—Case Reports—

Sialorrhea Successfully Treated by the Combined Use of Selective M1 and M3 Muscarinic Acetylcholine Receptor Antagonists

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Sialorrhea is often treated with anticholinergic agents, but they can have undesirable side effects such as drowsiness, sedation, and constipation. Effective medication that acts selectively on the salivary glands is needed.

We report the case of a patient with sialorrhea who was successfully treated by the combined use of pirenzepine and solifenacin (M1 and M3 muscarinic receptor antagonists, respectively). The patient was a 51-year-old man with mean unstimulated and stimulated salivary flow rates per 10 min of 6.1 mL and 41.7 mL, respectively (both were measured three times). $^{99m}TcO^{4-}$ salivary gland scintigraphy revealed characteristic spontaneous saliva secretion without stimulation. He was treated with *Scopolia* extract, escitalopram, solifenacin succinate, and the combined administration of solifenacin succinate and pirenzepine. A statistically significant decrease was observed from the pre-medication unstimulated and stimulated salivary flow rates only following the combined administration of solifenacin and pirenzepine.

The major muscarinic receptor subtype expressed in the salivary glands is M3; however, M1 is also present. A study using knockout mice demonstrated that the presence of either M1 or M3 receptors was sufficient for salivation. Thus, the combined use of selective M1 and M3 antagonists could provide a good treatment option for sialorrhea. (J Nippon Med Sch 2019; 86: 117–121)

Key words: sialorrhea, M1 and M3 muscarinic receptor antagonists, $^{99m}TcO^{4-}$ salivary gland scintigraphy

Introduction

Sialorrhea, also called hypersalivation, is characterized by an increased amount of saliva in the mouth. In the case of production sialorrhea (true sialorrhea), this is due to the hypersecretion of saliva, whereas in retention sialorrhea (false sialorrhea), the cause is the failure of the mechanisms that clear and remove saliva from the oral cavity. In patients with a normal salivary flow rate, the sialorrhea may be psychogenic.

Sialorrhea is treated medically with anticholinergic agents such as first-generation antihistamines, tricyclic antidepressants, and anticonvulsants. However, these medicines can cause undesirable side effects such as drowsiness, sedation, and constipation. There is a need for effective medication that shows higher selectivity for the salivary glands.

Here, we report a case of production sialorrhea successfully treated by the combined use of selective M1 and M3 muscarinic receptor antagonists. $^{99m}TcO^{4-}$ scintigraphy was useful for diagnosis, revealing the characteristic increased salivary excretion rate.

Case Presentation

A 51-year-old man was referred to our department with a 2-year history of sialorrhea. His medical history was unremarkable except for an allergy to cedar pollen and insomnia, and he was prescribed haloperidol for 10 days each month. He reported that his saliva was mucoid and that it was secreted spontaneously during the day but did not disturb him during sleep at night. Two months after the onset of sialorrhea, he experienced abdominal pain, diarrhea, and constipation. He was diagnosed with

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chronic gastritis and irritable bowel syndrome and he was prescribed dimethicone, which resulted in the alleviation of these gastrointestinal symptoms. He was prescribed Kampo traditional medicines for the sialorrhea; this resulted in no change in his condition, and therefore, he was referred to our department.

Physical examination revealed nothing remarkable. The unstimulated salivary flow (USR) rate and stimulated salivary flow rate (SSR) were measured three times on different days, with mean values of 6.1 mL/10 min and 41.7 mL/10 min, respectively. There is no standard threshold for hypersalivation, but in healthy Japanese men, the reported mean (range) values are 6.5 ± 3.4 mL/10 min (1.5-16.8 mL/10 min) for USR and 25.0 ± 6.9 mL/10 min (11.0-48.6 mL/10 min) for SSR[1]. Thus, the patient's USR was considered to be in the normal range, but his SSR was more than two standard deviations above the mean for healthy Japanese men.

In accordance with the regular protocol of our facility, $^{99m}TcO^{4-}$ scintigraphy was performed to evaluate the patient's salivary gland function. After an intravenous injection of 185 MBq $^{99m}TcO^{4-}$, sequential 3-min images were acquired for 45 min, with a few drops of lemon juice administered intraorally 20 min after the injection to stimulate salivation. Regions of interest for both parotid glands and both submandibular glands were drawn on the sequential images and a time-activity curve (TAC) was generated for each region.

