How Much Saliva Is Enough for Avoidance of Xerostomia?

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Key Words

Xerostomia · Hyposalivation · Dry mouth · Residual volume · Salivary film · Evaporation · Mucosal fluid absorption · Flow rate · Palatal dryness

Abstract

Xerostomia, the subjective sensation of dry mouth, occurs when the salivary flow rate is less than the rate of fluid loss from the mouth by evaporation and by absorption of water through the oral mucosa. Evaporation can only occur during mouth-breathing but could reach a maximum rate of about 0.21 ml/min at rest, although normally it would be much less. Water absorption through the mucosa can occur because saliva has one sixth the osmotic pressure of extracellular fluid, thus creating a water gradient across the mucosa. The maximum absorption rate is calculated to be about 0.19 ml/min, declining to zero as the saliva reaches isotonicity. A recent study found the residual saliva volume, the volume of saliva left in the mouth after swallowing, to be 71% of normal in patients with severe hyposalivation and whose mouths felt very dry. Saliva in the residual volume is present as a thin film which varies in thickness with site. The hard palate has the thinnest film and when this is <10 µm thick, evaporation during mouth-breathing and/or fluid absorption may rapidly decrease it to zero, resulting in xerostomia. This is also generally asso-

ciated with reduced secretion from the soft palate minor glands, which may contribute to the film on the hard palate. Thus, xerostomia appears to be due, not to a complete absence of oral fluid, but to localized areas of mucosal dryness, notably in the palate. Unstimulated salivary flow rates >0.1–0.3 ml/min may be necessary for this condition to be avoided.

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Xerostomia and Hyposalivation

In deciding how much saliva is enough for avoidance of the sensation of dry mouth, it is important to distinguish between xerostomia and hyposalivation [Nederfors, 2000]. Xerostomia is the subjective sensation of dry mouth, while hyposalivation is the objective finding of a reduced salivary flow rate. Patients with low salivary flow may experience many problems which include: xerostomia; an increase in caries, often at sites not normally prone to caries, such as the incisal edges [Odlum, 1991]; reduced clearance of bacteria and food, leading to mucosal soreness, gingivitis, cheilitis, fissuring of the tongue and infection of the salivary ducts; recurrent yeast infections; difficulty in chewing, speaking and swallowing; increased frequency of calculus deposition in the salivary ducts; burning mouth, and difficulty in retention of dentures [Sreebny et al., 1992].

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0008-6568/04/0383-0236\$21.00/0

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Several large studies [Dawes, 1987] have shown that the mean flow rate of unstimulated whole saliva is about 0.3 ml/min but with a remarkably large range, which was 0.008–1.85 ml/min in one study of 661 apparently healthy individuals who did not complain of xerostomia [Becks and Wainwright, 1943]. Clearly, the flow rate of saliva which is 'enough' varies considerably among individuals. However, Sreebny et al. [1992] and others regard an unstimulated salivary flow rate of <0.1 ml/min as evidence of hyposalivation. Food consumption normally stimulates salivary flow, and an inadequate flow during meals may make the swallowing of dry foods difficult. Sreebny et al. [1992] regard a stimulated flow rate of <0.5 ml/min to be evidence of hyposalivation in response to the chewing of paraffin wax.

Fluid Balance in the Mouth

Fluid enters the mouth from the ducts of the various salivary glands, while fluid loss may occur by swallowing, by evaporation or by absorption through the oral mucosa. Usually, the rate of fluid input exceeds the rate of fluid loss by evaporation or absorption through the oral mucosa, and the excess is periodically swallowed. The volume of saliva in the mouth varies from a mean of 1.07 ml (range 0.52–2.14 ml) prior to swallowing ($V_{\max}$) to a mean of 0.77 ml (range 0.38–1.73 ml) after swallowing [Lagerlöf and Dawes, 1984], which is the residual volume. When flow is unstimulated, the volume of saliva swallowed is about 0.3 ml with each swallow and if the unstimulated flow rate is 0.3 ml/min, the swallowing frequency will be about once per minute. The swallowing frequency is less during sleep [Lear et al., 1965], when the salivary flow rate is reduced, but whether the residual volume changes during sleep is unknown.

