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Case report

Aqueous penetration of topical tacrolimus

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ABSTRACT

Purpose: To evaluate the penetration of topical tacrolimus 0.05% into the aqueous humor.
Observations: A total of four patients scheduled for routine cataract surgery were included prospectively. We excluded patients with corneal pathology or ocular surface diseases. Topical tacrolimus 0.05% was compounded at our facility. It was dosed every 1 min for 5 min an hour before the aqueous was sampled. Aqueous samples were collected at the time of cataract surgery and were subjected to detection of presence and level of tacrolimus. There were 2 male and 2 female patients. The age range was 58–73 years with a mean age of 66 years. Tacrolimus was detected in the aqueous humor in all patients. The concentration of tacrolimus in the aqueous ranged from 2.6 to 5.6 ng/ml (mean 4.15 ± 1.18 ng/ml). In all patients, the aqueous tacrolimus concentration was greater than the minimal therapeutic level. The study was registered at clinicaltrials.gov (registration number is NCT02794610).
Conclusions and Importance: Tacrolimus was detected in the aqueous humor following topical application. Topical tacrolimus may be a promising steroid-sparing modality for the treatment of anterior uveitis.

1. Introduction

Tacrolimus is a potent macrolide immunosuppressant produced from the fermentation broth of a Japanese soil sample that contained the bacterium Streptomyces tsukubaensis.[1] Tacrolimus binds to FK506-binding protein in the T lymphocytes and inhibits calcineurin activity. Inhibition of T lymphocytes may lead to the inhibition of release of inflammatory cytokines and decreased stimulation of other inflammatory cells.[1] Based on the immunosuppressive properties of tacrolimus, several clinical trials were conducted to assess the efficacy of the topical preparation. Efficacy of systemic tacrolimus in experimental animals and humans made us study the ocular penetration of topical tacrolimus.[2–4] The main purpose of this study was to assess the ocular penetration and concentration of topical tacrolimus in the aqueous humor following topical application.

2. Findings

Four patients were included prospectively. The study included normal eyes only to evaluate the penetration of topical tacrolimus 0.05% into the aqueous humor. All patients were scheduled to undergo cataract surgery. Inclusion criteria included: adult patients 18 years or older and no anterior segment pathology. We excluded patients with corneal pathology, ocular surface disease or intraocular inflammation. Topical tacrolimus 0.05% was instilled to the eyes of each patient every 1 min for 5 min. The dosing schedule was selected based on the tolerance of the patients. Aqueous samples (0.2 ml) were collected 1 h following the last topical application and were subjected to detection of presence and level of tacrolimus. Tacrolimus concentration in the samples was measured by commercial tacrolimus chemiluminescent microparticle immunoassay. Tacrolimus eye drops were compounded by adding balanced salt solution to 1000 μg tacrolimus capsule (Prograf; Astellas Pharma Inc., Tokyo, Japan) to achieve 0.05% concentration. No preservative was added. The pH of the compounded solution was 7.5. The Protocol was approved by the Institution Review Board (IRB) of The Eye Center, Riyadh, Saudi Arabia. The study design complied with the standards set forth by the Declaration of Helsinki and written consents were obtained. The study was registered at clinicaltrials.gov (registration number is NCT02794610). There were 2 male and 2 female patients. The mean age was 66 years with age range of 58–73 years. Tacrolimus was detected in the aqueous humor of all patients 1 h following topical administration. The mean concentration of tacrolimus in the aqueous was 4.15 ± 1.18 ng/ml (ranging from 2.6 to 5.6 ng/ml).

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3. Discussion

The use of topical tacrolimus is of special interest to ophthalmologists as a steroid sparing agent.[1] Different forms and concentrations of tacrolimus have been assessed in the treatment of immune-mediated anterior segment inflammatory disorders including vernal keratoconjunctivitis, keratitis, ocular graft versus host disease, cicatrizing conjunctivitis and following corneal transplantation.[1] We have reported the efficacy of topical tacrolimus in the treatment of vernal keratoconjunctivitis and in keratopathy associated with autoimmune polyglandular syndrome.[5,6] The therapeutic level of tacrolimus required to control intraocular immune-mediated diseases has not been determined. Results of studies on organ transplantation however, may be extrapolated to the eyes with immune-mediated diseases. The studies demonstrated that the recommended minimal serum level of tacrolimus in patients undergoing organ transplantation is 2–10 ng/mL which can be considered a target concentration to control T-cell mediated diseases of the eye.[7–9] Topical tacrolimus was found to be effective in inhibiting endotoxin-induced uveitis and autoimmune uveitis in experimental uveitis models.[10,11] Topical use of tacrolimus in anterior uveitis remains to be demonstrated.

The function of aqueous humor to the eye is similar to that of blood to the whole body.[1] Based on the recommendation that minimal effective tacrolimus serum level in patients undergoing organ transplantation is 2–10 ng/mL, it is believed the same concentration of tacrolimus might be considered as the minimal therapeutic level for controlling ocular immune-mediated diseases.[8,9] Yuan and associates evaluated the aqueous humor concentration of tacrolimus 60 min following single topical administration of tacrolimus 0.05% in rabbits. 6 It was found to be above 10 ng/mL. Yalçındağ et al. evaluated higher concentration of the drug (topical tacrolimus 0.3%), they investigated the penetration of tacrolimus to the aqueous humor after topical administration of only one drop of 0.3% tacrolimus in rats.[12] Tacrolimus concentrations were determined in aqueous humor at 10 min after topical application, the mean concentration of tacrolimus was 35.16 ± 4.26 ng/ml (31–42 ng/ml) in aqueous humor.[12] Yalçındağ and associates also evaluated aqueous humor concentration of tacrolimus in human eyes using the 0.3% concentration.[13] The authors evaluated the concentration of tacrolimus in aqueous humor of 11 patients with ocular Behcet's disease following topical application. All patients received one drop of tacrolimus solution 0.3% every 6 h for 3 days. The mean aqueous humor tacrolimus concentration was found to be 12.49 ng/mL. However, the use of higher concentration of topical tacrolimus is associated with ocular surface irritation. In our study, we used topical tacrolimus concentration of 0.05 mg/ml which is lower than the dose used by Yalçındağ et al.[13] Our study is the second human study of this kind but we used lower concentration of topical tacrolimus compared to the previous study.

Tacrolimus has limited ocular penetration because of its hydrophobic nature and relatively high molecular weight (822 Da).[9] There have been several trials aimed at improving corneal penetration and prolonging precorneal retention time. Nanoscale drug delivery systems, such as nanoparticles, cubosomes, nanoemulsions, and liposomes, have shown to improve corneal penetration and increase retention time.[8,14] The microemulsion technique may provide a greater tacrolimus ocular bioavailability in the aqueous humor compared to a suspension formulation after topical ocular administration.[15] The variation of the detected concentration of tacrolimus in the aqueous humor in different studies may be due to differences in drug formulation, concentration, frequency of instillation and time of sampling. In all our patients, the aqueous tacrolimus concentration was more than 2 ng/ml which is the proposed lower limit for immuosupressive activity. More studies are required to evaluate optimum concentration, formulation and different dosage regimens to maintain therapeutic levels tacrolimus in the aqueous humor.

4. Conclusions

Tacrolimus was detected in the aqueous humor following topical application. Topical tacrolimus may be a promising modality for treatment of anterior uveitis. Larger case series are needed to determine the ocular penetration and appropriate dosage for topical use. This study suffers from certain limitations including the small number of patients and one time aqueous determination of tacrolimus.

Patient consent

Written consent was obtained from each patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: SS,FJ, KT.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2019.100582.

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