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In the Treatment of Sjögren's Syndrome

Rx Jögren®

Pilocarpine Hydrochloride Tablets USP 5 mg

Rational & Accurate Treatment

Product Datasheet

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Rational & Accurate Treatment

Pilocarpine Most Effectively Stimulates the Body's Own Multiorgan Secretions & Prevents the Long-term Complications of Sjogren's Syndrome[1]

- Significant increase in salivary flow by 2-3 fold (P<0.001)[1]
- Improvement in all oral symptoms by >25 mm on VAS scale[*2]
- Significant improvement as compared to artificial tears and lacrimal puncta occlusion[§3]
  - In the rose bengal test[∞]
  - In VAS scale (>55 mm)[#]
- No serious drug-related adverse experiences were reported[1]
- Offers relief of symptoms of whole-body dryness[1]

EULAR

Recommends pilocarpine for the treatment of mild or moderate dry mouth[4]

BSR

Recommends pilocarpine for the treatment of significant sicca symptoms[4]

Dosage[5]

- The recommended dose for adults is one tablet of 5 mg four times daily
- In case of non-responders, increase the dose up to 30 mg daily divided over the day

BSR - British Society for Rheumatology; EULAR - European Alliance of Associations for Rheumatology; VAS - Visual analogue scale; *. difficulty in speaking, difficulty in swallowing, feeling of dryness and quantity of saliva in the mouth; ∞. Rose bengal is a vital dye used to diagnose disorders of the external eye, particularly dry eye syndrome.
#. Changes from baseline in ocular symptoms were assessed on a 100 mm VAS. It was defined as an improvement of >55 mm for responses to the eye questionnaire. §. Lacrimal puncta occlusion is a mechanical treatment in which the tear drainage system is blocked in order to aid in the preservation of natural tears on the ocular surface.[6]

Ref.: 1. Arch Intern Med. 1999; 159(2): 174-181 2. Indian Journal of Rheumatology 2006; 1(3): 93-98 3. Ann Rheum Dis 2003; 62(12): 1204-1207 4. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020; PMID: 33048480. 5. Jogren pack insert as accessed on 1st Feb 2023 6. Cochrane Database Syst Rev. 2017; 6: CD006775

PREFACE

Sjögren's syndrome (SS) is a chronic, lifelong, systemic autoimmune disorder characterized by lymphocytic infiltration and malfunction of the exocrine glands such as salivary and lacrimal glands, resulting in dry mouth and eyes. Mainly affects middle-aged women (male/female ratio: 1:9), although it can occur at any age. Around 50% of RA patients are diagnosed with SS. Current treatments for Sjögren's Syndrome include artificial tear substitutes, saliva substitutes, parasympathomimetic drugs, immunosuppressive and/or immunomodulating therapy, NSAIDs, corticosteroids, DMARDs, biologics and surgical procedures. There is an inadequate response to the existing therapies in managing SS due to transient relief of symptoms, failure in preventing complications and a low patient compliance.

Pilocarpine, a US FDA approved parasympathomimetic agent showed improvement in symptoms of dry mouth and dry eyes as well as quality of life in patients with SS. It acts as a non-specific muscarinic acetylcholine receptor agonist and stimulates muscarinic receptors of exocrine glands such as salivary and lacrimal glands. Treatment with pilocarpine not only offers relief from dry mouth and dry eyes but also whole-body dryness. Till date, no artificial tear or saliva preparation has successfully duplicated the physiochemical properties of the body's own fluids well enough to provide a comparable degree of benefit.

In this booklet, we summarize the management of Sjögren's syndrome focusing on the role of pilocarpine and its clinical effectiveness.

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PRESCRIBING INFORMATION ON PILOCARPINE

1. COMPOSITION

Pilocarpine 5 mg Tablets

2. THERAPEUTIC INDICATIONS

- Alleviation of symptoms of salivary gland hypofunction in patients with severe xerostomia following irradiation for head and neck cancer.
- Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome.

3. DOSAGE AND ADMINISTRATION

- **For head and neck cancer patients:**

  The recommended initial dose for adults is 1 tablet of 5 mg three times daily.

  The maximal therapeutic effect is normally obtained after 4 to 8 weeks of therapy.

  For patients who have not responded sufficiently after 4 weeks and who tolerate the dose of 5 mg three times daily, doses of up to a maximum of 30 mg daily may be considered.

  However, higher daily doses are probably accompanied by an increase in drug-related adverse effects. Therapy should be discontinued if no improvement in xerostomia is noted after 2 to 3 months of therapy.

- **For Sjögren's syndrome patients:**

  The recommended dose for adults is one tablet of 5 mg four times daily.

  For patients who have not responded sufficiently to a dosage of 5 mg four times daily and who tolerate this dosage, increasing the dose up to a maximum of 30 mg daily, divided over the day, may be considered. Therapy should be discontinued if no improvement in the symptoms of dry mouth and dry eyes is noted after 2 to 3 months.

Special population

Use in the elderly: There is no evidence to suggest that dosage should be different in the elderly.

Paediatric population: The safety and efficacy of this medicinal product in the paediatric population have not been established.

Use in patients with impaired hepatic function: Patients with moderate and severe cirrhosis should start treatment on a reduced daily dosage schedule. Depending on

the safety and tolerability, the dosage may gradually be increased to the normal daily dosage schedule of 5 mg three times a day.

Use in patients with impaired renal function: Insufficient information is available to determine the importance of renal excretion of pilocarpine and its metabolites so as to recommend dosage adjustments for patients with renal insufficiency.

Method of Administration

- **For head and neck cancer patients:**

  Tablets should be taken with a glass of water during or directly after meals. The last tablet should always be taken in conjunction with the evening meal.

