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Xerostomia

Erosive potential of saliva stimulating tablets with and without fluoride in irradiated head and neck cancer patients

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ABSTRACT

Background: Patients irradiated in the head and neck region often suffer from severe dry mouth and use acidic saliva stimulating products, which may cause erosion of teeth.
Purpose: To determine saliva stimulating effects and erosive potential (EP) of acidic saliva stimulating tablets (Xerodent™) with and without fluoride in irradiated head and neck cancer patients.
Materials and method: Nineteen irradiated patients (median age 57 years) sucked Xerodent™ tablets with and without fluoride. Saliva collections were divided into three 10-min sessions in the sequence: unstimulated whole saliva, Xerodent™ stimulated saliva without fluoride, and with fluoride. Saliva pH was determined without loss of CO_2 and in combination with inorganic measures used to calculate the degree of saturation of hydroxyapatite (HAp) and fluorapatite (FAp). EP was determined directly in all saliva samples by monitored dissolution of HAp crystals.
Results: Saliva flow rates increased significantly (15-fold) when sucking both tablets ($p < 0.001$). Major changes in saliva composition caused undersaturation of HAp in some samples. However, no dissolution of HAp occurred in the saliva obtained with any of the two tablets. This was most likely due to the limited drop in pH resulting in saliva that was still supersaturated with respect to FAp.
Conclusion: Both Xerodent™ with and without fluoride were evaluated as non-erosive, however, for additional caries protection the fluoride variant is preferable.
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Saliva cleans, protects, and repairs the teeth and oral mucosa and is also important for speaking and swallowing. Thus severely impaired saliva secretion (hyposalivation) and the subjective feeling of dry mouth (xerostomia) can have serious impact on the oral health related quality of life. Patients suffering from hyposalivation also have greater risk of developing caries [1], which is loss of dental hard tissue by chemical processes involving bacteria, and dental erosion [2], which is loss of dental hard tissue through chemical processes not involving bacteria.

There are different causes of hyposalivation including diseases and side effects of medical treatments. Patients who have received radiotherapy for head and neck cancer often experience xerostomia and hyposalivation due to the destruction of major and minor salivary gland tissue by irradiation. Many of these patients therefore suffer from chronic dental problems with caries and erosion, infections and lesions in the oral mucosa, impaired speech, and reduced food intake [3–6]. Furthermore, elevated levels of bacteria on teeth and oral mucosa resulting from hyposalivation after radiotherapy in the head and neck area have also been related to increase the risk of osteoradionecrosis [6].

Dry mouth patients often prefer acidic foodstuffs such as candies and tablets for saliva stimulation because sour taste gives more saliva stimulation than any other taste and/or chewing [7]. However, such behaviour may lead to erosion of the teeth as well as caries if the foodstuffs contain sugar. Thus, demineralisation of tooth substance is accelerated in irradiated head and neck cancer patients, because their reduction in saliva pH and saturation with respect to the inorganic component of teeth (hydroxyapatite) caused by acids in foodstuffs is significantly greater than in healthy individuals [4].

During the last decades, a number of saliva stimulating products for relief of dry mouth have appeared on the market. One example is the acidic tablet Xerodent™ containing malic acid, phosphate and fluoride. The therapeutic strategy behind Xerodent™ is to stimulate the saliva production by the release of malic acid to the taste buds in patients suffering from dry mouth and impaired saliva flow. Because of its malic acid content, Xerodent™ tablets might have erosive potential in dry mouth patients especially when used on a daily basis. Nevertheless, phosphate and fluoride

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released from the Xerodent™ tablets, combined with buffering, calcium, and proteins from saliva, might play a compensative role, making these tablets non-erosive in the mouth of patients suffering from impaired saliva secretion.

Therefore, the aim of this study is to test the saliva stimulating effect of Xerodent™ in patients suffering from dry mouth after radiotherapy for head and neck cancer and further to test the erosive potential of Xerodent™ tablets with and without fluoride in human saliva at pH values corresponding to the pH values induced in the mouth when sucking the tablets.

Material and methods

Nineteen patients previously irradiated for head and neck cancer where the radiation field included the major salivary glands participated in this study. The patients were recruited from the Department of Oncology, Rigshospitalet, in connection with ordinary control visits and all were without recurrence of their former cancer. All patients gave informed consent to the protocol, which had been approved by the Ethical Committee of Copenhagen, Denmark (H-KF 03-001/03).

