− ORIGINAL ARTICLE −

Effect of 6-month administration of Cevimeline hydrochloride on salivary flow rate and s alivary components in primary Sjögren's syndrome patients

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一次性シェーグレン症候群患者の唾液分泌量と唾液成分に対する塩酸セビメリン投与後６ヶ月の効果

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Abstract : The aim of this study was to clarify pre- and post-cevimeline hydrochloride administrative changes of salivary flow rate and salivary components in primary Sjögren's syndrome (SS) patients. Twelve females who were diagnosed with primary SS were subjects in this study. Thirty milligrams of cevimeline hydrochloride was administered 3 times daily for 6 months. Whole stimulated saliva was collected from patients before and after administration. MMP(matrix metalloproteinase)-9 was measured by the sandwich-ELISA (enzyme-linked immunosorbent assay) method. The levels of Na^+, Cl^- and K^+ ions were measured by the ISE (ion-selective electrode) method. The level of Ca^{2+} ion was measured by the OCPC (ortho-cresolphthalein-complexone) method and amylase activity was determined by the enzyme coupling method. Whole stimulated saliva secretion was significantly higher ($p = 0.034$) after administration. Na^+,Cl^-,Ca^{2+} ions and MMP-9 levels were not different after administration. Amylase activity($p = 0.105$)and K^+ ion level($p = 0.105$)decreased but not significantly after administration. Therefore, Cevimeline hydrochloride at a dosage of 30 mg, 3 times daily may improve some symptoms of xerostomia in patients with primary SS, though there was no change of salivary components.

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抄録：この研究の目的は一次性シェーグレン症候群患者（pSS）の唾液分泌量と唾液成分に対する塩酸セビメリン投与前後の変化を調べることである。この研究の対象者は一次性ｐＳＳ患者12人であった。６ヶ月間１日３回30mgの塩酸セビメリンを投与した。試料としての全唾液は投与前後に集めた。Matrix Metalloproteinase-9（MMP－９）はsandwich-ELISA(enzyme-linked immunosorbent assay)方法で測定した。Na，Cl とＫイオンはOCPC(ortho-cresolphthalein-complexone)方法で測定し，アミラーゼ活性はEnzyme coupling法で測定した。その結果，全刺激唾液は投与後で有意に増加した（P = 0.034）。Na, Cl, Caイオンと MMP-9 レベルは投与後で変化がみられなかった。アミラーゼ活性（P = 0.105）とＫイオンレベル（P = 0.105）は投与後に減少傾向を示したが，有意差は認められなかった。それゆえ，塩酸セビメリン30mgの１日３回投与によって，一次性シェーグレン症候群患者（pSS）の唾液成分は変化しなかったが，口腔乾燥症状は改善する可能性が示された。

Introduction

Sjögren's syndrome(SS)is a systemic chronic autoimmune disease, characterized by symptoms of dry mouth and dry eyes, and can be primary or secondary to connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, and systemic sclerosis. Furthermore, it is said that SS is divided into primary and secondary classes according to symptoms and more prevalent in climacteric women. Pharmacotherapeutic approaches to xerostomia in SS include lubricating oral mucosa with saliva substitutes, treatment with immunosuppressive drugs and stimulating salivary gland activity with muscarine agents. Cevimeline hydrochloride(Saligren®, Evoxac®)is an acetylcholine analogue with high affinity for the muscarinic M3 receptor located on lacrimal and salivary gland epithelium and is an orally administered drug that relieves the symptoms in patients with SS[1]. In this study, we investigated the effect of cevimeline hydrochloride (Saligren®, Evoxac®) administration on salivary flow rate and salivary components in patients with primary SS.

Materials and Methods

1. Materials

Materials were as follows: Cevimeline hydrochloride (Saligren® Nippon Kayaku Inc. Japan; Evoxac® Daiichi-Sankyo Pharmaceutical Company Japan); MMP-9 enzyme-linked immunosorbent assay (ELISA) system kit (Amersham Bioscience, USA).

2. Subjects

The patients were diagnosed according to the preliminary classification criteria proposed by the Japanese Study Group on Diagnostic Criteria for primary SS[2]. Before administration of cevimeline hydrocloride, there were twelve female patients [average age 55.25±14.40 years (mean±S.D.)] with primary SS who had been referred to Niigata University, Medical and Dental Hospital. On the other hand, the control subjects were twenty one females [average age 54.00±9.76 years (mean±S.D.)]. All patients and control subjects gave informed consent and the Declaration of Helsinki (September 1989) was followed throughout the study. Statistical analysis was performed only on the patients in which enough saliva was available for measurements at all stages (before treatment, 1 month after treatment and 6 months after treatment).

3. Saliva sample

Patients were administered with 30 mg of Cevimeline hydrochloride 3 times daily for 6 months. Whole saliva was collected during stimulation by chewing paraffin for 10 min from patients between 9:00 am and 12:00 noon before administration as well as after administration at their first- and sixth-month visits.

The saliva of control subjects was collected in the same way as the patients. Immediately after the collection, the saliva was centrifuged at 12,000 rpm for 5 min at 4℃ to remove the precipitate. The supernatant was frozen quickly at -80℃ until use. The patients were asked not to eat on the day of examination. Except saliva flow rate measurement, the determination item numbers were not the same in all stages. The reason for this was the differences in the volume of saliva secretion among individuals. Therefore, for some patients, saliva volume was not enough to measure all items. The priority for measurement was MMP-9 ELISA assay.

4. One-step sandwich EIA system for MMP-9 ELISA assay

MMP-9 (Amersham Pharmacia Biotech Inc.) was