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Radiation-induced xerostomia: pathophysiology, clinical course and supportive treatment

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Abstract Xerostomia, or oral dryness, is one of the most common complaints experienced by patients who have had radiotherapy of the oral cavity and neck region. The hallmarks of radiation-induced damage are acinar atrophy and chronic inflammation of the salivary glands. The early response, resulting in atrophy of the secretory cells without inflammation might be due to radiation-induced apoptosis. In contrast, the late response with inflammation could be a result of radiation-induced necrosis. The subjective complaint of a dry mouth appears to be poorly correlated with objective findings of salivary gland dysfunction. Xerostomia, with secondary symptoms of increased dental caries, difficulty in chewing, swallowing and speaking, and an increased incidence of oral candidiasis, can have a significant effect on the quality of life. At present there is no causal treatment for radiation-induced xerostomia. Temporary symptomatic relief can be offered by moistening agents and saliva substitutes, and is the only option for patients without residual salivary function. In patients with residual salivary function, oral administration of pilocarpine 5–10 mg three times a day is effective in increasing salivary flow and improving the symptoms of xerostomia, and this therapy should be considered as the treatment of choice. Effectiveness of sialogogue treatment requires residual salivary function, which emphasizes the potential benefit from sparing normal tissue during irradiation. The hypothesis concerning the existence of early apoptotic and late necrotic effects of irradiation on the salivary glands theoretically offers a way of achieving this goal.

Key words Xerostomia · Ionizing radiation · Moistening agents · Saliva substitutes · Sialogogues

Introduction

Radiation therapy, in addition to surgery and chemotherapy, continues to be one of the primary modalities for treatment of head and neck cancers. In addition to the antitumour effect, ionizing irradiation causes damage in normal tissues located in the field of radiation. Radiation induces both functional and morphological changes in salivary glands and oral mucosa leading to xerostomia [50].

Xerostomia is generally accepted as the subjective complaint of a dry mouth, which is poorly correlated with objective findings of salivary gland dysfunction. Oral dryness can be a symptom of a systemic disease (e.g. Sjögren's syndrome and sarcoidosis), a side effect of anticholinergic, antiadrenergic, or cytotoxic drug treatment, or it can be due to radiation therapy of the head and neck region [1]. Apart from the discomfort induced by xerostomia, patients also suffer from fissures of the lips and tongue, decreased taste acuity and

difficulty in chewing, swallowing and speaking. In addition, xerostomia also causes mucositis, peridontal diseases, and a marked increase in dental caries [1].

Xerostomia is the most prominent long term symptom in many survivors of head and neck cancer. It affects their quality of life adversely in terms of health, comfort and function. Treatment options are largely palliative and generally offer only short term relief of symptoms.

In this article, the pathophysiology and clinical course of radiation-induced xerostomia will be discussed. Furthermore, symptomatic treatment options for oral dryness will be reviewed, with special emphasis on pilocarpine.

Pathophysiology of salivary dysfunction

The oral cavity and upper pharynx are lubricated and protected by saliva. A healthy adult produces up to 1.5 l saliva in 24 h. This complex secretion modulates microbial populations within the oral cavity, remineralizes teeth, aids in the preparation of the initial food bolus, and lubricates the oral mucosa [45]. Salivary glands and saliva are part of the mucosal immune system. Saliva contains antimicrobial substances such as lysozyme, lactoferrin and peroxidases and the antifungal histatins [1].

Humans have both major and minor salivary glands. There are three pairs of major salivary glands: the parotid, the submandibular and the sublingual. The parotid is a purely serous gland, whereas the submandibular and the sublingual contain both mucous and serous cells [45]. The three pairs of major glands provide most of the saliva secreted in response to an exogenous stimulus. Saliva from numerous minor glands lubricates the mucosa throughout the day [45]. Each gland is composed of a well-vascularized system of acini and ducts. The gland is divided into lobes and lobules by connective tissue septa which contain vessels, lymphatics, nerves and ducts. Clusters of secretory cells, the acini, make up the salivary parenchyma [45]. They transport water via solute-solvent coupling with sodium chloride. The acini contribute most of the protein to saliva. The ducts reasorb sodium and chloride to produce a hypotonic solution, and the ductal system then transports saliva to the mouth [50].

