New treatment of dry eye: the effect of calcium ointment through eyelid skin delivery

Kazuo Tsubota, Yu Monden, Yukiko Yagi, Eiki Goto, Shigeto Shimmura

Abstract

Aim—To demonstrate the efficacy of a petrolatum based calcium ointment applied to the lower lid skin in the management of dry eye.

Methods—In a controlled double masked study, the effects of water free petrolatum ointment containing calcium carbonate (10% w/w) on tear functional factors and ocular surface vital staining in dry eye patients were observed. Petrolatum without calcium carbonate served as control. Patients were instructed to place ointment to the lower lid skin twice a day. Evaluation of subjective complaints, fluorescein and rose bengal staining patterns, blink rate, tear evaporation and tear break up time (BUT) were performed before and 3 months after treatment. In order to demonstrate the movement of petrolatum from the skin to the tear film, petrolatum containing 1% sodium fluorescein was placed on the lower lid of four healthy volunteers, and the concentration of fluorescein in the tear film was followed up to 6 hours using an anterior fluorometer.

Results—Subjective symptoms significantly improved in both the calcium group ($p=0.001$) and control ($p=0.012$), while only the calcium group demonstrated a significant improvement in fluorescein ($p=0.043$), rose bengal ($p=0.021$) scores, and blink rate ($p=0.004$). Tear evaporation also significantly decreased in both the calcium group ($p=0.0004$) and control (0.043). BUT did not improve in either group.

Conclusion—Petrolatum based calcium ointment significantly improved symptoms, tear dynamics, and ocular surface staining in dry eye patients. However, some of the therapeutic effects may be due to lipids in the petrolatum vehicle. Petrolatum applied to the lower lid skin is an effective drug delivery system for slowly releasing drugs to the ocular surface.

(Br J Ophthalmol 1999;83:767-770)

or epidermal growth factor (EGF) are vital for the proper proliferation and differentiation of ocular surface epithelium.¹⁻⁵ When the tear supply is diminished, these components may not be adequately supplied to the ocular surface, especially in severe dry eye. A new hypothesis for the pathogenesis of dry eye includes the concept that the lack of tear components causes abnormal proliferation and differentiation of ocular surface epithelium.⁶ It is the common experience of many dry eye specialists that rose bengal and fluorescein staining patterns are worse in Sjögren's syndrome (SS) compared with non-SS dry eye, with increased lymphocyte infiltration as well as squamous metaplasia formation.^{7,8} Such differences cannot be explained by simple desiccation alone, and severe dry eye such as this seen in SS patients cannot be treated satisfactorily by artificial tear replacement or protective glasses.

Although various growth factors and cytokines have been given much attention, missing components may not be limited to proteins or vitamins, and may also include simple electrolyte ions. Tears contain ions which appear to be the main source of ions for the cornea and conjunctival epithelium. This hypothesis was proposed by MacKeen *et al*,⁹ Gilbard and Rossi,⁹ and Bernal and Ubels.¹¹ They emphasised that the ion content of tears play an important role in the maintenance of epithelium integrity. Since the calcium ion controls various gene expression as well as the formation of cell-cell adhesions^{12,13} this ion may be one of the most vital in tears involved in various physiological activities of the ocular surface. Recently MacKeen *et al* reported a unique drug delivery system that consists of applying petrolatum ointment vehicle to the lower eyelid, which melts at skin temperature and gradually moves over the skin onto the ocular surface; the movement of which was termed supracutaneous.¹⁴ In this paper, we have applied this method to continuously provide calcium ions to the tear meniscus for the treatment of dry eyes. In this study, a double masked study to test the efficacy of calcium ointment was performed, using the petrolatum ointment vehicle as control.

Department of
Ophthalmology, Tokyo
Dental College, Chiba,
Japan

K Tsubota
Y Yagi
E Goto
S Shimmura

Department of
Ophthalmology, Keio
University School of
Medicine, Tokyo, Japan

K Tsubota
E Goto
S Shimmura

Department of
Ophthalmology,
Kurume University
School of Medicine,
Kurume, Japan
Y Monden

Correspondence to:
Kazuo Tsubota, MD,
Department of
Ophthalmology, Tokyo
Dental College, 11-13
Sugano 5 Chome,
Ichikawa-shi, Chiba,
272-8513, Japan.

Accepted for publication
11 January 1999

Recent research on the interaction between tears and the ocular surface has revealed that important tear components such as vitamin A

Figure 1 Application of calcium ointment to the lower lid using a cotton tip applicator.

