Current Eye Research, 2013; 38(2): 229–236
© Informa Healthcare USA, Inc.
ISSN: 0271-3683 print / 1460-2202 online
DOI: 10.3109/02713683.2012.757323

informa
healthcare

ORIGINAL ARTICLE

Effectiveness of Dry Eye Therapy Under Conditions of Environmental Stress

Alan Tomlinson[1], Louise C. Madden[1], and Peter A. Simmons[2]

[1]*Vision Sciences, Glasgow Caledonian University, Glasgow, UK and* [2]*Consumer Eye Care Research & Development, Allergan LLC, Irvine, CA, USA*

ABSTRACT

Purpose: Dry eye is often characterized by increased tear evaporation due to poor tear film quality, especially of the lipid component of the tear film. Using an environmental chamber to induce environmental stress, this study compared the effect of three lubricant eye drops on various aspects of tear physiology in a crossover design (evaporation was the principal outcome measure).

Methods: Three eye drop formulas were tested: 0.5% carmellose sodium (Drop C), 0.5% carmellose sodium with added lipid (Drop C-L) and 1.0% glycerine with added lipid (Drop G-L). Nineteen control and 18 dry eye subjects used each product for 2 weeks, three times per day, in a random order, with a minimum 1-week washout between treatment periods. Tear evaporation, break up time, osmolarity, tear structure (by interferometry) and patient symptoms were assessed with the subjects adapted for 10 min in an environmental chamber controlled at 20% relative humidity and 22 °C. The treatment effects were analyzed using general linear model repeated measures analyses of variance.

Results: In dry eye subjects, evaporation, break up time, osmolarity and symptoms improved for all formulas ($p < 0.05$). Normal subjects showed some improvements: evaporation with C-L, osmolarity with C and symptoms with C-L and G-L. Change in evaporation was greater for both C-L and G-L versus C ($p < 0.05$), and there was a trend for C-L to reduce evaporation more than G-L ($p < 0.11$). There were no significant treatment effects on tear film structure.

Conclusion: Overall, the eye drop formula containing both carmellose sodium and lipid (C-L) produced a greater treatment effect on tear evaporation than the other formulations containing only one of these ingredients. This study also demonstrates the utility of a controlled environmental chamber in showing the difference in performance between dry eye treatments.

Keywords: Dry eye therapy, environment, humidity

INTRODUCTION

Dry eye disease, a complex group of conditions, is characterized by a dysfunction of one or more of the components of the tear film, and in 60% or more of patients there is the condition of evaporative dry eye.[1] Often exacerbated by adverse environmental conditions such as prolonged visual display unit use, low relative humidity (RH) and/or excessive wind or air conditioning,[2–5] studies have shown that such environments cause an increased rate of evaporation of the ocular surface tear film in both dry eye[6] and normal subjects.[7]

To fully understand the effect of the environment (specifically RH and temperature) on tear physiology, it is vital to control exposure conditions. Environment chambers work well in this instance, by controlling environmental stress (i.e. lowering RH) and can be used to assess the robustness of therapeutic interventions.[5,8–10]

Many dry eye sufferers find symptomatic relief of environmental dry eye symptoms through the use of ocular lubricants.[11–15] There are many ocular therapeutics on the market, with varying compositions. Some formulations contain an oil-in-water emulsion, intended to replenish both aqueous and lipid

Received 20 August 2012; revised 21 November 2012; accepted 25 November 2012; published online 4 January 2013

Correspondence: Alan Tomlinson, Department of Vision Sciences, Glasgow Caledonian University, 30 Cowcaddens Road, Glasgow G4 0BA, USA. Tel: +0044 141 331. E-mail: a.tomlinson@gcu.ac.uk

components of the tear film, leading to greater stability and a longer-lasting therapeutic benefit. This is achieved by the production of a more stable oily layer at the air–tear interface, to help prevent the evaporation of existing tears.[12,16,17]

The rationale of this study was to ascertain the therapeutic effect of chronic application (three times daily for 2 weeks) of three distinct types of artificial tear formulas: (1) a standard aqueous drop containing 0.5% carmellose sodium (Drop ''C''); (2) a drop with the same 0.5% carmellose sodium with added lipid (Drop ''C-L'') and (3) a drop without a lubricant polymer, containing 1.0% glycerine with added lipid (Drop ''G-L''). These were tested in dry eye and normal subjects exposed to conditions of environmental stress (low RH). The effects were assessed in terms of changes in symptoms and tear physiology, with tear film evaporation as the principal outcome measure.