- **For Sjögren's syndrome patients:**

  Tablets should be taken with a glass of water at mealtimes and bedtime.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients of the product.

Pilocarpine is contraindicated in patients with clinically significant, uncontrolled cardio-renal disease, uncontrolled asthma and other chronic disease at risk for cholinergic agonists.

Pilocarpine is contraindicated in cases where miosis is undesirable, such as in acute iritis.

5. SPECIAL WARNING AND PRECAUTIONS

Caution should be exercised in patients who are known or expected to sweat excessively and who cannot drink enough liquids, since dehydration could develop.

Pilocarpine has been reported to increase airway resistance in asthmatic patients. Also, patients with significant cardiovascular disease may be unable to compensate for transient changes in haemodynamics or heart rhythm induced by pilocarpine. Therefore, pilocarpine should be administered to patients with controlled asthma or significant cardiovascular disease only if the benefits are believed to outweigh the risks, and under close medical supervision.

Pilocarpine should be used with caution in patients with the following illnesses/pathologies:

- Chronic bronchitis and/or chronic obstructive pulmonary disease. These patients have hyperactive airways and may experience adverse effects due to increased bronchial smooth muscle tone and increased bronchial secretions.
- Known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis and biliary obstruction.

- Peptic ulceration, due to the risk of increased acid secretion.
- Underlying cognitive or psychiatric disturbances. Cholinergic agonists, like pilocarpine hydrochloride, may have dose-related central nervous system effects.
- Caution should be exercised when administering pilocarpine in patients with renal insufficiency.
- Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis.
- Pilocarpine should be administered with caution in patients with narrow-angle glaucoma.

6. DRUG INTERACTIONS

Pilocarpine should be administered with caution to patients taking beta adrenergic antagonists because of the possibility of conduction disturbances.

Concurrent administration of pilocarpine and drugs with parasympathomimetic effects is expected to result in additive pharmacologic effects.

Pilocarpine might antagonise the anticholinergic effects of other drugs used concomitantly (e.g. atropine, inhaled ipratropium).

While no formal drug interaction studies have been performed, the following concomitant drugs were used in at least 10% of patients in either or both Sjögren's efficacy studies: acetylsalicylic acid, artificial tears, calcium, conjugated estrogens, hydroxychloroquine sulfate, ibuprofen, levothyroxine sodium, medroxy progesterone acetate, methotrexate, multivitamins, naproxen, omeprazole, paracetamol, and prednisone. There were no reports of drug toxicities during either efficacy study.

In in vitro studies pilocarpine has been found to be an inhibitor of CYP2A6.

In vivo inhibition and therefore an interaction with CYP2A6 substrates (e.g. irbesartan, coumarin) cannot be ruled out.

7. USE IN SPECIAL POPULATION

Pregnancy: The safety of this medicinal product for use in human pregnancy has not been established. There are no known human data for the effects of pilocarpine on foetal survival and development. Studies in animals have shown reproductive toxicity. Pilocarpine is not recommended during pregnancy and in women of child bearing potential not using contraception.

Breastfeeding: Animal studies have shown excretion of pilocarpine in milk at concentrations similar to those seen in plasma. It is not known whether pilocarpine is secreted in human milk. A decision must be made whether to discontinue breast-

feeding or to discontinue from pilocarpine therapy.

Fertility: The effects of pilocarpine on male and female fertility are not known. Studies in mice, rats and dogs have shown adverse effects on spermatogenesis. A study in rats has also indicated a possible impairment of female fertility. The safety margin for the effects on fertility is unknown.

Based on the results of available studies in animals as a precautionary measure, Pilocarpine tablets should be administered to individual human males who are attempting to father a child, only, if the expected benefit justifies potential impairment of fertility.

8. EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Patients who experience dizziness during pilocarpine treatment should be advised not to drive or operate machinery.

Pilocarpine has been reported to cause impairment of depth perception and visual blurring. The latter may result in decreased visual acuity, especially at night and in patients with central lens changes. If this occurs, patients should be advised not to drive at night or perform hazardous activities in reduced lighting.

9. UNDESIRABLE EFFECTS

Most of the adverse experiences observed during pilocarpine treatment were a consequence of exaggerated parasympathetic stimulation. These adverse experiences were dose-dependent and usually mild and self-limited. However, severe adverse experiences might occasionally occur and therefore careful monitoring of the patient is recommended.

In controlled clinical trials the following adverse reactions were observed:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders: headache, dizziness

Eye disorders: lacrimation; blurred vision; abnormal vision; conjunctivitis; eye pain

Cardiac disorders: flushing (vasodilatation); hypertension; palpitations

Respiratory, thoracic and mediastinal disorders: rhinitis

Gastrointestinal disorders: dyspepsia; diarrhoea; abdominal pain; nausea, vomiting; constipation, increased salivation, flatulence

Skin and subcutaneous tissue disorders: sweating, allergic reactions, including rash, pruritus

Renal and urinary disorders: increased urinary frequency, urinary urgency

General disorders and administration site conditions: flu syndrome, asthenia, chills

There is no indication of a difference between older and younger patients receiving pilocarpine as regards reporting adverse experiences, except for dizziness, which was reported significantly more often by patients aged over 65 years.

The following adverse effects, which are due to the intrinsic pharmacological properties of pilocarpine, have been published in the medical literature: respiratory distress, gastro-intestinal spasm, atrio-ventricular block, tachycardia, bradycardia, cardiac arrhythmia, hypotension, shock, tremors, and mental status changes including memory loss, hallucinations, lability of affect, confusion and agitation.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above adverse drug reactions associated with the use of the above drugs. If such reactions are encountered, please report to Hetero Healthcare by writing the case or complaints to"drugsafety@heterohealthcare.com"

10. OVERDOSE

Overdose may lead to a 'cholinergic crisis' characterised by both muscarinic and nicotinic effects.