Materials and methods

SUPRACUTANEOUS DRUG DELIVERY

Calcium carbonate (10% w/w) was mixed with water free petrolatum ointment as previously reported.⁹ Water free petrolatum without calcium carbonate was used as control. The drug or control was dispensed randomly to the patients in a double masked manner so that neither patient nor doctor knew which ointment was used until the study was completed and the code broken. The lipid vehicle applied to the skin of the lower eyelids is transported supracutaneously to the inferior tear meniscus.¹⁴ Informed consent was obtained from all patients before the study, and the handling of human subjects complied with the tenets of the Declaration of Helsinki.

The patients were instructed to place ointment onto the lower lid skin twice a day (Fig 1) using a cotton tipped applicator. The test ointment used in this study was prepared according to the formulation as previously described by MacKeen *et al.*¹⁴ The evaluation of subjective complaints, ocular surface, and tear function tests were performed before the treatment and 3 months after the initiation of therapy.

In order to confirm the efficacy of supracutaneous delivery, four healthy volunteers were instructed to apply petrolatum ointment containing 1% sodium fluorescein to the lower eyelid as described. The intensity of fluorescein related fluorescence within the lower meniscus was measured quantitatively using an anterior fluorometer (FL 500, Kowa Company Ltd, Nagoya, Japan).

PATIENTS

Thirty six eyes of 18 patients with dry eye syndrome were recruited for this study, and treated with either calcium ointment or petrolatum vehicle only. Patients consisted of two males and 16 females with an average age of 55.1 (SD 10.5) years. Only patients with severe ocular complaints were recruited for this study owing to the fact that most patients with mild complaints did not want this additional treatment.

The diagnosis of dry eye was made by the dry eye criteria previously reported.¹⁵ Briefly, the diagnosis is based on the three criteria: (1) symptoms of dry eye, (2) abnormalities of tear dynamics determined by Schirmer test (5 mm), clearance test (8×), cotton thread test (10 mm), and tear break up time (BUT, 5

seconds), and (3) abnormalities of ocular surface determined by rose bengal (>3+) or fluorescein vital staining (>3+).^{8,15} When the patients met all three criteria, they were diagnosed as “definite dry eye”. Among the 18 dry eye patients, diagnosis of SS was made in seven patients according to Fox’s criteria.¹⁶

CLINICAL EVALUATION

Subjective complaints were evaluated by scores which the patients recorded on a scale of 0 to 100. The initial condition was scored as 100, and 0 signifies that no symptoms were present. To evaluate the effect of calcium ointment on the ocular surface, blink rates, tear evaporation, and tear BUT were used to analyse tear dynamics. Since the blink rate increases in dry eye because of increased stimulation or irritation,¹⁷ this factor can be useful in the evaluation of the ocular surface when the sensitivity of the cornea is intact. Corneal sensitivity was also measured by the Cochet-Bonnet aesthesiometer. One can expect a reduction in blink rate when the ocular surface irritation decreases. Since petrolatum is a lipid, a thicker lipid layer on the precorneal tear film may result in a decrease of tear evaporation. Tear evaporation was also measured quantitatively by the method we developed previously.¹⁸

The ocular surface was examined by a double staining method reported previously.¹⁹ In brief, 2 µl of preservative-free combined solution of 1% rose bengal and 1% fluorescein dye was instilled into the conjunctival sac. The severity of rose bengal staining was recorded in the temporal and nasal conjunctiva and the cornea, and then quantified on a scale of 0 to 3 points.²⁰ Thus, the maximum score obtained from the staining of one eye is 9. Fluorescein staining was graded in the cornea on a scale of 0 to 3 points for the top, middle, and bottom thirds of the cornea, for a total of 9 points.

Clinical evaluations were performed at the beginning of the study, and after 3 months of treatment. Statistical analysis was done by the Mann-Whitney U test for intergroup comparisons, and by Wilcoxon’s signed rank test for intragroup analysis for staining and symptom scores. Analysis for BUT, blink rate, and tear evaporation was done using the paired *t* test.

Results

SUPRACUTANEOUS DRUG DELIVERY

Application of petrolatum containing 1% sodium fluorescein to the lower lid increased fluorescein levels in the tear film for as long as 6 hours following application. An initial peak was observed at approximately 30 minutes, while concentrations at 6 hours were still at levels near 20% of peak concentration (Fig 2).

SUBJECTIVE SYMPTOMS

There were no significant differences in age or sex between the test and control groups. Tear function was also similar in both groups (Table 1). Corneal sensation did not change after 3 months’ use of calcium ointment or vehicle. The symptom score before treatment was standardised at 100, and significantly improved in both groups at the end of the study (Table 2).

Figure 2 Fluorescein levels in tear film of four healthy volunteers following application of 1% fluorescein ointment to the lower eye lid ($n=4$) (mean (SE)).