METHODS AND MATERIALS

Study Design

This study was three-armed, crossover and double blind in design. It was conducted according to the principles contained in the Declaration of Helsinki. Ethical approval was obtained from the Glasgow Caledonian University Ethics Committee, the Regional Ethics Committee (South East Scotland Research Ethics Committee 2) as well as the Medicines and Healthcare products Regulatory Agency of the United Kingdom (MHRA (Ref CI/2011/0007)). Written informed consent was obtained from all participants after explanation of the study procedures and requirements.

Subject Enrollment

Participants were initially enrolled by poster advertisement. Two groups of participants were recruited; those with dry eye and a group of age- and sex-matched normal controls. The initial dry eye inclusion criteria were <10 s using a Hir-Cal grid for non-invasive tear break-up time (NITBUT);[18] and <10 mm in 5 min for Schirmer (without anesthetic). The Schirmer value of less than 10 mm was in order to include mild dry eye cases. Our cutoff of 10 mm represents a severity level 2 in the DEWS Report. A cutoff of 5 mm is a level 3 or severe/Sjogren's dry eye. In addition, a grade of 1, 2 or 5 using the grading scale of Thai et al.[19] for thin-film interferometry and a score of ≥10 on the OSDI Questionnaire.[20] All test results had to exceed the above values. A negative response to any of these tests placed participants in the ''normal'' category.

A total of 38 participants were recruited for the study, 19 in each group (based on a power calculation (http://www.cs.uiowa.edu/~rlenth/Power/) obtained from pilot data from a previous study).[21] Due to loss to follow up, the final number included in the analysis was 37; 19 controls (7 male, 12 female; mean age ± SD 30 ± 12 years) and 18 dry eye participants (7 male, 11 female; mean age ± SD 41 ± 14 years).

Environmental Conditions

Participants were subjected to conditions in a controlled environment chamber (Weiss Gallenkamp, Loughborough, UK) located in Vision Sciences at Glasgow Caledonian University, Glasgow, UK. The environmental chamber is an isolated room 2.19 m wide, 2.3 m deep and 2.3 m high in which temperature and RH can be controlled between 5 °C and 35 °C and 5–95%. All measures were carried out after patient adaptation periods of 10 min to environmental conditions of 22 °C at a RH level of 20%.[21] These conditions differed from those normally found in the United Kingdom where ambient external humidity levels are between 70% and 90% (Met Office – MIDAS Land Surfac http://badc.nerc.ac.uk/view/badc.nerc.ac.uk__ATOM__dataent_ukmo-midas) and internal levels within our facility between 35% and 50% RH. Therefore the study conditions stressed the tear film, particularly of dry eye patients, leading to an increase in evaporation of around 33%.[22,23] The chamber's low environmental condition could have had an effect on tear film osmolarity (presumably higher in most subjects due to increased evaporation), but this effect should be equal between conditions for each subject (the advantage of a crossover design) and is unlikely to have affected the conclusions of the study.

Test Parameters

Tear Film Evaporation

Tear film evaporation rate was determined with a Servo-Med EP-Evaporimeter.[24] This measures the RH and temperature at two sensors separated by a known distance, above the evaporative surface. The ocular surface evaporation was calculated from measurements of fluid loss with the eyes open and closed to eradicate the contribution of sweat from the facial skin in the eye region.

Interferometry

The structure and quality of the tear film was assessed by observing the interference fringes of the lipid layer and recorded with a miniature slow motion video camera.[19] The grading scale developed previously in

our laboratory by Thai et al.[19] was utilized to grade the tear film distribution.

Non-invasive Tear Break Up Time
The HIR-CAL grid system[18] based on a modified Bausch and Lomb keratometer was used to measure a non-invasive tear break up time. The HIR-CAL grid was focused on the pre-corneal tear film and the time before the first distortion of the grid image was observed: three measurements were taken and the mean calculated.

Osmolarity
Tear osmolarity was measured using the OcuSense TearLab Osmometer.[25] Employing a single use, disposable test card mounted to a collection pen, tear samples are obtained by passive capillary action from the inferior-temporal tear meniscus. The pen monitored the collection process and provided an audible and visual signal when the sample of tear was complete. The pen was then docked into the reader, which calculated and displayed the osmolarity result.[25] All subjects had their osmolarity measured on both eyes at the first visit. The eye with the higher recording at that time was designated as the ''test eye'' and was measured at all subsequent visits.

