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ORIGINAL ARTICLE

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A phase II study of Biotene in the treatment of postradiation xerostomia in patients with head and neck cancer

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Abstract One of the major side effects of radical radiation therapy for head and neck malignancies is xerostomia, or dryness of the mouth. There is no clearly effective treatment for this condition, but we have observed that patients in our practice believe that their symptoms improve significantly when using two "over-the-counter" oral comfort products – Biotene (toothpaste, mouthwash and chewing gum) and Oralbalance gel. We decided to study these agents in a formal phase II study to evaluate their usefulness in patients with postirradiation xerostomia. Twenty-eight patients with post-irradiation xerostomia were entered on the study. All had biopsy-proven carcinoma of the nasopharynx, oropharynx, oral cavity, hypopharynx or larynx, and had received primary radiotherapy with curative intent ($\geq$50 Gy in 20 fractions) more than 4 months before study entry. More than 75% of both parotid glands were included in the primary radiation field. There was no clinical evidence of recurrent disease. Patients were provided with a 2-month supply of Biotene mouthwash, toothpaste, chewing gum and Oralbalance gel. Response was evaluated 1 and 2 months after study entry using a patient-completed visual analogue scale to assess the severity of xerostomia and its effects on quality of life. For analysis, the scored baseline was subtracted from the later scores to assess change. Patients with an increase of 10 mm from their baseline score on the visual analogue scale were classified as having responded to the treatment intervention, and those with an increase of $\geq$25 mm from their baseline score were classified as having experienced a major improvement in their symptoms. After 2 months of treatment, 15 patients (54%) reported an improvement in intraoral dryness and 10 of these patients (36%) reported a major improvement. Similar proportions of patients (46% some improvement, 25% major improvement) reported an improvement in their ability to eat normally. Seventeen patients (61%) reported an improvement in oral discomfort, and 12 of these (43%) had a major improvement in their symptoms. The results of this study suggest that the use of Biotene (mouthwash, toothpaste and chewing gum) and Oralbalance gel can improve many of the symptoms of radiation-induced xerostomia. A placebo effect could account for many of the observed improvements in symptoms, and in order to assess the role of these agents in the management of patients with postirradiation xerostomia a randomised phase III study is needed.

Key words Radiation therapy · Xerostomia · Phase II study

Introduction

Radiation therapy (RT) is one of the primary modalities of treatment in head and neck cancer and can be used either as definitive treatment or as adjunctive therapy after surgical resection of the primary tumour. Because of the location of most primary head and neck cancers and regional lymph nodes, the salivary glands of most patients are included in the irradiated volume. While RT can be very effective in the eradication of tumour in these patients, one of the major side effects of treatment is xerostomia, or dryness of the mouth [6]. RT damages the parenchyma of the salivary glands and produces secretory hypofunction. These effects are dose related and usually permanent, and the clinical syndrome is known as postirradiation xerostomia [1–3].

Patients with postirradiation xerostomia produce little or no saliva and, as a result, they frequently complain of oral discomfort and pain, as well as difficulty with chewing, swallowing and speech [2–4]. Food often has little or no taste, and these patients commonly present with nutritional problems. Also, they have a greatly increased incidence of oral infections and dental caries, and all of these effects can combine to significantly affect patients' quality of life [3]. There is no clearly effective treatment for this condition: saliva substitutes are generally ineffective and most patients prefer increased water consumption to their continued use. Since the completion of this study, pilocarpine hydrochloride has been approved for use in patients with postirradiation xerostomia, and various reports indicate that approximately 50% of patients may benefit from its use [5, 8].

In our institution many patients with postirradiation xerostomia use various over-the-counter oral comfort agents, including sugar-free chewing gums and mouthwashes, to alleviate their symptoms. We observed that a number of our patients reported a major improvement in their symptoms with two of these products – Biotene (toothpaste, mouthwash and chewing gum) and Oralbalance gel – and, consequently, we decided to study these agents in a formal phase II study to evaluate their usefulness. Biotene is available as an alcohol-free mouthwash, a sugar-free chewing gum, and a toothpaste, and Oralbalance is available as a moisturising gel [9]. Biotene is said to act by producing an antibacterial enzyme system in the oral cavity that penetrates the cell walls of plaque-forming bacteria, destroying them just under the gum line. Oralbalance moisturising gel is felt to prevent moisture loss, and thereby to soothe and protect dry oral tissues.