OBJECTIVE VARIABLES

Intergroup analysis did not reveal a significant difference in all objective factors between groups at the start of the study (Table 1). The blink rate was 67.0 (SD 24.3)/minute before the treatment in calcium ointment group. This frequency decreased significantly to 42.0 (19.9) after 3 months in the calcium ointment group. The vehicle also had a similar effect on blink rate (Table 2). Tear evaporation rate also showed a significant decrease at 3 months in both groups. Intergroup analysis of blink rate and tear evaporation did not reveal a significant difference. Both rose bengal and fluorescein staining of the ocular surface epithelium significantly decreased in the calcium ointment group, whereas no significant changes were observed in the control group (Table 2).

Discussion

A beneficial effect on the ocular surface was observed by the application of calcium ointment to the lower lid skin. Subjective grading scores improved in both the calcium ointment and vehicle groups. A decrease in tear evaporation rate was also observed in both groups, suggesting the petrolatum vehicle itself may have prevented desiccation from the pre-

corneal tear film. Among the objective clinical variables, improvements in vital staining scores were observed in the calcium ointment group only. This observation suggests that the addition of calcium offers an advantage over the application of petrolatum alone in terms of epithelial integrity. There were no complaints from either group concerning the use of ointment over the 3 month period, nor were any adverse effects observed related to the test ointment.

A recent hypothesis for the pathogenesis of dry eye⁶ proposes that in addition to simple desiccation, missing tear components may also contribute to the pathological changes of the ocular surface epithelium. Such tear components may include growth factors, vitamins, ions, or a combination of these factors. Since the calcium ion is one of the most important ions involved in the control of various cell functions, decreased calcium levels in the pre-corneal tear film may be involved in the pathogenesis of dry eye. Ubels *et al*²¹ reported the beneficial effect of artificial tears with bicarbonate ions. Gilbard and Rossi recently proposed the importance of other ions in artificial tears¹⁰; however, further studies are required to determine the precise roles of various ions in the tear film.

Vital staining with rose bengal and fluorescein only improved in patients receiving ointment containing calcium bicarbonate. Recent studies suggest that the ocular surface epithelium can express their own mucin such as Muc1.^{22 23} In addition to the mucin supplied by goblet cells, these transmembrane mucins may also have a role in maintaining the integrity of the ocular surface. In addition, it is well known that cell-cell adhesion mediated through cadherins or hemidesmosomes also require calcium.^{12 13} The improvement of the fluorescein staining may be mediated by the improvement in such intercellular junctions.

It is interesting to note that the vehicle group also had a beneficial effect on the treatment of subjective complaints and prevention of evaporation. Since the vehicle itself is lipophilic, interaction with the tear lipid layer may contribute to tear film stability. Thus the efficacy of calcium ointment may have been a combination of vehicle and calcium supply.

In summary, we have shown the beneficial effect of the application of calcium ointment via lower lid for the treatment of dry eye patients. Statistically significant improvements were observed in subjective symptoms, blink patterns, and vital staining of the ocular surface. We confirmed that petrolatum can reach the ocular surface supracutaneously, by simply applying a small amount of ointment to the lower eyelid. This mode of therapy is well tolerated by the patient, and provides a totally new therapeutic approach to providing steady levels of medication to the ocular surface. Although the number of patients and follow up periods in this study were limited, this treatment may offer additional benefits in the management of dry eyes.

Table 1 Age, tear function, and corneal sensitivity in the calcium ointment and control group

	Calcium ointment	Vehicle only
Age (male:female)	51.1 (11.4) (1:7)	59.8 (10.0) (1:9)
Schirmer test (mm)	5.9 (5.4)	5.4 (3.3)
Tear clearance	9.3+20.2-4.3	9.8+28.1-3.4
TFI	4.7+9.0-2.5	5.2+7.3-3.6
Cotton thread test (mm)	18.6 (6.5)	22.9 (6.5)
Corneal sensitivity (mm)	5.3 (1.1)	5.0 (1.0)

Table 2 Subjective and objective evaluation before and after calcium ointment application

	Calcium ointment			Vehicle only		
	Before	After	p value	Before	After	p value
Subjective	100	31 (19)	0.001	100	64 (27)	0.012
Blink (/min)	67.0 (24.3)	42.0 (19.9)	0.004	54.7 (23.4)	49.5 (18)	0.057
TEROS*	9.5 (6.6)	5.8 (4.3)	0.0004	7.8 (2.9)	4.5 (4.3)	0.043
BUT (s)	3.4 (2.2)	3.8 (2.7)	0.828	3.0 (1.7)	3.3 (1.5)	0.339
Rose bengal	4.0 (2.6)	2.6 (1.7)	0.021	3.4 (2.7)	3.3 (3.8)	0.917
Fluorescein	3.6 (2.2)	2.4 (2.2)	0.043	3.2 (2.6)	2.9 (2.9)	0.889

* 10^{-7} g/s.