Questionnaire
Symptomatology was evaluated with the validated OSDI questionnaire.[20] This is made up of 12 questions relating to dry eye symptoms, and assesses these on a scale of 0 to 100, with higher scores representing greater disability. A cut of score of $\geq$10 was used for dry eye symptoms.[20]

Study Protocol
Once enrolled in the study, the participants were randomly allocated the use of each of three drops; C (0.5% carmellose sodium (Refresh Tears® Lubricant Eye Drops, Allergan, USA)), C-L (0.5% carmellose sodium with added lipid (Optive Plus™ Lubricant Eye Drops, Allergan, USA)) or G-L (1.0% glycerine with added lipid (Refresh Ultra® Lubricant Eye Drops, Allergan, USA)). Participants used each product for 2 weeks, three times per day, with a minimum 1-week washout between treatment periods. All test parameters were measured at baseline and at 14 ± 2 days after initial use of each of the drops. At least 1 h had elapsed since the last drop instillation and all measurements were taken between 10 am and 4 pm.

Statistical Analysis

All statistical analyses were performed with the SPSS Version 18 (SPSS Inc., IBM Software, Portsmouth, UK) statistical software package. Descriptive statistics (reported as means $\pm$ standard deviation) were completed. To determine the relationship of the tear physiology measures before and after treatment with each of the three solutions, repeated measures analyses of variance (ANOVA) were used. Shapiro–Wilk normality testing was carried out before ANOVA was applied. Data was found to be normally distributed in this study, a general linear model (GLM) was adopted with the symptoms or tear physiology measures as the between-effect variables and time and patient type (dry eye or control) as the within-effect variable. These analyses allowed comparisons of the effect of treatment on individual physiological measures, as well as comparisons between therapies.

RESULTS

Comparisons of Symptoms and Tear Physiology Measures Before and After Treatment

A pattern of improvement in the tear physiology measures was observed over the treatment periods with all the solutions (Tables 1 and 2).

Comparisons of the tear physiology measures before and after treatment with the three solutions showed significant statistical changes *after* treatment for the following: (decreased) tear evaporation rate (with Drop C-L in controls ($p = 0.010$) and all solutions in dry eye ($p = 0.0001$) (Figure 1); (improved) symptoms (OSDI score) (with Drop C-L ($p = 0.013$) and Drop G-L ($p = 0.011$) in controls and all solutions for dry eye ($p = 0.001$); NITBUT (no change in controls and all solutions in dry eye (Drop C ($p < 0.0001$), Drop C-L ($p = 0.002$) and Drop G-L ($p = 0.008$)) (reduced) are osmolarity (Drop C for controls ($p = 0.031$) and all solutions for dry eye (Drop C = 0.003, Drop C-L ($p < 0.0001$) and Drop G-L ($p = 0.001$)). No significant changes in the tear stability by interferometry were found for either subject group with any treatment ($p > 0.05$).

Comparison of the Effects of Different Treatments on Symptoms and Tear Physiology Measures

Statistical analyses of the effectiveness of treatments with the three formulas for all participants were undertaken by applying a GLM repeated measure ANOVA (Table 3 and Figure 2).

Significant differences between the effects of the study treatments were found only for changes in tear evaporation rate; evaporation change (decrease) was greater with Drop C-L compared to Drop C ($p < 0.0001$) and with Drop G-L compared to Drop C ($p = 0.016$). The change (decrease) with Drop C-L

TABLE 1. Pre and post symptoms and tear physiology measures (mean ± SD) for the dry eye group ($N = 18$) with each therapy.

	Drop C		Drop C-L		Drop G-L	
	DE		DE		DE	
	Pre	Post	Pre	Post	Pre	Post
Evaporation ($g/m^2/s$)	49.91 ± 24.18	38.78 ± 18.91	50.29 ± 19.86	29.21 ± 13.6	54.99 ± 22.24	35.68 ± 15.84
NITBUT (s)	6.33 ± 2.16	8.69 ± 2.31	6.55 ± 2.50	9.88 ± 3.77	6.92 ± 1.24	8.66 ± 2.35
Interferometry (Grade)	1.39 ± 0.69	1.94 ± 1.30	1.72 ± 0.89	2.22 ± 1.35	1.28 ± 0.57	2.06 ± 1.30
Osmolarity (Osm)	329 ± 7	314 ± 16	326 ± 6	302 ± 12	329 ± 18	307 ± 15
Symptoms (OSDI score)	23.1 ± 15.3	15.9 ± 9.29	22.8 ± 14.8	12.2 ± 8.73	21.4 ± 13.8	13.8 ± 9.35

TABLE 2. Pre and post symptoms and tear physiology measures (mean ± SD) for the control group ($N = 19$) with each therapy.

