Salivary Function in Patients with Reflux Esophagitis: Effect of Cisapride

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Saliva plays an important role in esophageal acid clearance. Reduction in salivary function has been considered in the pathogenesis of reflux esophagitis. Cisapride, a prokinetic agent, has been reported effective for treating mild-to-moderate grade gastroesophageal reflux disease. Some studies have shown that cisapride increases saliva volume and acid-buffering capacity. The aim of this study was to evaluate the effect of cisapride on salivary gland function by means of dynamic salivary scintigraphy. **Methods:** Fifty-five patients with endoscopic reflux esophagitis (Savary-Miller Grades I-II) were enrolled in this study. In Group 1 (n = 29), patients were evaluated during the fasting state, both before and after cisapride treatment (5 mg, 3 times/day, before meals, for 2 wk). In Group 2 (n = 26), patients were evaluated during the postprandial state, both before and after cisapride treatment. Uptake ratio (UR) and excretion ratio (ER) of the salivary gland in each group were compared using the paired Student's t-test. **Results:** In Group 1, no significant differences were found in UR or ER after cisapride treatment. However, in Group 2, ER increased significantly after treatment ($p < 0.01$), but UR did not show any significant change. **Conclusion:** Cisapride can increase the secretion function of salivary glands during the postprandial phase but not the fasting phase.

Key Words: cisapride; reflux esophagitis; salivary function; scintigraphy

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Saliva plays an important role in the neutralization of gastric contents in the esophageal lumen (*1*). Restoration of esophageal intraluminal neutrality after reflux requires not only esophageal peristalsis but also the presence of saliva (*2*). Salivary flow is increased during esophageal acid perfusion, and saliva may act as an endogenous antacid to protect against symptomatic gastroesophageal reflux (*3*). Cisapride has been reported to be an effective prokinetic agent (*4,5*). This drug works synergistically with histamine-receptor blockers (*6*) to treat and prevent relapse of reflux esophagitis (*7*). In terms of esophageal acid clearance changes after cisapride treatment, increased salivary flow has been proposed as a possible mechanism (*8*).

Salivary scintigraphy was introduced more than two decades ago (*9*). Scintigraphic changes correlate well with sialographic abnormalities (*10,11*) and histopathologic changes (*12,13*). Using salivary scintigraphy, the major salivary glands can be examined noninvasively, simultaneously and continuously. This technique has gained widespread acceptance for evaluating a variety of salivary gland disorders (*14,15*). The purpose of this study was to evaluate the effect of cisapride on salivary function during both the fasting and postprandial phases in patients with reflux esophagitis using salivary scintigraphy.

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MATERIALS AND METHODS

Patients

From March 1996 to March 1997, a total of 55 patients with endoscopy-proven reflux esophagitis (Savary-Miller Grades I–II) were enrolled in this study. Patients with a history of gastric outlet obstruction, rheumatologic disease, salivary gland parenchymal disease, diabetes mellitus or local radiation to the neck were excluded. To evaluate the effects of cisapride in different phases, patients were divided randomly into two groups. In Group 1, fasting phase study (n = 29; 3 women, 26 men; age range 23–78 yr; average age 53.9 yr), salivary scintigraphy was performed in the fasting state. In Group 2, postprandial phase study (n = 26; 2 women, 24 men; age range: 28–68 yr; average age 52.4 yr), salivary scintigraphy was performed in the postprandial state. Cisapride, 5 mg, 3 times/day, before meals, was given for 2 wk. In Group 1, one further dose was given 30 min before injection of the tracer. In Group 2, one further dose was given 30 min before a meal and the tracer was injected after another 30 min. Patients were asked to refrain from all drugs known to affect salivary secretion such as cholinergics/anticholinergics, alpha-/beta-agonist/antagonist, opioids, antidepressants, antihistamines and antiparkinsonisms. Informed consent was obtained from all subjects, and the study protocol was approved by the ethics review committee of Taichung Veterans General Hospital.

