Journal français d'ophtalmologie (2016) 39, 156—163

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

Long-term tolerance of preservative-free eye drops containing macrogol hydroxystearate as an excipient☆

Tolérance à long terme d'un collyre sans conservateur contenant comme excipient du macrogol hydroxystearate

K. Viaud-Quentric, S. Lefranc-Jullien, L. Feraille, P.-P. Elena*

Iris Pharma, Les Nertières, allée Hector-Pintus, 06610 La Gaude, France

Received 24 June 2015; accepted 17 September 2015
Available online 29 January 2016

KEYWORDS
Macrogloglycerol hydrostearate 40;
Excipient;
Tolerability;
Ocular;
Eye drop

Summary
Purpose. — This in vivo animal study was conducted to assess the tolerability of macrogloglycerol hydrostearate 40 (MGH 40), commonly used as a solubilizing excipient in prostaglandin $F_{2\alpha}$ analogue eye drops without benzalkonium chloride.
Methods. — Twenty-eight (14 males and 14 females) New Zealand white albino rabbits in good health and with no signs of ocular irritation were randomly assigned to receive 25 μL instillations of a solution containing 10% MGH 40 in the right eye 3 times daily for either 3 or 6 months. Ocular examinations of the conjunctiva, cornea and iris (using an ophthalmoscope and slit-lamp), corneal sensitivity, and intraocular pressure were assessed in both the right (treated) and left (untreated) eyes throughout the study. General characteristics, hematology and serum biochemistry parameters were also assessed throughout the study and necropsy examinations were performed at study completion.

☆ The data included in this manuscript have been accepted for poster presentation at the annual meeting of The Association for Research in Vision and Ophthalmology (ARVO), Denver, Colorado, USA, 3—7 May 2015.

* Corresponding author.
E-mail address: pierre-paul.elena@iris-pharma.com (P.-P. Elena).

http://dx.doi.org/10.1016/j.jfo.2015.09.011

Results. — There were no treatment-related effects on the cornea, conjunctiva, iris, or intraocular pressure. Transient findings were generally seen in the untreated as well as the treated eye. Similarly, there were no treatment-related findings in either the hematology or serum biochemistry data or at necropsy. There were no differences based on gender.
Conclusions. — Long-term administration of a 10% MGH 40-containing formulation three times per day in a standard in vivo animal model was well tolerated and had no ocular or other effect.

MOTS CLÉS
Macrogloglycerol hydrostearate 40 ;
Excipient ;
Tolérance ;
Oculaire ;
Collyre

Résumé
Objectifs. — Cette étude animale a été réalisée afin d'évaluer la tolérance du macrogloglycerol hydrostearate 40 (MGH 40), utilisé comme excipient solubilisant des collyres, notamment pour les analogues de prostaglandines $F_{2\alpha}$, formulées sans chlorure de benzalkonium.
Méthodes. — Vingt-huit lapins albinos New Zealand ont été randomisés pour recevoir dans l'œil droit des instillations de 25 µL d'une solution contenant 10 % de MGH 40 trois fois par jour pendant 3 à 6 mois. Des examens à l'ophtalmoscope et la lampe à fente de la conjonctive, la cornée et de l'iris ont été réalisés et la sensibilité cornéenne et la pression intraoculaire ont été évaluées tout au long de l'étude dans l'œil traité ainsi que dans l'œil controlatéral. Les paramètres généraux, l'hématologie, la biochimie sérique et les organes lors de la nécropsie ont été évalués.
Résultats. — Au cours des 6 mois de traitement, à l'ophtalmoscope ou à la lampe à fente, aucun effet oculaire lié au traitement du collyre à base de MGH 40 10 % n'a été observé au niveau cornéen, conjonctival ou irien. Par ailleurs, aucun effet sur la pression intraoculaire ou la sensibilité cornéenne n'a été relevé. Au niveau systémique, aucun changement n'a été observé pour les paramètres hématologiques ou biochimiques ainsi qu'au niveau des organes lors de la nécropsie.
Conclusions. — L'administration long terme 3 fois par jour d'une formulation contenant 10 % de MGH 40, dans un modèle animal bien reconnu et validé, n'a permis d'objectiver aucun effet délétère et a permis de démontrer la très bonne tolérance du collyre.

Introduction

Excipients are inactive ingredients that can be intentionally added to pharmaceutical products and intended to be inert, i.e. to not exert a therapeutic effect. These are routinely used in a wide range of pharmaceutical products, including fillers, diluents, preservatives, flavoring or coloring agents. There have been occasional historical cases of excipients that have proven toxic, e.g. a sulfanilamide preparation using toxic diethylene glycol as a solvent (the so-called 'elixir sulfanilamide') that caused numerous mortalities in 1937. Cases such as this have led to the implementation of guidelines for the rigorous pre-clinical testing of excipients for safety in vitro and in animal models before any product is tested clinically [1].

New prostaglandin $F_{2\alpha}$ analogue, preservative-free eye drops containing macrogloglycerol hydrostearate 40 (MGH 40) are increasingly popular [2,3] as medication for the treatment of glaucoma since preservatives — such as benzalkonium chloride (BAK) — contained in earlier formulations have been shown to be inflammatory and poorly tolerated [4—6]. MGH 40 is used as a solubilizer in such formulations due to the low water solubility of prostaglandin analogues.

Based on data from in vitro evaluation using human corneal epithelial cells (HCE) [7] and data from an *ex vivo* eye irritation test (EVEIT) [8], it has recently been suggested that MGH 40 is a potential irritant when used in eye drops at a concentration of 5%. However, it has been shown that switching from BAK-preserved to a preservative-free product that contains MGH 40 decreases anterior chamber flare in patients with primary open-angle glaucoma [9] and a meta-analysis showed that an MGH 40-containing product results in significantly reduced intra-ocular pressure (IOP) in patients with ocular hypertension compared to a BAK-preserved product and additionally led to a reduced incidence of ocular redness [10].

This study was designed to evaluate a higher concentration of MGH 40 (10%) in a long-term non-clinical study to fully assess its potential ocular irritant effect and to definitively evaluate its safety in albino rabbits.

Materials and methods

Study design and animals

Twenty-eight (14 males and 14 females) New Zealand white albino rabbits, baseline mean weight 2.649 kg (males) and