	Drop C		Drop C-L		Drop G-L	
	Controls		Controls		Controls	
	Pre	Post	Pre	Post	Pre	Post
Evaporation ($g/m^2/s$)	16.88 ± 8.55	18.06 ± 13.83	15.68 ± 7.43	11.22 ± 4.66	14.95 ± 6.40	15.39 ± 10.93
NITBUT (s)	15.78 ± 4.78	15.52 ± 7.02	17.10 ± 4.29	18.05 ± 8.18	15.47 ± 4.18	14.57 ± 7.58
Interferometry (Grade)	3.79 ± 0.42	3.94 ± 2.61	3.68 ± 0.48	3.78 ± 0.42	3.63 ± 0.76	3.26 ± 1.14
Osmolarity (Osm)	305 ± 20.6	295 ± 9.5	299 ± 16	296 ± 11	297 ± 22	302 ± 9.5
Symptoms (OSDI score)	4.17 ± 4.17	2.85 ± 2.96	5.59 ± 5.14	1.97 ± 2.35	3.73 ± 3.44	1.64 ± 2.36

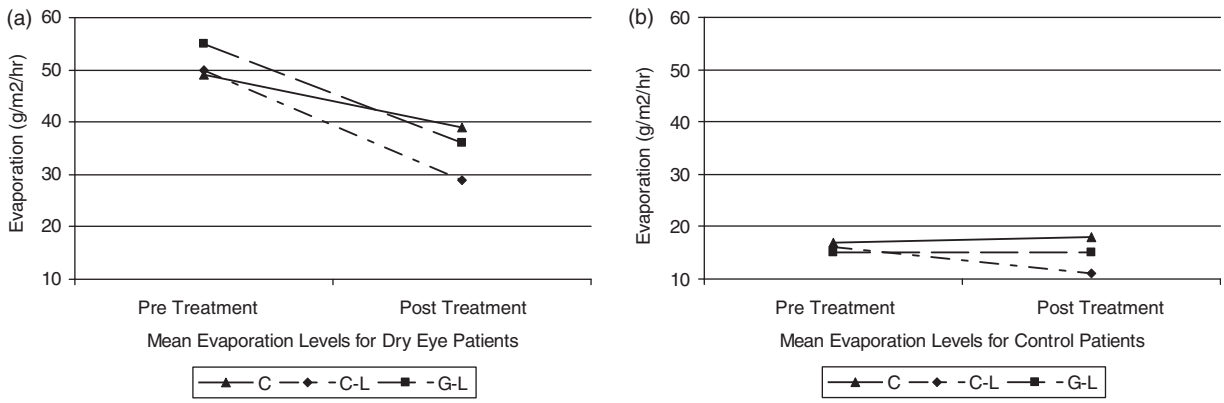

FIGURE 1. Estimated marginal means of evaporation rate pre and post treatment for each therapy. (a) Dry eye patient data. (b) Control patient data. The before and after data for other measures can be seen in Tables 1 and 2.

TABLE 3. Change in symptoms and tear physiology measures (mean ± SD of difference of pre–post therapy values for each subject) with each therapy.

	Drop C		Drop C-L		Drop G-L	
	DE	Control	DE	Control	DE	Control
Evaporation	11.12 ± 10.58	−1.17 ± 7.83	21.07 ± 10.91	4.45 ± 6.69	19.31 ± 13.52	−0.43 ± 9.63
NITBUT	−2.36 ± 2.12	0.26 ± 4.65	−3.3 ± 3.98	−0.95 ± 8.31	−1.75 ± 2.45	0.89 ± 8.75
Interferometry	−0.55 ± 1.42	−0.15 ± 2.60	−0.50 ± 1.65	−0.10 ± 0.57	−0.77 ± 1.59	0.37 ± 0.95
Osmolarity (Osm)	15.39 ± 8.65	10.58 ± 11.05	23.78 ± 6.24	4.95 ± 4.77	22.45 ± 2.42	−4.64 ± 12.77
Symptoms (OSDI score)	7.29 ± 5.98	1.32 ± 1.2	8.68 ± 6.05	3.62 ± 3.78	7.64 ± 4.47	2.08 ± 1.08

These changes are shown for the dry eye ($N = 18$) and control ($N = 19$) groups.

