

## Clinical Effects of Cevimeline Hydrochloride for The Treatment of Dry Mouth in 2 patients with Sjögren's Syndrome.

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**Abstract:** We report here 2 cases of patients with Sjögren's syndrome with dry mouth that were successfully treated with cevimeline hydrochloride. The first case was diagnosed as Sjögren's syndrome at our clinic, and the saliva secretion increased by more than three-fold following oral cevimeline hydrochloride. The second case was diagnosed at another hospital, and the saliva secretion was increased by more than two-fold by the medication.

**Key Words:** cevimeline hydrochloride, Sjögren's syndrome

### Introduction

Sjögren's syndrome is a chronic, autoimmune exocrinopathy that predominantly involves the lacrimal, salivary, and other exocrine glands, resulting in a decreased secretion<sup>1)</sup>. Most frequently, it affects women in the fourth and fifth decades and is characterized by xerostomia and keratoconjunctivitis sicca<sup>2)</sup>. Recently, the clinical effects of cevimeline hydrochloride have been evaluated as a remedy of dry mouth in patients with Sjögren syndrome<sup>3)</sup>. Cevimeline increases saliva production, with a selective affinity for the M3 muscarinic receptor<sup>4)</sup>. We report here 2 cases of patients with Sjögren's syndrome with dry mouth that were successfully treated with cevimeline.

### Case reports

**Case 1:** The patient was 66 years-old, when she presented at our hospital for the first time. Her chief complaint was xerostomia. The patient had experienced xerostomia since January 2002. She had taken several medicines, but her symptoms did not improve. Therefore, she visited our hospital in Oct. 2004. Her past medical history was remarkable for Guillaume-Barre syndrome. Her blood examination data revealed SS-A 115.2 and SS-B 6.3, and her sialography was Stage 1. According to the Japanese diagnostic criteria for Sjögren Syndrome in 1999, the patient was diagnosed with Sjögren's syndrome. Her total saliva before taking cevimeline was 1ml on a gum examination. She was then prescribed cevimeline at 30mg/ day, and 3 daily gargles of cevimeline gargle for 1 week. After 9 days, of taking cevimeline, the total saliva of this patient was 2ml on a gum examination. She has been continuously prescribed cevimeline at 60mg/ day and 3 daily cevimeline gargles since then. After 30days of taking cevimeline, her subjective symptoms of feeling a dry mouth were improved. After 150 days of taking cevimeline, her total saliva was increased to 3.3ml on a gum examination (Fig.1).

**Case 2:** The patient was 67 years-old, when she came to our hospital for the first time. Her chief complaint was xerostomia. This patient was diagnosed with Sjögren's syndrome by an

examination of the minor salivary gland via biopsy, and sialography at another hospital for about 6 years ago. The patient has had xerostomia for 6 years. Therefore, she visited our hospital in May 2005. Her past history included Progressive systemic sclerosis (PSS), Gastroesophageal Reflux Disease, and an allergy to drugs. Her total saliva before taking cevimeline was 0.7 ml on a gum examination. Therefore, she had been prescribed cevimeline at 30mg/ day and two daily gargles of cevimeline for 2 weeks. After 14 days of taking cevimeline, the total saliva of the patient was increased to 1ml on a gum examination. Since then, she had been prescribed cevimeline at 60mg/ day and one daily cevimeline gargle for 2 weeks since then. After 28 days of taking cevimeline, the total saliva of the patient increased to 1.1ml on a gum examination. Therefore, we have been continuously prescribing cevimeline at 90mg/ day since then. After 42 days of taking cevimeline, the total saliva of the patient increased to 1.6ml on a gum examination (Fig.1).

### Discussion

According to a report from the Ministry of Health, Labour, and Welfare in 2002, there are approximately 43,000 patients with Sjögren's syndrome in Japan. The diagnosis in Japan is often made according to the criteria established in 1999. The first case was diagnosed at our clinic, and the second case was at another hospital. This disease is found 20 times more frequently among women than in men, and the onset is usually between 40 and 50 years of age<sup>2)</sup>. The disease involves chronic inflammation of the exocrine glands, such as the salivary and lacrimal glands. Due to disturbed functions of these affected glands, various symptoms are manifested such as dry mouth, dry eyes, and hypersensitivity of the esophagus and respiratory tracts. It is often related to underlying conditions such as rheumatism and collagen diseases. Among patients with Sjögren's syndrome, 20-50% have rheumatoid arthritis, 20-45% have systemic lupus erythematosus (SLE), and 6-14% have systemic sclerosis (SSc). SSc is a chronic disease with sclerotization and fibrosis of the skin and all internal organs. The first case had high levels of rheumatoid factor, but

