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ORIGINAL ARTICLE

Effect of the H2 receptor antagonist nizatidine on xerostomia in patients with primary Sjögren's syndrome

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Abstract In Sjögren's syndrome (SS), oral dryness (xerostomia) is frequently the most bothersome symptom. An H2 histamine receptor antagonist is often administered to SS patients to treat associated superficial gastritis. The aim of the present study was to assess the ability of nizatidine, an H2 receptor antagonist, to also relieve xerostomia in patients with primary SS. Twenty-seven patients with primary SS were randomly assigned to receive nizatidine ($n = 14$, 300 mg a day) or another H2 blocker, famotidine ($n = 13$, 40 mg a day; control), were followed for eight -weeks, and were asked for both subjective and objective assessments of oral dryness using a visual analog scale (VAS; 1–100 mm) and the Saxon's test, respectively. Patients receiving oral nizatidine, but not famotidine, obtained significant objective relief from their xerostomia (Saxon's test; baseline, 0.57 g/2 min; after eight weeks, 0.90 g/2 min, $P < 0.05$). VAS scores indicated that nizatidine also provides mild improvement (20% improvement over baseline) of xerostomia-related clinical conditions, including mouth dryness and difficulty in chewing, tasting and swallowing food. Both drugs were generally well tolerated, without adverse effects. The present preliminary study suggests that nizatidine may represent a new option for the treatment of xerostomia in SS.

Keywords H2 receptor antagonist · Sjögren's syndrome · Xerostomia

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Abbreviations

SS	Sjögren's syndrome
VAS	Visual analog scale

Introduction

For patients with Sjögren's syndrome (SS), oral dryness (xerostomia) is frequently the most bothersome symptom, one that can cause significant morbidity and a reduction in a patient's perception of the quality of life [1, 2]. Furthermore, although awareness of the systemic nature of SS and the considerable morbidity associated with it has directed treatments toward disease modification, treatment of sicca symptoms such as xerostomia with immunomodulatory drugs has been unsuccessful. On the other hand, the most recent data show that systemic administration of a cholinergic agonist (e.g., pilocarpine and cevimeline) is effective for symptomatic treatment of dryness [3–7]. Cevimeline hydrochloride is a muscarinic cholinergic agonist that acts to stimulate secretion primarily via M1 and M3 receptors, which are prevalent in exocrine glands [8, 9]. Another compound, cisapride, increases salivary secretion by inducing the release of acetylcholine from post-ganglionic cholinergic neurons via serotonin receptors [10, 11]. Patients using cholinergic agonists, however, may experience a number of unpleasant side effects that may limit the efficacy of these medications [12]. However, the H2 receptor antagonist nizatidine appears to also have the ability to inhibit acetylcholinesterase, resulting in an increased availability of acetylcholine [13, 14], and was recently shown to stimulate salivary secretion in healthy volunteers [15]. This observation led us to speculate that nizatidine may have a beneficial effect without any adverse

effects in SS patients experiencing xerostomia. Therefore, the aim of the present study was to assess the efficacy and safety of nizatidine in the treatment of xerostomia in patients with primary SS.

Methods

Study design and population

An eight-week, single center, open-labeled, randomized controlled study was performed. A total of 27 primary SS patients, in whom salivary secretion (Saxon's test <2 g/2 min) was deemed impaired based on the American/European consensus group classification criteria for SS [16], were enrolled in this study. All patients were at least 18 years old. For eight weeks prior to the study, they made no changes in the dosage of their medications such as nonsteroidal antiinflammatory drugs, and were prescribed no immunosuppressive agents or agents affecting salivary secretion. At the time of the baseline visit (week 0), the patients were randomly assigned to receive nizatidine ($n = 14$, 150 mg twice a day) or famotidine ($n = 13$, 20 mg twice a day) as control because this H2 receptor antagonist is used all over the world, and were followed for eight weeks. The patients were evaluated prior to (baseline) and then after eight weeks of therapy. The primary outcome in this study was salivary secretion (Saxon's test) and a global improvement of xerostomia. At each visit, subjects were first instructed to take nothing by mouth for at least 60 min and then to chew a piece of preweighed gauze for 2 min, after which the gauze was weighed again. The change in the weight of the gauze represented the patient's salivary production during this 2-min period [17]. The effect of the study medication on salivary production was quantified by determining the difference between salivary production before and after the eight weeks of therapy. Participants were also asked to compare their overall clinical condition associated with xerostomia before and after therapy using a 100 mm visual analog scale (VAS). The parameters assessed included mouth dryness; desire to sip water when eating a meal; difficulty in speaking; and difficulty chewing, tasting and swallowing food. A 20% improvement or more against the baseline VAS score was considered to be a clinically positive improvement, although it would be difficult to define the improvement in the patient's clinical condition. The frequency of 50% improvements in VAS score was also examined. In addition, erythrocyte sedimentation rates (ESR), complete blood counts, and renal and liver function were evaluated throughout the study.

