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Effect of castor oil emulsion eyedrops on tear film composition and stability☆

Cécile Maïssa [a,*], Michel Guillon [a], Peter Simmons [b], Joseph Vehige [b]

[a] OTG Research & Consultancy, London, UK
[b] Allergan, Irvine, CA, USA

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ABSTRACT

Purpose: An emulsion eyedrop containing castor oil has been shown to modify the tear film lipid layer and increase tear film stability. The primary objectives of this investigation were to measure the prevalence of castor oil in the tear fluid over time and quantify the effects on the lipid layer. A secondary objective was to quantify the initial effects on ocular symptomatology.

Methods: The investigation was an open label pilot study on 5 normal and 10 dry eye subjects. A single eyedrop (Castor oil emulsion, Allergan) was instilled in each eye; the tear film appearance and composition were monitored for 4 h via in vivo visualisation using the Tearscope™ and post in vivo tear samples analysis by HPLC.

Results: Combined results for both normal and dry eye subjects showed that castor oil was detected up to 4 h after a single eyedrop instillation and associated with an increase in the level of tear film lipid. The relative amount of various lipid families was also changed. An increase in tear lipid layer thickness was significant up to one hour post-instillation for the symptomatic sub-population. The changes in tear film characteristics were associated with significantly lower symptoms up to four hours post-instillation for the symptomatic sub-population.

Conclusion: This pilot investigation showed that castor oil eyedrops achieved a residence time of at least four hours post-instillation, producing a more stable tear film and an associated significant decrease in ocular symptoms over the entire follow-up period for the symptomatic subjects.

1. Introduction

Dry eye is defined as a disorder of the tear film due to a deficiency in aqueous tear production and/or increased evaporative loss that leads to irritation of the ocular surface and is associated with symptoms of discomfort [1].

The prevalence rates reported in the literature are highly dependent upon the selection criteria used to diagnose dry eye subjects. Estimates in the prevalence of dry eye syndrome ranged from 14.4% to 34.0% [2–9] depending upon population biases and selection criteria. Additionally, an increased prevalence of dry eye with age [3,6], in women [3,6,10] and in contact lens wearers with estimates from 43% to 50.1% [2,3,11] has also been observed.

Treatments have been formulated to either restore tear volume or to increase tear film stability hence reducing tear evaporation. The most commonly used treatment for dry eyes consists of topically applied artificial tears and lubricants in the forms of eyedrops, gel or ointments. In a 2000 study by Nelson et al. [12], 87% of dry eye patients were reported to have used medications for dry eye in the previous 3 months, 56% reported using lubricant drops and 40% using lubricant ointments. The main active agents in traditional artificial tears products are viscosity enhancing agents used in a range of concentrations, in preserved or unpreserved formulations. Such products have been used in practice to help in the relief of the symptoms present in mild dry eye conditions, with more viscous products dedicated to more pronounced symptoms [13,14].

In the last few years, as a result of a better understanding of the complex aetiology of dry eye syndrome, more targeted, specialised treatments have emerged, either pharmacological compounds aimed at decreasing inflammation, improving lipid production and/or stimulating mucin and aqueous secretions from the ocular surface or treatments formulated to mimic the structure and function of natural tears.

A new emulsion eyedrop developed by Allergan, containing 1.25% castor oil stabilised within an aqueous demulcent formula, was initially used as a vehicle for cyclosporine ophthalmic emulsion 0.05% (Restasis®, Allergan), a pharmaceutical compound used to modulate inflammatory components in KCS and severe dry

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* Corresponding author at: OTG Research & Consultancy, Optometric Technology Group, 66 Buckingham Gate, London SW1E 6AU, UK. Tel.: +44 2072224224; fax: +44 2072224246.
E-mail address: cmaissa@otg.co.uk (C. Maïssa).

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eye cases. It is available in the US in slightly modified form as an artificial tear emulsion (Refresh Endura®, Allergan). This artificial tear solution falls into the category of eyedrops with targeted efficacy, aiming at treating all three layers of the tear film. Upon release the oil is thought to interact with the superficial lipid layer stabilising the tear film and reducing tear film evaporation, while the aqueous demulcent enhances the aqueous and mucin layers [15].

Interestingly, in clinical studies of Restasis® cyclosporine ophthalmic emulsion, the castor oil vehicle alone was reported to reduce some signs and symptoms of dry eye [16,17] and a pre-market study on the emulsion itself as an artificial tear on 73 mild to moderate dry eye subjects reported a significant increase in tear break-up time compared to baseline together with some improvements in signs and symptoms of dry eye after 90 days of usage [18].

Di Pascuale et al. [19] in a study on 5 normals and 10 aqueous tear deficient subjects reported a significant increase in tear lipid layer thickness and improved tear film spread time following the use of 1.25% castor oil emulsion eyedrop. Khanal et al. [20] measured reduced tear film evaporation with use of the 1.25% castor oil emulsion eyedrop, greater than that with a conventional aqueous drop. Further, Goto et al. [21] reported improved symptoms scores, increased tear break-up time and decreased tear evaporation after 2 weeks of six times daily treatment of homogenised castor oil compared to placebo for patients with non-inflamed obstructive meibomian gland dysfunction.