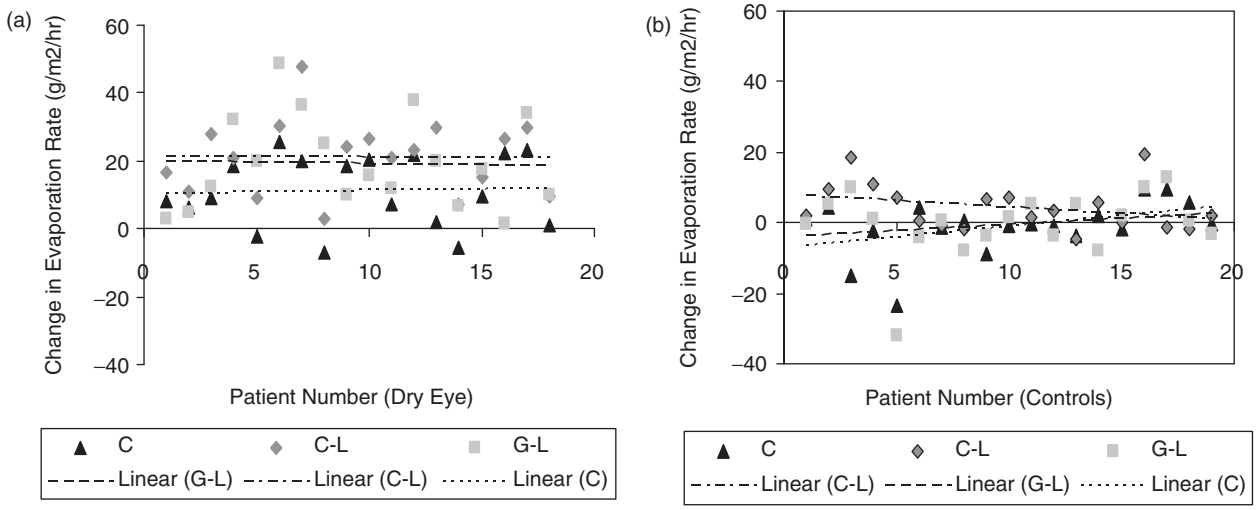

FIGURE 2. A comparison of the differences between treatment effects of solutions (change in evaporation) pre- and post treatment. (a) Dry eye patient data. (b) Control patient data. Dashed lines show regression line for each treatment.

compared to Drop G-L was significant at the 11% level ($p = 0.105$).

Statistical comparisons of the treatment effects of the solutions when used by dry eye patients alone showed a significantly greater reduction in evaporation with Drop C-L ($p < 0.0001$) and Drop G-L ($p < 0.0001$) than with Drop C (Figure 2).

DISCUSSION

Dry eye in the majority of cases is characterized by increased tear film evaporation – particularly in evaporative dry eye, but it is also a feature of many cases of aqueous deficiency dry eye.[1,22,23] This increase is due to poor tear film quality, especially of the lipid component of the tears. This inability of the lipid layer to effectively prevent tear fluid loss from the ocular surface is exacerbated by adverse environmental conditions such as low humidity. Dry eye patients are frequently prescribed artificial tears to help supplement the reduced volume of the tears in the dry eye. These supplements can take a number of forms[26,27] some of which are intended to enhance the lipid layer of the tear film. The primary objective of this study was to compare the effect of sustained treatment with three forms of lubricant eye drops on tear physiology and patient symptoms in normal control and dry eye subjects. Tear film evaporation was the principal outcome measure in the study.

The use of all formulations significantly improved tear evaporation rate, tear break up time, osmolarity and symptoms in dry eye patients – in line with other recent studies.[28] Some improvements may also be seen in control subjects.[11,16] To determine the differential effects of treatment with Drop C, Drop C-L and Drop G-L, the changes in tear parameters, post treatment were compared. The change in evaporation was greater for both Drop C-L (42%) and Drop G-L (34%) than Drop C (22%, $p < 0.05$), and there was a trend for Drop C-L to reduce evaporation more than Drop G-L ($p < 0.10$). There were no significant differential treatment effects on the tear film structure (by interferometry) or osmolarity.

The observed decrease in evaporation of up to 42% as a result of the frequent use of eye drops containing a lipid component supports the therapeutic strategy of inhibiting excess evaporation through enhancement of the layer. In prior studies of changes in tear film evaporation, some aqueous drops of varying composition have demonstrated reductions similar to our finding of 22%. McCann et al.[16] found a significant reduction over a 3-month period in tear evaporation with a sodium hyaluronate solution by ~26%, an hydroxypropyl methylcellulose (HPMC) containing solution reducing evaporation by ~21%; and Uchiyama et al.[29] reported a 13.2% reduction in tear film evaporation rate at 25–35% RH following a single application of a HP-Guar containing drop. In contrast, Khanal et al.[30] reported a 7% increase in evaporation following 1 month of use of a Hypromellose eye drop.