If evaporation of saliva and absorption of fluid through the oral mucosa did not occur, it would be expected that anyone with even a low flow rate of saliva would not experience xerostomia, since there would be no reason why the residual volume would not remain constant. The individual could simply reduce the swallowing frequency to compensate for the reduced rate of input of saliva. However, if the rates of fluid loss by evaporation of saliva and absorption of fluid through the oral mucosa are greater than the unstimulated salivary flow rate, the residual volume would be expected to decrease, although it would be temporarily increased if flow were stimulated or if a drink were consumed.

Rate of Water Evaporation from the Mouth

If the mouth remains closed during breathing so that no air passes through it, no evaporation of water from saliva will occur. However, with mouth-breathing, the rate of water evaporation from saliva will be influenced by the respiratory minute volume, the percentage of the inspired air which passes through the mouth, and the temperature and relative humidity of the inspired air.

Proctor [1977] reported that air inspired through the nose becomes almost saturated with water vapour and reaches a temperature of 33°C during the few seconds that it takes to reach the nasopharynx. Even when the ambient temperature is –20°C, the inspired air is heated to about 27°C by the time it reaches the nasopharynx. Air which passes through the mouth would presumably also be heated similarly and be brought to a high relative humidity from the fluid in saliva by the time the air reaches the pharynx.

According to Niinimaa et al. [1981], the proportion of the population who are mouth-breathers is 10–15%, and in such persons about 50% of the inspired air passes through the mouth. This is not unexpected, since the combined cross-sectional area of the nasal passages just posterior to the nostrils is only about 60 mm² [Proctor, 1986] and this area would be equalled by a quite small opening of the mouth. During normal conversation, by non-mouth-breathers, more than half the inspired air passes through the mouth [Camner and Bakke, 1980].

Given that the respiratory minute volume at rest is about 6 l/min [Ganong, 1999] and that air at 33°C and 100% relative humidity contains 35.68 g of water/m³ [Weast and Astle, 1978–1979], the maximum rate of water evaporation from saliva into inspired air that was initially dry would be as high as 0.21 ml/min in complete mouth-breathers. Inspired air which already contained some moisture would, of course, pick up fluid at less than that rate. The involvement of saliva evaporation in xerostomia has received little attention, although it is well known that certain animals, such as dogs, use water evaporation from the tongue, in place of sweat, as a means of body temperature control.

In winter, it is a common experience in cold climates, such as that of Winnipeg, that water drips from the nose as a result of condensation of water from expired air (which has 100% relative humidity at 37°C) as it is suddenly cooled at the nostrils. It seems possible that fluid may be supplied to the mouth by condensation of water on the lips from air which is expired orally when the ambient temperature is low. However, this does not seem

to have been tested. Theoretically, if it were possible to cool a region of a denture or an appliance, condensation of water from air expired through the mouth would provide an inexhaustible source of fluid for the mouth. Unfortunately, the power requirements for such a cooling system would appear to make it impractical for clinical use.

Rate of Water Absorption through the Oral Mucosa

The permeability of the oral mucosa can be characterized by a permeability coefficient, K_p (cm/min), derived from the relationship: $K_p = Q/[A(C_o - C_i)t]$ [Siegel et al., 1981], where Q (mol) is the quantity of permeant crossing the epithelium, A (cm²) is the area of the tissue, C_o and C_i (mol/l) are the concentrations of the permeant on the outside and inside of the mucosa and t is time (min).

There are relatively few studies of the permeability to water of human oral mucosa, and autopsy specimens have been employed, with tritiated water as the permeant. The advantage of tritiated water is that its concentration on one side of the mucosa (C_i) can be maintained very low in comparison with that on the other side (C_o). However, the K_p values for water are identical for transport in both directions across the oral mucosa, and there is no active transport. Thus, water can only diffuse across the oral mucosa if there is a concentration gradient.

Lesch et al. [1989] reported that the K_p for water movement across the oral mucosa was about 0.97×10^{-4} cm/min, but more recent values average about 4.8×10^{-4} cm/min [Healy et al., 2000; Howie et al., 2001] for different regions of the oral mucosa at 20°C.