Signs of overdose due to muscarinic effects may include abdominal cramps, diarrhoea, nausea and vomiting, involuntary defecation and urination, sweating, salivation, increased bronchial secretions, miosis, bradycardia and hypotension.

Nicotinic effects may include involuntary twitching, fasciculations and generalised weakness.

Parenteral atropine may be used as an antidote to the muscarinic effects. Supportive treatment should be given as required; artificial respiration should be instituted if respiratory depression is severe.

11. PHARMACOLOGICAL PROPERTIES

11.1. Mechanism of Action

Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. Pilocarpine, in appropriate dosage, can increase secretion by exocrine glands such as the sweat, salivary, lacrimal, gastric, pancreatic and intestinal glands and the mucous cells of the respiratory tract.

11.2. Pharmacodynamic Properties

Dose-related smooth muscle stimulation of the intestinal tract may cause increased

tone, increased motility, spasm and tenesmus. Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder and biliary duct smooth muscle may be enhanced.

Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist isvaso depression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

11.3. Pharmacokinetic Properties

Absorption: In a multiple-dose pharmacokinetic study in volunteers given 5 or 10 mg of pilocarpine hydrochloride three times daily for two days, the Tmax after the final dose was approximately 1 hour, the elimination $t_{½}$ was approximately 1 hour, and the mean Cmax were 15 ng/ml and 41 ng/ml for the 5 and 10 mg doses, respectively.

When taken with a high-fat meal, there was a decrease in the rate of absorption of pilocarpine from pilocarpine tablets. Mean T max were 1.47 and 0.87 hours and mean Cmax were 51.8 and 59.2 ng/ml for fed and fasted male volunteers, respectively.

Distribution: Pilocarpine is extensively distributed with an apparent volume of distribution of 2.1 L/kg. Data from animal studies indicates that pilocarpine is distributed into breast milk at concentrations similar to plasma. Preclinical data also suggests that pilocarpine can cross the blood brain barrier at high dose. Pilocarpine does not bind to plasma proteins.

Metabolism: Pilocarpine is primarily metabolized by CYP2A6 and has demonstrated a capacity to inhibit CYP2A6 in vitro. Serum esterases are also involved in the biotransformation of pilocarpine to pilocarpic acid.

Elimination: Approximately 35% of dose is eliminated as 3-hydroxypilocarpine in urine and 20% of dose is excreted unchanged in the urine. Mean elimination half-lives for pilocarpine is 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of pilocarpine hydrochloride, respectively.

Elderly: Pilocarpine area under the curve (AUC) values in elderly male volunteers were comparable to those in younger males. In a small number of healthy elderly female volunteers the mean AUC was approximately twice that of elderly and young male volunteers due to reduced volumes of distribution. However, the observed difference in pharmacokinetics was not reflected in the incidence of adverse events between young and elderly female patients. No dosage adjustment is required in elderly subjects.

Renal impairment: A pharmacokinetic study of pilocarpine in patients with mild and moderately impaired renal function showed that there was no significant difference in clearance and exposure compared with subjects with normal renal function.

CLINICAL EVIDENCES ON PILOCARPINE

1. **Oral Pilocarpine for the Treatment of Dry Eye in Patients with Sjögren's Syndrome**
   (Felberg S et al., Arq Bras Oftalmol 2022; 85(3): 269-276)

OBJECTIVE: To evaluate the efficacy of oral pilocarpine (20 mg daily) for the treatment of dry eye in patients with Sjogren's Syndrome. The frequency of side effects reported during the treatment was also investigated.

METHODS: In this placebo-controlled crossover study, 32 patients with Sjögren's syndrome were enrolled to receive either oral pilocarpine or placebo for 10 weeks. Following a 2-week washout period, the treatment was inverted for each patient for the same duration. Assessments included the quality of life National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), dry eye specific questionnaire Ocular Surface Disease Index, non-invasive breakup time, invasive breakup time with fluorescein, corneal and conjunctival staining patterns with the use of fluorescein and rose bengal staining, Schirmer's test, and tear ferning test.

RESULTS: According to the NEI-VFQ-25, there was statistically significant improvement in the quality of life following oral pilocarpine. Similar results were observed for ocular discomfort, as determined by the Ocular Surface Disease Index. All clinical tests showed favorable and statistically significant results following the use of oral pilocarpine. Regarding the analysis of tear samples, there was an improvement in the quality of tear film. This was evidenced by the modification of the patterns observed in the tear ferning test. Side effects were reported by 96.8% and 56.2% of the patients who received pilocarpine and placebo, respectively. Sweating was the most frequently reported side effect (67.74% versus 11.11%, respectively).

CONCLUSIONS: Although the treatment was associated with a high frequency of side effects, oral pilocarpine (20 mg daily) was able to relieve discomfort related to dry eyes in patients with Sjögren's syndrome and induce favorable structural changes in the tear film.

2. Clinical Study of Efficacy and Safety of Oral Pilocarpine in the Treatment of Severe Dry Eye Disease

(Kumar S et al., , International Journal of Pharmaceutical and Clinical Research 2021; 13(3): 411-417)

INTRODUCTION: Dry eye disease is a multi-factorial disease with varied presentation of foreign body sensation with or without visual disturbance. When its presentation is severe and refractory to conventional tear substitution treatment, it maybe it can lead to compromised quality of life.