The study protocol was approved by the Ethics Committee of the Showa University. All participants provided written informed consent.

Statistical analysis

Chi-squared analysis was used to compare categorical data between the nizatidine and famotidine groups. Differences in salivary secretion between the two groups were initially evaluated using repeated measures analysis of variance. Where the groups appeared to significantly differ, means were compared using Student's *t*-test. The Fisher's exact probability test was used to compare VAS scores between the two groups. Correlation between improved rates (%) of salivary secretion and relief from symptoms of mouth dryness was evaluated using the Spearman correlation test. Values of $P < 0.05$ were considered significant.

Results

There were no significant differences in the demographic variables, including salivary secretion at baseline and disease characteristics, between the patients in the nizatidine and famotidine groups (Table 1). Although the most frequently used medications were nonsteroidal antiinflammatory drugs, a few patients received low-dose prednisolone (<5 mg/day), and the usage of both medications was similar in the two groups.

Salivary secretion was evaluated using Saxon's test (g/2 min). As shown in Fig. 1, the tests indicated that patients receiving oral nizatidine obtained significant objective relief from their xerostomia (mean salivary secretion: baseline, 0.57 ± 0.39 g/2 min; after eight weeks of treatment: 0.90 ± 0.65 g/2 min, $P < 0.05$), whereas salivary secretion was not increased by famotidine (baseline, 0.68 ± 0.40 g/2 min; after eight weeks of treatment: 0.71 ± 0.44 g/2 min).

Table 1 Patient characteristics as baseline

	Nizatidine	Famotidine
Sex (M/F)	2/12	3/10
Age (years)	61.8 ± 13.7	59.8 ± 12.0
Disease duration (years)	3.2 ± 2.3	2.9 ± 3.0
Salivary secretion (g/ml)	0.57 ± 0.39	0.68 ± 0.42
Presence of xerophthalmia (%)	85.7	76.9
Anti SS-A antibody (U/ml)	56.0 ± 63.6	61.0 ± 58.1
Anti SS-B antibody (U/ml)	53.5 ± 76.1	56.7 ± 62.4
IgG (mg/dl)	1,918.3 ± 551.8	2,017.8 ± 397.0
ESR (mm/h)	41.7 ± 18.3	39.0 ± 28.1

Results shown are means ± SD. Saliva secretion was measured using Saxon's test

ESR erythrocyte sedimentation rate

There were no significant differences between the two groups for any of the parameters

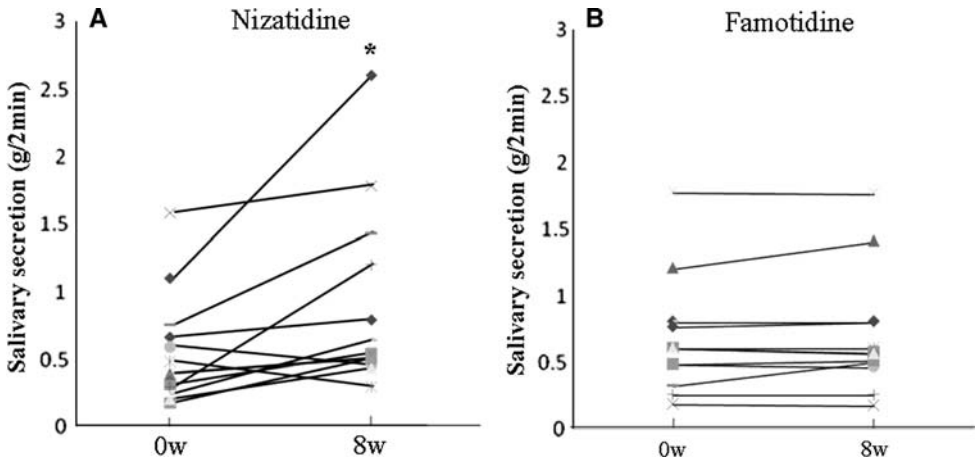

Fig. 1 Effects of H2 receptor antagonists on salivary secretion. Salivary secretion was assessed using the Saxon test (g/2 min) before and after eight weeks of treatment. In the nizatidine group, but not the famotidine group, salivary secretion was significantly increased after therapy (* $P < 0.05$, analyzed by repeated measures analysis of variance)