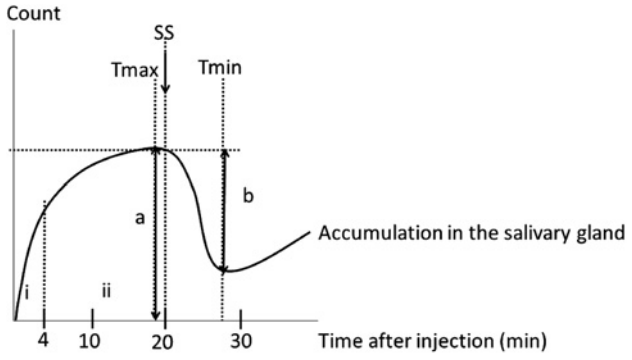

Fig. 1 A schematic time-activity carve (TAC) of normal $^{99m}TcO^{4-}$ salivary gland scintigraphy

A normal TAC (**Fig. 1**) showed an early fast-rising component, representing the vascular perfusion of the radiotracer into the gland, followed by a slow-rising component associated with the accumulation of the radiotracer into the striated duct cells. A stimulus to increase salivation is generally administered soon after the time of maximum accumulation (Tmax). Tmax and the time at minimum accumulation after stimulation (Tmin) are obtained from the TAC and the radiotracer counts in the salivary gland at these two times (a and b, respectively) are used to calculate the washout rate, defined as a/b × 100%. The washout rate provides an indication of the secretory function of the gland. At our facility, a washout rate >50% is considered normal.

For the present patient, the TAC images showed an apparently normal fast-rising component, but the following component declined slowly instead of the normal slow rise; this was due to excretion of the radiotracer into the oral cavity (**Fig. 2A**). Tmax was 7 min for both parotid glands and 4 min for both submandibular glands (**Fig. 2 B**); these time points were arrived at earlier than normal. The washout rates for the parotid glands were somewhat below the normal range (right, 40%; left 46%), and those for the submandibular glands were moderately decreased (right, 25%; left, 22%). These decreases were interpreted