Because of the location of the primary tumour and regional lymph nodes, the oral cavity, and salivary glands of most head and neck cancer patients are in the fields of radiation. As a result radiation-induced changes will occur in these tissues upon radiotherapeutic treatment of the tumour [28].

The tissues of the salivary glands are stable and have a low mitotic index [47]. Furthermore the cells of the salivary glands have slow turnover rates, which implies that the radiation damage may not become evident for months or years after therapy (late effects) [28, 47]. Based on this consideration, one would expect the cells of the salivary glands to be relatively radioresistant. However, changes in quantity and composition of saliva occur shortly after irradiation (early effects), indicating that the gland tissue is acutely radiosensitive, at least in a functional aspect [28, 47]. When major salivary glands are within the radiation field, salivary dysfunction develops immediately and predictably and in a radiation-dose-dependent manner.

A 50–60% decrease is salivary flow occurs during the first week. The saliva becomes viscous and mucoid, indicating that some mucous acini are still functional. Most patients experience the first signs of xerostomia at this stage. As radiation therapy continues and the total radiation dose increases, salivary function decreases further [50].

The hallmarks of irradiated salivary glands are acinar atrophy and chronic inflammation. Fibrosis and chronic inflammation are found in periductal and intralobular areas, whereas the ductal system remains relatively intact [19]. Degranulation, degeneration, and necrosis of serous acinar cells are observed 1 h after treatment with a dose of 2.5 Gy. At 6 h after single-dose irradiation, a parotid gland treated with doses of 2.5–7.5 Gy showed necrosis of serous cells, whereas with doses of 10.0–15.0 Gy whole acini were found to be lost [37]. The loss of salivary parenchyma is the most probable cause of decreased salivary flow [50]. Sialochemistry shows that both the acinar and the ductal functions are affected by radiation. Sodium and chloride levels are increased, suggesting that ductal reabsorption of these electrolytes is defective. Potassium, which is secreted by the ductal cells, remains normal. The primary salivary buffer bicarbonate is significantly decreased [50].

The extent of radiation-induced salivary dysfunction depends on several factors: radiation field, radiation dose, and initial volume and function of the salivary gland [13, 39, 55]. The radiation field, specifically the volume of gland tissue exposed, is an important determinant of salivary dysfunction and development of xerostomia [39, 49]. In some cases the field may be designed to spare the salivary glands while sterilizing the tumour. When possible, unilateral radiation fields may be used, which can preserve contralateral parotid function and cause less xerostomia compared with bilateral fields [13, 38]. Patients with tumours of nasopharynx, oropharynx, and unknown primary sites are generally irradiated in a bilateral manner. The major glands are often entirely within the field, and the irradiation then results in severe dysfunction. Individuals whose tumour location allows part of the major glands to be spared (such as laryngeal tumours, Hodgkin's disease, or non-

Hodgkin's lymphoma) have lesser dysfunction and development of xerostomia [39, 40].

Most patients with head and neck cancer receive a total dose of 50–70 Gy as a curative dose. Conventional treatments are given via fractionated radiotherapy over a 5- to 7-week period, once a day, 5 days a week, with a daily tumour dose of about 2 Gy [13, 28, 49]. After 2–3 weeks of this fractionated radiotherapy, the basal salivary secretion is grossly reduced [13, 28, 49]. Valdez followed the salivary function of six patients before, during, and after radiotherapy with 2.0 Gy per fraction [50]. They found that both resting and stimulated salivary functions of all patients decreased in a dose-dependent manner. The pattern of decline during radiation was similar for both parotid and submandibular/sublingual gland function. The dysfunction proved to be long lasting; no recovery has been found during the follow-up of 12 months. Earlier observations already showed the irreversible nature of the damage [5, 19]. It has been shown that acinar necrosis and gland atrophy progress until 6–8 months after therapy, and the patient's salivary function continues to decline during that time [5, 19]. In individual reports, a slight recovery of salivary function has been mentioned [13], but the majority of the studies show no recovery [12, 39, 41, 55].

