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CLINICAL INVESTIGATION

Clinical evaluation of the effect of diquafosol ophthalmic solution in glaucoma patients with dry eye syndrome

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Abstract
Purpose To investigate the effects of diquafosol on intraocular pressure (IOP) and dry eye symptoms in glaucoma patients with dry eye syndrome (DES).
Methods This study evaluated a total of 138 glaucoma patients with DES who were treated with diquafosol ophthalmic solution (DIQUAS®). Before treatment and 1, 4, 12, 36, and 52 weeks after treatment, IOP, ocular surface disease index (OSDI), tear film break-up time (BUT), Schirmer I test scores, fluorescein staining, conjunctival impression cytology, and adverse drug reactions were evaluated.
Results Throughout the treatment period, the mean IOP for all the patients remained stable after treatment with diquafosol (15.4 ± 2.8 mmHg at baseline and 16.0 ± 2.8 mmHg at 52 weeks). The mean OSDI score improved significantly at 4, 12, and 52 weeks after diquafosol treatment. The BUT and Schirmer I test scores were significantly increased after diquafosol treatment. The Oxford scheme score was significantly decreased at 1, 4, 12, 36, and 52 weeks after diquafosol treatment. A significant improvement in goblet cell density was observed after 4 weeks of treatment with diquafosol. Adverse drug reactions were reported in 22 (15.9 %) patients. There were no serious adverse drug reactions.
Conclusions Diquafosol was effective in improving objective and subjective symptoms and maintained a stable IOP in glaucoma patients with DES. Therefore, the addition of diquafosol treatment in glaucoma patients with DES or ocular surface side effects using anti-glaucoma medication may be beneficial.

Keywords Diquafosol · DIQUAS · Glaucoma · Dry eye

Introduction

Glaucoma is a group of ocular diseases with multifactorial etiologies. These diseases are clinically characterized by optic neuropathy and visual field loss [1]. Many treatment modalities, including molecular therapy, are aimed at arresting or reversing apoptotic damage to the optic nerve and retinal ganglion cells. However, the most important goal of glaucoma treatment is to reduce the intraocular pressure (IOP) that is typically elevated in glaucoma patients. To date, the only effective treatment for glaucoma is early drug therapy to decrease the IOP in the initial stages of the disease. There is a broad spectrum of medications that reduce the IOP. However, medical treatments that have minimal side effects are needed to promote compliance and allow for the continuation of therapy [2]. Forty-five to 60 % of glaucoma patients who use topical glaucoma eye drops over the long term develop ocular surface diseases, such as hyperemia, superficial punctate keratitis, a burning sensation, and dry eye syndrome (DES) [3]. Additionally, patients taking chronic topical anti-glaucoma medication are more likely to report dry eye symptoms, suggesting that they have significant ocular surface disease [4]. Therefore, glaucoma patients using topical glaucoma eye drops also need to use ocular surface disease (OSD) medication, such as artificial tears, lubricating gel and ointment, corticosteroids, or cyclosporine.

Diquafosol is a uridine triphosphate-related compound. Diquafosol is reported to be an agonist of the purinergic

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$P2Y_2$ receptor that is expressed in several ocular (including the cornea, conjunctival epithelium, goblet cells, ciliary body, trabecular meshwork, choroids, and retina) and pulmonary tissues, which is related to the mechanisms of G protein-mediated activation of phospholipase C and inositol. At the cellular level, the $P2Y_2$ receptor is known to contribute to water transfer and mucin secretion [5, 6]. In animal studies with rabbits, diquafosol has been shown to stimulate both water secretion from conjunctival epithelial cells and mucin secretion from conjunctival goblet cells via the $P2Y_2$ receptors [5, 7]. Diquafosol is also reported to prevent corneal epithelial damage in a rabbit dry eye model [8]. In a rat model of dry eye disease, diquafosol was demonstrated to improve tear secretion and restore the corneal epithelial barrier function [9]. Based on clinical studies, diquafosol ophthalmic solution (DIQUAS; Santen Pharmaceutical Co., Ltd., Osaka, Japan) was introduced into the market at the end of 2010 as a drug for treating dry eyes with a novel mechanism of action that involves the stimulation of tear and mucin secretion [10–12].

However, several animal studies demonstrate that the activation of the $P2Y_2$ receptor may increase IOP [13–15]. Ciliary epithelial cells are known to store and release ATP. This agonist can act on $P2Y_2$ receptors, modulating aqueous humor flow and IOP. Stimulation of the $P2Y_2$ receptor by uridine triphosphate (UTP) and its derivatives increased the IOP in rabbits, whereas $P2Y_2$ receptor antagonism or its silencing by means of a selective siRNA in the ciliary body substantially reduced the IOP, confirming the involvement of the $P2Y_2$ receptor in IOP elevation [13].

