Diclofenac Mouthwash as a potential therapy for reducing pain and discomfort in chemo-radiotherapy-induced oral mucositis

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Abstract

Aims: Oral and/or oropharyngeal acute mucositis during and after chemo-radiotherapy (chemo-RT) for head and neck squamous cell carcinoma (HNSCC) can be extremely painful, sometimes requiring nasogastric feeding to enable adequate nutrition. The MASCC/ISOO evidence- based guidelines recommend benzydamine mouthwash for mucositis prevention in RT (recently updated to include chemo-RT), and a Cochrane systematic review found other agents to be effective in prophylaxis. Diclofenac mouthwash is licenced for painful oral mucosal inflammatory conditions but to our knowledge has not been assessed in chemo-RT associated oral mucositis.

Method: A clinical observation and service evaluation study in 10 patients undergoing chemo-RT for HNSCC to assess the potential value of diclofenac mouthwash (0.74mg/ml) in reducing symptoms. Patients used 20ml of mouthwash up to 4 times a day starting in week 3 (of a 6 week course of treatment), recording pain and discomfort scores using a visual analogue scale on days 0, 1,7 and 14 (until the end of week 4). As per our current clinical practice, oral mucositis was not clinically scored as an outcome. Statistical analysis was performed using a one-way ANOVA.

Results: Using diclofenac mouthwash, 9/10 patients experienced pain score reduction from day 0 (mean score 6.75 +/- SD 1.83) to day 2 (5.05 +/- SD 1.62) and day 14 (4.09 +/- SD 1.96).

Conclusions: Diclofenac mouthwash may be beneficial for managing chemo-RT-induced oral mucositis. While a prospective randomised clinical trial is needed, it can be prescribed for this condition within its current licence.

Key words: oral mucositis, radiotherapy, diclofenac, mouthwash, pilot study.

Introduction

Oral mucositis is a common side effect that occurs during treatment for head and neck squamous cell carcinoma (HNSCC) with external beam radiotherapy (RT), and chemo-radiotherapy therapy (chemo-RT). Oral mucositis can progress to ulceration and sub-mucosal changes (1) and have a significant negative impact on the patient's quality of life and result in dysphagia, dehydration and poor nutrition (2).

Though many drugs are available, there is currently no approved therapy for oral mucositis (1). Various agents have been advocated for both prevention and symptom control. In their evidence-based clinical practice guidelines for mucositis secondary to cancer therapy (3), the Multinational Association for Supportive Cancer Care (MASCC) and International Society of Oral Oncology (ISOO) recommend that 0.2% morphine mouthwash and 0.5% doxepin mouthwash may be effective to treat pain due to oral mucositis in patients treated by chemo-RT.

Benzydamine (Difflam) mouthwash, a non-steroidal anti-inflammatory drug that acts by inhibiting pro- inflammatory cytokines including TNF-α is also recommended by MASCC and to prevent oral mucositis in patients with head

and neck cancer receiving moderate dose RT (up to 50 Gy). Recently this has been updated to include patients undergoing chemo-RT (4).

A Cochrane systematic review of interventions for preventing oral mucositis included 89 useable studies and evaluated various agents. Those with some benefit (with variable strength of evidence for use during chemotherapy, chemo-RT and RT regimes) included ice chips, amifostine benzydamine and Chinese medicine, honey and zinc sulphate (5).

A systematic review of the many natural products such as vitamins, plant extracts, chamomile, aloe vera, glutamine and manuka honey that have been used for both prophylaxis and symptom control in oral mucositis has recently been published by MASCC/ISOO and use of oral glutamine was suggested. (6)

Other methods including photo-bio-modulation (PBM) such as low-level laser therapy are also used by some for both prevention and/or treatment of oral mucositis. A recent MASCC/ISOO systematic review is available (7). Finally, several novel biological agents including recombinant human interleukin-11 and recombinant human keratinocyte growth factor-1 are currently undergoing phase II/III clinical trials and the results are awaited with interest. A recent comprehensive summary of these potential agents is available (1).

