yang 1996**, Taiwan, Morphine active control

• Both cross over trials
Mercandante 2000

- 10 patients
- 7 men 3 women 21-69 years
- Pain unrelieved by morphine
- Diagnosed with neuropathic pain
Mercandante 2000

- 2 doses ketamine IV bolus 0.25mg/kg and 0.5mg/kg as adjuvant vs. normal saline
- 2 day washout between treatments
- No rescue doses described
Mercandante 2000

• Outcomes
• Pain score at 30, 60, 90, 120, 180 minutes and adverse effects
• Pain score 0-10
Mercandante 2000

• Effectiveness
• 0.25mg/kg dose
• Pain score reduced after 30 mins vs. normal saline
• After 60 mins effect lessened but some benefit even after 180 mins noted
Mercandante 2000

- 0.5mg/kg dose
- Significant reduction at 30 mins and maintained throughout the 180 mins
Yang 1996

- 20 hospital patients
- 10 men 10 women 22-69
- Cancer pain effectively treated with morphine
Yang 1996

- Assessed intrathecal 1mg/kg ketamine as adjuvant vs. morphine alone
- Morphine dose titrated until stable 48 hours then randomly crossed over to morphine PLUS Ketamine or continued on morphine (control) alone, administered twice daily intrathecally
- No washout period
- Rescue doses available Morphine 5mg im
Yang 1996

- Outcomes
- Patient pain score 0-10
- Pain frequency
- Morphine dose
- Total morphine dose
- Total rescue doses
- Frequency of intrathecal titration
Yang 1996

- Co-administration of ketamine reduced the dose of morphine needed

- Was as effective as intrathecal morphine alone
Adverse effects

• No withdrawals in either study
• Hallucinations commonest treated with diazepam
• Mild effects including light flashes, buzzing in head, insobriety, drowsy, nausea and vomiting, dry mouth, confusion
Conclusions

- No evidence based conclusion due to small numbers
Other Reports

- 32 case studies
- Opioid AND ketamine
- 246 patients
- Various routes used po, im, s/c, iv, s/c infusion, epidural, intrathecal
- Various doses 1mg/kg/day s/c infusion to 600mg/day iv, 67.2mg/day intrathecal
- Various time scales 4 hours to 12 months
Case Studies

• Most used morphine, some fentanyl, hydromorphone, diamorphine or alone
• 16 reports described dramatic relief of refractory cancer pain
• Commonest adverse effects sedation and hallucinations
• One had sedation settling with opioid reduction
• Only 2 studies out of 32 had patient withdrawal
Case studies

- Inflamed infusion sites, nystagmus, hyperalgesia post cessation
- Post mortem – myelopathy post intrathecal infusion with vasculitis
- *Lloyd Williams 2000* - s/c infusion sites, 0.1% hydrocortisone cream to maintain sites
Therapeutic Review

- Rachel Quibell, Eric Prommer, Mary Mihalyo, Andrew Wilcock and Robert Twycross
- Journal of Pain and Symptom Management Volume 41, March 2011
- PCF 4 Chapter 13 Anaesthesia Page 593-600
Dose and Use
Advise long term ketamine only if “Burst” has failed
Due to renal tract concerns
Oral Ketamine

- 50mg/5ml
- Co-administration
- 10-25mg TDS/QDS and PRN
- Titrate up in steps to 100mg QDS
- Consider dose reduction if drowsy/psychomimetic issues
- Can be opioid sparing effect
Oral Ketamine

- Some centres attempt withdrawal over several weeks
- Benefit can persist without ketamine for weeks/months
“Burst Ketamine”

- Maximal dilution
- 0.9% saline
- 100mg/24 hrs.
- If not effective increase to 300mg/24 hrs.
- If not effective again, increase to 500 mg/24 hrs.
- Stop 3 days after last dose increment
- Prophylactic use
Other Routes

- Sublingual (s/l)
- Subcutaneous stats (s/c)
- Intravenous (IV)
- Continuous IV Infusion (CIVI)
Opioid reduction

• Some centres reduce regular opioid dose 25-50% when starting parenteral ketamine
Other Papers of Interest

• The use of Ketamine in severe cases of refractory pain syndromes in the palliative care setting: A case series
• Kerr et al, Buffalo, New York
• Journal Of Palliative Medicine, Volume 14, Number 9, 2011
• 4 complex cases, non-cancer
• Sub-anaesthetic doses unresponsive to escalating opioid doses
• Sickle cell, paraplegia, multiple issues including Chronic Obstructive Pulmonary Disease, Ischaemic heart disease, Raynaud`s, quadriplegia
• 2 used CIVI, 2 used CSCI Ketamine
• Conclusion – ketamine has a role in reducing opioid tolerance and hyperalgesia, few side effects
Kate Jackson et al, Victoria, Australia