OBJECTIVE: The purpose of this study is to effectively treat aqueous deficient, severe dry eyes with oral Pilocarpine, which is conventionally refractory to conventional tear substitute ocular instillation.

METHODS: 32 continuous cases of bilateral dry eye disease with severe symptoms, refractory to the conventional tear film substitute treatment and fitted in our inclusion criteria. All the patients were given oral Pilocarpine tablet of 5 mg once a day.

RESULTS: There were mean improvement of 4.37 mm in Schirmer's value and mean improvement of 3.03 seconds in TBUT. The result was analysed by using two tailed t- test and found to highly significant ($p<0.001$) for both TBUT and Schirmer's test. A few patients complained of sweating after taking the medicine which was relieved in few minutes.

DISCUSSION: Pilocarpine is widely used as sialagogue. Oral Pilocarpine is approved for management of dry eye in Sjögren's syndrome and has been ascertained to be effective in dry eye (6-11). Our study shows similar effect of improvement who were otherwise refractory to tear film substitutes without significant adverse effects. Though we do not rule out that many of them may be cases of Sjögren's syndrome.

CONCLUSION: Oral Pilocarpine (5 mg OD) is safe and effective in otherwise healthy individuals in relieving symptoms of severe dry eye disease in cases who are refractory to various tear film substitutes.

3. Salivary Glands and Periodontal Changes in a Population of Sjögren's and Sicca Syndrome Treated by Pilocarpine: A Pilot Study

(Depinoy T et al., Rheumatol Ther 2021; 8(1): 219-231)

INTRODUCTION: Oral administration of pilocarpine enhances salivary flow in sicca patients but its effect upstream on ultrasound (US) of salivary glands (SG) and downstream on periodontium remain unknown.

METHODS: Sicca patients were prospectively included. Echostructural and vascularization of SG were assessed using B mode and pulsed Doppler (USPD). Vascularization of SG was measured using resistive index (RI) before and after stimulation by lemon juice. Echostructure (measure of glandular length in cm2, evaluation of parotid and submandibular glands parenchymal abnormalities) was assessed at baseline (M0) and after 3 months (M3) of treatment with pilocarpine. A dental consultation was performed at M0 and M3 to evaluate changes in unstimulated salivary flow (USSF), stimulated salivary flow (SSF), and periodontal parameters such as modified gingival index (Lobene), plaque index (Silness), bleeding index, pocket depth, and pH.

RESULTS: Nineteen patients were included but only 11 received pilocarpine treatment for 3 months, as six stopped pilocarpine due to side effects and two were excluded for other causes. Among the 11 patients who completed the 3-month follow-up, five had primary Sjögren's syndrome according to the American-European's classification criteria. As expected, statistical differences were found concerning SSF ($p = 0.018$) and USSF ($p = 0.027$) between M0 and M3 while no statistical change in both SG echostructure and vascularization or periodontal evaluation was shown.

CONCLUSIONS: Pilocarpine improved SSF and USSF measurements in sicca syndrome but no ultrasonography of major salivary glands (SGUS) structural and vascular changes were detected as well as periodontal evaluation.

4. Pilocarpine for Sjögren's Syndrome-induced Dry Mouth and Dry Eyes: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

(Freige C et al., Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Jan 21)

Sjögren's syndrome is an autoimmune disease most frequently affecting women between 30 and 50 years of age. Sjögren's syndrome is often under-diagnosed but may affect up to 430,000 Canadians.

The cause of Sjögren's syndrome is currently unknown, however, one prevalent theory is that certain genetic factors coupled with an environmental stimulus (i.e., a virus) triggers the disease.

There are two main classifications of Sjögren's syndrome: primary and secondary. Patients are classified as having primary Sjögren's syndrome when there is no other autoimmune disease present. Patients are classified as having secondary Sjögren's syndrome when another autoimmune disorder, such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, is also present. Both types of Sjögren's syndrome are characterized by damage to exocrine glands such as the salivary, tear and mucous-secreting glands, which can result in dry eyes and dry mouth. Dry eyes can cause discomfort via a scratchy and gritty sensation. In rare, severe cases, vision impairment may occur due to damage to the corneal surface.2 Dry mouth occurs secondary to a diminished saliva production and can cause difficulty chewing and swallowing, *Candida* infections, tooth decay and sialolithiasis. Both dry eyes and dry mouth can be managed with a variety of non-pharmacological and non-prescription therapies. Pharmacological therapy with muscarinic agonists (i.e., pilocarpine, cevimeline) which stimulate exocrine glands, can also be used to alleviate the symptoms of dry eyes and dry mouth. Other symptoms of Sjögren's syndrome may include extraglandular manifestations such as lymphadenopathy, Raynaud phenomenon, and vasculitis.

This report aims to summarize the evidence regarding the clinical effectiveness, cost-effectiveness and evidence-based guidelines' recommendations for the use of pilocarpine in the treatment of Sjögren's syndrome-induced dry eyes and dry mouth.

5. Pilocarpine and Artificial Saliva for the Treatment of Xerostomia and Xerophthalmia in Sjögren Syndrome: A Double-blind Randomized Controlled Trial

(Cifuentes M et al., Br J Dermatol. 2018; 179(5): 1056-1061)

BACKGROUND: Sjögren syndrome (SS) is associated with xerostomia and xerophthalmia. Pilocarpine has been shown to stimulate the secretion of saliva.

OBJECTIVES: To investigate and compare the efficacy of pilocarpine and artificial saliva as symptomatic treatments for xerostomia and xerophthalmia in patients with SS.