Salivary Scintigraphy

After an overnight fast, patients in Group 1 were positioned supine with the neck slightly extended. A gamma camera (Apex 400; Elscint, Haifa, Israel) with a low-energy, medium-resolution, medium-sensitivity parallel-hole collimator (APC 34) was used. Each patient was slowly injected intravenously in the antecubital fossa with 5 mCi ^{99m}Tc-sodium pertechnetate. The camera and on-line computer immediately began recording 60 sec/frame images over the anterior view of the head including the bilateral parotid and submandibular glands. Total data collection time was 30 min. Fifteen minutes after injection, a 200-mg ascorbic acid tablet was placed on the dorsal surface of the tongue for salivary stimulation, and the study was continued for an additional 15 min. Regions of interest (ROIs) were chosen over four salivary glands. In Group 2 (postprandial phase study), a standard meal consisting of two fried eggs placed between two pieces of toast to form a sandwich was eaten 30 min before the scan. After finishing the meal, patients were asked to rinse their mouths thoroughly. The total meal weighed 300 g, and it contained 312 kilocalories: 28% protein, 15% lipid and 57% carbohydrate The morning dose of 5 mg cisapride was given to patients in both groups before the study.

Scintiscan Rating Parameters

Two parameters were used to evaluate salivary gland changes during scanning (*14*). The first parameter was uptake ratio (UR) that represented the function of saliva production in the major salivary glands (parotid and submandibular glands). UR from 1–5 min after intravenous injection of the tracer in the four major salivary glands was calculated by the following equation:

TABLE 1
Data of Fasting Phase Salivary Scintigraphy in Group 1

		Parotid glands	Submandibular glands
UR*	Pre-tx	1.75 ± 0.52	1.37 ± 0.23
	Post-tx	1.66 ± 0.29	1.32 ± 0.16
ER*	Pre-tx	57.1% ± 13.1%	46.5% ± 11.9%
	Post-tx	59.7% ± 12.2%	48.9% ± 11.9%

*No significant difference between pre-tx and post-tx.
UR = uptake ratio; ER = excretion ratio; tx = treatment with cisapride.

$$\frac{\text{total counts in ROIs of bilateral salivary glands at 5 min}}{\text{total counts in same ROIs of bilateral salivary glands at 1 min}}$$

The second parameter was excretion ratio (ER) that represented the function of saliva excretion in the major salivary glands. The maximal ER of the four major salivary glands for the sialagogue were calculated by the following equation:

$$\frac{\text{15-min mean counts in ROIs of bilateral salivary glands} - \text{lowest mean counts in ROIs of bilateral salivary glands after 200 mg ascorbic acid stimulation}}{\text{15-min mean counts in ROIs of bilateral salivary glands}} \times 100\%$$

Pretreatment and post-treatment studies were compared and processed together. Only one technologist, under a doctor's supervision, decided the accurate sizes of the ROIs over the salivary glands.

TABLE 2
Data of Postprandial Phase Salivary Scintigraphy in Group 2

		Parotid glands	Submandibular glands
UR*	Pre-tx	1.64 ± 0.52	1.33 ± 0.15
	Post-tx	1.70 ± 0.34	1.38 ± 0.23
ER†	Pre-tx	52.4% ± 28.9%	43.4% ± 17.8%
	Post-tx	65.7% ± 16.4%	54.0% ± 12.2%

*No significant difference between pre-tx and post-tx.
†Significant difference between pre-tx and post-tx ($p < 0.01$).
UR = uptake ratio; ER = excretion ratio; tx = treatment with cisapride.

Statistical Analysis

UR and ER of the parotid and submandibular glands were expressed as mean ± s.d. The differences between UR and ER in each group, before and after cisapride treatment, were evaluated by paired Student's t-tests.

RESULTS

After cisapride treatment, symptoms such as heartburn, bloating and acid regurgitation improved in 37/55 patients (67.3%). Endoscopic follow-up was not performed routinely except in patients with a poor response. Results of the salivary scintigraphic study are shown in Table 1 and Table 2. There were no significant differences in UR or ER of parotid glands (P) and submandibular glands (S), before or after cisapride treatment, in Group 1 [UR: 1.75 ± 0.52 versus 1.66 ± 0.29 (P), 1.37 ± 0.23 versus 1.32 ± 0.16 (S); ER: 57.1% ± 13.1% versus 59.7% ± 12.2% (P), 46.5% ± 11.9% versus 48.9% ± 11.9% (S)]. In Group 2, there was a significant increase in ER after cisapride treatment. ER increased from 52.4% ± 28.9% to 65.7% ± 16.4% in the parotid glands and from 43.4% ± 17.8% to 54.0% ± 12.2% in the submandibular glands after cisapride treatment ($p < 0.01$). However, the changes in UR values in Group 2 were not significant [1.64 ± 0.52 versus 1.70 ± 0.34 (P) and 1.33 ± 0.15 versus 1.38 ± 0.23 (S)]. The scintigraphic changes in a typical case in Group 2 are shown in Figure 1 and Figure 2.

