

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Mucositis: A Focus on Topical Analgesia

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Patient Case

TM is a 65-year-old male with advanced head and neck cancer with a history of COPD who elected hospice two weeks ago. In addition to systemic medications to manage pain, nausea, and constipation, he is prescribed inhalation therapies for COPD and palliative radiation to the head and neck.

The hospice physician managing TM's care reports that the radiation continues to improve symptoms of pain and difficulty breathing, swallowing and speaking however TM suffers with significant mucositis in his mouth and pharynx. He has tried Magic Mouthwash, but it makes him nauseous and exacerbates the local pain from the mouth sores. Viscous lidocaine 2% topically has been considered but TM does not like the taste. The physician wants to try a compound, doxepin mouth rinse, but is uncertain of the recommended dosing.

Introduction

Mucositis is mucosal ulceration affecting the oral, pharyngeal, laryngeal and/or the esophageal areas and caused most commonly by chemotherapy or radiation to the head and neck region. Mucositis is typically painful, initially consisting of a mild or moderate burning discomfort but can be slow to heal and progress to significant pain, reducing a person's ability to talk, drink, eat and/or swallow.^{1,2}

RISK FACTORS

- Chemotherapy associated with mucositis
 - Alkylating agents (e.g., melphalan, cisplatin)
 - Anthracyclines (e.g., doxorubicin, epirubicin)
 - Antimetabolites (i.e., cytarabine, fluorouracil, methotrexate)
 - Antitumor antibiotics (dactinomycin, bleomycin, mitomycin)
 - Taxanes (docetaxel, paclitaxel)
 - Topoisomerase inhibitors (e.g., etoposide, irinotecan)
 - Molecularly targeted agents (e.g., lenvatinib, sorafenib, sunitinib, regorafenib)
- Oral disease present prior to chemotherapy and/or radiation
- Dental conditions such as poor oral hygiene, caries and periodontal disease
- Local radiation of structures around the head or neck³

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Clinical Manifestations

Sequelae, in order of occurrence:

- Soft tissue erythema of buccal mucosa or soft palate with burning sensation in mouth
- Solitary elevated white patches that are slightly painful
- Epithelial sloughing leading to shallow ulcerations that coalesce to form larger lesions
- Pain, dysphagia and reduced oral intake
- Oral or gingival bleeding
- Severe cases can lead to infection or sepsis³

Grading, from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE):^{3,4}

- Grade 1 - Asymptomatic or mild symptoms; intervention not indicated
- Grade 2 - Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated
- Grade 3 - Severe pain, interfering with oral intake
- Grade 4 - Life-threatening consequences; urgent intervention indicated
- Grade 5 - Death

Prevention

- Proper oral hygiene can lessen severity^{1,3,5,6}
- Oral cryotherapy (holding ice chips in mouth during treatment) for select patients⁶
- Low-level laser therapy⁶
- Oral zinc supplements⁶
- Prescription palifermin (Kepivance®) is a parenteral recombinant human keratinocyte growth factor that can reduce the duration of mucositis for select patients receiving high dose chemotherapy and total body irradiation.^{1,5,6}

Non-Pharmacological Treatment

- Avoid irritating food or beverages (e.g., dry, salty, acidic, hard, hot)^{1,3}
- Limit diet to foods that do not require significant chewing³
- Avoid alcohol-containing oral rinses
- Proper oral hygiene (brushing teeth, flossing, water flossing on low setting)¹
- The oral cavity should be rinsed and wiped after meals³
- Dentures, removed, cleaned and brushed often to remove plaque³
- Oral rinses with a bland solution of salt and baking soda (one-half teaspoon of salt and one teaspoon of baking soda in a quart of water) every four hours^{1,3}

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Pharmacological Treatment

Viscous Lidocaine 2%^{3,5}

Labeled indication for topical anesthesia of skin and mucous membranes or stomatitis. Recommended dose is one tablespoon (15 ml), swish and spit solution for use in the mouth, or gargle and swallow for use in the pharynx. Frequent administration is needed for adequate pain relief - separate doses by at least 3 hours. Topical lidocaine is frequently combined with other agents in a mixture referred to as "Magic Mouthwash".

"Magic Mouthwash"

Despite lack of controlled studies evaluating efficacy of these combinations, "Magic Mouthwash" formulations are commonly used to manage pain from mucositis. It is important to note that not one formulation is proven superior to another.^{1,3} Available formulas include:

- First-Mouthwash BLM - Commercially available compound kit containing diphenhydramine, lidocaine, aluminum/magnesium hydroxide and simethicone
- Compound ordered from scratch – most common ingredients:
 - Antihistamine for pain relief (e.g., diphenhydramine)
 - Local anesthetic for pain relief (e.g., viscous lidocaine)
 - Antacid to enhance coating of the ingredients in the mouth (e.g., aluminum/magnesium hydroxide¹)

Other ingredients found in some compound formulas with less supportive evidence:

- Antibiotics to reduce bacteria around the lesion (e.g., chlorhexidine)¹
- Antifungal to prevent fungal growth (e.g., nystatin) - strength per dose of nystatin suspension typically used is sub-therapeutic and sugar content may feed fungus when used topically⁷⁻⁹
- Steroid to reduce inflammation (e.g., dexamethasone) - concern that long-term use may lead to oral candidiasis⁶

Ketamine Solution¹⁰⁻¹²

An open label, prospective, phase II study conducted by Shillingburg A, et al. evaluated oral ketamine 20mg/5ml (5ml ketamine 100mg/ml solution for injection diluted with enough sodium chloride 0.9% to make a final concentration of 20mg/ml). Thirty patients were instructed to swish 5ml for 30 seconds and expectorate, then repeat 4 times daily and every 4 hours as needed. Significant pain reductions and improvement in sleep quality were shown.¹⁰

A case report by Slatkin and Rhiner describes a woman with severe mucositis with related pain refractory to opioids who trialed ketamine 20 mg oral rinse in a clinic. The oral rinse was to be swished for 1 minute and expectorated, then repeated every 3 hours as needed for breakthrough pain. The patient reported that her overall pain decreased from a 9/10 to 3/10 (0 rating = no pain and 10 rating = the worst pain imaginable) after using ketamine.¹¹

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A retrospective chart review conducted by Ryan AJ, et al. evaluated 8 patients from 2005 to 2008 with refractory mucositis pain treated with 20mg/5mL ketamine mouthwash. Most patients were administered treatments every 4 hours as needed for an average of 6 days. Adverse events reported were mild confusion, hallucinations, nausea, and vertigo. The authors concluded that ketamine oral rinse may be a viable treatment option for refractory mucositis pain.¹²

Doxepin 0.5% Mouth Rinse¹³⁻¹⁵

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Mucositis Guidelines⁶ state that Doxepin 0.5% mouth rinse may be effective to treat pain due to oral mucositis. Doxepin mouth rinse is cited in the literature as early as 2001 by Epstein JB, et al concluding it can provide clinically significant pain relief in patients with mucosal damage from a variety of cancer treatments.¹³

Leenstra JL, et al later studied doxepin 0.5% rinse (25mg in 5ml solution) topically in a Phase III randomized, double-blind, placebo-controlled trial of patients receiving radiotherapy with or without chemotherapy and found that significantly more doxepin-treated patients experience greater mouth and throat pain relief compared to placebo.¹⁴

This same investigator joined others in a subsequent randomized, controlled trial including 275 patients undergoing radiotherapy, and found the use of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash reduced mucositis during the first 4 hours after administration by a statistically significant amount compared to placebo. Significantly more drowsiness, unpleasant taste and stinging or burning was reported with doxepin mouthwash than the combination mouthwash versus placebo. Fatigue was reported by 5 patients (6%) in the doxepin mouthwash group and no patients in the combination mouthwash group. Investigators concluded that further research is needed to assess longer-term efficacy and safety.¹⁵

Morphine 0.2% Mouthwash⁶

The MASCC/ISOO Mucositis Guidelines⁶ also cite morphine mouthwash as potentially useful for mucositis. Use of 2% morphine solution (2000 mg morphine chloride diluted in 1000 mL of water) 15ml swish for 2 minutes and expectorate, then repeat every 3 hours (up to six times a day) “may shorten the duration and intensity of mouth pain, even in the absence of significant systemic absorption”⁶ according to a 2002 randomized, controlled trial¹⁶ published in the journal *Cancer*. Twenty-six patients compared morphine mouthwash to a mixture of equal parts of viscous lidocaine, diphenhydramine, and magnesium/aluminum hydroxide – the study “demonstrated statistically significantly shorter duration and lower pain intensity with the morphine mouthwash.”⁶

Published in 2015, a similar randomized, controlled trial of 28 patients assigned to topical morphine or magic mouthwash concluded that “topical morphine is more effective and more satisfactory to patients than magic mouthwash (magnesium/aluminum hydroxide, viscous lidocaine, and diphenhydramine) in reducing severity of cancer treatment-induced oral mucositis”. The morphine group used the mouthwash of 2% morphine solution (20 mg morphine sulfate diluted in 100 ml of water), 10 ml swish

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for 2 minutes and expectorate, the repeat every 3 hours (up to six times a day). The magic mouthwash group followed the same instructions.¹⁷

Patient Case Continued

Considering TM has trialed both Magic Mouthwash and viscous lidocaine 2%, with nausea & pain exacerbation and unpleasant taste reactions, respectively, alternative topical agents need to be considered. Doxepin 0.5% mouth rinse is a compounded solution that has been cited in the literature in the cancer population with mucositis with fair efficacy however not without adverse effects that may be bothersome to TM. These include drowsiness, fatigue, unpleasant taste and mouth stinging or burning.

If TM is receptive to trialing this treatment, the trial dose was 25mg/5ml administered as a one-time dose swished in mouth for 1 minute and then expectorated. It may be reasonable to repeat the dosing however at the discretion of the prescriber with separation of doses by at least 6-8 hours and not exceeding maximum dosing for doxepin systemic use as trial safety data was not conclusive.

For additional information on this topic, please review these references:

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