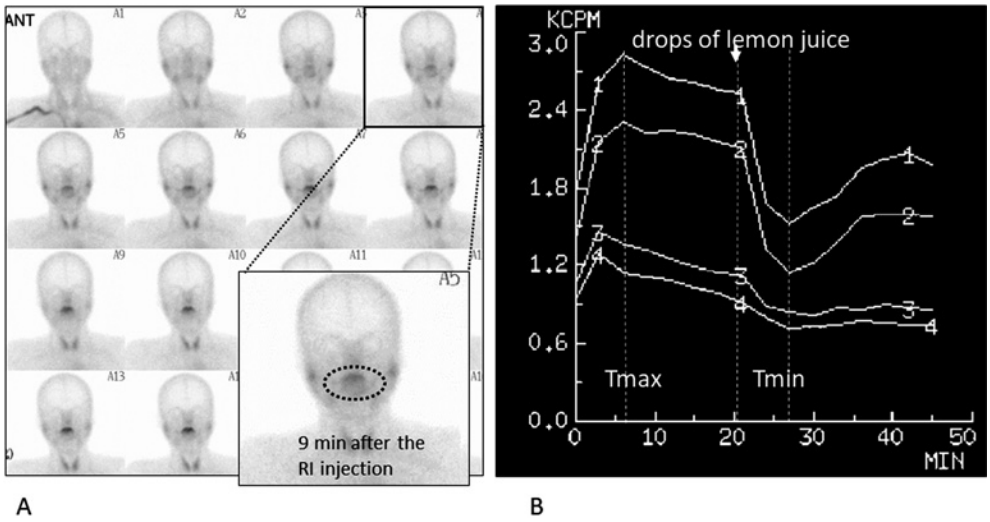

Fig. 2 The sequential 3-min images (2A) and TAC images (2B) of the present case

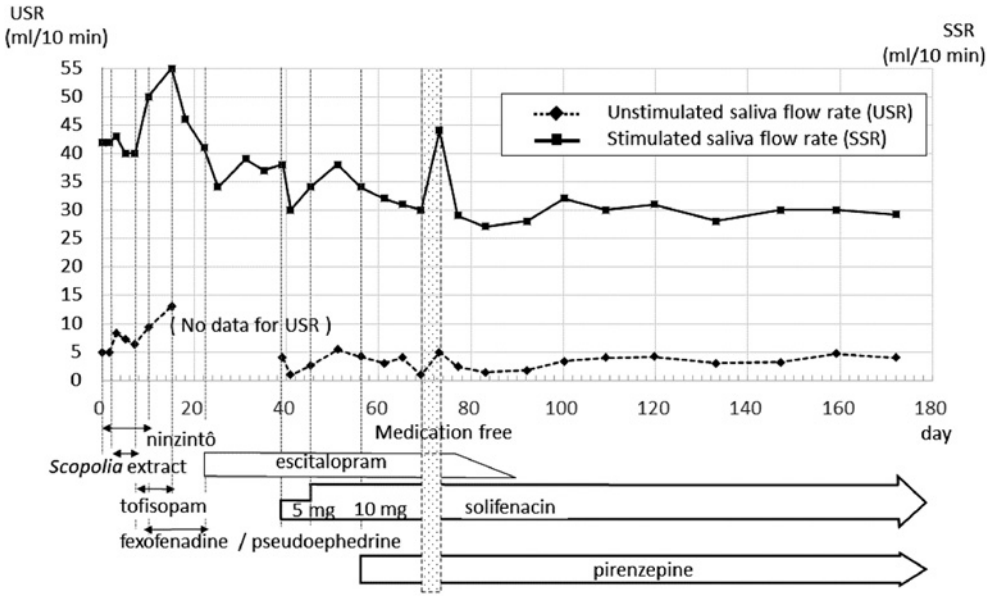

Fig. 3 Changes in unstimulated and stimulated saliva flow rate following medicine administration

as the result of the lower than normal Tmax values.

In summary, the patient's scintigraphic results showed spontaneous saliva secretion without stimulation, which indicated that the patient had production type sialorrhea.

Management and Outcome

The patient refused first-generation antihistamines and tricyclic antidepressants out of concern they would cause drowsiness. Therefore, from week 3 to 39 after the first visit, various medicines were administered: ninzintô (considered the first choice for sialorrhea among Kampo medicines), *Scopolia* extract (a nonspecific anticholinergic agent), tofisopam (an anxiolytic), fexofenadine/pseudoephedrine (to treat the pollen allergy), and escitalopram (a selective serotonin reuptake inhibitor). However, neither the salivary flow rate nor the patient's subjective symptoms showed any marked improvement (**Fig. 3**). At week 39, with the approval of the ethics committee of Tokyo Women's Medical University (approval no. 1600308), the off-label use of solifenacin succinate (trade name, Vesicare®) 5 mg/day was started. By week 41, the patient's USR had decreased from 4 to 1 mL/10 min and his SSR from 38 to 30 mL/10 min. At week 47, USR and SSR were found to have increased, so the dose of solifenacin was increased to 10 mg/day. From week 56, pirenzepine hydrochloride (trade name, Gastrozepin®), an antiulcer drug expected to reduce salivation, was also administered. At week 69, all drugs were stopped to determine the necessity of medication; however, by week 71 the USR and SSR had increased from 30 to 44 mL/10 min and from 1 to 5 mL/min, respectively. Solifenacin 10 mg/day and pirenzepine were, therefore, continued. Escitalopram was stopped at week 92 but neither USR nor SRR demonstrated a subsequent increase by week 172. There were no signs of side effects from the anticholinergic agents or recurrence of the irritable bowel syndrome.

We evaluated how much each medication reduced USR and SSR by comparing USR and SSR values in the periods during which no medication, escitalopram, 5 mg of solifenacin, 10 mg of solifenacin, and 10 mg of solifenacin with pirenzepine were taken. The statistical analyses were performed with JMP Pro 13.0.0 for Windows, using one-way analysis of variance and Tukey-Kramer HSD tests to evaluate the comparisons. Statistically significant decreases of USR and SSR from the pre-medication levels were observed only following the administration of 10 mg of solifenacin with pirenzepine (**Fig. 4**).

Discussion

This case highlighted two important clinical findings. First, for productive sialorrhea, the combined use of selective M1 and M3 muscarinic receptor antagonists was effective for reducing salivation without adverse effects. Second, $^{99m}TcO^{4-}$ salivary gland scintigraphy was useful for the pathophysiological evaluation of potential causes of the sialorrhea.

