UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

February 3, 2022 Vol. 3, No. 2

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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:

Ketamine Mouthwash for Oral Mucositis

Background:

Oral Mucositis (OM) is a common side effect of anti-cancer treatment and is characterized by erythema and ulceration of the GI tract. The MASCC/ISOO Clinical Practice Guidelines for the management of mucositis recommend basic oral care, topical morphine 0.2% mouthwash, systemic opioids and phototherapy for the treatment of pain from OM.

- At UPMC, we have the following options on-formulary: Doxepin 0.5% mouthwash and Magic swizzle (Diphenhydramine; Lidocaine Viscous 2%; and Maalox)
- We have the option to order PO ketamine (IV solution diluted with normal saline) for pain. Could we potentially add PO ketamine to our toolbox for oral mucositis?

Importance:

Oral mucositis is common in the oncology population and has a negative impact on quality of life. Palliative care clinicians should be aware of evidence related to treatment options.

The Literature:

Support Care Cancer. 2017 Jul;25(7):2215-2219

Treatment of severe mucositis pain with oral ketamine mouthwash

Objective: Assess the reduction in pain intensity of OM compared to baseline assessment as reported on numeric scale

Methods: open-label, prospective, phase II interventional study

- Patients with grade 3 or 4 OM (WHO scale) treated with ketamine mouthwash 20mg/mL, swish 5mL four times daily and every 4 hours as needed

Outcomes:

- Reduction in pain score (NRS 0-10) at baseline, 1 hour after first dose and then daily for 7 days, patient-reported onset (no effect, 0-15 min, 16-30 min, 31-45 min, 46-60 min or > 1 hour) and duration of effect (no effect, < 1 hour, 1-2 h, 2-3 h, 3-4 h, or > 4 h), reduction in opioid and topical lidocaine use, improvement in patient-reported sleep quality, safety and tolerability

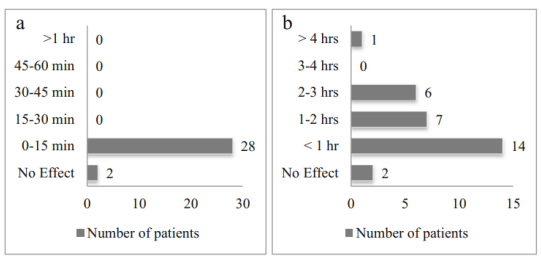
Results: n = 30

- Average time taking ketamine = 4 days (range 1-9), receiving a median of 3.5 doses of ketamine per patient/day (range 1-5.7)

Table 3 Endpoints

Objective	Baseline	1-h post		Day 1		Day 2		Day 3	
	Median (range)	Median (range)	*p* value	Median (range)	*p* value	Median (range)	*p* value	Median (range)	*p* value
Pain score at rest	6 (1–10)	4 (0–10)	<0.0001	5 (0–10)	0.005	3 (0–9)	0.0001	3 (0–8)	0.0003
Pain score when swallowing	9 (2–10)	6 (0–10)	0.0006	8 (1–10)	0.014	5 (0–10)	0.0001	4 (0–10)	0.0001
Sleep quality	5 (0–10)	n/a	n/a	6 (1–10)	0.006	6.5 (0–9)	0.019	6 (2–10)	0.034
IV morphine equivalents mg/24 h/pt	46 (0–242)	n/a	n/a	34 (0–202)	0.37	26 (1–230)	0.5	24 (0–173)	0.145
Lidocaine usages/day/patient	3 (0–5)	n/a	n/a	2 (0–8)	0.093	2 (0–5)	0.045	1 (0–4)	0.029

- Onset of effect (A) + Duration of action (B)



Conclusion: Ketamine mouthwash resulted in clinically meaningful and statistically significant reduction in pain scores

Pediatr Blood Cancer. 2020 Sep;67(9):e28573.

Ketamine mouthwash versus placebo in the treatment of severe oral mucositis pain in children with cancer: A randomized double-blind placebo-controlled trial

Objective:

- To test the efficacy of ketamine mouthwash in reducing OM in children

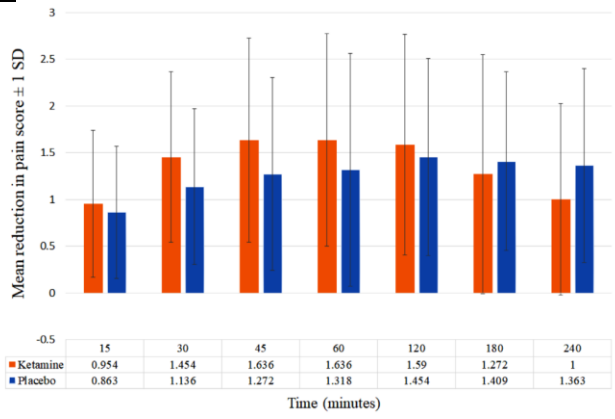
Methods:

- Children aged 8-18 with severe OM randomized to single dose of ketamine mouthwash 1mg/kg (of 4mg/mL solution) with a max dose of 40mg set or placebo
- Pain score noted at baseline and 15, 30, 45, 60, 120, 180, and 240 min time points after dose

Outcomes:

- Reduction in pain score, need for rescue medication, adverse events

Results: n = 44



- Mean OM pain score at 60 min decreased by 1.64 points (CI 1.13-2.14) in the ketamine group and 1.32 points (CI 0.76-1.87) in the placebo group (P = 0.425)
- Rescue pain medication at 60 min was required in 13.6% (n=3) of the ketamine group and 18.2% (n=4) in the placebo group (p = 1.000)
- No severe adverse events reported

Conclusion:

- Ketamine mouthwash (1mg/kg dose) did not significantly reduce OM pain or decrease the need for rescue pain medication

Bottom Line:

- RCT in children may have used doses lower than what is necessary to achieve adequate pain relief (100mg vs. 40mg max)
- Timing of daily pain scores can impact reported pain score in observational trial. We do not know when these pain scores were documented in relation to other activities (eating/drinking). Hard to generalize one snapshot in time from a daily pain score
- Outcomes at one hour are the likely most clinically significant because severity of mucositis will be closest to baseline
- Inpatient: PO ketamine on UPMC formulary for pain. There may be utility in utilizing as mouthwash (swish and spit) for OM. Currently, we do not have it already "pre-mixed" in the diluted form for its use this way. It still may be an option for patients who have tried other oral rinses without success
  - Could consider ordering doses 20mg-50mg to start, with instructions to dilute to 5 or 10mL and utilize for swish and **spit** only
- Outpatient: Collaborate with a compounding pharmacy like Hieber's or Asti's

CLINICAL PEARL: Ketamine oral rinse may be effective for refractory OM pain