DISCUSSION

Our data showed that cisapride can increase the excretion function of salivary glands during the postprandial phase. This result was consistent with the study conducted by Patel and Soffer (*16*), which showed that cisapride significantly enhanced the postprandial but not fasting salivary volume and buffer capacity, compared with a placebo in normal subjects. Improved salivary function after cisapride treatment may promote the healing of esophageal injury caused by reflux esophagitis due to saliva's inorganic and organic components (*17,18*).

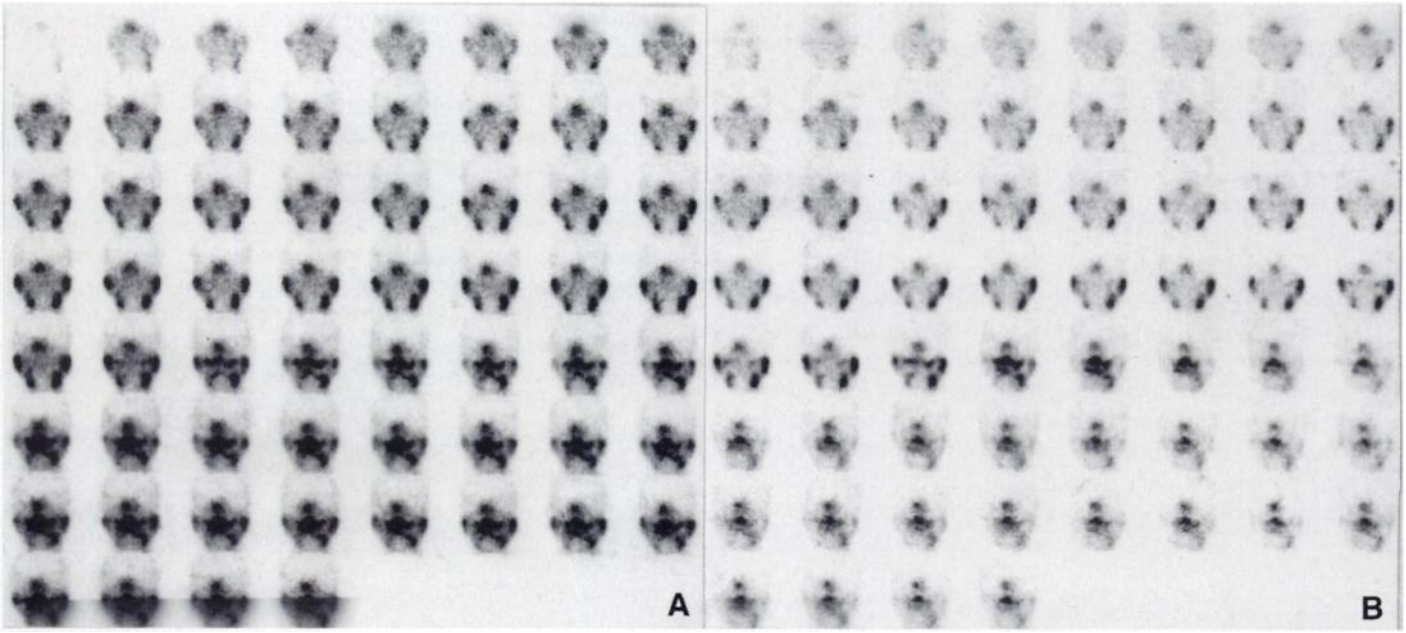

FIGURE 1. Original dynamic salivary scintigraphy of patient in Group 2 (postprandial study). (A) Pretreatment study. (B) Post-treatment study.