Patients and methods

Patients

All patients had biopsy-proven carcinoma of the nasopharynx, oropharynx, oral cavity, hypopharynx or larynx. All had received primary RT with curative intent (≥ 50 Gy in 20 fractions) which had been completed more than 4 months before study entry. More than 75% of both parotid glands had been included in the primary radiation field. There was no clinical evidence of recurrent disease. The median age was 59 years (range 38–80), and there were 20 men and 8 women. All patients gave a history of clinically significant problems with xerostomia and were accrued from the out-patient follow-up clinics of the head and neck service at the Princess Margaret Hospital. Patients who were taking antidepressants, pilocarpine or other drugs associated with anticholinergic side effects were excluded from this study, as were patients with other medical problems associated with xerostomia, such as Sjögren's syndrome. Informed consent was obtained from each patient, and the study was approved by the University of Toronto Human Subjects Review Committee.

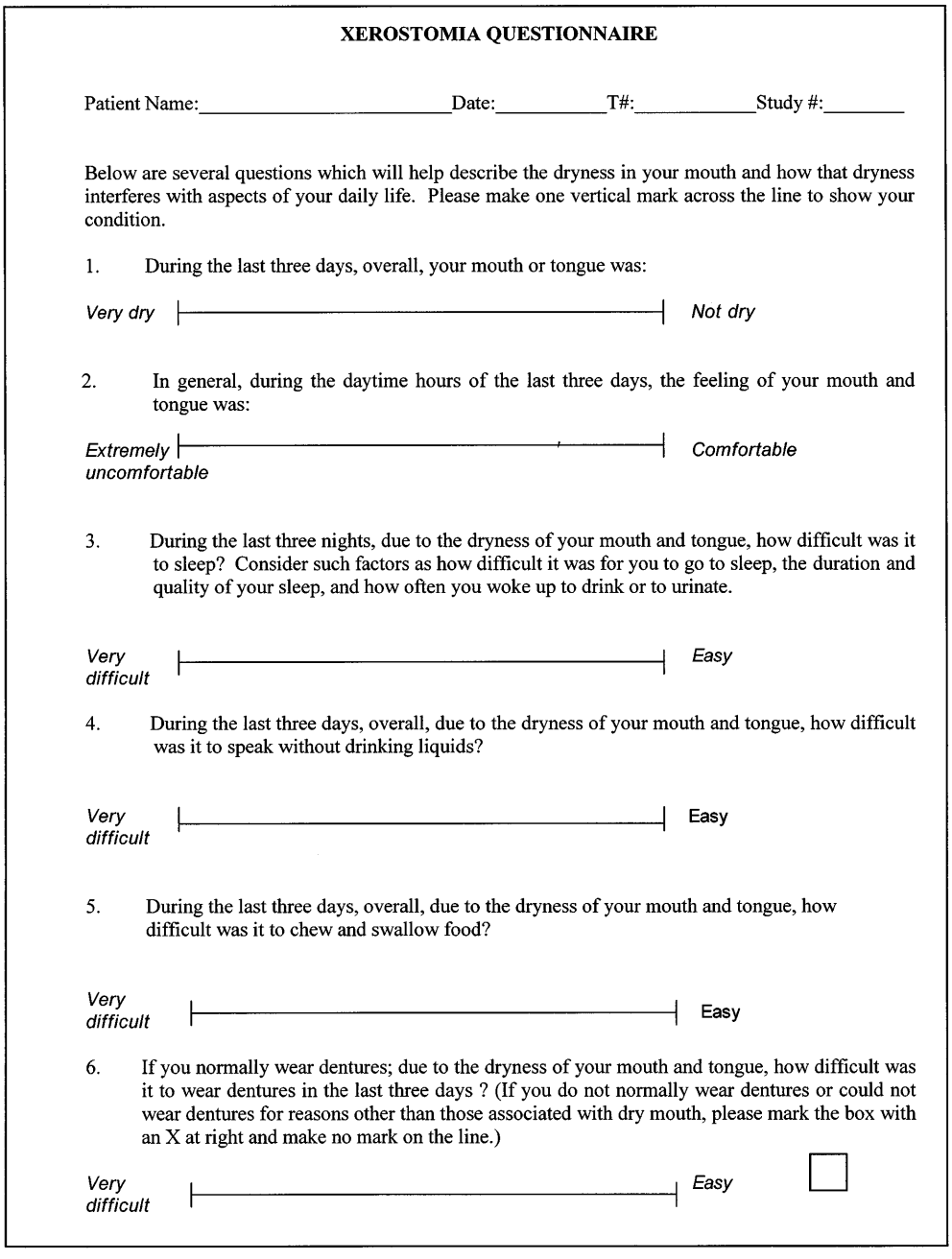
Treatment protocol

After entry on study, patients were supplied with a kit containing a 2-month supply of Biotene mouthwash, toothpaste and chewing gum, and of Oralbalance gel. Biotene toothpaste contains the main ingredients of a fluorinated toothpaste (monofluorophosphate, xylitol and sorbitol) as well as the major components of the lactoperoxidase system (lactoperoxidase, thiocyanate and glucoseodidase) [9]. Patients were also given a Biotene soft toothbrush to use with the toothpaste and full instructions on how to use these products. They were told to use the Biotene chewing gum as desired to relieve symptoms of dry mouth and throat. They were instructed to use the Oralbalance gel when they felt their mouths were uncomfortably dry, and to apply a half-inch ribbon of gel onto the tongue or directly onto the affected areas in the mouth. They were advised to brush with the Biotene toothpaste on rising in the morning, after eating, and at bedtime.

Prior to entry on study, evaluation included a general history and physical examination, in addition to a detailed head and neck examination. Patients also completed a questionnaire evaluating the severity of xerostomia and its effects on their quality of life. This was the same questionnaire as had been used in a phase III study of pilocarpine hydrochloride in a similar group of patients [5]. A 100-mm scale was used to record the responses to each of six questions. This scale was set up with negative responses on the left and positive responses on the right (Fig. 1). The patients marked their responses on the scale in relation to these extremes. For analysis the scored baseline was subtracted from the later scores to assess change. A patient with an increase of 10 mm from baseline score on the visual analogue scale was classified as having responded to the treatment intervention. Those with an increase of ≥ 25 mm from their baseline score were classified as having a major improvement in their symptoms.