DNA damage is believed to be responsible for classical clonogenic cell killing by ionizing radiation [42]. An early rupture of the plasma membrane occurs, resulting in release of cytoplasmic and nuclear material. These characteristic morphological changes are typical for the passive form of cell death called necrosis [52]. In addition, ionizing radiation activates a genetically regulated cell death process called apoptosis [31, 52]. Apoptosis, or programmed cell death, is a genetically based active process induced by a damaging stimulus (e.g. immunotoxins, cytotoxic drugs, ionizing radiation) or by deprivation of a viability factor (e.g. growth factors, hormones, cytokines). Apoptosis is morphologically characterized by cell shrinking, plasma membrane blebbing, and nuclear changes, including chromatin condensation and nuclear fragmentation [31, 52]. In contrast to necrosis, which induces inflammation of the tissue, apoptosis culminates in the rapid clearance of cells by phagocytosis without inflammation [7]. In the literature there is convincing evidence that ionizing radiation can induce apoptosis in vitro [9, 20, 37, 53]. Recently it has been demonstrated that therapeutic fractionated low-dose total-body irradiation induces prompt but long lasting apoptosis of circulating human lymphocytes in vivo [11]. Based on these observations we can speculate that both apoptosis and necrosis may play a part in the radiation-induced morphological changes of the salivary gland. The early effects on the serous gland characterized by disappearance of the acinar cells without inflammation could be due to apoptosis, whereas the late inflammatory reaction of the tissue could be subscribed to necrosis. In fact, these two distinct forms of cell death were demonstrated in lacrimal gland and parotid gland of rhesus monkeys after irradiation [20, 48]. Furthermore, there are suggestions in the recent literature that the stimulus for induction of apoptosis by radiation may differ from the stimulus for the induction of clonogenic cell killing [4, 34]. It has been shown that apoptosis can be triggered by chemical agents which mimics different types of molecular damage that are caused by ionizing radiation [4, 34]. Accordingly, it may be possible to differentially modify the apoptotic and the necrotic process so as to achieve increased tumour cell kill while normal tissues are protected, thus increasing the therapeutic ratio [9]. According to the same principle, salivary glands may be protected against radiation-induced xerostomia by pretreating the parotid acinar cells with an agent capable of inhibiting radiation-induced apoptosis [9].

Clinical course

Oral sequelae of radiotherapy in the head and neck region are the result of deleterious effects of irradiation on salivary glands, oral mucosa, bone, dentition, masticatory muscles and temporomandibular joints. The occurrence and the extent of these side effects depend upon the total irradiation dose, volume of the irradiated tissue, dose fractionation and the type of ionizing irradiation.

Xerostomia is the subjective complaint of a dry mouth, and can be caused by salivary gland dysfunction. The consequences of xerostomia include oral discomfort and difficulties with oral functioning, including speech [33]. Sequelae from hyposalivation also include alterations in the oral soft tissues, a shift in oral microflora, hyposalivation-related dental caries, and periodontal disease [54]. Mucosal alterations such as inflammation, atrophy and ulceration are also common [27]. Patients have low tolerance for dental prostheses because of tissue friability and lack of lubrication. Oral microbial populations shift, resulting in a high risk of caries and frequent occurrence of oral candidiasis [8, 12, 19]. Patients may also have abnormal swallowing patterns, in which the movement of a bolus from mouth to pharynx is slowed [24].

Salivary dysfunction may effect general health as well. Oral symptoms can alter food choices and may lead to nutritional compromise [2, 6, 56]. Recently, chronic oesophagitis was identified in patients with radiation-induced xerostomia [32]. The loss of salivary flow and decreased oesophageal pH may contribute to the development of gastro-oesphageal reflux disease [23]. Sleep disruptions occur when a patient awakens to moisten the dry mouth or to relieve the polyuria experienced with polydipsia [54]. Furthermore, polydipsia

and polyuria may result in emotional stress. Finally, patients with certain concomitant medical conditions may be subject to health risks from increased fluid intake [33].

