IATROGENIC XEROSTOMIA

Definition and terminology

Xerostomia means dry mouth (Greek ξερος: dry, στομα: mouth). Traditionally, the term has been used to describe both the subjective feeling of dry mouth, i.e. the patient's own conception of dry mouth, as well as the objectively assessed signs suggesting dry mouth (Table 1). More recently, it has been suggested that ”xerostomia” should be used in its first-mentioned connection as a subjective feeling of the patient, while expressions such as ”reduced salivary flow” and ”hyposalivation” should be used when discussing the objective condition of the patient by whom salivary flow rate has been measured and found to be reduced or even extinct. This terminological issue is further complicated by the fact that not all patients with objectively measured reduced salivary flow (hyposalivation) suffer from xerostomia and, vice versa, many patients who report subjective feeling of dry mouth (xerostomia) show salivary flow rates not meeting the criteria for hyposalivation. This is because not only the amount of saliva is responsible for adequate wetting of the oral surfaces, but also the quality of saliva is important.

Epidemiology

There are now population studies on the prevalence of xerostomia or reduced salivary flow. However, among elderly people, xerostomia has been reported in more than 50% of the subjects and 10 – 25% of the elderly experience it constantly. Patients who underwent cancer treatment and received radiotherapy to the head and neck region, where salivary glands are subjected to primary radiation, often suffer severe and irreversible xerostomia due to damage to the secretory tissue. It has been shown that the mean radiation dose received by a salivary gland is correlated with the reduction of salivary flow. The range of mean cumulative doses to cause irreversible functional reduction of the salivary glands included in the radiation portal, is from 26 to 39 Gy. In most conventional schedules both tumour and normal tissues (i.e. healthy tissues surrounding the tumour that are included in the radiation portal) receive a cumulative dose exceeding 40 Gy. Newer radiation techniques (three-dimensional conformal radiation therapy) are designed to shape the spatial distribution of the high radiation dose to the target area, thereby reducing the dose delivered to the normal tissues, including salivary gland tissue.
Other subjects that can be affected by dry mouth include patients with autoimmune diseases (in particular Sjögren's disease, in its secondary presentation often combined with rheumatic diseases), individual taking drugs (Table 2) and post-

menopausal women. In general, complaints of dry mouth are more common among women than men. In irradiated patients, xerostomia has a sudden onset, while in auto-immune diseases there is a more gradual development of a dryness sensation. In post-menopausal women, as well in patients suffering from drug-induced xerostomia, oral dryness usually is of a lesser extent as salivary secretion can often still be stimulated.

Clinical presentation

In addition to dry mouth with its characteristic consequences to the teeth and mouth mucosa as given in Table 1, reduced salivary flow may be associated with a variety of other symptoms. These are presented in Table 3.

Etiopathogenesis

Saliva is secreted from the salivary glands. There are three pairs of major glands and hundreds of minor glands. The major glands are: *the parotid glands*, situating in front and underneath the ear lobes, which duct ends in the buccal mucosa adjacent to upper molar teeth; *the submandibular glands* and *the sublingual glands*, both situating in the bottom of the mouth and delivery saliva through a common duct ending on the side of the tongue fraenulum, thus wetting the floor of the mouth. The major glands are responsible of the watery saliva flowing into the oral cavity when secretion is stimulated. In particular, parotid gland saliva is watery (serous) and contains high concentrations of amylase, a digestive enzyme causing starch to turn to glucose and fructose. Submandibular and sublingual saliva is ”mixed” with both serous and viscous (sticky) secretions. Mucins (a very large protein molecule with many sugar side chains) are responsible for the viscous behaviour of submandibular and sublingual secretions, a characteristic that is important for the well-being of the mucosa (moistening and protective function).

The minor salivary glands are situated in the oral mucosae over nearly all the mouth. They are particularly numerous in the palate and inner aspects of the lips. Their secretion is viscous and the function is to lubricate the mucous membranes. The secretion of the minor glands is active all the time, while the activity of the other glands follows a diurnal rhythm, so that the production of saliva is lowest during night and highest in the afternoon. The secretion of the parotid glands is reduced to zero during sleep, while the secretions of the submandibular and sublingual glands reduce to a basal level.