this was not diagnosed as rheumatism by the internists. The second case had a history of SSc. There is no difference in symptoms between primary Sjogren's syndrome without any other collagen disease and secondary Sjogren's syndrome with underlying collagen diseases. The medications for treating patients with Sjogren's syndrome include cevimeline hydrochloride, artificial saliva and tears, steroids, immunosuppressants, Chinese herbal medicines such as Ophiopogon tuber, expectorants such as bromohexine hydrochloride, salivary gland hormone, and plant alkaloids, but nothing works very well. Cevimeline hydrochloride works by directly stimulating muscarinic M<sub>3</sub> receptors in the acinar cells of the salivary gland, thus stimulating the secretion of serous saliva<sup>4</sup>. According to Iwabuchi et al.<sup>5</sup>, when 60-90 mg of cevimeline hydrochloride per day was administered for an average of 10 weeks, 8 cases out of 21 case (38.1%) showed a saliva secretion increase greater than 101%. When an increase greater than 51% was defined as "effective", 61.9% of the cases were determined to have experienced improvements. In the first case, the amount of saliva secretion was increased from 1 cc to 2.6 cc over 10 weeks, which is an increase of more than 101%. Improvements in eating and swallowing were also achieved during the same time. The second case was followed for only 6 weeks. The amount of saliva secretion increased from 0.7 cc to 1.6 cc, an increase of more than 101%, although the symptoms were not improved. Iwabuchi et al.<sup>5</sup> also reported an increase in saliva secretion of 33.2% if the medication was administered for 2 weeks, 60.2% for 4 weeks, and 97.1% for 16 weeks, respectively, and a longer period of medication use was correlated with an increased rate of saliva secretion. In the two cases we reported, the first case showed a 100% increase over 2 weeks. It kept increasing, and showed a 230% increase at the 21st week. The second case showed increases higher than those reported by Iwabuchi et al., with increases of 42.8% at the second week, 57.1% at the 4th week, and 128.5% at the 6th week, respectively. This may be due to a combination of the medications and mouth washing. This mouth washing method was developed by Nakamura et al<sup>6</sup>. One capsule

of cevimeline hydrochloride is dissolved in 50 mL of water, and the solution is gargled in the mouth for two minutes and then spat out. Saliva secretion at rest after 1-3 hours of mouth washing has been reported to increase by 20% with minimal side effects. Although Nippon Kayaku Co., Ltd. has reported that 30.9% of patients who were given cevimeline hydrochloride reported adverse events such as nausea and vomiting, Iwabuchi et al.<sup>5</sup> reported that 48.0% of patients using cevimeline hydrochloride experienced such adverse events. The two cases we report here did not experience any adverse effects. The first case was diagnosed as Sjogren's syndrome at our clinic, and the saliva secretion increased by more than three-fold following oral cevimeline hydrochloride. The second case was diagnosed at another hospital, and the saliva secretion was increased by more than two-fold by the medication. We plan to follow-up both cases in the future.

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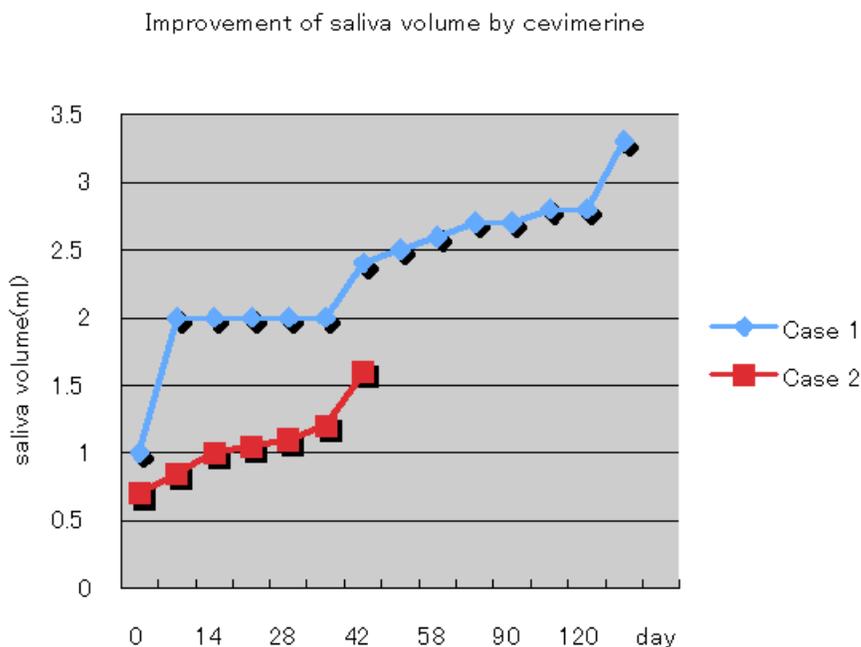


Fig.1. Improvement in the saliva volume induced by cevimerine