Patients were assessed with a detailed head and neck examination after 1 and 2 months on study, and they also completed the questionnaire on the severity of xerostomia. The primary measure of efficacy was based on the proportion of patients with an increase from baseline of at least 10 mm for the assessment of oral dryness. Patients who discontinued use of the products prior to the 1- and 2-month assessments were classified as nonresponders.

Fig. 1 Xerostomia questionnaire



XEROSTOMIA QUESTIONNAIRE

Patient Name:_____ Date:_____ T#:_____ Study #:_____

Below are several questions which will help describe the dryness in your mouth and how that dryness interferes with aspects of your daily life. Please make one vertical mark across the line to show your condition.

1. During the last three days, overall, your mouth or tongue was:

Very dry — *Not dry*

2. In general, during the daytime hours of the last three days, the feeling of your mouth and tongue was:

Extremely uncomfortable — *Comfortable*

3. During the last three nights, due to the dryness of your mouth and tongue, how difficult was it to sleep? Consider such factors as how difficult it was for you to go to sleep, the duration and quality of your sleep, and how often you woke up to drink or to urinate.

Very difficult — *Easy*

4. During the last three days, overall, due to the dryness of your mouth and tongue, how difficult was it to speak without drinking liquids?

Very difficult — Easy

5. During the last three days, overall, due to the dryness of your mouth and tongue, how difficult was it to chew and swallow food?

Very difficult — Easy

6. If you normally wear dentures; due to the dryness of your mouth and tongue, how difficult was it to wear dentures in the last three days ? (If you do not normally wear dentures or could not wear dentures for reasons other than those associated with dry mouth, please mark the box with an X at right and make no mark on the line.)

Very difficult — *Easy* ☐

Results

Between January and October 1996, a total of 28 patients were entered on study. Five patients discontinued use of the Biotene and Oralbalance products during the study, while 23 used the products as instructed for the duration of the study (1 developed tumour recurrence during the 2nd month of treatment and 4 found the products to be of no benefit). The median baseline severity of xerostomia score was 10 mm (range 9–74 mm; Table 1), indicating that these patients perceived that their mouth was markedly dry over the preceding 3 days. The baseline scores for the other questions are also shown in Table 1. Most patients found it difficult to chew and swallow food due to the dryness of their mouths (median score 14 mm), and many had considerable oral discomfort (median score 35 mm).

