Dr. Nicola Macpherson MD FRCPC (Anaesth)
Clinical Associate Professor, Department of Medicine, UBC
Associate Member, Department of Anaesthesiology, Pharmacology & Therapeutics, UBC
Assistant Professor, Academic Family Medicine, University of Saskatchewan
Clinical Assistant Professor, Family Medicine, Cumming School of Medicine, University of Calgary
Faculty/Presenter Disclosure

• Faculty: Dr. Nicola Macpherson
• Relationships with financial sponsors:
  • Grants/Research Support: None
  • Speakers Bureau: None /Honoraria:
    • University of British Columbia: Teaching honoraria 2004-18
    • University of Saskatchewan: Teaching honoraria 2014-17
    • Victoria Hospice: Teaching honoraria for Medically Intensive Course 2012-18
    • BC FP Anaesthesia Network: Teaching honorarium for 2017 Refresher Course for General Practitioner Anesthetists
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  • Patents: None
  • Other: None
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- This program has received financial support from N/A in the form of N/A
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Potential for conflict(s) of interest:
- Dr. Nicola Macpherson has received no payment/funding, etc. from:
  - Any organization supporting this program (apart from a speaking honourarium) AND/OR
  - Any organization whose product(s) are being discussed in this program.
Mitigating Potential Bias

• All teaching has been unrestricted by course organizers
Non-Financial Potential Bias

Based upon data from the largest ongoing prospective cohort study in history, with \( n \) approaching 107 billion, there is a very high likelihood (\( RR = \infty, p<0.0001 \)), that I will die.

I want to be comfortable.
Speaker Disclosure
At the conclusion of this presentation, participants will be able to:

1. Describe the circumstances where a trial of ketamine is worth considering.
2. Describe an evidence-informed method of administering parenteral ketamine to maximize success.
3. Consider developing a protocol or guideline for ketamine infusion appropriate for your organization.
Ketamine

Ketamine is FDA approved for IM or IV administration as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation.

Use in chronic pain, palliative medicine and psychiatry is “off-label”
Ketamine as a General Anaesthetic

Useful as a GA for trauma (i.e. unstable) patients because it:

- Preserves sympathetic reflexes
- Supports BP in patients in shock
- Does not interfere with respiratory drive

Can be used in resource-poor settings where intubation and ventilation are unfeasible

Patients can be monitored by non-anaesthesiologists
Ketamine

Derivative of PCP ("Angel Dust") synthesized by Belgian chemist C.L. Stevens in 1963
Patented by Parke Davis in 1966
First used on U.S. soldiers during the Vietnam War
Approved by the FDA ("released for civilian use") in 1970
The NMDA Receptor

Adapted from AnaesthesiaUK
Ketamine Mechanism of Action

• Known mostly as an NMDA antagonist, but also:
  • Reduces the presynaptic release of glutamate
  • Interacts with opioid receptors, esp. mu and kappa
  • Monoaminergic antagonist
  • Muscarinic and nicotinic antagonist
  • Local anaesthetic properties via inhibition of neuronal sodium channels at high doses

Ketamine

• In North America, and the UK, ketamine is available as a racemic mixture that contains equal amounts of the two isomers (S and R forms)

• The S enantiomer is available in Germany, Austria, Italy, Netherlands
  • The S isomer has twice the analgesic potency, and fewer psychomimetic effects than the R isomer
Ketamine as an adjuvant to opioids for cancer pain

28 June 2017

The benefits and harms of adding low-dose ketamine to strong pain-killers such as morphine for the relief of cancer pain are not yet established

High-dose ketamine does not appear to be effective and may be associated with serious side effects
Evidence?