Global assessment of xerostomia showed that significantly more patients in the nizatidine group than in the famotidine group achieved a 20% improvement in VAS score related to the sensation of mouth dryness (71.4 vs. 15.4%, $P < 0.05$; Fig. 2). Moreover, patients taking nizatidine also reported improved (20% improvement in VAS score) abilities to chew, taste and swallow food (Fig. 2). On the other hand, no significant differences between the groups were seen in the ability to speak or the desire to sip water (Fig. 2). Notably, prominent relief from xerostomia symptoms, as indicated by a 50% improvement in VAS score, was also observed significantly more frequently in the nizatidine group than the famotidine group ($P < 0.05$; Fig. 3). Additional analysis revealed that there is a significant positive correlation between improved rates of salivary secretion and relief from symptoms of mouth dryness in patients receiving oral nizatidine (Fig. 4). Both drugs were generally well tolerated, with no adverse effects on either their symptoms or clinical laboratory findings.

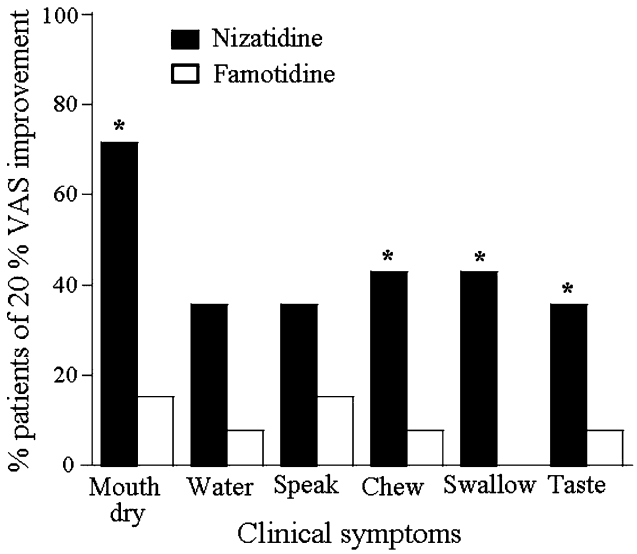

Fig. 2 Percentages of SS patients reporting a 20% improvement in clinical symptoms associated with mouth dryness. Using a 100 mm visual analog scale (*VAS*), patients were asked to assess clinical symptoms. After eight weeks of therapy, a 20% or more improvement in the VAS score over baseline was considered a positive response. *Water* means the desire to sip water, *Speak* means difficulty in speaking, *Chew* means difficulty in chewing, *Swallow* means difficulty in swallowing food, *Taste* means difficulty in tasting food. Significantly more patients in the nizatidine group than in the famotidine group obtained relief from the symptoms of mouth dryness and reported an improved ability to chew, swallow and taste food (* $P < 0.05$, analyzed by Fisher's exact probability test)

Discussion

In terms of the primary outcome measure in this trial, administration of nizatidine to SS patients stimulated significantly more salivary secretion than famotidine. Comparisons of the outcomes showed statistically significant relief from mouth dryness as well as an improved ability to chew, taste and swallow food. On the other hand, nizatidine had little or no effect on the desire to sip water or difficulty in speaking. Although statistically significant, the weakness of nazatidine's effect on some oral symptoms may reflect the fact that our patients had established SS for a mean of 3.2 years, which means that at least some irreversible destruction of glandular tissue had already occurred. In SS, deficient secretion from salivary and lacrimal glands, leading to xerostomia and xerophthalmia, respectively, is attributable to both a reduction in the number of secretory units and dysfunction of the residual secretory units [18, 19]. Perhaps a stronger clinical response might be observed if SS were treated at an earlier stage of the disease, when there is more active inflammation.