METHODS: A double-blind randomized controlled study was performed. A total of 72 patients with SS were assigned randomly to receive 10 drops of pilocarpine (5 mg) or 10 drops of artificial saliva orally, three times daily for 12 weeks. Whole saliva and tear flow were evaluated at baseline and periodically throughout the study to provide a global assessment of dryness and to report any adverse effects.

RESULTS: Patients receiving pilocarpine had a statistically significant improvement in their salivary flow ($P < 0.001$), lacrimal flow ($P < 0.001$) and their subjective global assessment ($P < 0.001$), compared with patients who received artificial saliva. The most common side-effects were sialorrhoea and nausea.

CONCLUSIONS: Pilocarpine is more effective than artificial saliva for enhancing salivary and lacrimal secretion in patients with SS. This is the first study to compare the efficacy of pilocarpine and artificial saliva for the treatment of xerostomia and xerophthalmia in SS.

6. The Effectiveness of Pilocarpine Hydrochloride for Dry Mouth Symptoms of Sjögren's Syndrome – Examining the Adjustments on the Number of Times of its Administration

(S. Toya et al., *International Journal of Oral and Maxillofacial Surgery 2015; 44(1): e298)*

OBJECTIVES: Pilocarpine is the representative drug for the treatment of dry mouth symptoms of Sjögren's syndrome. However, as indicated in its directions for use, it causes a high incidence of such side effects as excessive perspiration, so its continuous administration presents difficulty at times.

METHODS: With 47 patients of Sjögren's syndrome as subjects, we conducted a retrospective study to determine the most effective dosage and frequency of its administering. The subjects were divided into two groups for testing two different patterns of administration – one of which for making adjustments on the number of administration of the normal dose of 5 mg tablet per time and the other group, for making adjustments on the number of administration of 2.5 mg which was half the 5 mg tablet. Each week, we made adjustments by increasing or decreasing the dose. Our findings indicated that the group for the pattern of making adjustments on the number of times in administering 2.5 mg dosage was the group that was superior with respect to the incidence of excessive perspiration of side effects, as observed by the Saxon Test – the rate of improvement in the average saliva secretion and the rate of improvement dry mouth symptoms in the average on the Visual Analogue Scale.

FINDINGS AND CONCLUSIONS: The above results suggested that the treatment of dry mouth symptoms of Sjögren's syndrome, using the method of adjusted administration of 2.5 mg/time, was more effective.

7. Effect of Oral Pilocarpine in Treating Severe Dry Eye in Patients with Sjögren Syndrome

(Kawakita T et al., Asia Pac J Ophthalmol (Phila) 2015; 4(2): 101-105)

OBJECTIVE: The aim of this study is to evaluate the efficacy and safety of oral pilocarpine in treating severe dry eye unresponsive to conventional conservative treatment in patients with Sjögren syndrome.

METHODS: A prospective study.Oral doses of pilocarpine were administered for at least 3 months to patients with Sjögren syndrome complicated by established dry eye of great severity unresponsive to conventional conservative treatment.

RESULTS: Subjective eye symptoms (dry eye sensation and eye pain), fluorescein staining scores, rose Bengal staining scores, and tear film breakup time measurements improved significantly after 1 month and 3 months of oral treatment with pilocarpine, whereas no significant improvement was noted in Schirmer I testing.

CONCLUSIONS: Oral administration of pilocarpine was useful in treating severe dry eye unresponsive to conventional conservative treatment in patients with Sjögren syndrome from the standpoint of efficacy and safety. Thus, we conclude that oral pilocarpine is effective as a new option in treating severe dry eye.

8. Efficacy of Cevimeline vs. Pilocarpine in the Secretion of Saliva: A Pilot Study

(Brimhall J et al., Special Care in Dentistry 2013; 33(3):123-127)

OBJECTIVES: To determine the efficacy and compare the side-effects of cevimeline and pilocarpine in the secretion of saliva in patients with xerostomia.

METHOD: A randomized, cross-over, double blind study was designed. Fifteen patients with diagnosis of xerostomia were assigned to take either 5 mg of pilocarpine or 30 mg of cevimeline three times a day for four weeks. Salivary flow rates were measured during the initial baseline, first and second month appointments. Statistical analysis was carried out with ANOVA and post hoc t-tests.

RESULTS: Twelve patients completed both medication treatments. Although both medications proved to increase salivary secretion, there was no significant difference between pilocarpine and cevimeline. Also, the perceived side-effects between the two medications were similar.

CONCLUSION: Both medications increased the secretion of saliva at the end of four weeks. However, there was a slightly higher increment in saliva with pilocarpine. However, the difference was not statistically significant.

9. Efficacy and Safety of Orally Administered Pilocarpine Hydrochloride for Patients with Juvenile-Onset Sjögren's Syndrome

(Tomiita M et al., Mod Rheumatol 2010; 20(5): 486-490)

ABSTRACT: The number of patients with juvenile-onset Sjögren's syndrome (SS) has recently increased. However, there is no drug that is safe and effective for the xerostomia that occurs in patients of this age group. We evaluated the efficacy and safety of orally administered pilocarpine hydrochloride for juvenile- onset SS patients. Five female patients, aged from 9 to 16 years, received 5-10 mg/day for 4 weeks. On days 1 and 28, salivary production was measured by the Saxon test, and patients completed subjective self-evaluations of xerostomia symptoms and were asked about changes in water intake and overall improvement of dry mouth on day 28. After 4 weeks of pilocarpine administration, salivary production increased significantly in all patients, and overall status was assessed as "improved" in all patients. One patient had excessive sweating. No serious adverse events or laboratory examination abnormalities correlated with pilocarpine administration were found. In conclusion, the results of this study suggest that orally administered pilocarpine is safe and effective for treating xerostomia in juvenile-onset SS patients. This is the first report of the efficacy of pilocarpine for juvenile SS patients; further evaluations are needed to confirm our result.

