

# Mouth and Eye Dryness After Use of Sildenafil: A Case Report

## Sildenafil Kullanımı Sonrasında Ağız ve Göz kuruluğu: Bir Olgu Sunumu

### AUTHORS / YAZARLAR

#### Yılmaz Sezgin

Department of Family  
Medicine, Sürmene State  
Hospital, Trabzon,  
Turkey

#### Muhammet Ali Kılıç

Department of Family  
Medicine, Ulubey State  
Hospital, Uşak, Turkey

#### Tolga Günvar

Department of Family  
Medicine, Dokuz Eylül  
University School of  
Medicine, Izmir, Turkey

#### Vildan Mevsim

Department of Family  
Medicine, Dokuz Eylül  
University School of  
Medicine, Izmir, Turkey

### ABSTRACT

This case report intended to draw attention to different etiological factors and treatment of dryness of mouth and eye. The patients was diagnosed as dry mouth and dry eye. Sjögren's syndrome screening was negative. The patient received sildenafil 100 mg two months and four months ago. On physical examination the patient's skin moist, redehyes, anxious and tired-looking. The patient serum vitamin B12 level was 216 pg/ml. So we adviced vitamin B12 treatment. Dry mouth improved in the second month of treatment. The patient's dry eye complained continued. Sildenafil and vitamin B12 deficiency can disrupt the neural transmission with different mechanisms. As a result, sildenafil and vitamin B12 deficiency together may cause dry mouth and dry eye.

Keywords: : mouth dryness, dry eye, sildenafil, vitamin B12 deficiency

### ÖZET

Bir olgu sunumu ile ağız ve göz kuruluğunun farklı etiyolojik faktörlerine ve tedavisine dikkat çekmek amaçlanmıştır. Hasta kuru ağız ve kuru göz tanısı almıştır. Sjögren sendromu taraması negatif gelmiştir. Hasta, iki ay ve dört ay önce 100 mg Sildenafil almıştır. Fizik muayenede hastanın derisi nemli, gözleri kızarıklık, anksiyöz ve yorgun görünümündü. Serum vitamin B12 seviyesi 216 pg/ml olması nedeniyle vitamin B12 tedavisi önerildi. Tedavinin ikinci ayında ağız kuruluğu düzeldi. Hastanın göz kuruluğu devam ediyordu. Sildenafil ve vitamin B12 eksikliği farklı mekanizmalarla sinirsel iletimi bozabilir. Sonuç olarak sildenafil ve vitamin B12 eksikliği birlikte kuru ağız ve kuru göze neden olmuş olabilir.

Anahtar kelimeler: ağız kuruluğu, kuru göz, sildenafil, vitamin B12 eksikliği

### Introduction

Autoimmune diseases such as sarcoidosis and sjögren syndrome; anticholinergics, antihistamines, tricyclic antidepressants drugs and systemic side effects of radiotherapy and chemotherapy treatment applications causes mouth and eye dryness. In addition the factors that affect the synthesis of myelin or neuromediators blocking sensory, motor and autonomic neural transmission can cause the dry mouth and dry eye. For cases dryness last more than a month it was stated that inflammation in the eye can cause permanent loss of function in lacrimal glands (1).

Most of saliva is secreted by submandibular and parotid glands, and a small quantity by sublingual glands. In addition a sufficient amount of saliva is secreted by the submucosal glands located on lips, cheeks, palate, tonsils, molar and retromolar area. In adults, 1000-1500 ml of saliva is produced (2). Concentration of saliva is more hypotonic than plasma sodium and chloride ions. Salivary glands are controlled by dominantly parasympathetic autonomic nervous system and partly the sympathetic nerve impulses to initiate excretory function. Saliva consists of the fluid part produced by parasympathetic stimulation and protein part produced by sympathetic stimulation (3). Acetylcholine, substance P and alpha-receptors affected by norepinephrine causes

