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SHORT REPORT

Infectious diseases

Kinetics of hydrocortisone sodium phosphate penetration into the human aqueous humor after topical application

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Abstract

Aim of the study: Hydrocortisone is a soft steroid with low anti-inflammatory properties and a short duration of action, used to manage several ocular conditions. The clinical benefits and side effects associated with hydrocortisone are well documented, but its basic pharmacokinetic in the eye is yet to be fully elucidated. The purpose of this study is to investigate the anterior chamber penetration capabilities of hydrocortisone when used in different concentrations as eye drops treatment.

Materials and Methods: This is a double-blind, single-centre, randomised clinical trial performed at the Department of Medicine and Surgery of the University of Perugia (Italy) on consecutive patients who undergone phacoemulsification with intraocular lens implantation. Patients were randomly assigned on the morning of surgery to receive a single instillation of 0.33% (group A) or 0.001% (group B) hydrocortisone sodium phosphate solution. Group of patients C did not receive any treatment and was used to measure the hydrocortisone endogenous levels. Before surgery, one aliquot of aqueous humor for each patient was aspirated. The time of collection for each sample was recorded. Hydrocortisone concentrations were then stratified into six interval classes of 30 minutes each.

Results: The mean concentration of hydrocortisone was significantly higher in group A (25.2 ± 12.4 ng/mL) compared with group B (7.11 ± 1.51 ng/mL) and compared with the mean hydrocortisone endogenous levels (3.92 ± 1.18 ng/mL) ($P < .0001$). No statistically significant differences of hydrocortisone mean concentrations between group B and the mean endogenous levels were found.

Conclusions: Considering the frequent need for prolonged topical steroid therapies and the possible consequent undesirable side effects, ophthalmologists should consider the lowest clinically effective dose of hydrocortisone useful to obtain the desired therapeutic effect and in an adequate time, to minimise the amount of steroids into the anterior chamber and to avoid side effects like intra-ocular pressure increase or cataract development.

1 | INTRODUCTION

Ophthalmic eye drops of steroids are widely used to manage several ocular conditions, such as conjunctivitis, uveitis and diabetic macular edema.[1-4]

Steroids on the market for topical ocular administration have different concentrations of the active ingredient and different formulations (solutions, suspensions, gels): this can lead to a different efficacy and amount penetration in the anterior chamber.[5] This aspect has a relevant importance since the use of effective steroid drugs with reduced side effects related to their penetration in the humor aqueous is a therapeutic need; consequently, their correct use in the clinical practice should be elucidated.

In the last years, the interest is growing towards topical "soft steroids", such as loteprednol and hydrocorticosteroids, which are mostly used in chronic diseases because of their higher safety profile.[6,7] This class of steroids is particularly indicated in chronic eyes pathologies when a long-term treatment is required, to avoid the typical side effects of conventional steroids used topically, such as the risk of cataract development and the increase in intra-ocular pression.[6,8]

Hydrocortisone is a soft steroid with low anti-inflammatory properties and a short duration of action. The clinical benefits and side effects associated with hydrocortisone are well documented,[9] but its basic pharmacokinetic in the eye is yet to be fully elucidated. Indeed, to the best of our knowledge, the pharmacokinetic profile of hydrocortisone has been investigated only in in vivo animal models[10] or in humans after subconjunctival injection.[11]

The purpose of this study is to investigate the anterior chamber penetration capabilities of hydrocortisone used in different concentrations as eye drops treatment, for a more conscious use of this soft steroid to treat ocular disease conditions.

2 | PATIENTS AND METHODS

2.1 | Subject and study design

This is a double-blind, single-centre, randomised clinical trial performed at the Ophthalmology Section of the Department of Medicine and Surgery of the University of Perugia (Italy). This study involved consecutive patients of both genders aged >18 years with a cataract who underwent phacoemulsification with intraocular lens implantation.

Exclusion criteria were any previous ocular surgery and a history of uveitis or trauma, and eye diseases, such as corneal pathologies, hypertension or glaucoma, pseudoexfoliation syndrome and those receiving any ophthalmic therapy.