Salivary output and flow rate values are highly individual. Salivary secretion is a complicated process regulated by the autonomic nervous system, so that both the

parasympathetic and sympathetic nerves stimulate the secretory units of the salivary glands. The nervous regulation is affected by the psychic state and alertness of the patient. Stress and tension cause a sensation of a dry mouth, while salivation is increased by merely thinking of something delicious or sour, such as imagining the sucking of a lemon.

The general body fluid balance is of key importance for salivary secretion because the watery saliva in particular is dependent on osmotic pressure of body fluid. Thus, dehydrated patients have less saliva.

There are hundreds of drugs that interfere with salivary secretion, mostly inhibiting salivary output. Examples of such drug categories are given in Table 2. Basically the more drugs a patient uses daily, the more prone he/she is for xerostomia and reduced salivary flow (Fig. 1).

Diagnosis

Salivary flow rates of whole saliva (pooled saliva that can be collected by e.g. a drooling or spitting method) and glandular saliva (separate collection of secretions of the parotid and submandibular/sublingual glands) can be obtained without stimulation (resting saliva) and after mechanical (chewing) or gustatory (e.g. citric acid) stimulation. In this way, it can be easily deduced whether sufficient saliva is secreted under resting conditions. In addition, assessment of salivary gland function shows to what extent stimulation of the salivary flow is possible, which salivary glands still can be stimulated to a significant flow, and in which cases supportive oral care (stimulation therapy) might be successful. When successful stimulation of saliva flow is not possible, only palliative oral care can be provided.

The assessment of resting flow needs collection of saliva under peaceful, quiet circumstances with as few outer stimuli as possible. It is commonly measured by having the patient seated undisturbed and asking him/her to let all saliva coming in the mouth to flow into a receptacle without any chewing movements. The collection time should be long enough for a reliable reading; from 5 to 15 minutes depending on the patient's secretory capacity. A commonly applied clinical reference limit for reduced resting whole salivary flow rate is 0.1 ml/min when the free flowing method is used for measuring. Values below this threshold indicate reduced flow rate or hyposalivation.

Stimulated whole salivary flow can be measured with several means of stimulation. Citric acid drops on the tongue surface cause saliva to flow, as does chewing. Standard piece of paraffin wax (2 g) is a commonly used method for assessment of stimulated salivary flow rate. Here the patient is again seated undisturbed and given

the paraffin wax to chew at a constant rate of approximately once a second. Saliva secreted during the first 30 seconds is discarded (to remove debris and food remnants), and collection into a receptacle is then started and continued for usually 5 minutes so that the patient spits all saliva into the receptacle. The clinical reference limit for paraffin-wax stimulated whole salivary flow rate is 0.7 ml/min. Thus, values below this threshold indicate hyposalivation or reduced flow rate.

Treatment

Drinking enough fluid daily is of key importance to a patient with dry mouth. The amount of recommended daily fluid intake of an adult is 1.5 - 2 L. Elderly patients seldom drink that much, and the clinician may therefore need to remind the patient to drink enough throughout the day. Because the patient's medication is often the cause of hyposalivation, the drugs should be checked, together with the physician in charge, in order to assess if an alternative, less xerostomic, drug or drug combination can be prescribed. Unfortunately this is seldom possible. Therefore, local remedies to relieve xerostomia and oral dryness need to be considered. Table 4 gives examples of preparations used to relieve xerostomia.

Medical therapy for hyposalivation is rarely considered a first approach, as many patients find relief by gustatory or mechanical stimulation of the salivary glands. Cholinergic drugs such as pilocarpine tablets (5 mg two to four times daily) are available in many countries and they suit patients with no contraindications for using such preparations. These include irradiated patients who are otherwise healthy and some patients with Sjögren's syndrome. Also the use of cevimeline has been advocated (with probably less side effects than pilocarpine), but this drug is not available yet in Europe. Acupuncture has been reported as resulting in some relief of the dryness related complaints.

When the function of the salivary glands is nearly completely destroyed, stimulatory measures can have no effects. In these cases some palliation can be obtained by wetting the oral tissues with home-made or commercially available products, including special tooth pastes, oral gels, mouthrinses and saliva substitutes (Table 4). Not all patients rate the effectiveness of saliva substitutes higher than that of moistening the mouth with water, although it is known that water is a very poor agent for prolonged moistening of the oral mucosa, as short after moistening the oral mucosa feels dry again. Therefore it is worthwhile to assess the effect of various saliva substitutes in each individual patient.