Unstimulated saliva has an osmotic pressure which is about one sixth of that of extracellular fluid (ECF). Thus, there is normally a concentration gradient for water to pass from saliva through the oral mucosa. However, if the saliva were not continuously replenished, the concentration of salivary electrolytes would increase with time, and the net rate of diffusion of water would fall exponentially and cease when the saliva was isotonic with ECF.

For calculation of the maximum rate of water transfer across the oral mucosa, it is necessary to calculate the difference in the molar concentrations of water in saliva and in ECF. ECF is isotonic with 0.9% NaCl, whereas unstimulated whole saliva is isotonic with about 0.15% NaCl. Thus, the molarities of water in ECF and saliva must be about the same as those in the two salt solutions.

The molecular weight of water is 18.0153 and the densities of 0.9 and 0.15% NaCl at 20°C are 1.0046 and 0.9993, respectively [Weast and Astle, 1980–1981]. A 0.9% NaCl solution contains 991 g of water in 1,000 g of solution, or 55.0088 mol of water/1,000 g. To convert the 1,000 g to millilitres, division by the density gives 995.421 ml. Thus, the molarity of the water in ECF = $55.0088 \times 1,000/995.421 = 55.2618$ mol/l. A similar calculation for 0.15% NaCl yields a water molarity of 55.3863. Thus, the difference in water molarity between saliva and ECF is 0.1245 mol/l.

Since the surface area of the oral mucosa averages 178 cm² [Collins and Dawes, 1987], the maximum rate of water transfer from saliva across the oral mucosa will be: 4.8×10^{-4} cm/min $\times$ 178 cm² $\times$ 0.124 mol/l = 0.0106 mol/min or 0.19 ml/min.

In this calculation there are uncertainties in that the K_p value: (1) was derived at room temperature rather than mouth temperature, (2) is for tritiated water rather than H₂O, (3) was measured on autopsy mucosa rather than on fresh mucosa and (4) is for ventral tongue mucosa rather than being a weighted average of all sites (Lesch et al. [1989] found site specificity in K_p values).

A computer simulation, iterative at 1-second intervals, shows that with the normal residual volume, it would take <6 min to reach 95% of isotonicity if no further saliva entered the mouth.

Although water would be expected to pass across the mucosa into the mouth when the mucosal epithelium is dry, this does not seem to occur, possibly because distortion of the epithelial cells by the drying obliterates the water channels normally present.

Saliva as a Thin Film

Collins and Dawes [1987] measured the surface area of the mouth and found it to be 214.7 ± 12.9 cm² (mean $\pm$ SD, $n = 20$). From the values for the residual volume and V_{max} determined by Lagerlöf and Dawes [1984], they calculated that if the saliva were evenly distributed throughout the mouth, it would be present as a thin film, varying from 72 to 100 μ m in thickness after and before swallowing, respectively. This calculation assumes that opposing surfaces in the mouth, such as the palate and the dorsum of the tongue, are in contact with each other, except for the interposition of the fluid film. Subsequent investigators have usually measured the fluid thickness on individual surfaces not in contact with other surfaces, and thus the values which they obtain would be expected to aver-

age, over the mouth as a whole, 36–50 μm , only half of those calculated by Collins and Dawes [1987].

Kleinberg and his colleagues have recently provided some very important data on the thickness of the salivary film at many different sites in the mouth. DiSabato-Mordarski and Kleinberg [1996a] found marked site-specific variation in the thickness of the surface fluid layer on the oral mucosa, with mean values ranging from 70 μm on the posterior dorsum of the tongue to 10 μm on the hard palate. The maximum film thicknesses in embrasures and occlusal fissures are larger than these values [DiSabato-Mordarski and Kleinberg, 1996b], but the rate of fluid turnover in these sites is uncertain.

Wolff and Kleinberg [1998] reported that in patients with or without a dry mouth and an unstimulated flow rate of >0.1 ml/min, the mean mucosal fluid thicknesses were 27.8 and 41.8 μm , respectively. In those with a dry mouth, the hard palate and the lips had the lowest fluid thicknesses, and values of at least 10 μm on the palate appeared necessary to avoid complaints of dry mouth.