Diclofenac, a powerful non-steroidal anti-inflammatory drug, has been used topically for musculoskeletal disorders and pain (8). Its mechanism of action is

via cyclo-oxygenase-2 (COX-2) inhibition, reducing angiogenesis and induction of apoptosis. More recently, diclofenac mouthwash (0.74mg/ml) has been assessed for painful oral mucosal conditions and following periodontal surgery (9,10). It is currently licenced in the UK (and in other countries) for symptom control of painful inflammatory conditions of the oral mucosa (Figure 1). We regularly prescribe this mouthwash to help control oral symptoms in patients with HNSCC undergoing chemo- RT but to date only have anecdotal evidence of its potential benefit.

Methods

No ethical committee approval was required for this clinical observation/service evaluation study in a small group of 10 head and neck cancer patients as our practice was not changed. Ten patients who were undergoing intensity modulated RT (IMRT) treatment (65Gy in 30 fractions) for tongue base (n=6) or tonsillar SCC (n=4) were included. Eight of the primary tumours were staged as T2 while two were T4a. Eight patients had positive neck nodes at the time of diagnosis. Seven patients had concurrent chemotherapy during RT while 3 patients had RT only. Patients were only included if they were not already using opioid analgesia during the period of evaluation. Patients were prescribed the mouthwash from the beginning of week 3 (of a 6 week course of treatment), and were instructed to use 20ml and to gargle for 1-2 minutes up to 4 times per day, before spitting it out. Patients were asked to score their discomfort during 14 days of using the mouthwash on a sheet containing a visual analogue scale (VAS) with 0 for no

pain to 10 for unbearable pain at day 0 (before using the mouthwash for the first time), day 1, day 2, day 7 and day 14 (until the end of week 4 of therapy). All scores were put on an Excel spread sheet. The mean and SD were calculated and the results were analysed using a single way ANOVA. No formal scoring system was used to assess oral mucositis severity during treatment as this is not the routine practice of the oncologists in our unit.

Results

Seven men and three women completed VAS while using diclofenac mouthwash during their cancer treatment. The mean age was 71 years (range 54 - 87 years). Initial assessment of the VAS sheets found that 9/10 patients experience some improvement in their oral mucositis symptoms using diclofenac mouthwash over the 2-week period of observation (Figure 2). A statistically significant difference was found between the mean VAS scores over the 2 week period (ANOVA F-stat 5.83, P= 0.0083) (Table 1).

Discussion

Oral mucositis can be an extremely debilitating complication of chemo-RT treatment for HNSCC. Many drugs and other agents have been tried for both the prevention and treatment of oral mucositis with varying success. Currently recommendations including the use of benzydamine have been published by MASCC/ISOO (3,4,6,7). Our preliminary observations suggest that diclofenac mouthwash might have some benefit in the symptom control of this painful

condition. In some respects, this is not surprising given its anti-inflammatory properties which also account for the therapeutic benefits of both aspirin and benzydamine in painful sore throats (8). However, the longer term use of anti-inflammatory agents can be associated with oral mucosa irritation, sensitization and paradoxical worsening pain.

In addition to the small size of our pilot study (10 patients), a potential confounding factor is the progressive development and worsening of oral mucositis in many patients as the cancer treatment continues over several weeks. A prospective randomised clinical trial is being considered, but the study design will need careful planning to take in to account the likelihood of worsening mucositis during RT or chemo-RT treatments, and the need for opioids to control pain in some patients.

However, given that diclofenac mouthwash is available and is licenced for use in painful inflammatory oral mucosal conditions, and to date has not received attention by MASCC/ISOO or others, we wanted to use this paper to raise awareness of its potential use and benefit in RT-induced oral mucositis.

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Table 1 Summary of results showing mean, standard deviation (SD) and ANOVA for the 10 patients who participated in this study.

Data Summary				
Days from start of mouthwash	**N**	**Mean**	**Std.Dev.**	**Std.Error**
Day 0	10	6.75	1.83	0.58
Day 2	10	5.05	1.62	0.51
Day 14	10	4.09	1.96	0.59

ANOVA Summary					
Source	**Degrees of Freedom DF**	**Sum of Square SS**	**Mean Square MS**	**F-Stat**	**P- Value**
Between Groups	2	37.68	18.84	5.72	0.0083
Within Groups	28	92.26	3.30		
Total:	30	129.93			

Figure 1. Commercially available diclofenac mouthwash.

Figure 2. Visual analogue scores of the 10 patients at Day 0, 2 and 14.