The combined use of M1 and M3 antagonists reduced salivation. The options for sialorrhea include conservative treatment (such as postural changes and biofeed-

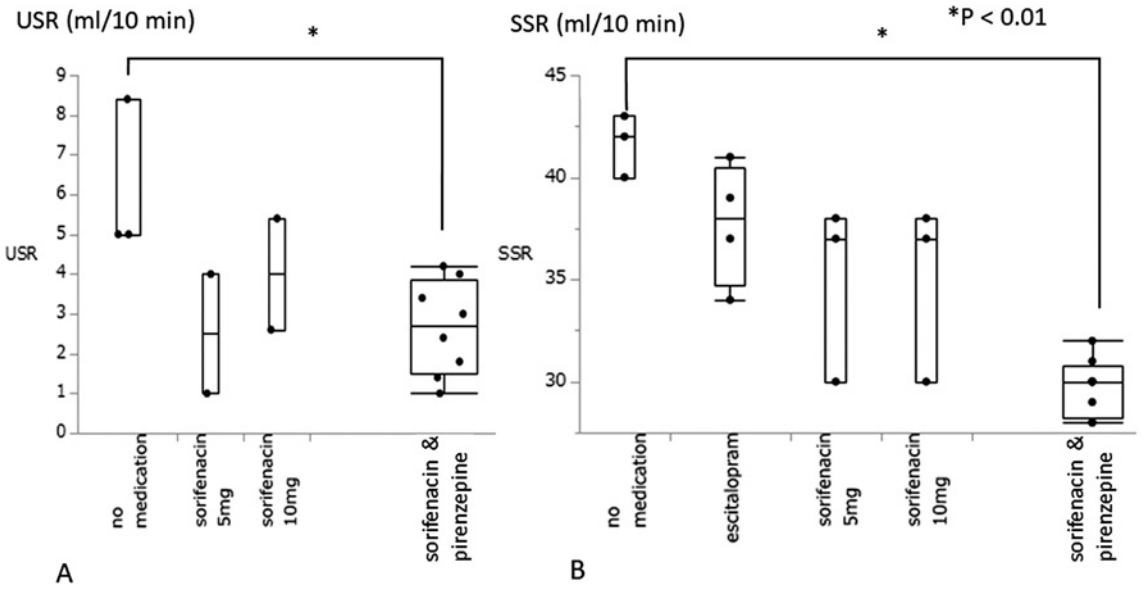

Fig. 4 Comparison of USR and SSR between each medication

back), medication with anticholinergic agents, the injection of botulinum toxin into the salivary glands, and surgical interventions such as salivary gland excision, salivary duct ligation, and duct rerouting. Among anticholinergic agents, oral glycopyrrolate and sublingual drops of 1% atropine solution have been reported to be beneficial for drooling in patients with Parkinson's disease (PD)[2,3]. The injection of botulinum toxin into the salivary glands reduces salivary secretion by inhibiting cholinergic parasympathetic and postganglionic sympathetic activity; this has been confirmed to be effective for symptomatically controlling drooling in PD in the current recommendations of the International Parkinson and Movement Disorder Society[4]. However, these medications are not available in Japan, so we initially gave the patient other anticholinergic agents, including *Scopolia* extract; these were not effective.

It is generally agreed that the increases in the flow of saliva evoked by cholinergic stimulation are mainly mediated by activation of the M3 muscarinic receptor. Selective M3 muscarinic receptor antagonists, which are anticholinergic agents, would therefore be expected to selectively minimize salivary secretion. Solifenacin is a selective M3 antagonist developed for treating contraction of an overactive bladder. A dry mouth is one of its adverse effects. This was shown in a study of 1,223 patients treated with Vesicare® 10 mg, in which the most common side effect was dry mouth (27.6%)[5], whereas side effects associated with the central nervous system or cardiovascular are rare.

The findings of the present case suggested that the combined use of selective M1 and M3 muscarinic receptor antagonists was more effective than the administration of M3 antagonists alone. In addition to M3 muscarinic receptors, M1 muscarinic receptors are also expressed in the salivary glands[6]. A study using M1 or M3 receptor single-knockout mice and M1/M3 receptor double-knockout mice demonstrated that the presence of either M1 or M3 receptors was sufficient for mediating robust pilocarpine-induced salivation, whereas this was abolished in the M1/M3 receptor double-knockout mice[7]. We therefore expect the result for our case would be generalizable to other cases of sialorrhea.