With lipid-containing drops, prior reports have shown some similarity to the present findings: McCann et al.[16] observed a 45% reduction with an emulsion drop from a high baseline value; while Khanal et al.[30] reported 22% reduction with a formula similar to the presently-tested G-L under ambient environment test conditions.

The target reduction in evaporation sought in therapy for dry eye is in the order of 46% for evaporative cases and 24% in aqueous tear deficiency; this is based upon a recent meta-analysis of the inputs and outputs of the lacrimal system indicating that the evaporation rates in the normal average $13.57 \times 10{-}7$ g/cm^2/s, those for aqueous tear deficiency $17.91 \times 10{-}7$ g/cm^2/s, and in evaporative dry

$25.34 \times 10{-}7\ g/cm^2/s$.[22] Thus, the current observation of 42% reduction with Drop C-L under stressed conditions should provide a clinically useful improvement in tear film function.

Both of the tested lipid-based formulas, C-L and G-L, contain the same lipid, castor oil; the key difference in the case of C-L may be the presence of the established demulcent polymer carmellose sodium (although there are other differences in excipients). In prior studies, carmellose sodium has been shown to improve signs and symptoms of dry eye[31,32] and has demonstrated some superiority over other polymeric demulcents, including hyaluronic acid solutions.[33] It is likely that the presence of carmellose sodium in the C-L formula has improved overall tear stability, as demonstrated in these earlier studies, leading to additional positive effects on tear evaporation.

It is not clear from the current literature what the optimum type or amount of lipid should be in a lubricant eye drop designed to enhance the lipid layer in evaporative dry eye patients. In the current investigation, Drop C-L contains the same type (castor oil) but less total quantity as drop G-L, suggesting that only a relatively small amount of lipid may be needed to adequately improve lipid layer function. Other lipid formulations have made use of mixtures of mineral oils (Soothe, Bausch & Lomb. Rochester, NY, USA; Systane Balance, Alcon, Fort Worth, TX, USA), or alternatively soybean oil and phospholipid (Emustil, SIFI). Clinical comparisons between these formulas have been limited: Scaffidi and Korb[34] did demonstrate greater lipid layer thickening with a 5.5% mineral oil emulsion compared with a 1.25% castor oil emulsion, at least over a relatively brief time after drop instillation. However, no differences in overall clinical benefit were reported in that contra lateral eye study. Clearly, further comparative work addressing the effect of lipid containing tear supplements on standard signs and symptoms of dry eye would be useful.

The literature reports that the thickness of the lipid layer in the healthy eye ranges between 50 and 180 nm.[35,36] Similarly, the exposed area of ocular surface has been reported to range from 2.25 to 3.75 cm.[2,37] Therefore by simple calculation, the total volume of lipid in the tear film of the healthy eye ranges from approximately 0.01 to 0.07 μL. In a 50 μL eye drop, this amount is equivalent to a lipid content of 0.15% by volume (or less); therefore formulations containing 1% lipid or greater may be supplying excess lipid that could contribute to blur or irritation. In a recent multi-center clinical trial comparing the overall clinical performance of formula C-L with G-L (reported at ARVO 2012 by Simmons et al.[21]), reports of blur, visual disturbance and instillation site pain or discomfort were reduced with C-L (with <1% oil) versus G-L (with >1.0% oil).

The present study demonstrated a reduction in osmolarity in dry eye subjects with all therapies, with Drop C-L showing the greatest decrease (7%; from 326 mOsm/l to 302 mOsm/l). This reduction in osmolarity with therapeutic intervention correlates well with a recent study, which reported a 9% reduction in variation of osmolarity from 341 to 307 mOsm/l post treatment (cyclosporine A) over a 3-month study period.[28] Of the 18 dry eye subjects participating in this study, all demonstrated a response to each therapy (Drop C, Drop C-L and Drop G-L) by a decline in tear hyper-osmolarity; with a large proportion demonstrating a ''normalization'' of osmolarity (<308 mOsm/l) after 3 months of treatment (respectively 38%; 56% and 56% of dry eye patients had iso-osmolarity with Drop C, Drop C-L and Drop G-L). This agrees with previous reports examining the clinical utility and variability of objective tests over time, and supports the hypothesis that efficacious dry eye therapy should achieve a stable and low tear film osmolarity.[28]

In contrast, for normal subjects, changes with treatment in osmolarity varied greatly, from a decrease of 10.58 mOsm in the C group to an increase of 4.64 mOsm in the G-L group, with a high degree of variability. Under the conditions of environmental stress used in the present study, this suggests that there may be considerable variability in the degree of adaptability of the lacrimal feedback system in these normal subjects.

