UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Oral Ketamine for Pain

Background:

Ketamine is a rapid-acting non-barbiturate anesthetic. It's mechanism for pain relief is through noncompetitive NMDA receptor antagonism, where it blocks glutamate to inhibit the "pain pathway." It can be used via intravenous, subcutaneous, intrathecal, oral, rectal, intranasal routes to mitigate symptoms such as pain and depression. Side effects are common with ketamine use, including but not limited to: psychotomimetic phenomena, hypertension, tachycardia, and urinary tract toxicity. It is thought that oral ketamine has less side effect burden than IV/SUBQ/intrathecal routes. Oral ketamine (PO ketamine) is typically compounded by mixing injectable solution with flavoring into an oral syringe. Oral ketamine has been used for refractory pain, even in setting of the paucity of evidence of efficacy.

Importance:

Pain is one of the most common symptoms in our palliative care population. It is important for palliative care clinicians to be aware the evidence for all the possible tools in our toolbox to mitigate pain.

The Literature:

JAMA Oncol. 2018 Jun 1;4(6):870-872

Oral ketamine vs placebo in patients with cancer-related neuropathic pain: a randomized clinical trial

Objective: To determine if oral ketamine is beneficial for neuropathic pain

Outcomes: Primary: Duration of analgesic benefit, defined as improvement of 5 points or more in index pain score compared with baseline score, Secondary: Mean and worst pain, mood, adverse events

Methods: multicenter, double-blind RCT oral ketamine versus placebo in patients with cancer related neuropathic pain

- Ketamine starting dose 40mg/day titrated to max 400mg/day, received stable dose for 16 days
- Patients without analgesic benefit were removed from the study
- Maintenance of analgesic benefit considered failed if opioid dose increased during 16 day period

Results: Intention to treat analysis (n=214, median age: 58 years, 65.8% female, 74.7% patients had cancer in readmission and this pain was likely chronic, chemotherapy-induced neuropathy)

- Median duration of analgesic benefit for ketamine group was 0 days (95% CI, 0-1 day) and for placebo group was 0 days (95% CI, 0-4 days)
- No difference between QOL, anxiety/depression

Variable	Ketamine Hydrochloride	Placebo	Median Difference, Ketamine – Placebo (95% CI)[a]	*P* Value		
				Secondary Outcomes	AUC Analyses	
					Unadjusted[b]	Adjusted[c]
Secondary Outcomes						
Patients with analgesic benefit at day 4, %	34 (31.8)	39 (36.4)	NA	.47	NA	NA
Patients with an analgesic benefit at day 16, %	24 (22.4)	27 (25.2)	NA	.63	NA	NA

- Adverse effects did not differ between groups, most common ADE were cognitive disturbance, dizziness, fatigue, nausea and somnolence

Conclusion: Ketamine was equivalent to placebo for cancer-related neuropathic pain

Eur J Pain. 2010 May;14(5):466-72.

Use of oral ketamine in chronic pain management: a review

Objective: To provide overview of available evidence regarding efficacy and safety of oral ketamine in chronic pain management

Methods: Literature search (1966-2009); n=22 articles, majority were case reports or case series

- 4 studies were comparative studies with greater than N=1

Results:

- Quantitative analysis impossible given small number of trials and heterogeneity of data
- Two common ways to initiated PO ketamine: start directly with PO ketamine, low dose and titrate based on clinical effect or start with IV ketamine and switch to equipotent dose of PO ketamine
    - Median of dose ration between equianalgesic potency of ketamine SC to PO was 1:1
    - Average doses to maintain analgesic effect was 3-4 doses of PO ketamine per day
- No consistent dose-response relation, daily doses ranged from 45-1000mg/day
- Among case reports 90% of patients had positive results regarding efficacy of ketamine compared to 25% efficacy rate in the "larger" comparative controlled studies
- Most common ADE: sedation, somnolence, dizziness, hallucinations, dissociative feeling, blurred vision

Conclusion: Lack of efficacy/safety evidence does not support routine use of oral ketamine for chronic pain. Oral ketamine may have a limited place as add-on therapy in complex chronic pain patients if other therapeutic options have failed

CLINICAL PEARL: PO ketamine seems to be generally safe to use for pain management, although strong evidence for efficacy is lacking

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Anesthesiology. 1999 Jun;90(6):1528-33.

Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management

Objective: To evaluate the role of PO ketamine or transdermal nitroglycerin polymer as co-adjuvants to oral morphine compared to morphine alone or with NSAID + oral morphine in cancer pain therapy

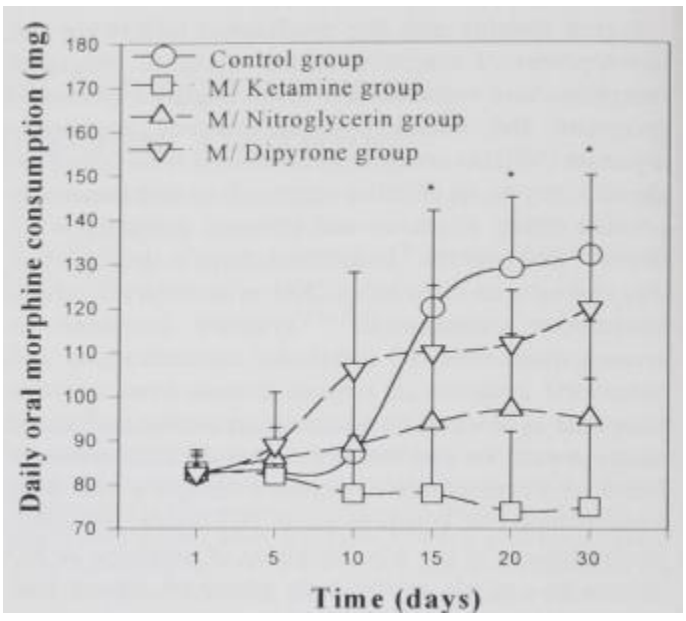
Outcomes: Primary: Changes in reported pain (VAS) after ketamine added

Methods: RCT, cancer patients receiving morphine 80-90mg/day (n=60) randomized into 4 groups:

- Morphine plus nitroglycerin 5mg patch daily or ketamine 0.5mg/kg PO Q12H or dipyrone 500mg PO Q6H, compared to morphine 10mg Q12H PO alone
- Patients were able to utilize morphine for breakthrough to keep VAS < 4
- VAS and morphine requirements were noted on days 1, 5, 10, 15, 20, 30

Results:

- Efficacy:
  - VAS scores similar across groups during study time periods
  - Reduced morphine doses in the ketamine group



- Safety
  - Somnolence highest in control group (group that required more breakthrough morphine)
  - Ketamine fairly well tolerated; 2 instances of hallucination

Conclusion:

- Ketamine is effective co-analgesic, potentially having opioid-sparing effects

Bottom Line:

- PO ketamine may be better tolerated (less side effects) than IV routes of administration given likely reduced bioavailability of PO formulation
  - Less likely to have issues with tachycardia/hypertension with oral doses, but would still monitor
- No standard dose-response has been established
- Ketamine may not have much of a role for chemotherapy-related neuropathy (especially in setting of stable disease)
- PO formulation needs to be compounded at compounding pharmacy, like Asti's or Hieber's
- IV formulation used to make PO ketamine tastes terrible… counting on our compounding pharmacy colleagues to help mask this terrible taste!
- Ketamine may be useful as a co-analgesic and may decrease overall opioid requirements if patients find beneficial
- Could be used for refractory pain, would start low with dosing and titrate slowly based on clinical response and tolerability…

CLINICAL PEARL: PO ketamine seems to be generally safe to use for pain management, although strong evidence for efficacy is lacking