In vivo ocular tolerance of a new preservative-free eye drop formulation in rabbits

Quentric Yann; Viaud-Quentric Karen; Lefranc-Jullien Solveig; Feraille Laurence; Elena Pierre-Paul; Iris Pharma La Gaude France

Introduction

Due to low water solubility of drugs, solubilizers have to be added to the ocular formulation. Macrogol 15 hydroxystearate (MGH 40) is frequently used in pharmaceutical formulation as solubilizer and it is recently used for new formulation in eye drops. This new formulation seems to be well tolerated. Pauly et al. recently reported that preservative free (PF) latanoprost (Monoprost®) containing a concentration of 5% MGH 40 had a good tolerability, when applied topically in a rabbit model or in 3D HCE cell construct model. A clinical phase III trial with two parallel groups Monoprost® versus Xalatan® showed that Monoprost® was non inferior for intracocular pressure lowering efficacy with less frequent and severe conjunctival hyperemia. However, recent in vitro studies investigating PF formulations in glaucoma drugs have indicated that Monoprost® had induced signs of cellular damage. The concentration of the solubilizer MGH 40 in Monoprost® was presumed to cause many of the detrimental cellular effects in HCE-2 cells, although mildly increased apoptotic cells were detected and on rabbit cornea cultured on artificial anterior chamber (EVEIT system).

In order to assess the accuracy of these models, we performed a long term study in rabbits with high level of MGH40.

Material and method

Twenty-eight (28) male and female New Zealand White albino rabbits were involved in this study and assigned to two groups of 14 animals (7 male and 7 female) corresponding to the 3-month and 6-month time-points. A formulation containing 10% MGH 40 was instilled in the right eye, three times daily. The left eyes served as control. Ocular signs were evaluated daily over a 4 –week period, then once a month(b). Blood was collected at 3-month and 6-month time-points and then once a month(b) throughout the study period.

Body weight, Hematological and Biochemical Parameters

The body weight was measured once a week throughout the study period. Blood was collected at 3-month and 6-month time-points and hematological and biochemical parameters were analyzed. There were slight alterations in the biochemical parameter (slight increase of urea at 3 months, which was not observed at 6 months), however they were within the normal range.

Corneal sensitivity

The corneal sensitivity was measured using an esthesiometer of Cochet-Bonnet. No difference was observed between treated and control group. All animals had need less than 4 mechanical stimuli to have a blinking reflex which is commonly observed.

Histological analysis

Some minor focal changes attributed to repeated instillations were observed. Theses changes consisted of slight signs of irritation (extravasated lymphocytes) in conjunctival or limbus stroma. No other microscopic findings were observed in the ocular structures.

Conclusions

A formulation with MGH 40 10% 3 times a day was well tolerated and the ocular surface remained normal after 6-month exposure. Thus, results obtained in vitro/ex vivo with the new prostaglandin preservative free formulation containing 5% MGH 40 seem to be not predictive of in vivo tolerance. MGH 40 is a good solubilizer for topical use. This may be useful for the formulation of a variety of lipophilic and hydrophobic drugs that hitherto have not been available as eye drops.

References