Treatment

Radiation-induced xerostomia results from partial or complete destruction of the salivary glands. Therefore, the goal of treatment is to provide symptomatic relief of mucosal dryness with saliva substitutes or to increase the flow of saliva with moistening agents and/or sialogogues [33] (Table 1).

Saliva substitutes

Various commercial products have been designed to moisten and lubricate the oral mucosa. Saliva substitutes duplicate the properties of normal saliva. Levine et al. list the potential constituents of artificial saliva including carboxymethylcellulose (CMC), mucins, sorbitol or xylitol, mineral salts, fluorides and preservatives [36]. A product that includes sorbitol and CMC has been shown to provide considerable relief without significant side effects [46]. However, most patients prefer water as an oral lubricant [1]. Mucolytic agents that decrease the viscosity of secretions have also been used with some success [16].

Several limitations must be considered in recommending commercial preparations [33]. One concern is the high cost to the patient when these products are used for an extended period of time. Furthermore, the taste of the product, which may change with the effects of therapy, is a subjective complaint of many patients. However, the major disadvantage of saliva substutes is the temporary nature of the relief provided.

Table 1 Symptomatic treatment of radiation-induced xerostomia

Without residual salivary function
Saliva substitutes
With residual salivary function
Moistening agents
Sialogogues
Pilocarpine
Neostigmine
Nicotinic acid
Potassium iodide
Bromhexine
Carbacholine
Anetholetritione

Moistening agents

Chewing sugarless gum, sucking sugarless candies, or taking frequent sips of liquids are the most common methods of relieving oral dryness [33]. Unfortunately, these measures provide only temporary relief of dryness. The inconvenience and the possible embarrassment that may result from their frequent use can be a source of irritation to the patient. A major disadvantage is the nocturnal oral dryness and nocturia that may awaken the patient from a restful sleep [33]. An additional caution is that oral mucosal damage stemming from pressure and osmolarity can accompany the chronic use of oral lozenges and hard candy [3].

Sialogogues

Sialogogues, defined as systemic salivary gland stimulants [57], are also used to treat the symptoms of xerostomia. Sialogogues increase the flow of saliva and therefore require functional salivary gland parenchyma in order to be effective. While a significant proportion of the salivary glands may be damaged by radiation therapy, it is rare for all the minor and major glands to be totally compromised. The residual function of the salivary glands can be evaluated by measuring salivary gland flow rate and salivary gland scintigraphy [57]. A number of substances have been previously used as a sialogogue (e.g. neostigmine, nicotinic acid, potassium iodide, bromhexine), but pilocarpine proved to be the most effective substance [57] and it is approved for the treatment of radiation-induced xerostomia in several European countries and in the USA.

Pilocarpine is a naturally occurring parasympathicomimetic alkaloid derived from the leaves of plants of the genus *Pilocarpus*. Because of its muscarinic-cholinergic properties it has a broad spectrum of pharmacological effects, including diaphoretic, miotic and central nervous system actions. It increases the secretion from the exocrine glands, including the sweat, salivary, lacrimal, gastric, pancreatic and intestinal glands. It also increases the tone and the motility of smooth muscles of the different organs. The pilocarpine-induced vasodilatation in the salivary glands and consequently the increase in salivary secretion is mediated by cholinergic-muscarinic receptors [57]. Pilocarpine-stimulated secretions have been found to be similar in composition to normal salivary secretions [33]. The clinical efficacy of pilocarpine as a salivary stimulant has been investigated in patients with salivary gland dysfunction or radiation-induced xerostomia in several double-blind placebo-controlled studies (Table 2).