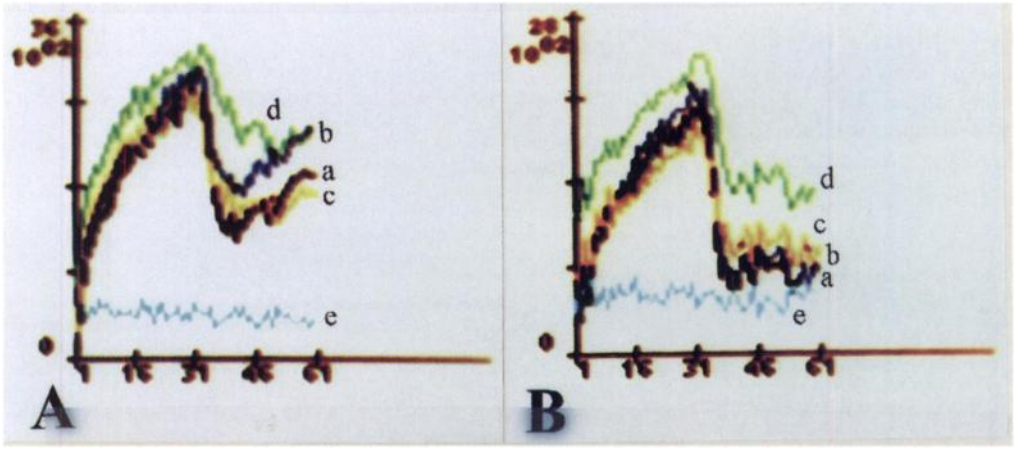

FIGURE 2. Dynamic salivary scintigraphy of same patient as in Figure 1 (A) pretreatment and (B) post-treatment with cisapride. a/b: right/left parotid glands. c/d: right/left submandibular glands. e: background activity. Excretion ratio increased from 50% to 77% in parotid glands and from 44% to 59% in submandibular glands after cisapride treatment. No significant changes in uptake ratio.

Normally, 1–1.5 liters of saliva are secreted daily, mostly from the parotid and submandibular glands. In the resting state, saliva is secreted at a low basal rate. The flow of saliva increases during eating and mastication because of cholinergic stimulation (*19*). The production of saliva is elicited by cholinergic, alpha-adrenergic and peptidergic (substance P) stimulation. There was no difference in the resting salivary function among esophagitis patients, young control subjects and age-matched control subjects in terms of salivary volume, bicarbonate and N-acetylneuraminic acid concentration (*20*). However, salivary secretory response to esophageal mechanical and chemical stimuli was impaired in patients with reflux esophagitis (*17,18*). A broad array of drugs may reduce salivary secretion (*21*). To avoid drug effects on salivary secretion, detailed drug histories were taken in this study.

Objective techniques for quantifying saliva production and gland function include collecting secretions from gland orifices and sequential salivary gland scintigraphy. Although major gland saliva collection remains the most widely accepted method of assessing secretory function, this technique requires special training. Scintigraphy with ^{99m}Tc-sodium pertechnetate is a readily available, minimally invasive, diagnostic test used to evaluate salivary gland function. It has been used to diagnose a variety of salivary disorders (*22–24*). The scintiscan is a particularly valuable tool because it produces a visual dynamic measure of gland function, which allows for differentiation of uptake and excretion abnormalities.

Salivary function may have implications for gastroesophageal reflux disease (GERD). Although development of GERD is thought to be multifactorial, the two most important causative factors are the potency of injurious agents in refluxed fluids and their duration of contact with the esophageal mucosa (*25*). Esophageal acid clearance is thought to be a two-stage process of esophageal emptying and acid neutralization (*2*). For this reason, the esophageal clearance mechanism is an important defense against developing GERD (*26*). Normal salivary flow decreases the time acid is in contact with the esophageal mucosa. The buffering ability of saliva is supplied primarily by carbonate and secondarily by proteins and phosphates (*27*). The capacity for acid neutralization of saliva is directly related to its bicarbonate content. Increased salivary flow results in increased bicarbonate concentration and, therefore, increased acid neutralization. The secretory response of salivary epidermal growth factor to esophageal mechanical and chemical stimulation, mimicking the natural episode of gastroesophageal reflux, is impaired in patients with reflux esophagitis (*28*).