10. Successful Treatment of Dry Mouth and Dry Eye Symptoms in Sjögren's Syndrome Patients with Oral Pilocarpine: A Randomized, Placebo-Controlled, Dose-Adjustment Study

(Papas AS et al., J Clin Rheumatol 2004; 10(4): 169-177)

BACKGROUND: Sjögren's syndrome is characterized by the presence of xerostomia and/or xerophthalmia. Pilocarpine, a muscarinic cholinergic agonist, has been proven to be efficacious in treating radiation-induced xerostomia (up to 30 mg/day) and symptoms of dry mouth in Sjögren's patients (up to 20 mg/day).

OBJECTIVE: To compare the safety and efficacy of oral pilocarpine (dose-adjusted) versus placebo in the treatment of dry eye and dry mouth symptoms in Sjögren's syndrome at 6 and 12 weeks.

METHODS: In this 11-center, 256-patient placebo-controlled study, the safety and efficacy of oral pilocarpine (20 mg to 30 mg daily) for relief of Sjögren's-related dry mouth and dry eye symptoms was assessed. Changes in symptoms and salivary flow were measured over 12 weeks.

RESULTS: Compared with placebo, salivary flow was significantly increased in the pilocarpine group ($P \leq 0.0001$) after the first dose and throughout the study. Significant improvement in patients' global assessment of dry mouth ($P \leq 0.0001$) with relief in 5 of 7 separate oral symptoms ($P \leq 0.02$) was reported by the treated patients throughout study. Minimal differences in 3 of 8 ocular symptoms were noted at 6 weeks (5-mg dose), but at 12 weeks (5- to 7.5-mg dose), the pilocarpine group demonstrated both significant improvement in global assessment of dry eyes ($P \leq 0.0001$) and relief in 6 of 8 related symptoms ($P \leq 0.04$). The drug was well tolerated at both doses. The most common pilocarpine-related side effects were sweating, urinary frequency, flushing, and chills.

CONCLUSIONS: Significant relief in dry mouth symptoms was noted at 20 mg/day, and significant relief in ocular symptoms, including lower artificial tear requirement, was noted after the dose was increased to 30 mg/day.

11. Oral Pilocarpine for the Treatment of Ocular Symptoms in Patients with Sjögren's Syndrome: A Randomised 12 Week Controlled Study

(Tsifetaki N et al., Ann Rheum Dis 2003; 62(12): 1204-1207)

OBJECTIVE: To evaluate the efficacy and side effects of oral pilocarpine for the treatment of ocular symptoms in patients with primary Sjögren's syndrome (SS).

METHODS: A 12 week, single centre, randomised controlled study was performed. Twenty nine patients were randomly assigned to receive oral pilocarpine (5 mg twice a day), 28 only artificial tears, and 28 inferior puncta occlusion. Patients receiving oral pilocarpine and those with inferior puncta occlusion also received artificial tears. Patients were evaluated at baseline and throughout the study for their subjective global assessment of dry eyes and for their objective assessment of dry eyes (Schirmer's-I test, rose bengal test, and imprint test).

RESULTS: Patients taking oral pilocarpine had significant improvement in subjective global assessment of dry eyes, as was evaluated by improvement of >55 mm on a visual analogue scale (VAS) for responses to the eye questionnaire, compared with patients treated with artificial tears ($p<0.001$) and those with inferior puncta occlusion ($p<0.05$). Furthermore, patients receiving oral pilocarpine also showed greater objective improvement, as measured by the rose bengal test ($p<0.05$), while Schirmer's-I test showed no differences between the treated groups. Commonly reported adverse events were headache, increased sweating, nausea, and vomiting in the pilocarpine group, while one patient in the inferior puncta occlusion group had blepharitis and was withdrawn from the study.

CONCLUSIONS: 10 mg of pilocarpine daily given to patients with SS for 12 weeks had a beneficial effect on subjective eye symptoms, as evaluated by improvement >55 mm on a VAS. Additionally, an improvement of rose bengal staining was noted, but an increase in tear production, as measured by the Schirmer-I test, was not substantiated.

12. Oral Pilocarpina for Dry Eye in Sjogren's Syndrome

(Arroyave CP et al, Investigative Opthalmology & Visual Science 2003; 44(13): 2454)

PURPOSE: To investigate the safety and efficacy of oral pilocarpine for the treatment of dry eye signs and symptoms associated with Sjogren's syndrome (SS).

METHODS: Thirty patients with signs and symptoms of dry eye associated with SS were evaluated with Schirmer test, rose of Bengal and a dry eye questionnaire before and after treatment with an 8-week course of oral pilocarpine 5 mg three times daily.

RESULTS: In a global evaluation a statistical significant number of patients (28/30) 93% showed improvement (p< or = 0.001) Only 3 (10%) patients experienced diaphoresis, which was described as "mild" and occurred at a median of 8 days (range 2-14 days) after starting the medication and lasted for a median of 29 days (2-56 days). There were no other adverse events and no patient needed to discontinue the medication due to intolerance.

CONCLUSIONS: The signs and symptoms of dry eye associated with Sjogren's syndrome improved significantly after treatment with oral pilocarpine.

13. Usefulness of Basal and Pilocarpine-Stimulated Salivary Flow in Primary Sjögren's Syndrome

(Rosas J et al, Rheumatology (Oxford). 2002; 41(6): 670-675)

OBJECTIVES: To examine salivary function in patients with primary Sjögren's syndrome (SS) by assessing unstimulated and stimulated flows using 5 mg of pilocarpine in a 5% solution, in order to define their clinical usefulness in the evaluation of xerostomia in patients with primary SS as well as to identify those factors related to the increase in salivary flow after pilocarpine stimulation.