Pilocarpine 5–10 mg three times daily was effective in stimulating salivary secretion and improving symptoms of xerostomia, including difficulty in swallowing,

Table 2 Double-blind, placebo-controlled clinical studies with pilocarpine in the treatment of radiation-induced xerostomia (*tid* 3 times daily, *qid* 4 times daily)

Daily dose	Regimen	Duration of treatment	No. of patients	Results	Reference
20/30 mg	tid/qid	3 months	12	Symptomic improvement after 3 months	[22]
15 mg	tid	5 months	10	Positive responses after 1 month in 9/10	[18]
7.5/15/30 mg	tid	3 months	162	Subjective and overall improvements	[35]
15/30 mg	tid	3 months	207	Overall improvements: placebo group 25%, 15-mg group 43%, 30-mg group 54%	[30]
15 mg	tid	3 months	20	Overall improvement in 12/17	[10]
20 mg	qid	3 months	9	Subjective and objective improvements	[51]
7.5/15/30 mg	tid	1 month	262	Overall improvements at all dosages	[44]
15/30 mg	tid	3 months	207	Overall improvements	[44]
15 mg	tid	1 month	9	Subjective improvement in 7/9	[14]
18 mg	tid	1 month	24	Subjective improvement in 18/24	[29]

chewing and speaking, in a significantly higher percentage of patients than placebo [17, 18, 21, 22]. In a double-blind, placebo-controlled, cross-over study, 5 mg pilocarpine in patients with subjective xerostomia and documented salivary gland dysfunction increased salivary flow of the parotid gland within 30 min following administration, with a maximum flow at 45 min [17]. Flow rates slowly decreased, reaching baseline values within 3 h. When pilocarpine was administered flow rates were 10 times that with placebo, which produced no difference from baseline [17]. In a double-blind, placebo-controlled study in 39 patients with radiation-induced xerostomia, unstimulated major salivary gland output was significantly increased in 26 of 39 patients after initial exposure to pilocarpine 5 mg, and 27 of 39 patients showed symptom improvement after 1 month of treatment with pilocarpine 5 mg three times daily [18]. At 6 months after treatment patients were still experiencing relief of their symptoms [18]. A double-blind, cross-over study in 12 subjects with xerostomia caused by irradiation was performed by Greenspan and Daniels [21, 22]. Patients were given pilocarpine 2.5 mg tablets (2–3 tablets 3–4 times daily) or placebo for 90 days. Patients taking pilocarpine showed a measurable increase in parotid and whole flow rates, which was statistically significant at 90 days [21, 22]. In a large multicentre study in 207 patients, the overall severity of xerostomia was reduced in a significantly higher percentage of patients following 12 weeks of treatment with pilocarpine 5 mg three times daily (54%) than in those receiving placebo (25%) [30]. Pilocarpine treatment was associated with an increased ability to speak without requiring liquids, and a reduced need for oral comfort agents. The percentage of patients with an increase in whole and unstimulated parotid salivary flow rates was also higher in pilocarpine recipients than in those who received placebo, but the objective findings of salivary secretion did not correlate with symptomatic relief [30]. LeVeque et al. [35] demonstrated in a multicentre, randomized, placebo-controlled, dose-titration study of 162 patients with radiation-induced xerostomia that pilocarpine in a dose of at least 5 mg is effective and safe in reducing symptoms of dry mouth in patients treated with irradiation for head and neck cancer. In this study, the dose of pilocarpine was titrated from 2.5 mg to 10 mg three times daily, depending on patient response at each visit. There was a statistically significant improvement in overall symptoms of dry mouth in the pilocarpine groups treated with 5 or 10 mg, but there were very few objective responses to the drug [35]. Preliminary results of a small double-blind placebo-controlled study indicate that pilocarpine administration during irradiation therapy may reduce the severity of xerostomia. In this study nine patients were treated with pilocarpine 5 mg three times daily for 3 months starting the day before irradiation therapy. It appeared that the pilocarpine-treated patients had a smaller loss in salivary gland function and fewer symptoms of xerostomia following irradiation than those receiving placebo [51].

Pharmacokinetic studies performed by the company that manufactures pilocarpine showed that the peak plasma concentrations after 2 days of oral treatment with 5 and 10 mg three times daily were 15 and 41 μg/l, respectively, and were reached in 1.25 and 0.85 h, respectively [25, 26]. Pilocarpine is eliminated predominantly in the urine, with an elimination half-life of 0.76 or 1.35 h following administration of a 5- or 10-mg dose, respectively, three times daily [25, 26].