### Corresponding Author / İletişim için

Dr. Yılmaz Sezgin, MD  
Sürmene State Hospital, Trabzon, Turkey  
E-mail: drysezgin@gmail.com

Date of submission: 25.01.2015 / Date of acceptance: 30.07.2015

secretion with more amount of fluid and low amount of amylase by increasing the amount of calcium ion in serous acinar cells. In contrast beta receptors affected by norepinephrine, and vasoactive intestinal polypeptide increases adenosine monophosphate in acinar cells and causes amylase rich secretion (4). Parasympathetic stimulation causes saliva with a low protein concentration and sympathetic stimulation may cause a high susceptibility to dryness by creating saliva rich in protein with less amount of saliva (5). Calcium agonists increase the volume of saliva (6-8). Aldosterone increases the potassium content of saliva while reducing the sodium content (9).

Dry eye prevalence varies between 5% to 35% (10) and incidence increases with age (11). It is more common in women (12). Tear drops consist of mucin, aqueous and lipid parts. Mucin secreted from goblet cells of conjunctiva spreads to hydrophobic surface of corneal epithelial cells. The aqueous portion is secreted from lacrimal glands. It contains lysozyme, lactoferrin, immunoglobulins and these serve to protect against microorganisms. The aqueous liquid helps the passage of oxygen to avascular cornea. The lipid part secreted from Meibomian glands provides some surface lubrication and prevents against evaporation. Normal tear secretion rate is 1.2  $\mu\text{l}/\text{min}$  and normal tear volume is 6.2  $\mu\text{l}$ . The 16% portion of tears changes for every minute (13). Dry points caused by some reasons like evaporation stimulates the nerve endings on the surface of the cornea, allows for the twinkle reflex. Contaminated mucin layer with the movement of the upper eyelid is transferred to the lower fornix and removed with the lacrimal drainage system. When the eyelids are opened, aqueous and lipid layers spread on the surface, creates a new layer of tears. Secretory functions of lacrimal glands are under the control of the autonomic nervous system. Parasympathetic nervous system stimulation of lacrimal glands increases secretion of water, protein and electrolytes but sympathetic nervous system stimulation decreases in opposite (14). Mediators which are involved in parasympathetic stimulation, show the effects by increasing the amount of intracellular calcium ion in secretory glands. It is shown that Sildenafil, a phosphodiesterase inhibitor, increased sympathetic activation (15) and block

calcium channels at heart muscle (16,17). Among 27,906 sildenafil users four individuals with keratoconjunctivitis sicca caused by sildenafil were stated on March 12, 2012 FDA report. Vitamin B12 deficiency causes degeneration at the dorsal and lateral corticospinal pathways due to defects in the synthesis of myelin. Vitamin B12 deficiency results in a symmetrical ataxia, weakness, spasticity, clonus in the arms and legs, as well as personality changes, irritability, dementia, memory loss, loss of vibration and position sense; sense of taste, smell and sight defects (18). Orthostatic hypotension, impotence, urinary retention, alongside constipation, diarrhea, atrophic glossitis; painful, smooth red tongue can be seen (19). Our goal is to draw attention to a phenomenon common in primary care "different etiological factors and treatment of mouth and eye dryness" with a case.

### Case

46 years old, unmarried men who suffer from dryness of the mouth and eyes admitted to our clinic. Complaints beginning approximately 45 days before the approval, he attended to doctor according to results of the Schirmer test and the doctor ordered the artificial eye drops treatment. Because of ongoing complaints patient is screened for Sjogren's syndrome by rheumatology section but did not take a diagnosis. Result of salivary gland biopsy taken by Ear, Nose and Throat department: "The number of focus/ investigated area ratio is not enough for Sjögren's syndrome" has been reported. Patient has history of taking Sildenafil 50 mg two tablets two months and four months ago. Gastric biopsy made due to reflux complaints was normal. He had history of 15 pack-years of smoking and quit smoking for two months. He uses alcohol as a social drinker, has an allergy to spring flowers and pollens. During the daytime patient attends the university and he is working at night. Patient was using artificial tears and cyclosporine eye drops for dry eyes. On physical examination he was anxious, tired looking, has hyperemic eyes, his skin moisturized. Blood pressure, body temperature and pulse of the patient was evaluated in the normal range, thyroid function tests were within normal limits. Vitamin B12 level was

216 pg/ml, so he was ordered vitamin B12 treatment. In the second month of treatment his dry mouth recovered but dry eye did not improve.