Cisapride is the most recent prokinetic agent for treating a variety of gastrointestinal motility disorders involving the smooth muscle extending from the esophagus to the colon (*29*). Cisapride exerts its effects by increasing the physiologic release of acetylcholine from postganglionic nerve endings of the myenteric plexus by the 5-HT_4 receptor (*30*). Cisapride may improve factors that contribute to the pathophysiology of GERD. The effects of cisapride include an increase in the amplitude of esophageal contractions, enhancement of acid clearance, an increase in low esophageal sphincter pressure, improvement in gastric emptying and enhancement of coordination between the stomach and pylorus (*24,25*). Its reported effects on esophageal motility have varied (*31–35*). Different doses, routes and phases (fasting or postprandial) have been used in previous studies and have been thought to be the main causes of variability in the reported effects of cisapride on esophageal motility. Cisapride cannot decrease the number of reflux episodes (*8*) or change the esophageal transit time (*36,37*). The esophageal acid exposure time was also reported unchanged after a 3-day loading dose of cisapride, although the acid clearance was enhanced (*8*). Reduction in the volume of refluxate with each reflux episode and/or an increase in salivary flow has/have been proposed as the explanation for improved acid clearance. A recent study with a 14-day cisapride treatment reported that esophageal acid exposure decreased with an increase in the mean number of contractions per minute during reflux episodes (*38*). Thus, both increased salivary flow and contraction frequency during reflux episodes may be involved in preventing prolonged acid contact with the esophageal mucosa during cisapride treatment.

The mechanism of cisapride for increasing salivary function remains unclear. Cisapride may affect salivary function either directly by stimulating postganglionic neurons or indirectly by affecting vagal afferents from the myenteric plexus. Further studies are needed to define the exact mechanism. The reason that cisapride treatment does not increase salivary gland function during the fasting phase remains unknown. It may be due to the low dose (5 mg, 3 times/day, before meals) of cisapride used or the small number of patients in this study. There were also differences between the fasting and postprandial phases in other studies of the effects of cisapride on esophageal function (*8,39*). Further evaluation is needed to determine the reason for the differences between the phases. UR of the salivary glands during salivary scintigraphy is dependent on blood flow and salivary parenchymal function. The results from our study indicated that cisapride cannot affect the blood flow to salivary glands or change their parenchymal function. Cisapride is not recommended for improving xerostomia in patients with a salivary parenchymal disease such as Sjögren's syndrome.

CONCLUSION

Our results with dynamic salivary scintigraphy in patients with reflux esophagitis showed that cisapride enhances salivary gland secretion during the postprandial phase. This indicates that cisapride improves both the gastroesophageal motor function and the salivary function and enhances esophageal acid clearance in patients with reflux esophagitis.

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Radioiodine Secretion in Tears

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Lacrimal secretion of radioiodine has been suspected from previous scintigraphic observations. We semiquantitated radioiodine secretion in the tears of a thyroid-ablated patient with an artificial eye while the patient was on thyroxine treatment. **Methods:** After an oral dose of 555 MBq (15 mCi) ^{123}I, 12 tear samples were collected over 24 hr by using Schirmer papers. Radioactivity in each sample was determined in a well counter 27 hr after radioiodine ingestion and was corrected for decay and counting efficiency. **Results:** Radioactivity was detectable at 15 min and at up to 24 hr after radioiodine ingestion and peaked at around 60 min (215 Bq/μl or 39×10^{-6} % of the administered dose/μl. Considering a tear-flow rate of 1 μl/min, the total radioactivity secreted in the first 4 hr was estimated to be 56 kBq, representing about 0.01% of the administered dose. **Conclusion:** An appreciable amount of ingested radioiodine could be secreted in tears. The potential damage of the lacrimal gland after high doses of ^{131}I treatment deserves further study.

Key Words: radioiodine secretion; tears; Schirmer test; thyroid cancer

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Several nonthyroidal tissues such as the gastric mucosa, intestine, choroid plexus, placenta and mammary, salivary and sweat glands have the ability to concentrate iodide (*1*). Radioiodine has been detected in fetal blood, breast milk, cerebrospinal fluid, sweat and salivary, gastric and nasopharyngeal secretions (*2*). Radioiodine uptake was observed in the lacrimal sac in a patient with dacrocystitis (*3*) and in the orbital cavity in a patient with an artificial eye (*3*).

We examined whether radioiodine is detectable in tear samples obtained after the ingestion of ^{123}I radioiodine.

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