This study was supported by grants from the Oral Health Science Center at Tokyo Dental College and from the Ministry of Health and Welfare. Support was also awarded by the Medical School Faculty and Alumni Grants of Keio University Medical Science Fund.

- 1 Tsubota K. The importance of the Schirmer test with nasal stimulation [letter]. *Am J Ophthalmol* 1991;111:106-8.
- 2 Ohashi Y, Motokura M, Kinoshita Y, et al. Presence of epidermal growth factor in human tears. *Invest Ophthalmol Vis Sci* 1989;30:1879-87.
- 3 van Setten G, Viinikka L, Tervo T. Epidermal growth factor is a constant component of normal human tear fluid. *Graefes Arch Clin Exp Ophthalmol* 1989;22:184-7.
- 4 Ubels J, Loley K, Rismondo V. Retinol secretion by the lacrimal gland. *Invest Ophthalmol Vis Sci* 1986;27:1261-9.
- 5 Wilson S. Lacrimal gland epidermal growth factor production and the ocular surface. *Am J Ophthalmol* 1991;111:763-5.
- 6 Tsubota K, Goto E, Fujita H, et al. Treatment of dry eye by autologous serum application in Sjögren's syndrome. *Br J Ophthalmol* 1999;83:390-5.
- 7 Tsubota K. SS dry eye and non-SS dry eye: what are the differences? In: Homma M, Sugai S, Tojo T, Miyasaka N, Akizuki M, eds. *Sjögren's syndrome*. Amsterdam: Kugler, 1994: 27-31.
- 8 Tsubota K, Toda I, Yagi Y, et al. Three different types of dry eye syndrome. *Cornea* 1994;13:202-9.
- 9 McKeen D, Roth H, Doane M. Ocular drug delivery by the lid (lower lid delivery). *Invest Ophthalmol Vis Sci* 1996;37: S77.
- 10 Gilbard J, Rossi S. An electrolyte-based solution that increases corneal glycogen and conjunctival goblet-cell density in a rabbit model for keratoconjunctivitis sicca. *Ophthalmology* 1992;99:600-4.
- 11 Bernal D, Ubels J. Artificial tear composition and promotion of recovery of the damaged corneal epithelium. *Cornea* 1993;12:115-20.
- 12 Schwarz MA, Owaribe K, Kartenbeck J, et al. Desmosomes and hemidesmosomes: constitutive molecular components. *Annu Rev Cell Biol* 1990;6:461-91.
- 13 Buxton RS, Magee AI. Structure and interactions of desmosomal and other cadherins. *Semin Cell Biol* 1992;3:157-67.
- 14 McKeen D, Roth H. Revolutionary method of ocular drug delivery. *Invest Ophthalmol Vis Sci* 1995;36:S166.
- 15 Toda I, Shimazaki J, Tsubota K. Dry eye with only decreased tear break-up time is sometimes associated with allergic conjunctivitis. *Ophthalmology* 1995;102:302-9.
- 16 Fox R, Saito I. Criteria for diagnosis of Sjögren's syndrome. *Rheum Dis Clin North Am* 1994;20:391-407.
- 17 Tsubota K, Hata S, Okusawa Y, et al. Quantitative videographic analysis of blinking in normal subjects and patients with dry eye. *Arch Ophthalmol* 1996;114:715-20.
- 18 Tsubota K, Yamada M. Tear evaporation from the ocular surface. *Invest Ophthalmol Vis Sci* 1992;33:2942-50.
- 19 Toda I, Tsubota K. Practical double vital staining for ocular surface evaluation. *Cornea* 1993;12:366-7.
- 20 Bisterveld O, Holland U. Diagnostic tests in sicca syndrome. *Arch Ophthalmol* 1969;82:10-4.
- 21 Ubels J, McCartney M, Lantz W, et al. Effects of preservative-free artificial tear solution on corneal epithelial structure and function. *Arch Ophthalmol* 1995;113:371-8.
- 22 Inatomi T, Spurr-Michaud S, Tisdale A, et al. Human corneal and conjunctival epithelia express MUC1 mucin. *Invest Ophthalmol Vis Sci* 1995;36:1818-27.
- 23 Inatomi T, Spurr-Michaud S, Tisdale A, et al. Expression of secretory mucin genes by human conjunctival epithelia. *Invest Ophthalmol Vis Sci* 1996;37:1684-92.