### Discussion

As we know calcium agonists increase the secretion of saliva (5); dryness of mouth and eye can be due to inhibitor effect of Sildenafil on calcium channels (16,17). Also Sildenafil's sympathetic stimulation on secretory glands (15) controlled by autonomic nervous system may contribute to the dryness of the mouth and eyes. Myelin synthesis defects due to a lack of vitamin B12 (18) causing deterioration of the parasympathetic nervous system may act on the glands may have led to the development of dry mouth and dry eye. The causes of eye dryness being rarely reported in Sildenafil users, and although vitamin B12 deficiency is common, lack of knowledge about dryness of the mouth and

eyes due to vitamin B12 deficiency; so we should mind that both sildenafil and vitamin B12 deficiency impairs neural stimulation via different mechanisms on glands showing their effect simultaneously together. After cessation of Sildenafil and starting vitamin B12 treatment, improvement in xerostomia was seen, but eye dryness did not improve. So this suggests that inflammation in dry eyes lasting for more than a month results in a permanent loss of function in the lacrimal glands (1).

Finally keeping in mind that multifactorial approach to primary care cases with mouth and eye dryness can contribute to prevent symptoms from being obstinate to avoid labour loss and to prevent wasting the economical sources.

*The summary of this article was presented as a poster on The Family Medicine Research Days in Istanbul, at 13-15 April 2012.*

### References

- Zoukhri D. Effect of inflammation on lachrymal gland function. *Exp Eye Res* 2006;82(5):885-98.
- Carlson GW. The salivary glands. embryology, anatomy, and surgical applications. *Surg Clin North Am* 2000;80(1):261-73.
- Romanenko VG, Nakamoto T, Srivastava A, Begenisich T, Melvin JE. Regulation of membrane potential and fluid secretion by Ca<sup>2+</sup>-activated K<sup>+</sup> channels in mouse submandibular glands. *J Physiol* 2007;581(Pt 2):801-17.
- Ono K, Inagaki T, Iida T, Hosokawa R, Inenaga K. Effects of pilocarpine and cevimeline on Ca<sup>2+</sup> mobilization in rat parotid acini and ducts. *J Med Invest* 2009;56(Suppl 1):375.
- Hattori T, Wang PL. Calcium antagonists cause dry mouth by inhibiting resting saliva secretion. *Life Sci* 2007;81(8):683-90.
- Tiffany JM. The normal tear film. *Dev Ophthalmol* 2008;41(1):1-20. doi: 10.1159/000131066
- Phillips BG, Kato M, Pesek CA, Winnicki M, Narkiewicz K, Davison D, et al. Sympathetic activation by sildenafil. *Circulation* 2000;102(25):3068-73.
- Chiang CE, Luk HN, Wang TM, Ding PY. Effects of sildenafil on cardiac repolarization. *Cardiovasc Res* 2002;55(2):290-9.
- Shinlapawittayatorn K, Chattipakorn S, Chattipakorn N. Effect of sildenafil citrate on the cardiovascular system. *Braz J Med Biol Res* 2005;38(9):1303-11.
- Dharmarajan TS, Norkus EP. Approaches to vitamin B12 deficiency; early treatment may prevent devastating complications. *Postgrad Med* 2001;110(1):99-105.
- Maralcan, M, Ellidokuz, E. Vitamin B12 deficiency [in Turkish]. *Güncel Gastroenteroloji* 2004;8(3):199-204.