• Since 1990, many articles on the use of ketamine in various cancer and non-cancer pain types have been published.
• The more rigorous the study, the more ambiguous the effectiveness.
• Is there still a role for ketamine in palliative patients?
Disclaimer

• My personal bias is that ketamine works for SOME patients, but:
  • We have not figured out which ones
  • We have not figured out the right dose and
  • We have not figured out what route work best for which pain types
• Lots of letters and editorials arguing the issue
• It has been used in ways as simple as intermittent nasal spray for incident pain up to 5 day coma therapy for CRPS 1
Ketamine Coma Therapy –
The Future of Palliative Medicine?
Tread Carefully

- Evidence for use in psychiatry (severe depression, PTSD)
- Clinics sprouted up, often with no psychiatrists
- Trials in ER for agitation
- “Sanctioned”, but often without consent
- Lots of bad press

Controversial US ketamine trial sparks ethics complaint

Advocacy group alleges that emergency medical workers in Minnesota gave patients ketamine injections without consent, despite known risks.
Prospective, multicenter, unblinded, open-label audit

39 patients (with a total of 43 pains), over 18 mos. (1998-99)

Short duration (3 to 5 days) ketamine infusion

“Burst” Ketamine for Refractory Cancer Pain: An Open-Label Audit of 39 Patients

Kate Jackson, MB BS, DTM&H, FRCA, FAcHPM, Michael Ashby, MB BS, MRCP, FRCR, FRACP, MRACMA, FAcHPM, Peter Martin, MB BCh, BAO, Dip PallMed, MMed, FAcHPM, Maria Pisasale, MB BS, BHA, FRACMA, AFCHSE, FAcHPM, David Brumley, MB BS, FRACGP, FAcHPM, and Barbara Hayes, MB BS, DipRACOG, MPHC, FAcHPM

McCulloch House, Monash Medical Center and Department of Medicine (K.J., M.A., P.M.), Monash University, Clayton; Mercy Hospice Inc. (M.P.), Sunshine; Gandarra Palliative Care Unit (D.B.), Ballarat; and Melbourne Extended Care and Rehabilitation Service (B.H.), Parkville, Victoria, Australia
The overall response rate was 29/43 (67%) 15/17 somatic, 14/23 neuropathic pains, and 0/3 visceral pains responded. After cessation of ketamine, 24/29 maintained good pain control, with a maximum documented duration of eight weeks. 5 of the initial 29 responders experienced a recurrence of pain within 24 hours, and ketamine was recommenced.
The Effectiveness and Adverse Effects Profile of “Burst” Ketamine in Refractory Cancer Pain: The VCOG PM 1-00 study

Kate Jackson, Michael Ashby, Deb Howell, Jennifer Petersen, David Brumley, Phillip Good, Maria Pisasale, Simon Wein, and Roger Woodruff

- Prospective single-arm study (March 2002 to May 2004)
- Enrolled a further 44 patients from an expanded group of centres using the same “burst” protocol
- To ascertain whether the early promising results would continue to be seen as local experience with this protocol increased
Not Quite as Good Second Time Around

• The overall response rate was 22/44 (50 percent)
• 4 participants (9 percent) had a complete response, becoming pain-free
• This is a good success rate for refractory cancer-associated pain that has failed to respond to a combination of:
  • Anti-inflammatory (steroids and/or NSAID)
  • Opioid dose escalation
  • +/- At least one anti-neuropathic adjuvant
• This was achieved with an acceptable AE profile and with a protocol that is applicable for use in most palliative care units - at least in Australia
Meanwhile, a 25 hour drive away...

Editor’s Comment: This report of a single case study is presented in unusual detail because of the exceptional promise of the technique described, and the importance of further study. Complex Regional Pain Syndrome challenges our most informed and skillful interventions. The field is replete with reports of promising “cures” that fail to be replicated. We hope that this report will stimulate further studies of this intervention in carefully constructed studies of a larger series, with randomization, before conclusions can be drawn.
“Walking” Hypothesis

• In the late 1990s Correll postulated that prolonged infusions of sub-anesthetic doses of ketamine might reverse abnormal cellular mechanisms that were maintaining CRPS.

• He observed that sub-anesthetic doses of ketamine can:
  • Result in remission of CRPS pain in some patients
  • Be safely given to fully conscious and fully ambulating inpatients on a general medical ward

• Initially presented as a poster at the 1999 Australian Pain Society Meeting, Fremantle, Western Australia
• 33 Patients
• Ketamine started at 10 mg/hr
• Titrated to feeling of inebriation (15-50 mg/hr)
  • Average maximum infusion rate 23.4 mg/hr (562 mg/day)
• Discontinued as follows:
  • After 12–24 hrs of complete CRPS pain relief; or
  • 24 hrs after an initial partial response that would not improve any further; or
  • After 48 hours of a continuous lack of improvement in the pain score
• Duration <1 to 20 days
Subanesthetic Ketamine Infusion Therapy

