Doxepin for radiation therapy-induced mucositis pain in the treatment of oral cancers

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Abstract

Radiotherapy (RT), an integral part of the oncologic treatment for patients with head and neck cancer, can cause adverse side effects such as oral mucositis (OM). Pain from OM can impact a patient's quality of life and interrupt RT treatment schedules, which decreases the probability for achieving cancer cure. Conventionally, RT-induced OM pain is treated with analgesics and/or mouthwash rinses. Doxepin, a traditional tricyclic antidepressant with analgesic and anesthetic properties when applied topically to the mucosa, has been shown to lower OM pain in multiple single-arm trials (Epstein *et al.*) and more recently, in a placebo-controlled crossover study (Leenstra and Miller *et al.*). Currently, a placebo-controlled study (Sio and Miller *et al.*) using doxepin for esophagitis pain caused by RT to the thorax is underway. Doxepin will also be further compared with *magic* mouthwash and a placebo solution in a three-arm trial (Miller and Sio *et al.*) with head and neck cancer patients with OM pain caused by RT. Doxepin may represent a new standard for treating RT-induced OM pain in the future.

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Introduction

While the use of radiotherapy (RT) in the treatment of various solid cancers has become increasingly effective due to technological innovations, numerous acute and chronic treatment-related adverse effects impact the patients' quality of life.[1-3] A significant majority of head and neck cancer patients treated with radiation, with or without chemotherapy, experience painful oral mucositis (OM).[1,4] Erythema and pain caused by OM, which manifests as traumatized ulcers within the oral cavity and oropharynx, can occur due to rapid mucosal breakdown as a result of RT.[1,4] Radiobiologically, the oral mucosa is an early responding tissue for RT and shares a similarly high α–β ratio compared with the head and neck tumor itself.[5] Usually occurring within 14 days after the start of external beam RT, OM is an acute toxicity which can rapidly diminish a patient's quality of life.[1,2] OM and its associated pain can deter patients from eating and subsequently deplete their nutritional intake, which may eventually lead to hospitalization. The open sores resulting from OM pose an increased risk for infection. Furthermore, OM may interrupt scheduling and dosing for cancer therapy, which compromises treatment efficacy.[1,2,6-8]

There is no uniform management for OM, though various standards currently exist.[9] Widely used treatment options include antimicrobial rinses, mucosal coating agents, and systemic and topical anesthetics and analgesics, which often include opioid derivatives.[4,10-12] Topical analgesics such as lidocaine, benzocaine, and diphenhydramine usually reduce pain for up to 30 min, though contact with the ulcerated layer of oral mucosa often causes stinging and taste impairment.[12,13] Doxepin, an antidepressant, has recently been shown to produce temporary local anesthesia, followed by more durable analgesia when used topically.[14] In recent pilot trials, doxepin has been shown to reduce the frequency and severity of OM complications in cancer patients.[8,15-17]

Background

Doxepin

Doxepin, a tricyclic antidepressant, is Food and Drug Administration (FDA)-approved for the treatment of depression, anxiety, and moderate pruritus.[17] It works as an antidepressant by increasing concentration levels of serotonin and norepinephrine at the presynaptic neuronal membrane level.[17-19] When used topically, it has been shown to have sequential or concurrent anesthetic and analgesic effects.[18] In rodent models, it has been demonstrated to substantiate the effect of opioid analgesics and produce local anesthetic activi-

ty.[18,20-22] While not fully understood, the mechanism of action may be explained through doxepin's suppressive action on pain stimuli in cutaneous nociceptors as a sodium channel blocker.[18] Doxepin may also modulate N-methyl-D-aspartate receptors that regulate spinal nociception.[19,23]

Completed trials

A number of symptom control trials have been completed to evaluate the efficacy of doxepin in patients with OM undergoing cancer therapy (Table 1).[8,16,24]

Two non-randomized, open-label trials by Epstein *et al.* have shown significant anesthetic and analgesic properties of doxepin in patients with OM.[8,15-17] In the first trial, 51 patients with OM pain caused by cancer therapy-related side effects were enrolled.[8] All patients' baseline lesions and erythema were assessed using the oral mucositis assessment scale (OMAS) at rest and also after most recent food intake. Patients were instructed to swish 5 mL of an aqueous doxepin suspension (5 mg/mL) containing 0.1% alcohol and sorbitol for one minute and then spit out the rinse. A visual analogue scale (VAS) was used to evaluate the patient's discomfort (pain, stinging, taste, and drowsiness) at 5 and 15 min, and then hourly for up to 4 h.[8] Compared to baseline, doxepin attenuated pain by a maximum of 75% (P<0.0001). Patients noticed instantaneous pain relief; 5 min after using the rinse, patients reported an average pain reduction of 41% (P<0.0001). Patients experienced pain relief lasting for a median of 145 min. However, 16 patients (31%) complained of mild burning or stinging after using the doxepin rinse.[8]

In the second trial by Epstein *et al.*, 9 patients with OM pain due to cancer therapy were enrolled and treated with the same doxepin rinse. Similar questionnaires including OMAS and VAS were also applied. Patients used the doxepin rinse 3 to 6 times daily as needed, and were assessed at the beginning of the trial and after a week.[15,16] Similar to the results of the initial trial, patients reported immediate pain reduction of 2 points on the VAS within 5 minutes (P=0.008). The pain reduction was significantly lower than baseline for up to 120 min after the first doxepin dose. After a week of daily usage of doxepin, the median reported baseline pain scores on the VAS were not significantly different from the previous visit (P=0.41). Taste alteration, stinging, and drowsiness also remained the same. However, most patients still reported that the overall pain reduction was instant and long-lasting.