Wolff and Kleinberg [1999] induced dry mouth in healthy volunteers by pharmacological means and found that the mean onset of oral dryness occurred when the total salivary flow rate had been reduced to just less than 50% of normal, a value in accordance with the findings of Dawes [1987]. When the volunteers experienced dryness, the pattern of variation in fluid film thickness at different sites was the same as that at baseline, with all sites showing a reduced thickness. Again, the surface of the hard palate had the lowest fluid thickness with values <10 μm . Wolff and Kleinberg [1998, 1999] have emphasized the importance of dryness of the palatal mucosa for the sensation of oral dryness. The anterior part of the hard palate contains very few minor salivary glands, and a fluid coating is dependent on tongue movements for transfer of fluid from other regions of the mouth.

Niedermeier et al. [2000] have summarized in English a great deal of their excellent work, originally published in German, which demonstrates the importance of the palatal mucous gland secretions for retention of the upper denture and that dry mouth and burning mouth syndrome are likely to occur when the flow rates from these glands are <6 $\mu\text{l}/\text{cm}^2$ of palatal mucosa/min. In persons not wearing dentures, these secretions probably also contribute to the film of saliva covering the mucosa of the hard palate.

Discussion

An important conclusion from the above analysis of fluid balance in the mouth is that commonly used ways of measuring the flow rate of whole saliva are not assessing the total fluid output by the different salivary glands. Rather they assess the net output of saliva after loss of fluid by evaporation and/or by mucosal absorption. That these latter two processes are clinically significant is suggested by the fact that patients with a low salivary flow rate usually experience a dry mouth, rather than maintaining a normal residual volume and swallowing less frequently.

In a recent study by Dawes and Odum [2004], the mean residual volume was found to be reduced by 29% in patients with severe hyposalivation and who stated that they had a very dry mouth. This, along with the studies of Kleinberg and colleagues, shows that such patients do certainly not have a complete lack of oral fluid. It emphasizes the probable importance of localized areas of dryness in the mouth, and especially on the hard palate, for the condition of xerostomia. Saliva production by the palatal minor salivary glands appears to be particularly important for providing an adherent fluid film on the hard palate. The latter site and anterior dorsum of the tongue are where xerostomia symptoms are most pronounced. If there the film thickness is <10 μm [Wolff and Kleinberg, 1999], the fluid will be very susceptible to removal by absorption and by evaporation during mouth-breathing as the palate and anterior dorsum of the tongue will be the main areas to receive initial contact with the inspired air.

Non-pharmacological ways for the dry-mouth patient to reduce the severity of the condition include: keeping well hydrated to maintain maximum unstimulated salivary flow; avoiding mouth-breathing as far as possible to reduce evaporation of saliva; using a humidifier to increase the relative humidity during the winter months, and especially in the bedroom, since mouth-breathing commonly occurs during sleep; avoiding tobacco, caffeine and alcohol to reduce their drying or diuretic effects; avoiding mouthwashes containing alcohol; using sugar-free chewing gum or candy to stimulate salivary flow, and using water or saliva substitutes.

While several clinical trials suggest that pilocarpine, which stimulates salivary flow, is effective in relieving dry mouth in some patients [Brennan et al., 2002], this drug also has some undesirable side-effects. A recently developed preventive measure for patients about to receive radiation treatment for cancer of the pharynx or larynx is the transfer of one submandibular gland to the submental

region, to shield it from the radiation beam [Jha et al., 2003]. So far, over 60 patients in Canada have successfully received this treatment, which maintains flow from at least one major salivary gland. Interestingly, the transferred gland appears to undergo hypertrophy, in a similar way to residual rat salivary glands after selective desalivation [Schwartz and Shaw, 1955].

In conclusion, saliva is probably 'enough' for avoidance of xerostomia if its flow rate exceeds the rate of fluid loss by mucosal absorption and evaporation. In practice, the unstimulated flow rate may need to be at least 0.1–0.3 ml/min. Because of an increase in the survival rate for

patients with head and neck cancer and an increase in the elderly population, there is an increased need for further research on the alleviation of xerostomia and for treatment of the deleterious effects of this condition.

Acknowledgements

I thank Dr. H.D. Gesser, University of Manitoba, and Dr. C.A. Squier, University of Iowa, for useful discussions on mucosal water absorption, and Dr. O. Odum, University of Manitoba, for her clinical insights.

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