Previous reports have shown tear osmolarity reduction after therapy can be accompanied by an improvement in symptoms.[28,38] This was also shown in the present study, with all formulations improving patient symptoms, particularly those complaining of dry eye. The improvement in OSDI scores was found to be higher with Drop C-L than with the other two therapies, in both dry eye and control patients. As in the tear evaporation results, this may be due to the inclusion of both carmellose sodium and lipid in this formula. Further, the reduced level of lipid in this eye drop compared to other formulas may have improved its level of patient acceptance and tolerability, as reported in larger clinical trials with the same formula.[39]

CONCLUSION

Overall, the eye drop formula containing both carmellose sodium and lipid produced a greater treatment effect as measured by decreased tear film evaporation than the other solutions containing only one of these ingredients. This study also demonstrates the utility of a controlled environmental chamber in providing the ''stress test conditions'' for investigating the differences in in-eye performance of dry eye therapies.

DECLARATION OF INTEREST

This work was supported by an unrestricted research grant to Professor Tomlinson from Allergan LLC.

REFERENCES

1. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea 2012; 31(5):472–8.
2. Schlote T, Kadner G, Freudenthaler N. Marked reduction and distinct patterns of eye blinking in patients with moderately dry eyes during video display terminal use. Graefes Arch Clin Exp Ophthalmol 2004;242:306–312.
3. Backman H, Haghighat F. Indoor-air quality and ocular discomfort. J Am Optom Assoc 1999;70:309–316.
4. Abelson MB, Ousler 3rd GW, Nally LA, Welch D, Krenzer K. Alternative reference values for tear film break up time in normal and dry eye populations. Adv Exp Med Biol 2002;506:1121–1125.
5. Ousler 3rd GW, Abelson MB, Nally LA, Welch D, Casavant JS. Evaluation of the time to ''natural compensation'' in normal and dry eye subject populations during exposure to a controlled adverse environment. Adv Exp Med Biol 2002;506:1057–1063.
6. McCulley JP, Aronowicz JD, Uchiyama E, Shine WE, Butovich IA. Correlations in a change in aqueous tear evaporation with a change in relative humidity and the impact. Am J Ophthalmol 2006;141:758–760.
7. Uchiyama E, Aronowicz JD, Butovich IA, McCulley JP. Increased evaporative rates in laboratory testing conditions simulating airplane cabin relative humidity: an important factor for dry eye syndrome. Eye Contact Lens 2007;33:174–176.
8. Abelson MB, Ousler 3rd GW, Nally LA, Emory TB. Dry eye syndromes: diagnosis, clinical trials and pharmaceutical treatment–'improving clinical trials'. Adv Exp Med Biol 2002;506:1079–1086.
9. Abelson MB, Kaplan AP. A randomized, double-blind, placebo-controlled comparison of emedastine 0.05% ophthalmic solution with loratadine 10 mg and their combination in the human conjunctival allergen challenge model. Clin Ther 2002;24:445–456.
10. González-García MJ, González-Sáiz A, de la Fuente B, Morilla-Grasa A, Mayo-Iscar A, San-José J, et al. Exposure to a controlled adverse environment impairs the ocular surface of subjects with minimally symptomatic dry eye. Invest Ophthalmol Vis Sci 2007;48:4026–4032.
11. Khanal S, Simmons PA, Pearce EI, Day M, Tomlinson A. Effect of artificial tears on tear stress test. Optom Vis Sci 2008;85:732–739.
12. Khanal S, Tomlinson A, Pearce EI, Simmons P. Effect of an oil in water emulsion on the tear physiology of patients with mild to moderate dry eye. Cornea 2007;26:175–181.
13. Korb DR, Scaffidi RC, Greiner JV, Kenyon KR, Herman JP, Blackie CA, et al. The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms. Optom Vis Sci 2005;82:594–601.
14. Nepp J, Schauersberger J, Schild G, Jandrasits K, Haslinger-Akramian J, Derbolav A, et al. The clinical use of viscoelastic artificial tears and sodium chloride in dry-eye syndrome. Biomaterials 2001;22:3305–3310.
