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A comparison of artificial saliva and pilocarpine in radiation-induced xerostomia

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Abstract

Twenty patients with radiation-induced xerostomia were entered into a prospective randomized crossover study comparing a mucin-based artificial saliva (Saliva Orthana) and a mouthwash containing pilocarpine (5 mg three times a day). Overall the patients found that the pilocarpine mouthwash was more effective than the artificial saliva in relieving their symptoms ($p = 0.04$), and 47 per cent of the patients wanted to continue with this treatment after the study had finished.

Key words: Xerostomia; Radiotherapy; Pilocarpine; Saliva, artificial

Introduction

One of the major complications of head and neck radiotherapy is chronic xerostomia. Saliva has a number of functions, and xerostomia may result in oral discomfort and problems with taste, mastication, deglutition and speech. It may also predispose to dental caries and other oral infections such as *Candida albicans* (Greenspan, 1990).

The only substances licensed for the treatment of radiation-induced xerostomia in the UK are the artificial salivas. However, there is now considerable evidence that pilocarpine is also useful in this condition (Greenspan and Daniels, 1987; Fox *et al.*, 1991; Joensuu *et al.*, 1993; Johnson *et al.*, 1993; Le Veque *et al.*, 1993). This study is, as far as we know, the first to compare an artificial saliva with pilocarpine in the treatment of radiation-induced xerostomia.

Materials and methods

The 20 patients in this study were all treated at the South East London Radiotherapy Centre, comprising the Radiotherapy Departments of Guy's, King's College and St Thomas' Hospitals. The mean age of the patients was 63.4 years (range 46–82 years) and there were 12 males and eight females.

Sixteen of the patients had primary head and neck carcinomas, and four non-Hodgkin's lymphomas. All were treated with radical intent, the mean dose being 55.4 Gy (range 35–65 Gy). None of the patients had xerostomia prior to their radiotherapy.

The study was of crossover design, each patient received a three-month treatment with a mucin-based artificial saliva (Saliva Orthana), and a three-month treatment with a mouthwash containing pilocarpine. None of the patients were receiving treatment for xerostomia at the start of the study, and there was a one-week washout period between the two treatments. The order in which the treatments were given was randomly allocated.

Saliva Orthana is administered by a spray. The recommended dose is 2–3 sprays when required and the patients were advised to use it regularly (and frequently).

There is currently no commercial oral preparation of pilocarpine in the UK. The mouthwash used in our study was prepared by the pharmacy at St Thomas' Hospital using a formula from the University of Otago (Ferguson *et al.*, 1991). The dose used was 5 mg three times a day and patients were advised to swallow any remaining fluid.

The patients were reviewed at the beginning, halfway through, and the end of each treatment period. On each occasion they had their pulse and blood pressure measured and were asked to complete both a questionnaire and visual analogue scales. The questionnaire referred to symptom improvement and side effects, and the visual analogue scales to the specific symptoms of xerostomia, dysphagia and dysgeusia (Figure 1).

The data was analysed using a *t*-test for paired differences, and the results checked for any period or crossover effect.

Results

Seventeen of the 20 patients completed both parts of the study. The three remaining patients withdrew because of

Fig. 1
Example of visual analogue scale (V.A.S.) used in study.

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TABLE I
SIDE EFFECTS EXPERIENCED BY PATIENTS IN STUDY

Treatment	Side effects	No. of patients (n = 20)
Artificial saliva	Headache	2
	Oral discomfort	2
	Nausea	1
Pilocarpine mouthwash	Nausea	4
	Sweating	3
	Lacrimination	2
	Headache	1
	Oral discomfort	1
	Intestinal colic	1
	Blurred vision	1
	Rhinorrhoea	1
	Urinary frequency	1

side effects (Table I): one patient developed nausea with both treatments, one headaches with the artificial saliva, and the other nausea and local irritation with the pilocarpine mouthwash.

Twelve of the 17 patients felt that the pilocarpine mouthwash had helped their symptoms, whilst only eight felt that the artificial saliva had (t-test; $p = 0.04$). Of these 12 patients, 10 preferred the pilocarpine mouthwash to the artificial saliva, and eight wanted to continue with the treatment after the study (Table II).