$^{99m}TcO^{4-}$ salivary gland scintigraphy was useful for diagnosing sialorrhea. Sialorrhea and drooling are generally exhibited by patients with neurological disorders such as PD, cerebral palsy, and amyotrophic lateral sclerosis. Usually, subjective tools such as the Unified Parkinson's Disease Rating Scale, Part II are used to evaluate the severity of sialorrhea in these patients, because objective tools are considered to be time-consuming and unable to evaluate the psychosocial impairment[8]. However, these assessment tools are insufficient for elucidating the onset mechanism and are unsuitable for patients with mild sialorrhea. $^{99m}TcO^{4-}$ scintigraphy is widely used for the semi-quantitative evaluation of salivary gland function, especially for diseases that reduce salivation, such as Sjogren's syndrome. Two studies have evaluated sialorrhea with $^{99m}TcO^{4-}$ scintigraphy. Cros et al.[9] categorized sialorrhea into three types by functional scintigraphic studies: deglutition disorders, ptyalomania, and primary hypersecretion at rest. These correspond to retention sia-

lorrhea, psychogenic sialorrhea accompanied by spitting of saliva, and production sialorrhea, respectively. Scintigraphic findings of primary hypersecretion at rest indicated saliva secretion that occurred early and without obvious stimuli. Kishimoto et al.[10] reported a case of production sialorrhea that required resection of the bilateral submandibular glands. Scintigraphy indicated low accumulation in the bilateral submandibular glands with early excretion of the radiotracer to the oral cavity. The authors explained this as the speed of salivation overwhelming the radiotracer accumulation. In the present case, the scintigraphy showed spontaneous saliva secretion without stimulation, similar to the findings of Cros et al.'s primary hypersecretion at rest and Kishimoto et al.'s case.

Sialorrhea and drooling are common symptoms in patients with neurological disorders. We expect the combined use of selective M1 and M3 antagonists will become a good treatment option for these patients. Patients who present with sialorrhea without obvious drooling are often considered, without sufficient objective evaluation, to have psychogenic sialorrhea. $^{99m}TcO^{4-}$ salivary gland scintigraphy is helpful for diagnosing these patients' condition and ensuring they receive adequate treatment.

Conclusion

We reported here a case of production sialorrhea with no underlying disease. $^{99m}TcO^{4-}$ salivary gland scintigraphy showed characteristic spontaneous saliva secretion without stimulation. The combined use of selective M1 and M3 muscarinic receptor antagonists was effective for reducing both USR and SSR.

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Conflict of Interest: The authors have no conflicts of interest, and no financial disclosures to report.

References

1. Yamamoto K, Kurihara M, Matsusue Y, Imanishi M, Tsuyuki M, Kirita T: Whole saliva flow rate and body profile in healthy young adults. Arch Oral Biol 2009; 54: 464–469.
2. Arbouw ME, Movig KL, Koopmann M, Poels PJ, Guchelaar HJ, Egberts TC, Neef C, van Vugt JP: Glycopyrrolate for sialorrhea in Parkinson disease A randomized, double-blind, crossover trial. Neurology 2010; 74: 1203–1207.
3. Hyson HC, Johnson AM, Jog MS: Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. Mov Disord 2002; 17: 1318–1320.
4. Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, Sampaio C: The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011; 26: S42–80.
5. VESIcare (solifenacin succinate) tablets full prescribing information: Revised: February 2016; 16A001-VES-WPI Astellas Pharma US, Inc.
6. Ryberg AT, Warfvinge G, Axelsson L, Soukup O, Gotrick B, Tobin G: Expression of muscarinic receptor subtypes in salivary glands of rats, sheep and man. Arch Oral Biol 2008; 53: 66–74.
7. Gautam D, Heard TS, Cui Y, Miller G, Bloodworth L, Wess J: Cholinergic stimulation of salivary secretion studied with M1 and M3 muscarinic receptor single- and double-knockout mice. Mol Pharmacol 2004; 66: 260–267.
8. Srivanitchapoom P, Pandey S, Hallett M: Drooling in Parkinson's disease: a review. Parkinsonism Relat Disord 2014; 20: 1109–1118.
9. Cros P, Parret J, Peyrin J, Freidel M, Dumas P: Sialorrhees Apport des exomens isotopiques. Rev Stomatol Chir maxillofac 1979; 80: 319–324 (in French).
10. Kishimoto A, Kin Y, Minami T, Nakagawa N, Tada N, Ino C: A case of true hypersalivation Otologia. Fukuoka 2006; 52: 97–103 (in Japanese).

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