Included patients were randomly assigned to one of the following groups on the morning of surgery:

- Group A: patients received a single instillation of hydrocortisone sodium phosphate 3.040 ug/mL solution (Cortivis, 0.33%; Medivis Srl, Tremestieri Etneo).
- Group B: patients received a single instillation of hydrocortisone sodium phosphate 10 ug/mL and sodium hyaluronate 2.00 mg/mL solution (Idroflog, 0.001%; Alfa Intes).
- Group C: Control group. Patients did not receive any treatment.

The study protocol was approved by the local ethics committee (CER Umbria, register number 3500/19), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2 | Study procedures

All interventions were performed in treatment-blind by the same experienced surgeon (CC). Before the surgery, a drop of the hydrocortisone product was instilled in the eye to be operated on and the moment of instillation was recorded. The patients' pupils were dilated by introducing a phenylephrine and tropicamide insert (Mydriasert, Théa Farma SpA) into the eyelid fornix about 60 minutes before surgery. Topical anesthesia (lidocaine 4%) was applied three- or four-times, and then immediately before surgery an aliquot of 40-120 mL of aqueous humor was aspirated by means of paracentesis using an insulin syringe. The aqueous humor sample was promptly transferred to Eppendorf vials and immediately stored at −20°C. The time of collection for each sample was recorded.

Hydrocortisone concentrations were stratified into six interval classes of 30 minutes each, based on the time between the eye drop instillation and the aqueous humor collection. Samples obtained by patients of the study group C were used to evaluate the mean endogenous concentration of hydrocortisone.

2.3 | Liquid chromatography–mass spectrometry analysis

Hydrocortisone concentrations were obtained by liquid chromatography–mass spectrometry (LC/MS) analysis. LC separation was achieved by gradient elution with a mobile phase of acetonitrile and water in an Ascentis® Express C18, 2.7 μm column (Supelco).

MS analysis was performed using an Agilent 6530 Q-TOF mass spectrometer (Agilent Technologies, Inc). Hydrocortisone and D4-hydrocortisone were identified as $[M\text{-}H]^-$ ions based on accurate mass and MS/MS spectra.

Quantitative data were obtained using Agilent MassHunter quantitative analysis software (ver. B.09.00). The limit of quantification and the limit of detection of the drug were found experimentally as 0.5 and 0.01 ng/mL, respectively.

2.4 | Statistical analysis

Continuous variables were summarised by mean values and the standard deviation (SD). One-way ANOVA followed by *post-hoc* analysis has been applied to evaluate the experimental results.

3 | RESULTS

A total of 154 Caucasian patients (86 were females, 56%) were included in the study: 88 in group A (mean age ± SD: 78.0 ± 5.6 years), 56 in group B (mean age ± SD: 76.2 ± 6.8) and 10 in group C (mean age ± SD: 76.8 ± 5.3). Overall, the mean concentration of hydrocortisone was significantly higher in group A (25.2 ± 12.4 ng/mL), compared with group B (7.11 ± 1.51 ng/mL) and compared with the mean hydrocortisone endogenous levels (3.92 ± 1.18 ng/mL; $P < .0001$).

No statistically significant increase of hydrocortisone mean concentrations in the aqueous humor was observed in group A with respect to group B at 0-29 minutes (5.3 ± 2.9 vs 6.0 ± 0.3 ng/mL, respectively) and at 30-59 minutes (15.0 ± 6.8 vs 7.2 ± 2.3 ng/mL, respectively) and to endogenous concentrations. A statistically significant increase in hydrocortisone was observed in group A at the other time points, if compared with group B (60-89 minutes: 35.2 ± 20.2 ng/mL in group A, 9.0 ± 5.3 ng/mL in group B; 90-119 minutes: 35.2 ± 22.5 ng/mL in group A, 8.2 ± 5.0 ng/mL in group B; 120-149 minutes: 33.4 ± 20.3 ng/mL in group A, 7.3 ± 3.5 ng/mL in group B; 150-180 minutes: 26.9 ± 20.0 ng/mL in group A, 4.8 ± 3.7 ng/mL in group B).

There were no statistically significant differences of hydrocortisone mean concentrations between group B and the control group, in any of the time intervals considered (Figure 1).

4 | DISCUSSION

This study demonstrates that the eye drops hydrocortisone concentration significantly conditioned its penetration in the anterior chamber.