- 25/33 patients had complete pain relief
  - 18 for more than 3 months
  - 10 for more than 6 months
- 6/33 had partial relief
- 2/33 had no relief
- 12 patients had a repeat cycle
  - 12/12 had complete relief
    - 7 for more than a year
    - 4 for more than three years
- 2 patients had a third treatment
  - Results not reported
Inpatient Ambulatory Therapy
Biological End-Point – Titrate to Effect

“The onset of the feeling of mild inebriation was our endpoint to cease any further increase in the infusion rate. Based on [our] earlier work, we knew the effective infusion dosage would likely lie in the range of 10–30 mg/hr. We also knew that the effective treatment period on average would take about 2–5 days.”


Correll GE. Personal communication and unpublished work. Anaesthetics Department, Mackay Base Hospital, Mackay, Queensland, Australia. Poster presentation at the 1999 Australian Pain Society Meeting. Fremantle, Western Australia.

Inpatient Ambulatory Therapy
• 28-year-old man with metastatic pancreatic neuroendocrine cancer with severe, intractable pain
• He was initially treated with hydrocodone before rotating through oral morphine, oxycodone, hydromorphone, and methadone, all with poor pain control
• Started on hydromorphone IV PCA at home, titrated over several weeks to 100 mg/h with 50 mg demand doses q 15 min PRN while continuing on methadone 60 mg po q8h

• Given a bolus of 25 mg IV Ketamine, which decreased his pain to 3/10 within 10 minutes
• Ketamine IV infusion started at 0.3 mg/kg/h and increased to 0.4 mg/kg/h after 5 hours
• During the next 20 hours, the continuous rate of IV hydromorphone was decreased from 100 mg/h to 0 mg/h in a gradual, stepwise fashion
Course in Hospital and Beyond

• Over the course of treatment, his opioid requirements decreased by 99% and pain ratings by 50%

• On the day of discharge, pain was rated at 5/10 on methadone 40 mg PO q8h and PRN hydromorphone IR 32 mg PO (on average using 4 doses per day).

• He did well on these doses and maintained good pain control for the next 4 weeks
  • Functional decline
  • Died at home 10 days later
Long-Term Ketamine Therapy

- CSCI? CIVI? Oral?
- Stop ketamine and use PRN IV “reboots”?
- Monitor LFTs
  - Occasional ↑LFTs have been noted in patients treated at infusion rates of ketamine > 30 mg/hr given for ≥ 14 days
  - All LFT abnormalities resolved when ketamine D/C’d
  - LFT abnormalities recur when re-challenged
- Long term use can cause ulcerative cystitis
- Long term nasal use can cause anosmia
Long-Term Ketamine Therapy

- Based on animal studies that have shown neuronal degeneration and death in the retrosplenial cortex and other specific regions of the adult rat brain:
  - Suitable neuroprotective agents should be considered whenever ketamine therapy is undertaken for the purpose of treating CRPS
  - Clonidine has become the agent of choice for preventing the potential complications of ketamine

Role of Magnesium

• When inactive, the NMDA receptor is blocked by a Mg ion
• When stimulated the Mg plug is dislodged, allowing calcium influx into the cell
• IV Magnesium sulfate (30-50 mg/kg) has been used
  • As part of multimodal opioid-sparing anaesthetic techniques
  • In treatment of neuropathic pain

Putting it All Together

• Patient selection:
  • Suspected Opioid-Induced Hyperalgesia
  • High doses of opioids, with further titration limited by side effects

• Test / Loading Dose:
  • Ketamine 0.3 mg/kg, mixed in 100 ml NS over 15 min
  • “Rapid Reduction of Suicidal Thoughts in Major Depression”: 0.5 mg/kg, mixed in 100 ml NS over 40 min


Putting it all Together

• Infusion:
  • 10 - 50 mg/hr for 2 - 5 days at “two special coffee feeling”
• “Replacing the magnesium plug”
  • MgSO₄: 30-50 mg/kg over 30 minutes
• Then wat??
  • Depends on what your HA, and Home Care programs / hospices can support
QUESTIONS?