Pilocarpine is well tolerated in clinical trials, but the cholinergic properties of low-dose pilocarpine mean that prudence is required in its administration. During clinical trials mild adverse effects were reported by patients, such as sweating, chills, nausea, dizziness, rhinitis, flushing, asthenia, increased lacrimation and gastrointestinal tract disturbance [30, 44, 57]. Sweating was the most common side-effect and occurred in 37–65% of the patients treated with pilocarpine 5 mg three times daily and in 80% of the patients treated with 10 mg three times daily. This side effect caused 5.5%

and 29% of the patients, respectively, to withdraw from therapy during the first 3 months of the therapy period [30]. No significant effects have been observed on heart rate, blood pressure, or cardiac conductivity. However, pilocarpine is not recommended in patients with current or recent histories of cardiovascular diseases, unstable hypertension, or gastrointestinal ulcers [33]. Pilocarpine treatment is contraindicated in patients with uncontrolled asthma, acute iritis or narrow-angle glaucoma. Caution should be taken when coadministrating pilocarpine to patients treated with b-adrenergic antagonists or parasympathicomimetics or anticholinergic drugs [57].

It is concluded that pilocarpine is an effective and safe agent for the treatment of radiation-induced xerostomia. However, the lack of correlation between changes in salivary function and subjective relief of symptoms in some studies indicate that still more research is needed on the pharmacological mechanism of pilocarpine in the treatment of xerostomia.

Apart from pilocarpine, few drugs with cholinergic properties have been studied in the treatment of xerostomia. Joensuu et al. [29] studied the effect of carbacholine in 24 patients with radiation-induced xerostomia and compared it with the results of pilocarpine treatment. Patients were treated with oral pilocarpine solution 6 mg three times daily and, after a 4-week drug-free period, with carbacholine 2 mg tablets three times daily. Basal and stimulated salivary flow rates were measured before the start of drug treatment and after 1 week and 12 weeks of drug treatment. On a subjective linear scale, both pilocarpine and carbacholine improved mouth moistness. Although 6 of the 16 patients preferred carbacholine and only 1 patient preferred pilocarpine, more prospective randomized comparative trials are needed to prove superiority of either of these drugs [29].

Anetholetritione (ANTT), another chemical sialogogue, has been shown to alleviate the symptoms of xerostomia and increase the secretion of saliva in patients with Sjögren's syndrome [15]. In addition, a synergistic effect of ANTT and pilocarpine has been found in nine patients with xerostomia [14]. Patients who had not responded to salivary stimulation by physical means showed significant increases in salivary flow when ANTT 25 mg three times daily was administrated starting 1 week before the use of pilocarpine 1% solution. The authors postulated that ANTT increased the number of muscarinic receptors and that this was why it therefore, interacted with pilocarpine in a synergistic manner. They concluded that the two agents could be beneficial when used together in patients who did not respond to either drug alone [14].

General support measures

In general, patients also should be advised to maintain a balanced diet and avoid foods that irritate unprotected mucosa [43]. For example, caffeine-containing beverages, which can cause dehydration, fruits, especially of the citrus family, which can cause burn sensation, and alcohol-containing mouth rinses should be avoided [1].

Furthermore, patients can also benefit from oral hygiene counselling and nursing care [28].

Conclusions

In conclusion, there is at present not a causal treatment for radiation-induced xerostomia. Temporary symptomatic relief can be offered by moistening agents and saliva substitutes, and are the only options for patients without residual salivary function. Furthermore, in patients with residual salivary function, pilocarpine 5–10 mg three times daily is effective in increasing salivary flow and improving the symptoms of xerostomia. Accordingly, this therapy should be considered as the treatment of choice. However, a treatment adressing the cause of xerostomia might be possible if a means could be found to prevent the atrophy of the secretory cells. Further research concerning the modulation of apoptotic and necrotic cell damage during irradiation may hopefully improve the therapeutic potential and diminish damage to the salivary glands.

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