A dentist and a head and neck surgeon made an oral examination of all patients, recording the dental status, the status of the oral mucosa, and the status at the site of the previous tumour. The patients were interviewed prior to examination concerning their smoking habits, dietary intake, medication and their subjective feeling of dry mouth and graded according to RTOG–EORTC scoring criteria for late radiation induced salivary gland morbidity [8]. Further the clinical files were examined concerning the tumour location, histology and treatment performed. The experiment for each patient was performed during daytime in 1 day. To ensure an even background level of fluoride in saliva, the patients were supplied with mineral water and non-fluoride toothpaste 2 days prior to the experiment. The patients were not allowed to eat or drink for an hour before the saliva collection.

The study was performed as an open label study for the investigators, while the patients were blinded regarding the fluoride content of the tablets. Two tablets were tested: one tablet without fluoride and one tablet containing 0.25 mg of fluoride. Prior to sucking the tablets, unstimulated saliva was collected for 10 min and then the non-fluoride tablet was sucked for 10 min. The tablet was then removed from the mouth. After 1 h of resting, including intake of water and banana, the fluoride-containing tablet was sucked for 10 min.

Loss of CO_2 was avoided by collecting saliva through a glass tube into a vial containing paraffin oil [9]. By weighing the saliva collection vials before and after saliva collection flow rates were calculated in g/min, which is almost equivalent to ml/min [10]. All saliva samples were stored on ice for a maximum of 30 min before they were analysed for P_{CO2} and pH on a standard blood gas analyser (Radiometer ™, Denmark). The erosive potential was determined as previously described by Jensdottir et al. [4]. Briefly, after saliva was depleted of CO_2 the pH was adjusted to the lowest pH level obtained in response to sucking the tablets. Hereafter pure hydroxyapatite (HAp) crystals were added to the saliva and the pH change, if any, was recorded continuously for 5 min. In case there was no pH rise, the Xerodent™ was assessed as non-erosive and the process ended. In case the pH increased, the Xerodent™ tablet was assessed as erosive and the process continued to quantify the amount of HAp lost in the Xerodent™ containing saliva [11]. Sodium and potassium were determined by atomic absorption spectroscopy (AAS) in the absorption mode and total calcium by AAS in the emission mode. Chloride and phosphorous were determined spectrophotometrically. Phosphorus was determined by the molybdic reaction and chloride by the mercury–chloride and iron–TPTZ reaction. Finally fluoride was determined potentiometrically by use of electrodes. Calibrations and standards were greater than sample concentrations, or diluted sample concentrations, at all times and all samples were measured at least twice. The saliva degree of saturation [(ionic product/solubility product)^(1/18)] with respect to hydroxyapatite (DS_{HAp}) and critical pH with respect to HAp was determined by a computer program as previously described [4,12]. Likewise the saliva degree of saturation with respect to fluorapatite (DS_{FAp}) was also determined using a computer program [13].

Statistical analyses were done with Excel and the R statistical program [www.r-project.org]. In tables and figures data are presented as mean ± standard deviation. During statistical analyses pH and critical pH were expressed in concentrations and then averaged for mean results as $[-\log_{10}((\Sigma 10\text{^}-pH_X)/n)]$. DS_{HAp} and DS_{FAp} were also transformed for statistics as $\log_{10}(DS_{HAp})$ and $\log_{10}(DS_{FAp})$ and then averaged for mean results as $[10\text{^}((\Sigma \log_{10} DS_X)/n)]$. Following transformation the differences between all variables of interest obtained for tablets with and without fluoride showed normal distributions and therefore the two tablets were compared by paired *t*-tests. Differences for dichotomised count data were analysed by the Fisher exact test. The level of significance was set at $p < 0.05$.

Results

Characteristics of the patients are shown in Table 1. Seven females and 12 males with a median age of 57 years participated in the study. At the time of the study four patients were smokers, eight were former smokers, and seven patients had never smoked. Radiotherapy had been given at a total dose of 66 ± 2 Gy in 2 Gy fractions with 5–6 fractions per week. Ten patients were unilaterally irradiated, six patients bilaterally with conventional technique, and three bilaterally with intensity modulated radiotherapy. The irradiated volumes included varying parts of the oral cavity and the major salivary glands, and also some or all of the lymph node

Table 1
Patient characteristics.

Characteristic	
Gender	
Male	12
Female	7
Former tumour localization	
Oral cavity	4
Oropharynx	11
Salivary glands	3
Unknown primary	1
Radiation fields	
Unilateral	10
Bilateral – conventional	6
Bilateral – intensity modulated radiotherapy (IMRT)	3
Dietary intake	
Ordinary diet	13
Soft diet	5
Liquid diet	1
Dental problems	
None	13
Increased caries	4
Osteoradionecrosis	2
Xerostomia (RTOG–EORTC)	
Grade 0	2
Grade 1	9
Grade 2	3
Grade 3	5
Grade 4	0

RTOG–EORTC is scoring criteria for late radiation induced morbidity of various tissues including the salivary glands (www.rtog.org).