Despite the overall preference for the pilocarpine mouthwash over the artificial saliva, improvement in dysgeusia was the only specific symptom recorded on the visual analogue scales which achieved significance (t-test; $p = 0.04$) (see Table III). The data in Table III was calculated from the change in position of the patient's mark on the visual analogue scale. This change was expressed as a percentage of the length of the scale as a whole.

All the results were analysed for period and carry over effects, but none was found, i.e. the results obtained were independent of the order in which the treatments were given.

Discussion

Radiation-induced xerostomia may be managed with either saliva substitutes such as water, glycerine and the artificial salivas, or with saliva stimulants such as sour, hard boiled sweets, chewing gum or the pharmacological sialogogues (Greenspan, 1990).

The artificial salivas available in the UK are based on either mucin or carboxymethyl cellulose. Mucin is a normal component of saliva and there is some evidence that the mucin-based artificial salivas are more effective than carboxymethyl cellulose-based ones (S'Gravenmade *et al.*, 1974; Visch *et al.*, 1986). There are a significant number of patients with radiation-induced xerostomia who do not gain any benefit from the artificial salivas

TABLE II
PATIENTS' SUBJECTIVE OPINIONS ABOUT TREATMENTS

Treatment	Preferred treatment (n = 17)	Continuation of treatment after study (n = 17)
Pilocarpine mouthwash	10	8
Artificial saliva	4	3
Neither treatment	3	6

TABLE III
PATIENTS' OBJECTIVE OPINIONS ABOUT TREATMENTS

Symptoms	Mean changes in visual analogue scale (%)		t-test of difference between mean changes in visual analogue scale
	Pilocarpine mouthwash	Artificial saliva	
Xerostomia	+ 22.5%	+ 15.2%	$p = 0.32$
Dysphagia	+ 11.0%	+ 5.6%	$p = 0.47$
Dysgeusia	+ 18.4%	+ 1.0%	$p = 0.04$

(Visch *et al.*, 1986), and those who do need to use them repeatedly because of their short duration of action. The artificial salivas are not usually associated with side effects.

Pilocarpine is the most commonly used pharmacological sialogogue (Ferguson, 1993). It is primarily a muscarinic agonist, although it does have some effect on the beta-adrenergic receptors within the salivary glands (Ferguson, 1993). The saliva produced is similar in consistency to normal saliva (Fox *et al.*, 1986).

There does not appear to be a correlation between increased saliva production and symptom improvement (Fox *et al.*, 1991; Johnson *et al.*, 1993; Le Veque *et al.*, 1993). This may be due to a number of factors including individual patients' sensitivity to small increases in saliva production, and changes in the composition of the saliva produced (i.e. more mucin) (Fox *et al.*, 1991; Johnson *et al.*, 1993; Le Veque *et al*, 1993).

It may take up to 12 weeks for a response to be seen with pilocarpine (Greenspan and Daniels, 1987; Johnson *et al.*, 1993; Le Veque *et al.*, 1993). Saliva production is greatest one hour after a dose and the increase in saliva lasts for about four hours (Fox *et al.*, 1991).

The dose used in this study (5 mg three times a day) appears generally to be effective in relieving symptoms without producing unnecessary side effects (Fox *et al.*, 1991; Johnson *et al.*, 1993; Le Veque *et al*, 1993). However, the response to pilocarpine is variable and some patients require either a larger or smaller dose to control their symptoms, or side effects, respectively (Ferguson, 1993; Le Veque *et al.*, 1993). The side effects seen are mainly the result of generalized parasympathetic stimulation e.g. sweating, rhinitis, urinary frequency (Johnson *et al.*, 1993; Le Veque *et al.*, 1993). With the doses used there are no significant effects on the cardiovascular system.

Conclusions

Radiation-induced xerostomia causes a great deal of morbidity and should be actively managed. Patients who do not respond to saliva substitutes should be offered pilocarpine as it has now been shown to be both effective and *safe in the treatment of this condition.*

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