As a guide for the palliative treatment of hyposalivation the following recommendations can be used:

- *Severe hyposalivation*: A saliva substitute with gel-like properties should be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of natural saliva, such as substitutes containing xanthan gum and mucin (particularly bovine submandibular mucin) should be applied.
- *Moderate hyposalivation*: If gustatory or pharmacological stimulation of the residual salivary secretion does not provide sufficient amelioration, saliva substitutes with a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.
- *Slight hyposalivation*: Gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.

Prognosis and complication

Unfortunately, dry mouth and xerostomia are chronic conditions with little prospect of permanent resolution. Therefore, it is important that the patient understands the condition and learns to cope with it. Only in select cases xerostomia may subside. These include menopausal women whose reduced saliva flow may increase after the new hormonal balance when the climacteric is over. Some women with severe xerostomic symptoms benefit from hormone replacement therapy, but not all. Similarly, hyposalivation caused by irradiation may slowly subside provided that the tumour dose has not been targeted directly onto the salivary glands and the cumulative dose to the salivary glands does not exceed the critical limit of radiation injury to cause irreversible damage. As stated earlier, if the reduced salivary flow is a side effect of necessary medication, this can be changed. The patient's physician needs to be consulted whether alternative drugs with less mouth-drying effect might be available and suitable to the patient. The complications of reduced salivary flow are listed in Tables 1 & 3. Because the oral cavity is an important source of infection and saliva is one of the key defensive factors in the mouth, the lack of saliva may reflect in rampant caries or mucosal infections.

Prevention

Due to the aetiology of xerostomia and hyposalivation these conditions can seldom be prevented. All the remedies given in Table 4 must therefore be provided to the

patient in order to keep the teeth and mouth mucosa healthy. In addition, xerostomia patients with hyposalivation need frequent dental check-ups so that the dental diseases are controlled. Because these patients are also liable to dental erosion, acid beverages and acidic foodstuffs should be avoided. Daily oral hygiene should be taken care meticulously. In dentate patients frequent applications of neutral fluoride preparations are advocated.

Table 1. Symptoms and signs of dry mouth

• Saliva is viscous and foamy • Lips are cracked and fissured • Tongue is dry, burning and painful, may be lobulated or fissured • Cheeks are dry and may look pale • Mouth mucosa in general appears thin and has lost its glistening, mouth mirror and tongue blade attach easily at examination • Swelling of salivary glands • ”Milking” saliva from the glands produces only minor amounts of it • Taste disturbances	• Excessive dental caries, caries lesions often located at sites which normally do not show signs of decay, such as approximal surfaces of lower anterior teeth, tooth cusps, and cervical regions of the teeth • Dental erosion (chemical wear) and cracking of tooth enamel, amongst others related to the combined effect of a lower pH and buffer capacity of saliva • Retention of food remnants in the mouth and dentition due to decreased clearance by saliva flow. Food remnants often can be observed for hours to more than a day after a meal. • Candidiasis (may appear as red or white lesion or removable plaque, or as cheilosis)

Modified from Sreebny 1996, Närhi et al. 1999 and Vissink et al. 2003.

Table 2. Examples of medications that may cause xerostomia

• Anticholinergic agents e.g. scopolamine, biperidine, atropine • Medications with anticholinergic effects e.g. disopyramide, clonidine, metoprolol, amitriptyline, levomepromazine, melperone, selegiline • Psychotropic agents e.g. diazepam, tsopiclone	• Medications causing changes in fluid and electrolyte homeostasis e.g. cyclothiazide, furosemide • Antineoplastic agents e.g. methotrexate, cyclophosphamide • Others e.g. bromhexine

Table 3. Non-oral symptoms often associated with dry mouth

• ”Thirst”, i.e. an increased need to moisten the oral mucosa • Difficulty with eating and swallowing • Difficulty with speech • Dryness of throat • Persistent cough • Dryness of nose • Dryness of eyes	• Nocturnal oral discomfort as the patients often awake because of their oral dryness • Dryness of skin • Constipation • Dryness of urogenital mucosa such as vagina • General symptoms: weakness, fatigue, joint pain, swelling and stiffness, generalized aching, weight loss, depression

Modified from Sreebny 1996, Närhi et al. 1999 and Vissink et al. 2003.

