

A SCINTIGRAPHIC INVESTIGATION OF THE PRECORNEAL RESIDENCE TIME OF FOUR HYALURONIC ACID FORMULATIONS AND A CARBOXYMETHYLCELLULOSE FORMULATION IN PATIENTS WITH MILD DRY EYE SYNDROME

Blythe Lindsay, Tamara Jones, Bridget O'Mahony, Ben Browne*, Stuart Osborne*, Peter Chapman**, David Lloyd**, Clive Wilson†, Bio-Images Research Ltd, *Department of Ophthalmology, Glasgow Royal Infirmary, **Optogenesis Europe, †Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, UK

INTRODUCTION

The use of gamma scintigraphy to assess the precorneal residence of ophthalmic formulations is well established¹. The technique provides a quantitative measurement of the precorneal distribution over time and the proportion of the dose that has drained down the lacrimal duct.

Previous studies have shown good corneal retention of a 0.2% w/v hyaluronic acid solution². In this study, gamma scintigraphy was used to measure and compare the precorneal residence of four commercially available ophthalmic formulations containing different concentrations of hyaluronic acid and with a standard 0.5% w/v carboxymethylcellulose formulation.

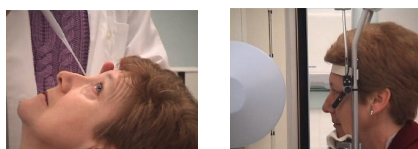


Figure 1 Administration of formulation and positioning during imaging

METHODS

CLINICAL STUDY

Design

Single-centre, randomised, analyst-blind, five-way crossover study.

Subjects

20 patients (ten females, ten males) with diagnosed mild Dry Eye syndrome, age range 36 to 68 (mean 48.1 +/- 9.1).

Diagnosis was made by questionnaire and ophthalmological examination.

Investigational Products

The following formulations were investigated:

- 0.5% w/v carboxymethylcellulose, Refresh (0.5% CMC)
- 0.1% w/v hyaluronic acid, Fermavis (0.1% HA)
- 0.15% w/v hyaluronic acid, i-Com (0.15% HA)
- 0.18% w/v hyaluronic acid, Vislube (0.18% HA)
- 0.4% w/v hyaluronic acid, lalurex (0.4% HA)

Formulations were aseptically labelled on the day of dosing with ^{99m}Tc-DTPA (1MBq per 25µl dose). The labelling had no significant effect on the rheological properties of the formulations.

Dosing

Subjects were dosed according to a randomisation schedule. A single drop (25 µl) of the appropriate test preparation was instilled into one eye using a calibrated positive displacement pipette. The same eye was dosed on each occasion. Each study arm was separated by a seven-day washout period.

Imaging Schedule

Subjects were seated at an ophthalmic table positioned 75mm from a low energy high resolution collimator with chin and forehead supported. A dynamic view was recorded for 10 minutes post dosing. Subsequently static views were collected every 5 minutes for a period of 30 minutes then every 15 minutes until 2 hours post dose.

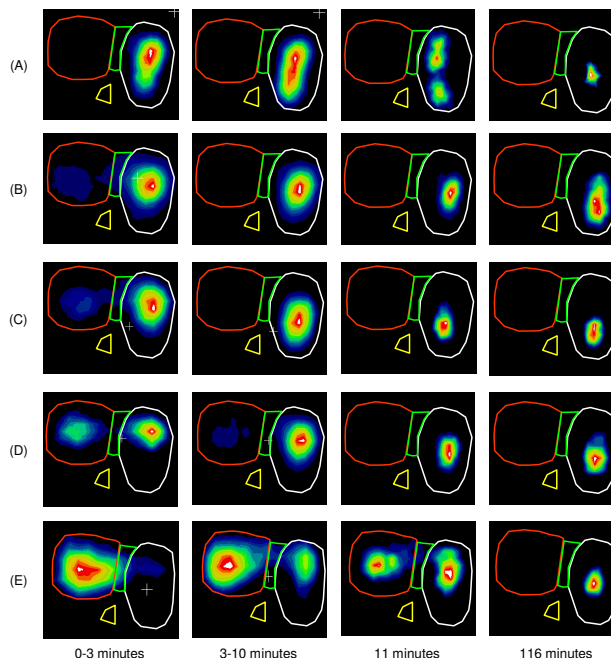


Figure 2 Images from a single subject showing the distribution of radiolabelled ophthalmic formulations at 0-3 minutes (summed dynamic images), 3-10 minutes (summed dynamic images), 11 minutes (static image) and 116 minutes (static image). The corneal ROI is shown in red, inner canthus in green, lacrimal duct in white and background in yellow. A = 0.5% CMC, B = 0.1% HA, C = 0.15% HA, D = 0.18% HA, E = 0.4% HA.

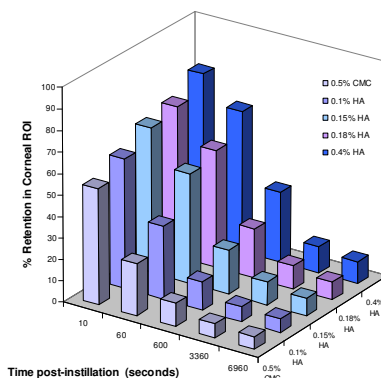


Figure 3 Graph of mean % retention in corneal ROI

ANALYSIS

Images were analysed using the WebLink[®] image analysis program. The dynamic images were summed to produce an overall picture of the label distribution. Regions of interest (ROI) were constructed for each eye, including the cornea, inner canthus, lacrimal duct and background (Figure 2). All counts were background and decay-corrected to express clearance and normalised to count rate at the time of instillation. Any hot spots due to contamination of eyelashes or surrounding skin were determined by construction of additional ROI and corrected for in the final analysis. AUC and T₅₀ were calculated using a validated Microsoft Excel spreadsheet.

AUC ₀₋₆₀₀	0.5% CMC	0.1% HA	0.15% HA	0.18% HA	0.4% HA
Mean	10106	13784	19255	23829	30097
SD	6455	9004	13341	10015	13662
Min	2069	1414	3935	8116	6874
Max	28083	36977	54825	51990	57066

T50	0.5% CMC	0.1% HA	0.15% HA	0.18% HA	0.4% HA
Mean	24	84	421	316	322
SD	13	162	1427	874	304
Min	9	9	6	15	8
Max	46	643	6296	3981	1045

Figure 4 AUC₀₋₆₀₀ (%.s) and T₅₀ (s)

RESULTS

All compounds were well tolerated and no reflex tearing was noted.

The hyaluronic acid formulations showed greater retention in the corneal ROI than carboxymethylcellulose (Figure 2). The percentage retention increased with increasing hyaluronic acid content (Figures 3). This is supported by the AUC data (Figure 4).

Analysis of the T50 indicated that hyaluronic acid formulations persisted longer on the corneal surface than carboxymethylcellulose (Figure 4).

CONCLUSION

Formulations containing hyaluronic acid have greater retention on the corneal surface than those containing carboxymethylcellulose and increasing the concentration of hyaluronic acid appears to result in better retention.

REFERENCES

- 1 Wilson, C. G. (1999). *Pharmaceutical Science & Technology Today* 2(8): 321-326
- 2 Snibson, G. R., J. L. Greaves, *et al.* (1992). *Cornea* 11(4): 288-93

Bio-*i*images