The proportions of patients reporting a significant (>10 mm) and major (>25 mm) improvement in the various parameters compared to baseline at one and two months are shown in Fig. 2. After 2 months using

Table 1 Baseline patients' scores on xerostomia questionnaires

	Mean score	Median score	Range
Oral dryness over past 3 days	22.6	10	9–74
Oral discomfort over past 3 days	39.2	35	3–82
Difficulty in sleeping over past 3 nights	48.8	50	3–97
Difficulty in speaking over past 3 days	31.4	21	2–94
Difficulty in chewing and swallowing food over past 3 days	27.7	14	4–93
Difficulty in wearing dentures over past 3 days	63.3	61	17–97

the Biotene and Oralbalance, 15 patients (54%) reported a significant improvement in the sensation of intraoral dryness, and 10 of these patients (36%) reported a major improvement with a >25 mm change in their sensation of intraoral dryness as compared with the baseline assessment. Similar proportions of patients (46% significant improvement, 25% major improvement) reported an improvement in their ability to eat normally after 2 months on treatment. Seventeen of the 28 patients (61%) reported a significant improvement in oral discomfort, and 12 of these (43%) had a major improvement in their symptoms.

Ten of the 28 patients (36%) noticed a significant improvement in their ability to speak, while 8 of these 10 patients (29%) experienced a major improvement. A similar proportion of patients noted an improvement in their ability to go to sleep and stay asleep and not be affected by persistent xerostomia necessitating continual ingestion of liquids. Of the 14 patients who wore dentures, 7 (50%) noticed a sufficient improvement in their intraoral dryness to make wearing their dentures more comfortable.

At the end of the 2 months on study, 10 patients expressed a wish to continue using these products. No adverse effects were noted of the Biotene or Oralbalance gel.

Discussion

Xerostomia is the most common symptom in patients treated with radical RT for head and neck cancer. Its effects on patients' quality of life are often severe. Oral discomfort and difficulties with oral functioning, including speech, are common. Simple activities such as telephone conversations or participation in meetings can become major ordeals for these patients [2–4]. In addition, periodontal disease is frequently seen, and patients often have a low tolerance for dental prostheses because of tissue friability and lack of lubrication. Oral symptoms frequently alter food choices and nutritional compromise is common. Also, patients often complain of sleep disruption because of the need to awaken to moisten their mouth or to pass urine (secondary to increased fluid ingestion).

The goal of treatment of radiation-induced xerostomia is to provide symptomatic relief of mucosal dryness with saliva substitutes, or to increase the production of saliva with moistening agents or sialagogues.

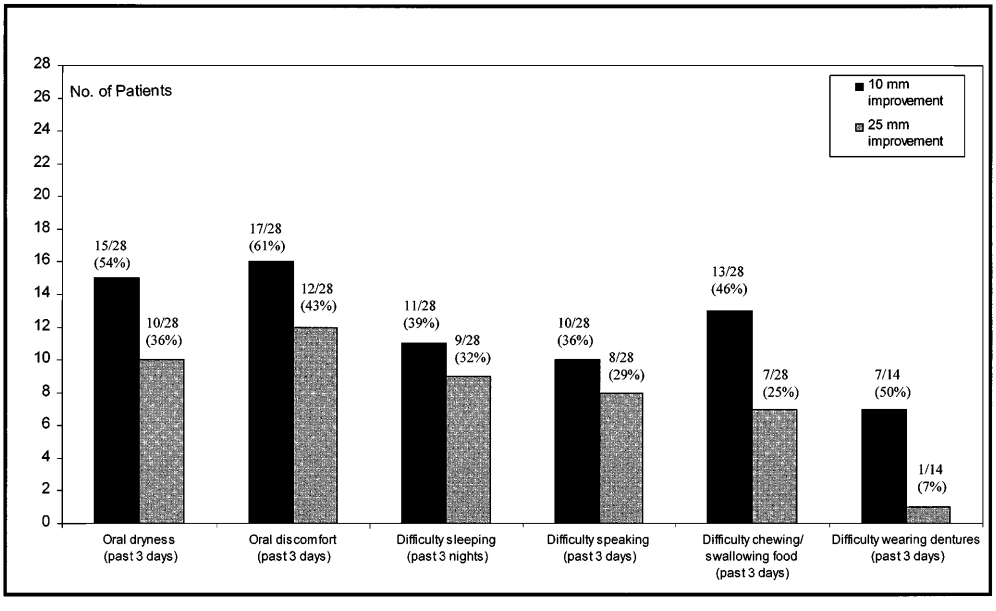


Fig. 2 Improvement from baseline scores on xerostomia questionnaire after 2 months of treatment

The results of this study show that the use of Biotene (mouthwash, toothpaste and chewing gum) and Oralbalance gel can improve many of the symptoms of radiation-induced xerostomia. More than half of the patients noted a definite improvement in oral dryness after 2 months' use of these products, and a substantial proportion (36%) reported a major improvement in their symptoms. In addition, many patients noted a major improvement in oral discomfort, which is frequently a troublesome symptom for these patients. Also, approximately half of the patients reported an improvement in their ability to eat normally.