Table 4. Remedies and preparations for relieving xerostomia.

• Frequent fluid intake • Sugarless chewing gum • Sugarless lozenges and hard candies • Acid tasting substances (e.g. vitamin C tablet, lemon pastilles, be careful in dentate patients) • Saliva substitutes (special preparations sold over-the-counter in a pharmacy. Best effects have been reported by the xanthan gum or mucin containing ones)	• Olive or peppermint oil (recommended as small amounts to be taken into the mouth several times daily) • Avoidance of irritating food stuffs or oral hygiene preparations • Pharmacological stimulation (e.g. pilocarpine, cevimeline, carbachol, anetholetrithione)

Modifed from Närhi et al. 1999, Nieuw Amerongen and Veerman, 2003, Guggenheim and Moore 2003 and Vissink et al. 2003.

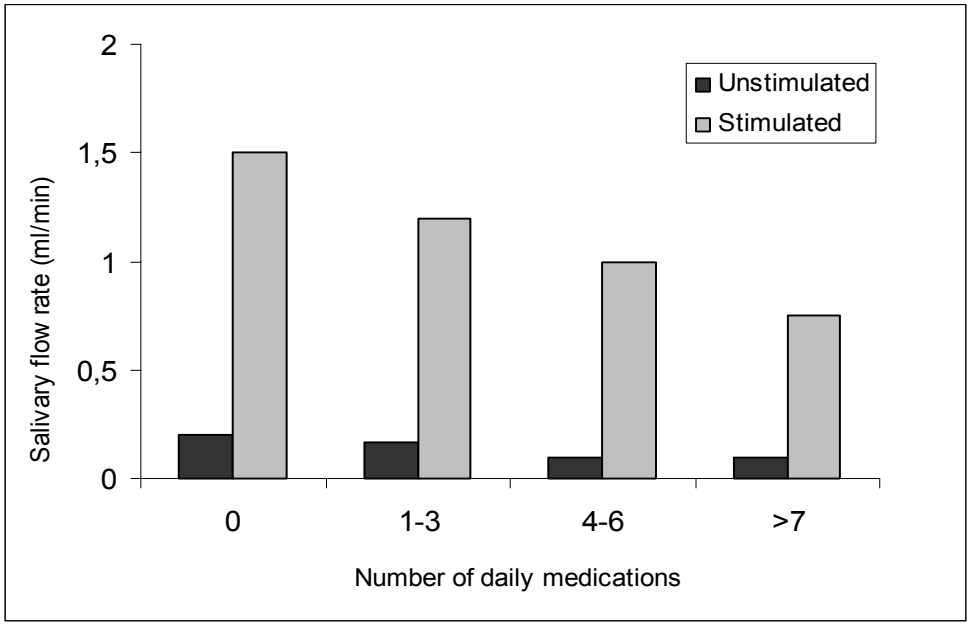

Figure 1. The more the patient needs to take concomitant drugs daily the less saliva is secreted. The black bars show the effect of increasing number of drugs daily on unstimulated salivary flow, the grey bars represent stimulated salivary flow (after chewing paraffin-wax). (Modified graph from Närhi et al. 1999)

Further reading

1 Guggenheim J, Moore PA. Xerostomia. Etiology, recognition and treatment. J Am Dent Assoc 2003; 134: 61-69.

2 Närhi TO, Meurman JH, Ainamo A. Xerostomia and hyposalivation. Causes, consequences and treatment in the elderly. Drugs Aging 1999; 15: 103-116.

3 Nieuw Amerongen AV, Veerman ECI. Saliva – the defender of the oral cavity. Oral Dis 2002; 8: 12-22.

4 Nieuw Amerongen AV, Veerman ECI. Current therapies for xerostomia and salivary gland hypofunction associated with cancer therapies. Support Care Cancer 2003; 11: 226-231.

5 Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 97: 28-46

6 Jensen SB, Pedersen AM, Reibel J, et al. Xerostomia and hypofunction of the salivary glands in cancer therapy. Support Care Cancer 2003; 11: 207-225.

7 Vissink A, Burlage FR, Spijkervet FKL, et al. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med 2003;14: 213-225.