• 2001 – “Burst” Ketamine for refractory cancer pain: an open label audit of 39 patients (J. Of Pain and Symptom Management Vol. 22 No 4 p834)

• 2010 – The effectiveness and adverse effects profile of “Burst” Ketamine in refractory cancer pain (J. of Palliative care Autumn 2010;26,3)
2001 Study

- Multi centre unblinded open label audit39 patients
- 18 month study, 4 Pall Care Centres
- Short duration Ketamine (3-5 days)
- 100mg-300mg-500mg per 24 hours CSCI
- 43 pains
- 29 responded
- **Response rate 67%**
- 24/29 maintained good pain control (8 week max.)
2001 Study

- 12 had adverse Psychomimetic effects
- Dose related
- Cancer patients
- Taking opioid, NSAIDS and neuropathic agents
- Suggested need for further investigation into the place of Ketamine in cancer pain management
2010 Study

- The VCOG PM1-100 Study
- Multi centre study
- **Response rate 22/44 i.e. 50%**
- 100mg-300mg-500mg per 24 hrs. CSCI
- Would the early promising results continue
- Open label study of effectiveness and incidence of adverse effects (AE)
- 53 patients registered, 44 eligible
- aged 35-82, 21 men 23 women
2010 Study

- 77% needed 300mg or more, 41% needed 500mg
- Response rate dropped to 50% but 9% had complete response (pain free)
- Ketamine role not purely for neuropathic pain, but bone metastases with nerve damage
- Dose related AE
- Cardiovascular stability noted
2010 Study Conclusions

- Need RCTs
- Blinded
- Limited opportunities in Palliative Care
- Difficult to blind with AE being noticeable
- The lack of level I and II evidence should NOT preclude the use of Ketamine Burst Treatment
Other Nuggets

- Burst Ketamine to reverse opioid tolerance in cancer pain
- Case reports
- Hyper excited opioid excess state
- Ketamine as co-analgesic OR reversal of opioid tolerance
Ketamine Mouthwash 1

- Cooney et al
- EAPC 2011
- Palliative Care Department, Dooraradoyle, Limerick
- Retrospective study 12 months
- Patients who received the mouthwash
- Dose, number of doses, duration, concurrent analgesics, adverse effects
Ketamine Mouthwash 2

- Received Ketamine 20mg in 10ml Bioxtra mouthwash, 6 hourly, swish and spit
- All were head and neck, post radiotherapy (DXT)
- Useful and safe
- Mild stinging when first used only
Ketamine Mouthwash 3

- Slatkin et al, *Pain Medicine, Volume 4, number 3, 2003*
- Duarte, California
- Topical ketamine in the treatment of mucositis pain
- Case study, 32 year old lady, DXT
- Unclear if local or systemic effect
- Anti-inflammatory? Sodium channel?
• Possible hyperalgesic effect of opioids
• NMDA receptor involved
• Development of this reversed/shifted by NMDA antagonists
• Wind up – increased neuronal response to repeated stimuli – Ketamine inhibits this wind up
• Reversal of central changes
• “resets the nerve system”
A Randomised Controlled Trial

- D. Currow, J Hardy et al

- Brisbane, Sydney, Adelaide

- Randomised double blind controlled multi centre study of subcutaneous ketamine in the management of cancer pain
Currow and Hardy et al

- Stable opioid dose
- Severe pain
- Adequate co-analgesics
- Randomised to Placebo or Ketamine
- 100-500mg per 24 hrs. CSCI
- Response greater than 2 point drop in BPI scale

- Pain score day 6 end point
• Results
• 185 patients
• March 2008 - February 2011
• High placebo response 26/92 (28%) with no difference between placebo and active arms
• Trial does NOT support the role of s/c Ketamine in the treatment of cancer pain in advanced cancer
Urinary tract damage

- Storr et al, Cumbria, Palliative Medicine, 2009; 23: 670-672
- Describes 3 cases developing significant urological symptoms
- Case 1 - oral 50mg QDS
- Case 2 – oral 170mg QDS
- Case 3 – oral 200mg QDS
- Temporal link
Refactory Depression