More recently, the North Central Cancer Treatment Group's (NCCTG [Alliance for Clinical Trials in Oncology]) phase III randomized, double-blind trial conducted by Leenstra and Miller *et al.* (NCCTG-N09C6) compared the treatment benefits of using doxepin versus placebo for 140 patients who developed OM pain while undergoing head and neck RT.[24] This was the first placebo-controlled trial to determine the efficacy of doxepin oral rinse as an analgesic for patients with OM caused by RT. This trial also attempted to determine the side effects of doxepin oral rinse and patient preference for the continuation of doxepin treatment. The patients were randomized to receive a single dose of either doxepin (5 mg/mL) or placebo on day 1, and were then given the option to cross over to receive the other treatment on the following day. Patients answered a numerical analog questionnaire (on a scale from 0 to 10) which assessed pain, taste, burning sensation, and drowsiness at various time points after rinsing, for up to 4 h. After the scheduled testing, the patients were unblinded and given the choice to continue doxepin treatment. The area under the curve (AUC) analysis of average mouth and throat pain reduction over time showed significant pain relief for patients after using the doxepin rinse ($\Delta = -9.1$) compared to the placebo group ($\Delta = -4.7$, P<0.001).[24] AUC analysis also showed that patients preferred the taste of placebo over doxepin (P=0.002). Furthermore, at the two-hour mark, patients noted an increased drowsiness score by 1.1 units for doxepin versus the placebo (P=0.02).[24] A majority of the patients (63%) expressed a desire to continue doxepin treatment after the trial, despite reporting bad taste and drowsiness.[24]

Current doxepin studies

As a pilot effort organized by the Mayo Clinic Cancer Center, a double-blind, randomized trial (MC13C1, Sio, Miller *et al.*), has currently completed accrual of patients to compare doxepin *versus* a placebo rinse in the treatment of esophagitis-related pain in patients receiving RT to the thorax with or without chemotherapy. Patient response to doxepin and placebo will be assessed using a crossover design by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and Radiation Therapy Oncology Group (RTOG) acute toxicity criteria, over two separate daily testing sessions. This trial primarily aims to determine if doxepin can reduce radiation-induced esophagitis pain, based on its previously demonstrated benefit in patients with mucositis-related pain caused by RT to the oral cavity.[24] A secondary objective of this trial is to assess the systemic tolerability of doxepin in patients receiving chemoradiotherapy or RT-based treatments, as the doxepin solution will be swallowed and ingested in this clinical study by patients who may not have clinical depression or anxiety (the current FDA-approved indications for doxepin use).

Table 1. Trials that determined the efficacy of doxepin for treating oral mucositis pain secondary to cancer therapy.

Author(s)	Number of patients	Trial Design	Pain evaluation Time point	Acute pain reduction after doxepin	Side effects
Epstein *et al.*[8] (2006)	51	One arm	4 h	41% (avg.) drop from baseline after 5 min (P<0.0001)	Minimal discomfort
Epstein *et al.*[16] (2008)	9	One arm	4 h, Day 1 and Day 8	2 unit (median) drop from baseline after 5 min (P=0.008)	No change after a week from baseline
Leenstra, Miller *et al.*[24] (2014)	140	Randomized Two arm crossover	4 h, Day 1 and Day 2*°	2 unit (avg.) drop from baseline after 30 min	Bad taste, stinging, drowsiness
Sio, Miller *et al.* (MC13C1) (Current)	50 Planned	Randomized Two arm crossover	4 h, Day 1 and Day 3*	Trial results pending	Trial results pending
Miller, Sio *et al.* (A221304) (Current)	240 Pending accrual	Randomized Three arm	4 h°	Trial results pending	Trial results pending

*Includes a crossover phase; °includes an optional continuation phase.

Led by Miller and Sio, a recently approved Alliance phase III trial, A221304, is now currently accruing patients nationally. This double-blind, randomized, placebo-controlled three-arm trial seeks to expand on the findings of NCCTG-N09C6 with the addition of DLA (diphenhydramine, lidocaine, and antacids) mouthwash. Despite the regular clinical use of the DLA rinse, there is limited evidence for its efficacy.[25] Also called *Magic* mouthwash or First® mouthwash, the DLA mouthwash contains three active ingredients which may potentially alleviate mucositis pain: diphenhydramine hydrochloride (an anti-histamine with anesthetic properties), lidocaine hydrochloride (an anesthetic with antipruritic properties when applied topically), and an antacid. There has not been a placebo-controlled trial in evaluating the effects of DLA mouthwash on patients with OM pain secondary to RT for their head and neck cancers. A previous clinical trial with DLA rinse compared its effectiveness with chlorhexidine and a soda rinse in treating chemotherapy-induced mucositis; it showed no significant difference among the three treatment arms.[26] The A221304 trial will compare OM pain reduction and adverse effects of doxepin and DLA mouthwash to a placebo in head and neck cancer patients undergoing RT to the oral cavity.

Conclusions

Presently, guidelines set by the Multinational Association of Supportive Care in Cancer (MASCC) suggest the potential use of doxepin mouthwash for the treatment of OM pain based on case reports and clinical examples.[27] Managing RT-induced OM remains an active area of research in cancer symptom control, as treatment-related oral and gastrointestinal mucosal side effects and symptoms can significantly reduce quality of life, limit cancer treatment, and subsequently jeopardize oncologic and clinical outcomes of our patients. A number of completed trials have established the potential role of doxepin in reducing OM pain in patients undergoing RT with or without chemotherapy. Future studies may be needed, in addition to the currently ongoing studies to further define and solidify the role of doxepin and its potentially efficacious use for OM and esophagitis-induced pain caused by RT. The results of these studies may strengthen and help update the MASCC guidelines in the future.

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