Sjögren's syndrome patients often present an ill-defined gastropathy with symptoms of epigastric pain and dyspepsia [20]. Chronic atrophic gastritis is a common finding in SS, though these patients often exhibit superficial gastritis and high pepsinogen I levels [21]. Protective agents and/or H2 antagonists are often used to treat these gastric

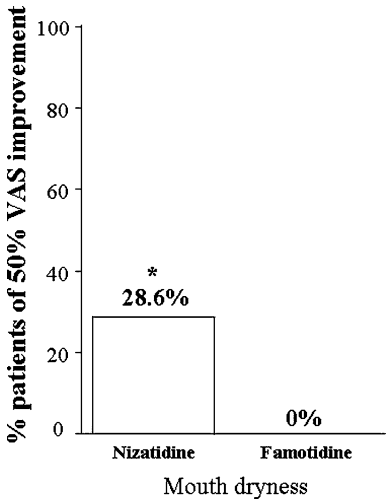

Fig. 3 Percentages of SS patients reporting a 50% improvement in clinical symptoms. Significantly more patients in the nizatidine group than in the famotidine group obtained symptomatic relief of mouth dryness leading to a 50% improvement in VAS score (* $P < 0.05$)

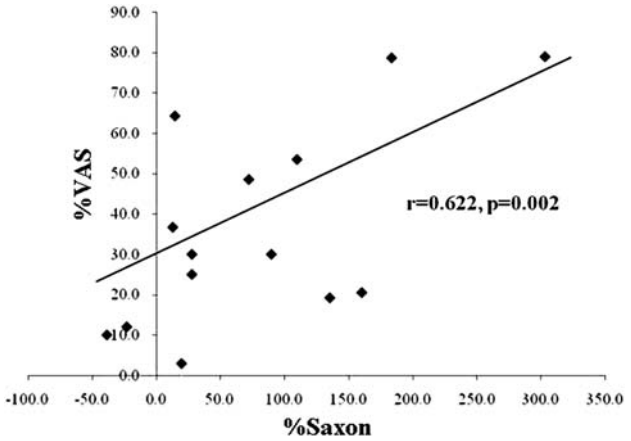

Fig. 4 Correlation between improved rates of salivary secretion and relief from symptoms of mouth dryness in SS patients with nizatidine. A significant positive correlation was found ($r = 0.622$, $P = 0.002$, analyzed by the Spearman correlation test). Each point represents an individual patient

manifestations of SS. It is noteworthy that the H2 antagonist nizatidine also shows an ability to inhibit acetylcholinesterase, thereby increasing the availability of acetylcholine [13, 14]. Evidence suggests that this acetylcholine acts via muscarinic receptors to upregulate secretion from salivary glands [15]. One would therefore expect that administration of an H2 receptor antagonist would be a particularly appropriate and reasonable approach to treating xerostomia in SS patients with superficial gastritis and, perhaps, other gastropathies.

Both xerostomia and xerophthalmia in SS patients can be treated locally [2, 4]. Pilocarpine was recently shown to have beneficial effects on salivary secretion and is now being used in clinics [3]. However, some adverse effects, including gastrointestinal symptoms, have been reported by patients taking pilocapine [3]. Among the medications used to regulate general immune responses in SS patients, D-penicillamine has a small effect on salivary symptoms [22]. Similarly, cyclosporin A and methotrexate provide some subjective relief from xerostomia [23, 24]. These agents exert no objective effect on clinical symptoms or serological parameters in SS patients, however [24]. Furthermore, there is no clinical evidence that these medications provide relief from the sicca symptoms seen in patients with either primary or secondary SS, and there is a risk of adverse effects with these generally acting drugs. By contrast, nizatidine was well tolerated with no adverse effects on either the clinical symptoms or laboratory findings in the present clinical trial.

Nizatidine, as well as pilocarpine, acts as a symptomatic therapy on xerostomia, and may have no significant immunological effects on inflamed salivary glands. Therefore it will be necessary to develop a more effective and safer therapy targeting dysregulated immunological abnormalities in the salivary glands seen in patients with SS. Although a double-blind, controlled study will be required to confirm the efficacy of nizatidine, the present preliminary study suggests that it may represent a new option for the treatment of xerostomia in SS patients.

Conflict of interest None of the authors have any conflicts of interest in connection with this work.