- Intravenous Ketamine “Burst” for refractory depression in a patient with advanced cancer
- Stefanczky-Saphieha et al, J. Palliative Medicine, Vol. 11, No.9, 2008, Toronto
- Studies in non cancer suggest NMDA antagonist role in rapid improvement from severe depression, even single Iv doses
- Burst Ketamine used with success for major depressive disorder in advanced cancer
- Suggest RCTs
Role of Ketamine in Analgesia

- Literature review, Legge et al, West Virginia, USA
- American society of consultant pharmacists vol.21, issue 1, 2006
- Medline, Cochrane

- Conclusion
- Useful with Opioids
Palliative Sedation Letter

• J. of Pain and Symptom management
• Vol.36 no.4 October 2008
• Carter et al, Bristol
• Case study
• 100mg IV, 300mg agitated, settled with 500mg rapidly IV
• Monotherapy role (?)
Conversion from s/c to oral

- J. of Pain and Symptom management. Vol.41, No.6, June 2011
- Benitez-Rosario et al, Tenerife
- A strategy for conversion from s/c to oral Ketamine in Cancer Patients: Effect of a 1:1 Ratio
- 29 patients enrolled
- Stable on s/c ketamine
Conversion from s/c to oral

- Converted to oral ketamine for maintenance
- Mean s/c dose 300mg/24 hours
- Used 1:1 ratio
- Given TDS
- Close monitoring
- No adverse effects reported
And finally from me……
Hocking and Cousins

• Systematic review
• Ketamine in chronic pain management: an evidence based review
• Anaesthetic Analgesia. 2003;97:1730-1739
• Good therapeutic response to parenteral ketamine suggests oral response
Ketamine Standards and Guidelines

Dr Sarah Fradsham
General principles in the Use of Ketamine
Introduction

- Ketamine is a drug used for the induction and maintenance of general anaesthesia.

- Ketamine has a role in treatment of pain unresponsive to standard treatments (e.g. neuropathic, inflammatory, ischaemic, procedural pains)\(^1,2,3\)

- Ketamine is a dissociative anaesthetic with analgesic properties at sub-anaesthetic doses\(^3,5\)
• The NMDA receptor channel is involved with sensitisation of the dorsal horn neurones which transmit pain signals.

• Prolonged stimulation (pain) causes hyper excitability and reduced opioid responsiveness, hyperalgesia and allodynia⁴.
• Ketamine is a potent NMDA receptor channel blocker, as well as other actions on the following channels – calcium, sodium, dopamine, cholinergic, noradrenergic, serotonergic reuptake and opioid-like effects and anti-inflammatory effects$^6,7$
• Ketamine has been used as an analgesic in many clinical settings including post-operative, chronic non-cancer pain, cancer pain, and procedural pain (e.g. burns dressings) and painful mucositis\textsuperscript{8,9}.

• in cancer pain, ketamine has been used mainly **ORALLY (PO)** or **SUBCUTANEOUSLY (CSCI)**
Subcutaneous use can be “Burst” (see below) or more prolonged subcutaneous use.
Side effects are dose related. 40% occurrence with CSCI, less so with PO.
Ketamine abuse is common on the “street” and associated with adverse media attention as a result.
• Ketamine can cause urinary tract problems, tachycardia, hypertension and intracranial hypertension and Psychomimetic side effects e.g. vivid dreams, hallucinations, altered body image and mood. These psychomimetic side effects can be managed with Midazolam and/or haloperidol. Co-administration is recommended \textsuperscript{11,12} (see manufacturers PI)
• Ketamine undergoes extensive first pass metabolism

• Mainly to Norketamine

• As an analgesic it is equipotent to parenteral ketamine$^{10}$
• Less than 10% is excreted unchanged, half in the faeces and half renally.

• Norketamine is renally excreted and long term use leads to hepatic enzyme induction and enhanced ketamine metabolism.
Formulations and Supply

- Oral solution
- Made to order
- Sugar free
- Made to order
- Martindale e.g. 50mg/5ml (other strengths are available)
- Different flavours
- Unlicensed
Preparation of oral Ketamine: Pharmacy Guidelines

- Use 100mg/ml 10ml vials (cheapest)
- To prepare 100ml 50mg/5ml oral solution

- 10ml vial of ketamine 100mg/ml
- 90ml purified water
- Refrigerate
- Use within a week of manufacture
- Not recommended to do in ward environment
• Injectable preparations
• Pfizer
• 10mg/ml 20ml ampoule
• 50mg/ml 10ml ampoule
• 100mg/ml 10ml ampoule
• Off label
Guidelines
Guidelines