15. Prabhasawat P, Tesavibul N, Kasetsuwan N. Performance profile of sodium hyaluronate in patients with lipid tear deficiency: randomised, double-blind, controlled, exploratory study. Br J Ophthalmol 2007;91:47–50.
16. McCann LC, Tomlinson A, Pearce EI, Papa V. Effectiveness of artificial tears in the management of evaporative dry eye. Cornea 2012;31(1):1–5.
17. Pearce EI, Tomlinson A, Blades KJ, Falkenberg HK, Lindsay B, Wilson CG. Effect of an oil and water emulsion on tear evaporation rate. Adv Exp Med Biol 2002;506:419–423.
18. Hirji N, Patel S, Callander M. Human tear film pre-rupture phase time (TP-RPT) – a non-invasive technique for evaluating the pre-corneal tear film using a novel keratometer mire. Ophthalmic Physiol Opt 1989;9:139–142.
19. Thai LC, Tomlinson A, Simmons PA. In vitro and in vivo effects of a lubricant in a contact lens solution. Ophthalmic Physiol Opt 2002;22:319–329.
20. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118(5):615–21.
21. Madden LC, Tomlinson A, Simmons PA. Effect of Humidity Varations in a Controlled Environment Chamber on Human Tear Evaporation Rate Following Dry Eye Therapy. Eye and Contact Lens, in press.
22. Khanal S, Tomlinson A, Diaper CJ. Tear physiology of aqueous deficiency and evaporative dry eye. Optom Vis Sci 2009;86:1235–1240.
23. Tomlinson A, Doane MG, McFadyen A. Inputs and outputs of the lacrimal system: review of production and evaporative loss. Ocul Surf 2009;7:186–198.
24. Trees GR, Tomlinson A. Effect of artificial tear solutions and saline on tear film evaporation. Optom Vis Sci 1990;67:886–890.
25. Sullivan B. Clinical resorts of a first generation lab-on-chip nanolitre tear film osmometer. Ocul Surf 2005;3:S117.
26. Foulks GN. DEWS report. Ocular Surf 2007;5, in press.
27. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci 2011;52(4):2050–2064.
28. Sullivan BD, Crews LA, Sönmez B, de la Paz MF, Comert E, Charoenrook V,et al. Clinical Utility of Objective Tests for Dry Eye Disease: Variability Over Time and Implications for Clinical Trials. Cornea 2012;31:1000–8.
29. Uchiyama E, Di Pascuale MA, Butovich IA, McCulley JP. Impact on ocular surface evaporation of an artificial tear solution containing hydroxypropyl guar. Eye Contact Lens 2008;34:331–334.
30. Khanal S, Tomlinson A, Pearce EI, Simmons PA. Effect of an oil-in-water emulsion on the tear physiology of patients with mild to moderate dry eye. Cornea 2007;26:175–181.
31. Grene RB, Lankston P, Mordaunt J, Harrold M, Gwon A, Jones R. Unpreserved carboxymethylcellulose artificial tears evaluated in patients with keratoconjunctivitis sicca. Cornea 1992;11:294–301.
32. Simmons PA, Vehige JG. Clinical performance of a mid-viscosity artificial tear for dry eye treatment. Cornea 2007;26:294–302.
33. Guillon M, Maissa C, Ho S. Evaluation of the effects on conjunctival tissues of Optive eyedrops over one month usage. Cont Lens Anterior Eye 2010;33(2):93–9.
34. Scaffidi RC, Korb DR. Comparison of the efficacy of two lipid emulsion eyedrops in increasing tear film lipid layer thickness. Eye Contact Lens 2007;33:38–44.
35. Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. Adv Exp Med Biol 1994;350:293–298.

36. Korb DR, Greiner JV, Glonek T, Whalen A, Hearn SL, Esway JE, et al. Human and rabbit lipid layer and interference pattern observations. Adv Exp Med Biol 1998;438:305–308.
37. Tiffany JM, Todd BS, Baker MR. Computer-assisted calculation of exposed area of the human eye. Adv Exp Med Biol 1998;438:433–439.
38. Nelson JD, Farris RL. Sodium hyaluronate and polyvinyl alcohol artificial tear preparations: a comparison in patients with keratoconjunctivitis sicca. Arch Ophthalmol 1988;106:484–487.
39. Simmons PA, Carlisle-Wilcox C, Beard B, Chen R, Liu H, Vehige JG, et al. Mechanism of lipid release and clinical performance of an advanced lipid-containing artificial tear formulation (E Abstract 2361). The association for research in vision and ophthalmology. Vol. 53, 6–10 May, Fort Lauderdale, FL: Invest Ophthalmol Vis Sci; 2012.