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Xerostomia. Development, properties and application of a mucin-containing saliva substitute

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CHAPTER 8

SUMMARY

The physiological importance of saliva in human becomes obvious when saliva is secreted to a too large (hypersalivation) or a too small (hyposalivation) extent. The reduced salivary secretion results in a wide scale of complaints such as a dry and burning sensation of the mouth, and difficulties in chewing, swallowing, speaking and sleeping. To combat these complaints, the lack of saliva has to be compensated. A large number of remedies has been developed to reduce or prevent these complaints. The majority of these remedies can only be applied in patients in whom salivary flow can be increased. The other remedies are meant as a (partial) saliva replacement. The effect of all these remedies is not optimal for a large group of patients; further investigations were needed.

To treat patients suffering from a reduced salivary flow effectively, an investigation was carried out. The aims of this study were:

1. Development of a saliva substitute which approximates the chemical and physiochemical properties of human whole saliva;
2. Development of a suitable method of application;
3. Evaluation of the meaning of the developed substitute for the patient.

Chapter 2 reviews the morphology and innervation of the salivary glands, and the composition and function of saliva. Only those aspects are mentioned, which are of importance for a better understanding of the results of a decreased salivary flow and for composing a saliva substitute. The most important components of human whole saliva are water, glycoproteins and the electrolytes sodium, potassium, calcium, magnesium, phosphate and chloride. The main functions are the moistening, protection and lubrication of the soft and hard oral and pharyngeal tissues.

The causes and main consequences of the reduced salivary secretion are discussed in Chapter 3. A large number of physiological and pathological processes can cause a reduction of the salivary flow, but mostly to a minor extent. The most severe forms of xerostomia are observed after radiation of malignant tumours in the head and neck region, in particular if the salivary glands are completely included in the treatment portals, in Sjögren's syndrome and after the use of certain medicines (e.g. cytostatics, antihypertensives and psychotropic medicaments). The most pronounced results of xerostomia are dry and burning sensation of the mouth, difficulties in chewing, swallowing, speaking and sleeping, progressive carious destruction of the teeth and frequently occurring oral infections.

In Chapter 4 some remedies are listed which are used in patients suffering from xerostomia. A curative therapy should be prescribed if possible. For the other patients only a symptomatic treatment remains. The latter is made up of the

stimulation of the salivary secretion by means of gustatory (a.o. citric acid, vitamine C), tactile (a.o. chewing gum) and pharmacological (a.o. anetholtrition, pilocarpine) sialogogues and/or the application of mouthwashes and more complex saliva substitutes. These saliva substitutes have been developed to take over the functions of saliva, this has only partially been succesful.

Chapter 5 describes the development of the mucin(glycoproteins)-containing saliva substitute. The mucin material was preferred to the other viscosity-increasing expedients, because precisely these glycoproteins determine the rheologic and wetting behaviour of human whole saliva. The most pronounced difference of the carboxymethylcellulose(CMC)-containing saliva substitutes is the substitution of CMC and sorbitol by animal glycoproteins (pig gastric mucin (PGM) and bovine submandibular mucin (BSM)) and xylitol. Subsequently the wetting, rheological, remineralizing, buffering and osmotic properties of the developed substitute are compared with those of the CMC-containing saliva substitutes and human whole saliva.

The wetting behaviour of all those liquids was determined by means of contact angle measurements on human ground and polished enamel (in vitro) and human oral mucosa (in vivo). From these measurements it was concluded that:

1. the contact angles of water and CMC- or mucin-containing saliva substitutes are significantly lower than those of human whole saliva on ground and polished enamel, indicating the better wetting of the prepared enamel by the former;
2. the contact angle of water on human mucosa is significantly higher than that of human whole saliva indicating that water is a poor wetting agent for the oral mucosa;
3. the contact angles of the CMC-preparations and human whole saliva are comparable on the human mucosa, although the ratio γ^d/γ^p differs greatly;
4. the contact angles of the mucin-preparations and human whole saliva are comparable on the human mucosa; the ratio γ^d/γ^p is comparable. This indicates that the mucin-preparations are better wetting agents of the oral mucosa than human whole saliva.

The rheological behaviour of all these liquids was determined by means of measuring the apparent viscosity of these mixtures as a function of shear rate (in vitro). From these measurements it was concluded that:

1. the CMC-containing saliva substitutes are non-Newtonian liquids within the range of shear rates studied. In all cases the apparent viscosity decreases slightly with increasing shear rate;
2. artificial saliva containing BSM or a mixture of BSM and PGM qualitatively approaches the visco-elastic properties of human whole saliva.

The remineralizing behaviour of all these liquids was determined by means of hardness measurements (rehardening) on softened human enamel. The softened enamel was exposed to the testing liquids during some hours or days (in vitro). From these measurements it was concluded that:

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1. saliva substitutes containing calcium, phosphate and fluoride have potentially rehardening properties;
2. the rehardening is better in the case of CMC-containing saliva substitutes than in that containing mucin;
3. the addition of CMC, mucin, sorbitol or xylitol to an aqueous solution containing calcium, phosphate and fluoride decreases the rehardening potency.
4. the addition of sorbitol reduces the rehardening potential to a greater extent than the addition of xylitol.

In addition, the mucin- as well as the CMC-containing saliva substitutes both have a minor buffering capacity (phosphate component in the substitutes), which was much lower than that of human whole saliva. The osmolality of all substitutes tested exceeds that of saliva; in the case of the CMC-containing saliva substitutes it even resembles or exceeds that of blood, which may cause a dehydration of the oral mucosa.

In Chapter 6 a new method of application is introduced, the intra-oral artificial saliva reservoir. When applying artificial saliva in this way the oral cavity is continuously moistened for a period of, on average, four hours. The intra-oral artificial saliva reservoir can be applied in dentulous and edentulous patients. In edentulous patients the reservoir is located in a thickening of the oral side of the upper denture and in the bulk of a lower denture. In a dentulous patient the reservoir is clasped like a palatal prosthesis to the dentition. The reservoir may be applied in patients, who:

1. can manage artificial saliva well;
2. have sufficient volume for a reservoir in the oral cavity;
3. can tolerate a reduced oral space.

Chapter 7 shows the effect of the developed substitute on the patient's complaints of xerostomia. In the first part of this chapter the effect of the developed substitute was compared to that of commercially available CMC-containing substitutes in a clinical trial. From this study it could be concluded that the majority of the patients preferred the mucin-containing saliva substitute. Subsequently in the second part of this chapter it was investigated whether the mucin-containing substitute was an effective relief bringing remedy for the patient suffering from xerostomia. From this study it was concluded that:

1. the application of the mucin-containing saliva substitute reduces the sensation of a dry mouth as well as improving oral functioning (in particular chewing, swallowing, speaking and sleeping);
2. the patient's perceived emotional impact concerning oral functioning improves;
3. the application of the mucin-containing saliva substitute reduces the number of restrictions in the daily functioning of the patient, resulting in a more normal functioning of the patient (a.o. improvements in social contacts, communication and working).

In conclusion it can be stated that:

1. the developed mucin-containing saliva substitute exceeds the rheological and wetting properties of the available CMC-containing saliva substitutes;
2. for a limited group of patients (see Chapter 6), the developed method of application can guarantee a continuous wetting of the oral cavity for about two hours;
3. the developed mucin-containing saliva substitute is an effective, relief bringing remedy.

CHAPTER

SAMENVATTING

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