Castor oil eyedrops are lipid eyedrops which beneficial effects are thought to be associated with a modification of the lipid layer properties. The objectives of this pilot study were primarily to measure the prevalence of castor oil in the tear fluid over time and quantify the effects of the castor oil eyedrops on the tear film lipid layer of normal and dry eye subjects. A secondary objective was to quantify the initial effects of the emulsion eyedrop on ocular symptomatology.

2. Materials and methods

2.1. Test products

The test product was an investigative formula of a new emulsion eyedrop containing a polar oil (castor oil) within a aqueous demulcent formula. The castor oil primarily consists of the triglyceride of ricinoleic acid. The demulcent aqueous phase consists of polysorbate 80 (demulcent and emulsifier), carbomer 1342 (gelling agent and emulsifier) and glycerin (demulcent and tonicity agent). The non-preserved formula was dispensed in unit-dose plastic ampoules. The modality of use of the test product was a single instillation by the investigator. The test product, which was an investigational product, was used under a clinical trial exemption (CTX) from the Medicines and Healthcare products Regulatory Agency.

2.2. Subjects

Non-contact lens wearers were randomly enrolled in this research study. The test population included both normal subjects ($n = 5$) and subjects who complained of dry eye ($n = 10$). The McMonnies questionnaire was used to assess the symptomatology of the subjects at the enrolment visit [22]. The dry eye group (Symptomatic group) was defined as those subjects with a score ≥ 40 and the remainder were classified as normal (Asymptomatic group).

Subjects were excluded if they showed signs of ocular infection or anomaly and if ocular medication was currently being used. Systemic diseases, general medications and systemic allergy with possible ocular components were also grounds for exclusion. All subjects signed an informed consent and experimental procedures were reviewed and approved by an ICH-GCP independent ethics committee.

2.3. Clinical test procedures

The *in vivo* evaluation of the tear film characteristics was carried out using a slit-lamp observation system with the Tearscope™ lighting system allowing the different layers of the tear film to be visualised non-invasively.

The lipid layer was observed over the whole corneal surface; the mixing patterns observed within the lipid layer were classified upon their appearance. Lipid mixing patterns, that are transient or of the open meshwork type, are considered to be of poor efficacy and characteristics of a thin lipid layer (~15 nm), close meshwork layer mixing patterns are viewed as average in efficacy and flow and subsequent layer mixing patterns, characteristics of a thick lipid layer (~30–80 nm) are considered optimal [23].

The Non-Invasive Break-Up Time (NIBUT) was taken as the quantification of the pre-ocular tear film stability. Three successive measurements of the NIBUT were recorded; the smallest value recorded (Minimum NIBUT), representing the worst case, and the median value (Median NIBUT) were used for statistical analysis.

The tear prism height was measured as an indication of tear volume pre- and post-eyedrop instillation. The measurement was made immediately below the central part of the inferior cornea using the graduated slit opening on the biomicroscope.

Subjective tolerance and satisfaction were evaluated in terms of ocular comfort, subjective vision and ocular symptomatology during four hours post-instillation. Ocular comfort and subjective vision were recorded on dedicated continuous 50-point scales with the following descriptive anchors (0 = Very poor; 8 = Poor; 17 = Less than satisfactory (below average); 25 = Satisfactory; 33 = Better than satisfactory; 42 = Good; 50 = Excellent). Ocular symptomatology was monitored in terms of ocular dryness, grittiness, burning sensation, scratchiness and itchiness. All symptoms were recorded on continuous 50-point scales with anchors (0 = Constantly; 8 = Very Often; 17 = Often; 25 = Sometimes; 33 = Rarely; 42 = Very rarely; 50 = Never) [24,25].

The other parameters recorded during the clinical examination were not efficacy parameters but were carried out for legal and safety purposes. Visual acuity measurement and safety slit-lamp biomicroscopy with sodium fluorescein and lissamine green vital stains instillation were carried out before eyedrop instillation and four hours post-eyedrops instillation.

2.4. Laboratory procedures

Tear samples were collected at the test visit at regular intervals before and after single eyedrop instillation (15 min, 1 h and 4 h) from both the right and left eyes. The tear samples were collected from the lower tear prism of each eye using sterile disposable surgical eye sponges for the overall lipid profiling and glass microcapillaries for the quantification of castor oil by the investigators, trained in the techniques and who paid particular attention not to stimulate reflex tearing. Sampling of tear in the left eye took place after sampling in the right eye. Approximately 2 μl of tears was collected from each eye.

The tear samples from the right and left eyes were analysed by two different High Performance Liquid Chromatography (HPLC) methods. The amount of castor oil present in the tear film was quantified from the right eye tear samples which were analysed by HPLC, using a technique optimised for fatty acids/triglyceride separation with a reverse phase column and UV detection at 205 nm. The height and area of the peak characteristic of castor oil were recorded. The presence of castor oil in the tear samples