References

1. Soto-Rojas AE, Kraus A. The oral side of Sjogren syndrome. Diagnosis and treatment. A review. Arch Med Res. 2002;33:95–106.
2. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. Arch Intern Med. 2004;164:1275–84.
3. Vivino FB, Al-Hashimi I, Khan Z, LeVeque FG, Salisbury PL 3rd, Tran-Johnson TK, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. Arch Intern Med. 1999;159:174–81.
4. Wall GC, Magarity ML, Jundt JW. Pharmacotherapy of xerostomia in primary Sjogren's syndrome. Pharmacotherapy. 2002;22:621–9.
5. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, et al. Cevimeline for the treatment of xerostomia in patients with Sjogren syndrome: a randomized trial. Arch Intern Med. 2002;162:1293–300.
6. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum. 2002;46:748–54.
7. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjogren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis. 2005;64:347–54.

8. Iga Y, Arisawa H, Ogane N, Saito Y, Tomizuka T, Nakagawa-Yagi Y, et al. (±)-*cis*-2-Methylspiro[1,3-oxathiolane-5,3′-quinuclidine] hydrochloride, hemihydrate (SNI-2011, cevimeline hydrochloride) induces saliva and tear secretions in rats and mice: the role of muscarinic acetylcholine receptors. Jpn J Pharmacol. 1998;78:373–80.
9. Fox RI, Konttinen Y, Fisher A. Use of muscarinic agonists in the treatment of Sjogren's syndrome. Clin Immunol. 2001;101:249–63.
10. Neya T, Itano N, Mizutani M, Yamasato T, Takaki M, Nakayama S. The effect of cisapride on neural 5-HT receptors in guinea-pig isolated ileum. Eur J Pharmacol. 1984;106:221–2.
11. Taniyama K, Nakayama S, Takeda K, Matsuyama S, Shirakawa J, Sano I, et al. Cisapride stimulates motility of the intestine via the 5-hydroxytryptamine receptors. J Pharmacol Exp Ther. 1991;258:1098–104.
12. Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med. 1993;329:390–5.
13. Kounenis G, Voutsas D, Koutsoviti-Papadopoulou M, Elezoglou V. Inhibition of acetylcholinesterase by the H2-receptor antagonist nizatidine. J Pharmacobiodyn. 1988;11:767–71.
14. Ueki S, Seiki M, Yoneta T, Aita H, Chaki K, Hori Y, et al. Gastroprokinetic activity of nizatidine, a new H2-receptor antagonist, and its possible mechanism of action in dogs and rats. J Pharmacol Exp Ther. 1993;264:152–7.
15. Adachi K, Ono M, Kawamura A, Yuki M, Fujishiro H, Kinoshita Y. Nizatidine and cisapride enhance salivary secretion in humans. Aliment Pharmacol Ther. 2002;16:297–301.
16. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis. 2002;61:554–8.
17. Kohler PF, Winter ME. A quantitative test for xerostomia. The Saxon test, an oral equivalent of the Schirmer test. Arthritis Rheum. 1985;28:1128–32.
18. Fox RI, Stern M, Michelson P. Update in Sjogren syndrome. Curr Opin Rheumatol. 2000;12:391–8.
19. Hansen A, Lipsky PE, Dorner T. New concepts in the pathogenesis of Sjogren syndrome: many questions, fewer answers. Curr Opin Rheumatol. 2003;15:563–70.
20. Sheikh SH, Shaw-Stiffel TA. The gastrointestinal manifestations of Sjogren's syndrome. Am J Gastroenterol. 1995;90:9–14.
21. Ostuni PA, Germana B, Di Mario F, Rugge M, Plebani M, De Zambiasi P, et al. Gastric involvement in primary Sjogren's syndrome. Clin Exp Rheumatol. 1993;11:21–5.
22. ter Borg EJ, Haanen HC, Haas FJ, Bistervels JH, Huisman FW, Kerckhaert JA, et al. Treatment of primary Sjogren's syndrome with D-penicillamine: a pilot study. Neth J Med. 2002;60:402–6.
23. Drosos AA, Skopouli FN, Costopoulos JS, Papadimitriou CS, Moutsopoulos HM. Cyclosporin A (CyA) in primary Sjogren's syndrome: a double blind study. Ann Rheum Dis. 1986;45:732–5.
24. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjogren's syndrome. Clin Exp Rheumatol. 1996;14:555–8.