METHODS: We investigated the clinical and immunological characteristics of 60 consecutive patients with primary SS. All patients fulfilled four or more of the preliminary diagnostic European criteria for SS. We measured unstimulated (basal) salivary flow (BSF) in all patients. In patients with BSF </=1.5 ml, stimulated salivary flows (SSF) were also measured after stimulation with an ophthalmic 5% pilocarpine solution (0.1 ml=5 mg, administered sublingually). SSF was also measured after oral administration of 50 mg anetholetrithione (ANTT) in the same patients. These stimulated salivary flows were measured 1, 2 and 3 h after the stimulus.

RESULTS: Of the 60 patients, 55 were women and five men, with a mean age at the SS onset of 61 yr (range 18-82 yr). The mean BSF for SS patients was 1.40+/-0.17 ml. Fifty (83%) patients showed a BSF less than 1.5 ml. The stimulated salivary flow after 1 h was 3.23 ml in the pilocarpine group and 0.57 in the ANTT group (P<0.001); after 2 h it was 1.32 ml in the pilocarpine group and 0.52 in the ANTT group (P=0.02) and after 3 h it was 0.80 ml in the pilocarpine group and 0.41 in the ANTT group (P=0.046). No clinical or immunological differences were found between SS patients with BSF more or less than 1.5 ml, although patients with a BSF less than 1.5 ml showed a parotid scintigraphy class III or IV more frequently (42 vs 0%, P=0.01). SS patients with a pilocarpine SSF less than 1.5 ml had a longer duration of SS (73.3 vs 31.3 months, P=0.03) and a higher prevalence of positive anti-Ro/SS-A (70 vs 36%, P=0.038), anti-La/SS-B (65 vs 32%, P=0.038), parotid scintigraphy class III-IV (79 vs 9%, P<0.001) and positive salivary gland biopsy (90 vs 43%, P<0.001).

CONCLUSION: The study of xerostomia using basal and pilocarpine SSF is simple to perform, acceptable to patients and needs no special equipment. We describe a significant increase in SSF using a solution of 5% pilocarpine in comparison with salivary flow obtained after stimulation with ANTT. Twenty-two of the 46 patients with low BSF

had stimulated flows over 1.5 ml. These 'responder' patients showed a shorter duration of sicca symptoms, a lower frequency of positive immunological markers and milder grades of scintigraphic patterns and lymphocytic infiltrates in salivary gland biopsies. This subset of patients probably maintain a residual capacity of their salivary glands, as opposed to the 'non-responder' patients, who had a longer duration of sicca syndrome evolution with more severe involvement of the salivary glands.

14. Effect of Pilocarpine Mouthwash on Salivary Flow

(Bernardi R et al, Braz J Med Biol Res. 2002; 35(1): 105-110)

ABSTRACT: Pilocarpine is a cholinergic agonist that increases salivary flow and has been used to treat xerostomia. Oral intake is the most frequent route of administration. Adverse effects are dose-dependent and include sudoresis, facial blushing and increased urinary frequency. The objective of the present study was to evaluate the effects of topical pilocarpine solutions as mouthwashes on salivary flow and their adverse effects on healthy subjects. Forty volunteers received 10 ml 0.5, 1 and 2% pilocarpine solutions or 0.9% saline in a randomized, double-blind, placebo-controlled manner. Salivation was measured before and 45, 60 and 75 min after mouth rinsing for 1 min with 10 ml of saline or pilocarpine solutions. Vital signs were measured and ocular, gastrointestinal and cardiovascular symptoms, anxiety and flushing were estimated using visual analog scales. There was a dose- dependent increase in salivation. Salivation measured after 1 and 2% pilocarpine (1.4 ± 0.36 and 2.22 ± 0.42 g, respectively) was significantly ($P<0.001$) higher than before (0.70 ± 0.15 and 0.64 ± 0.1 g), with a plateau between 45 and 75 min. Cardiovascular, visual, gastrointestinal and behavioral symptoms and signs were not changed by topical pilocarpine. Mouth rinsing with pilocarpine solutions at concentrations of 1 to 2% induced a significant objective and subjective dose-dependent increase in salivary flow, similar to the results reported by others studying the effect of oral 5 mg pilocarpine. The present study revealed the efficacy of pilocarpine mouthwash solutions in increasing salivary flow in healthy volunteers, with no adverse effects. Additional studies on patients with xerostomia are needed.

15. Effects of Pilocarpine on Salivary Flow in Patients with Sjögren's Syndrome

(Rhodus NL et al, Oral Surg Oral Med Oral Pathol. 1991; 72(5): 545-549)

ABSTRACT: Pilocarpine, a muscarinic-cholinergic agonist drug, has been reported to stimulate salivary flow in patients with salivary gland dysfunction. Previous studies involved heterogeneous groups of patients with salivary gland dysfunction and examined the short-term, single-dose, tablet form of pilocarpine. In this single-blind, placebo-controlled study we examined the long-term effects of pilocarpine administration on patients with definitively diagnosed Sjögren's syndrome (SS). Nine subjects with SS who received pilocarpine, and nine age- and sex-matched SS control subjects who received a placebo, participated. Baseline predosing sialometric and clinical data were obtained for all subjects. The study group used 2% pilocarpine as a liquid ophthalmic drop preparation, four drops three times per day, for 6-weeks. Identically appearing placebo solution with the same dosing schedule and duration was used for the control subjects. Sialometric and clinical examinations were performed. The results indicated a significant overall increase in both whole unstimulated salivary flow (0.15 +/- 0.03 ml/min in study subjects vs 0.02 +/- 0.001 ml/min in control subjects; p less than 0.001) and parotid stimulated salivary flow (0.14 +/- 0.04 ml/min in study subjects vs 0.009 +/- 0.002 ml/min in control subjects; p less than 0.001) in the pilocarpine group as compared with the placebo group. The results of this study support the use of pilocarpine to increase salivary flow in patients with SS.