• Ketamine for pain control should be initiated by a Palliative care physician experienced in the use of ketamine. This is usually done in a specialist palliative care inpatient unit. [Level 4]

• The majority of the evidence for the use of ketamine for pain control supports the use of ‘burst’ ketamine. This is therefore recommended as first line treatment. Long term ketamine is only recommended if burst ketamine has failed due to concerns regarding urinary tract toxicity. [Level 4]

• Suggested doses and regimes are described in Table 1.
Table 1 - Doses and Regimens [Level 4]
• **Compatibility in syringe drivers [Level 2]**
• For subcutaneous regimens it is recommended that ketamine is diluted with sodium chloride 0.9%.
• When giving subcutaneous ketamine via a syringe driver it is compatible with morphine plus additional drugs when mixed with sodium chloride 0.9%\textsuperscript{13}.
• Box A describes compatibility data for drug mixtures containing ketamine.
Guidelines - Monitoring

- Ketamine can cause tachycardia and intracranial hypertension. Due to this the 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. [Level 4]

- If the pulse rate rises above 20bpm from baseline or above 100bpm or the the blood pressure rises by 20mmHg on consecutive readings, a dose reduction should be considered. If the pulse rate or blood pressure does not return to baseline readings with a dose reduction then ketamine should be discontinued. [Level 4]
As ketamine has an ‘opiate sparing’ effect, patients should be monitored for signs of opiate toxicity. During the dose titration phase this should include twice daily monitoring of respiratory rate along with blood pressure and pulse rate as described above. The patients conscious level should also be monitored and if there is any concern regarding opiate toxicity the patient should be reviewed by a clinician and consideration of a dose reduction of the regular opiates should be made. [Level 4] (see opiate reduction below)
Guidelines- Monitoring

- 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 doses are needed. 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 ongoing effectiveness of pain control. [Level 4]

- For those patients maintained on long term ketamine reassessment should be carried out by a palliative care specialist monthly or sooner depending on symptoms or clinical need. [Level 4]
**Guidelines- Opioid reduction**

- As ketamine has an opiate sparing effect a dose reduction of 25% should be considered in those patients commencing parenteral or oral ketamine or if patients develop signs of opiate toxicity. [Level 4]

- All units commencing ketamine should ensure naloxone is available for use in the case of respiratory depression associated with opiate overdose/toxicity. [Level 4]

- Use of ketamine is not recommended in patients on transdermal opioids due to the risk of opiate toxicity. In these patients an opiate conversion should be considered prior to commencing ketamine. [Level 4]
Guidelines - Conversions [Level 4]

- Evidence regarding conversions is limited however, when converting from PO ketamine to Subcutaneous ketamine for use in a CSCI, a conversion of 1:1 is suggested.
- PO ketamine undergoes extensive first pass hepatic metabolism to norketamine which provides the main analgesic effect. The maximum blood concentration of norketamine is greater after PO administration than after parenteral administration therefore when converting from SC:PO a conversion of 3:1 is suggested.
- In both cases, there should be the provision for close monitoring and ability to alter the dose as necessary.
Ketamine can cause undesirable psychomimetic effects such as hallucinations, euphoria, 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. [Level 4]

- Suggested doses include Haloperidol 2mg-5mg po nocte or 2mg-5mg via CSCI over 24hrs or Midazolam 5mg-10mg via CSCI. [Level 4]
Guidelines - Urinary Toxicity

• Ketamine has been linked to urinary tract toxicity including interstitial cystitis, papillary necrosis and renal impairment.

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

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

When a patient is discharged on ketamine standardised information should be given to the patients, GP and community pharmacist. [Level 4]
Guidelines Discharge

- Units should liaise with the patients GP and community pharmacy prior to discharge to confirm future supplies of ketamine. [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. [Level 4]
- Units should consider the use of a ketamine card to be given to patients on discharge to inform other health professionals that the patient is on ketamine. [Level 4]
Standards
Standards

• The decision to commence ketamine, the indication and regimen to be used should be clearly documented in the patient’s case notes. [Grade D]

• Prior to commencing ketamine, the patient’s 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. [Grade D]

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

• Ketamine should always be prescribed in milligrams (mg). [Grade D]
Standards

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

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

• Patients discharged on ketamine (oral or subcutaneous) should have at least monthly follow-up with a Palliative Medicine clinician experienced in the use of ketamine. [Grade D]

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


12. Palliative Care Formulary 4


14. Dickman A. Drugs in palliative care. OUP.
Time to hear from the experts...
Any Questions?