While the results in this report are encouraging, the limitations of this phase II study must be borne in mind. It is possible that a placebo effect of treatment could account for a considerable proportion of the benefit of therapy observed. In a double-blind phase III study of pilocarpine in patients with postirradiation xerostomia, 25% of those treated with placebo reported an increase of over 25 mm from baseline, using the same visual analogue instrument as in this study [8]. In addition, this study assessed the benefit of these agents in only 28 patients for a short period of time. We did not evaluate their effect on the oral microflora or on periodontal disease. In order to assess the role of these agents in the management of patients with postirradiation xerostomia, a randomised phase III study incorporating these end-points is needed. The fact that only 10 patients wished to continue these products after study completion may indicate a low convenience of treatment and this also needs to be explored.

Prevention of postirradiation xerostomia would, of course, be preferable to treatment, and various approaches to achieving this are being investigated. The extent of radiation-induced salivary dysfunction is influenced by several factors, including radiation dose, the pretreatment function of the salivary gland, and the extent of the radiation fields (especially the volume of the salivary gland tissue receiving full-dose RT). The partial exclusion of the parotid gland from high-dose irradiation has been reported to be efficacious in reducing post-RT symptoms from xerostomia. Nishioka et al. reported on 45 patients with carcinoma of the nasopharynx treated with the three-field RT technique, which reduced the dose given to the superficial lobe of the parotid glands by >60% compared with the standard lateral opposed-pair technique [7]. Forty percent of these patients had no or mild xerostomia, in comparison to a 100% incidence of moderate to severe symptoms of oral dryness in a historical cohort of 33 patients treated using a lateral opposed-pair technique. Similar results have been reported from other centres [1]. Another approach to the prevention of radiation-induced xerostomia is the use of radiation protectors such as WR-2721 to attempt to preserve some salivary-gland function. Preliminary reports are encouraging but their effectiveness has yet to be determined. Pilocarpine has been reported to be effective in preventing the development of severe post-RT xerostomia when given concomitantly during RT [10]. In addition, the severity of radiation-induced mucositis during RT has been reported to be much less in patients receiving concomitant pilocarpine. We are currently performing a double-blind, placebo-controlled study of oral pilocarpine in patients receiving radical RT for head and neck cancer to assess the effect on post-treatment xerostomia as well as on the acute toxicity of RT.

Treatment with saliva substitutes has been disappointing, with the major disadvantage being the temporary nature of the relief provided. Also, the taste of the products, which may be affected by the effects of RT, is a major complaint of many patients. There has been renewed interest recently in the use of sialagogues to stimulate any residual functional salivary-gland tissue after RT. While a major proportion of patients' salivary tissue can be damaged by RT, it is unusual for all the minor and major salivary glands to be compromised. A number of agents have been used in the past as sialagogues (e.g., neostigmine, bromhexine), but more recently pilocarpine hydrochloride has been approved for treatment of radiation-induced xerostomia in several countries. It is a naturally occurring cholinergic parasympathicomimetic alkaloid with a broad range of pharmacological effects, such as increased secretion from the exocrine glands, including the sweat, salivary, lacrimal, gastric, pancreatic and intestinal glands. The clinical efficacy of pilocarpine hydrochloride has been evaluated in two large placebo-controlled randomised trials, and approximately 50% of patients given 5–10 mg three times a day noted an improvement in the sensation of oral dryness [5, 8]. Saliva production was also improved but it did not correlate with symptomatic relief. Pilocarpine administration was also associated with an increased ability to speak without requiring liquids and a reduced need for oral comfort agents. The major adverse effect noted by patients was sweating, and 29% of patients taking 10 mg three times a day withdrew from the studies because of adverse effects. As pilocarpine, Biotene and Oralbalance work by different mechanisms, it is certainly possible to use them together and the combination may be more effective than either treatment used alone.

The effects of postirradiation xerostomia on a patient's quality of life are usually severe and last for the duration of the patient's life. Management and prevention are best done in a multidisciplinary head and neck cancer unit with the involvement of radiation oncologists, dentists, dental hygienists, pharmacists, nurses and other health care professionals. While this study has suggested a benefit to Biotene and Oralbalance in the treatment of these patients, further research is clearly necessary in this area.

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