Notes:

In the Treatment of Sjögren's Syndrome

Jögren®

Pilocarpine Hydrochloride Tablets USP 5 mg

Rational & Accurate Treatment

EULAR

Recommends pilocarpine for the treatment of mild or moderate dry mouth.

BSR

Recommends pilocarpine for the treatment of significant sicca symptoms.

Abridged PI: COMPOSITION: Each film-coated tablet contains 5 mg of pilocarpine hydrochloride. **INDICATIONS:**• Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome. •Alleviation of symptoms of salivary gland hypofunction in patients with severe xerostomia following irradiation for head and neck cancer. **DOSAGE:** • **For Sjögren's syndrome:** The recommended dose for adults is one tablet of 5 mg four times daily. For patients who have not responded sufficiently, increasing the dose up to a maximum of 30 mg daily, divided over the day, may be considered. • **For head and neck cancer:** The recommended initial dose for adults is 1 tablet of 5 mg three times daily. The maximal therapeutic effect is normally obtained after 4 to 8 weeks of therapy. For patients who have not responded sufficiently, doses of up to a maximum of 30 mg daily may be considered. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients of the product. Pilocarpine is contraindicated in patients with clinically significant, uncontrolled cardio-renal disease, uncontrolled asthma and other chronic disease at risk for cholinergic agonists. Pilocarpine is also contraindicated in in acute iritis. **WARNINGS & PRECAUTIONS:** Caution should be exercised in patients who are known or expected to sweat excessively and who cannot drink enough liquids, since dehydration could develop. Pilocarpine has been reported to increase airway resistance in asthmatic patients. Also, patients with significant cardiovascular disease may be unable to compensate for transient changes in haemodynamics or heart rhythm induced by pilocarpine. Therefore, pilocarpine should be administered to patients with controlled asthma or significant cardiovascular disease only if the benefits are believed to outweigh the risks, and under close medical supervision. Pilocarpine should be used with caution in patients with the following illnesses/pathologies: • Chronic bronchitis and/or chronic obstructive pulmonary disease. These patients have hyperactive airways and may experience adverse effects due to increased bronchial smooth muscle tone and increased bronchial secretions. • Known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis and biliary obstruction. • Peptic ulceration, due to the risk of increased acid secretion. • Underlying cognitive or psychiatric disturbances. Cholinergic agonists, like pilocarpine hydrochloride, may have dose-related central nervous system effects. • Caution should be exercised when administering pilocarpine in patients with renal insufficiency. • Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis. • Pilocarpine should be administered with caution in patients with narrow angle glaucoma. **USE IN SPECIFIC POPULATIONS: Pregnancy:** There are no known human data for the effects of pilocarpine on foetal survival and development. Pilocarpine is not recommended during pregnancy and in women of child bearing potential not using contraception. **Lactation:** It is not known whether pilocarpine is secreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue from pilocarpine therapy. **Pediatric Use:** The safety and efficacy of pilocarpine in the pediatric population have not been established. **Geriatric Use:** There is no evidence to suggest that dosage should be different in the elderly. **Renal Impairment:** Insufficient information is available to determine the importance of renal excretion of pilocarpine and its metabolites so as to recommend dosage adjustments for patients with renal insufficiency. **Hepatic Impairment:** Patients with moderate and severe cirrhosis should start treatment on a reduced daily dosage schedule. Depending on the safety and tolerability, the dosage may gradually be increased to the normal daily dosage schedule of 5 mg three times a day. **ADVERSE EFFECTS:** Most of the adverse experiences observed during pilocarpine treatment were a consequence of exaggerated parasympathetic stimulation. These adverse experiences were dose-dependent and usually mild and self-limited. However, severe adverse experiences might occasionally occur and therefore careful monitoring of the patient is recommended. In controlled clinical trials the following adverse reactions were observed: • **Nervous system disorders:** headache, dizziness • **Eye disorders:** lacrimation; blurred vision; abnormal vision; conjunctivitis; eye pain • **Cardiac disorders:** flushing (vasodilatation); hypertension; palpitations • Respiratory, thoracic and mediastinal disorders: rhinitis • **Gastrointestinal disorders:** dyspepsia; diarrhoea; abdominal pain; nausea, vomiting; constipation, increased salivation, flatulence • **Skin and subcutaneous tissue disorders:** sweating, allergic reactions, including rash, pruritus • **Renal and urinary disorders:** increased urinary frequency, urinary urgency • **General disorders and administration site conditions:** flu syndrome, asthenia, chills. There is no indication of a difference between older and younger patients receiving pilocarpine as regards reporting adverse experiences, except for dizziness, which was reported significantly more often by patients aged over 65 years. The following adverse effects, which are due to the intrinsic pharmacological properties of pilocarpine, have been published in the medical literature: respiratory distress, gastro-intestinal spasm, atrio-ventricular block, tachycardia, bradycardia, cardiac arrhythmia, hypotension, shock, tremors, and mental status changes including memory loss, hallucinations, lability of affect, confusion, and agitation.

EULAR - European Alliance of Associations for Rheumatology; **BSR** - British Society for Rheumatology; **PI** - Prescribing information

Ref.: Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Jan 21.

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