In particular, the high concentration of hydrocortisone induces a high penetration of the drug into the anterior chamber. Indeed, in the group of patients treated with the highest concentration of hydrocortisone, a 6.6-times higher level of hydrocortisone was found at peak, detected between 60 and 120 minutes after the instillation, compared with the mean endogenous concentration. In group A patients, the steroid amount persists at a relatively stable high concentration until around 150 minutes, followed by a slow decrease.

Otherwise, in the group treated with the low hydrocortisone concentration solution, the hydrocortisone amount remained almost stable during the study period. This amount was not significantly different from hydrocortisone endogenous levels, which are normally present in the aqueous humor to preserve the immune-privilege status of the anterior chamber, together with TGF-β2 and the a-melanocyte-stimulating hormone (a-MSH).[12,13]

The implications of this study lie in the use of hydrocortisone-based preparations in the daily clinical practice for the treatment of various eye diseases. The penetration capacity of drugs in ophthalmology was a neglected aspect for a long time, but recently, this topic has been addressed by numerous studies and the ability of antibiotics, steroids and NSAIDs to penetrate the anterior chamber has been extensively evaluated.[14-21]

These studies were often correlated with the definition of therapeutic capabilities of the different compounds to optimise their use and promote a correct therapeutic attitude.[15,22-24]

Our results suggest that high concentrations in the eye drops are required to significantly change the concentration of hydrocortisone in the anterior chamber. Even if the complications or adverse effects related to both the low- and high-concentration treatments were not studied, we can suggest that eye drops with a low concentration of hydrocortisone could represent an adequate and safe option for a prolonged treatment in those conditions when we can observe a mild-to-moderate chronic ocular surface inflammation associated with lacrimal tears alteration, as dry eye disease or after routine cataract surgery, as their administration does not appear to change the anterior chamber concentration of hydrocortisone.[25,26]

This study presents some limitations, including the relatively low number of samples and the lack of in-depth analysis of the anti-inflammatory activity and toxic effect of the hydrocortisone concentration observed in the anterior chamber. This aspect should be evaluated in future studies on larger samples.

To conclude, considering the frequent need for prolonged topical steroid therapies and for the possible consequent appearance of undesirable side effects, ophthalmologists should consider

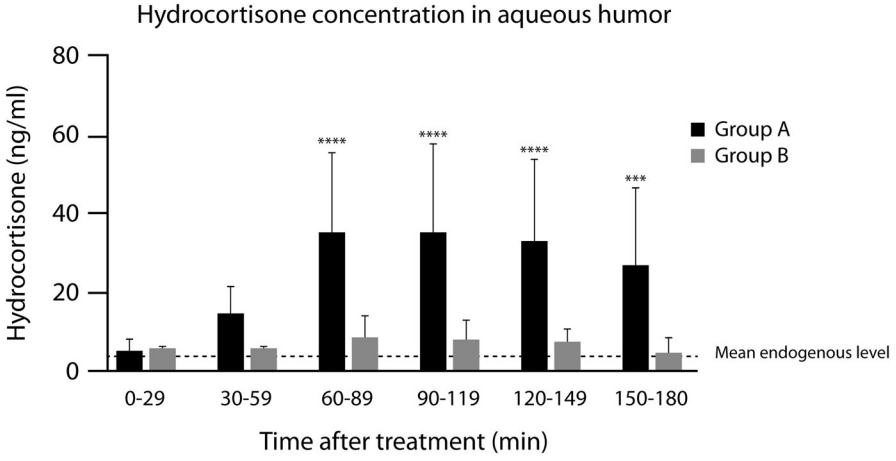

FIGURE 1 Hydrocortisone concentrations in aqueous humor after treatment with hydrocortisone sodium phosphate 3.040 μg/mL (group A) or hydrocortisone sodium phosphate 10 μg/mL (group B). Mean endogenous concentrations of hydrocortisone were measured in group C patients (no treatment, dashed line). Mean ± standard deviations are represented. ****$P < .0001$; ***$P < .001$

the lowest clinically effective dose of drug useful to obtain the desired therapeutic effect and, in an adequate time, to minimise the amount of steroids into the anterior chamber and to avoid side effects, such as intra-ocular pressure increase or cataract development.

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DISCLOSURES

The authors have declared no conflicts of interest.

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