To the best of our knowledge, there are no clinical studies on the adverse effects of diquafosol, such as IOP elevation, in patients with glaucoma. The purpose of the current clinical study was to investigate the effects of diquafosol on IOP and dry eye symptoms in glaucoma patients with DES.

Subjects and methods

This study was a prospective, observational case series conducted at the Dong-A Medical Center in Korea from March 2014 to February 2015. In a total of 138 glaucoma patients with DES, the following were evaluated: IOP, ocular surface disease index (OSDI), tear film break-up time (BUT), Schirmer I test scores, fluorescein staining, and conjunctival impression cytology. The Institutional Review Board of Dong-A University approved this study. The research protocol adhered to the tenets of the Declaration of Helsinki for clinical research. Written informed consent was obtained from all participants after explanation of the purpose and possible consequences of the study.

Eligible patients met the following criteria: clinically diagnosed with primary open-angle glaucoma or normal tension glaucoma that had been treated with topical glaucoma eye drops for 6 months or longer, in one or both eyes. Additionally, the inclusion criteria for DES were as follows: age $\geq$20 years and mild to moderate dry eye corresponding to dry eye severity level 1 or 2, as suggested by the Delphi Panel Consensus for Dry Eye Management and the International Dry Eye Workshop (DEWS). The definition of modified dry eye severity level 1 was as follows: (1) mild to moderate symptoms and no signs; and (2) mild to moderate conjunctival signs. Dry eye severity level 2 was defined as follows: (1) moderate to severe symptoms; (2) tear film signs; (3) mild corneal punctuate staining; (4) conjunctival staining; and (5) visual symptoms [16, 17].

Patients with a history of previous ocular surgery, including glaucoma surgery and laser ocular procedures, history of using eye-drops except anti-glaucoma medications, ocular trauma, contact lens use, punctual occlusion or diathermy, or eye disease, including active inflammation of the eye, history of allogeneic hematopoietic stem cell transplantation, refractive corneal surgery, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, or chemical or thermal burns, were excluded from the study. Patients were also excluded if they had any other ocular diseases, had any systemic diseases, took medication that could cause dry eyes, or were pregnant at the time of the study. One eye from each subject was used for the analysis, and when both eyes had the same glaucoma diagnosis and visual field progression, the right eyes were used for the analysis. Patients were instructed to use diquafosol 6 times daily in both eyes.

During the study, 6 visits were scheduled, which included a combined screening/baseline visit followed by visits at 1, 4, 12, 36, and 52 weeks of treatment. At each visit, the following ocular procedures, except conjunctival impression cytology, were performed: IOP measurement, OSDI measurement, BUT measurement, Schirmer I test, and fluorescein staining. Additionally, conjunctival impression cytology was performed at the screening/baseline visit and at 4, 12, 36, and 52 weeks.

The same examiner assessed the IOP during the day, at a specified time, using Goldmann applanation tonometry, and the average of three measurements was used in the analyses.

The ocular symptoms were graded according to the OSDI (Table 1) [18]. The OSDI includes an overall score and 3 subscale scores for ocular symptoms (3 items), vision-related function (6 items), and environmental triggers (3 items). Each OSDI item is scored using a Likert-type scale that ranges from 0 to 4 points, where 0 indicates "none of the time" and 4 indicates "all of the time."

Table 1 Ocular surface disease index: OSDI questionnaire

	Always	Most of the day	Half of the day	Occasionally	Never
How often did you experience any of the following eye symptoms in the past week?					
Photophobia?	4	3	2	1	0
Sensation of sand?	4	3	2	1	0
Pain or burning sensation?	4	3	2	1	0
Blurred vision?	4	3	2	1	0
Diminished visual acuity?	4	3	2	1	0
When did your eyes have these symptoms?					
Reading?	4	3	2	1	0
Driving?	4	3	2	1	0
Using the computer?	4	3	2	1	0
Watching TV?	4	3	2	1	0
When did your eyes feel dry during the past week?					
Discomfort with wind?	4	3	2	1	0
Dry?	4	3	2	1	0
Air-conditioned environment?	4	3	2	1	0

OSDI ocular surface disease index

The following formula for calculating the OSDI scores was used: (the sum from all of the answers × 100/the total number of questions answered × 4). The overall and subscale OSDI scores ranged from 0 to 100. Based on the OSDI scores, the patients were categorized as having a normal ocular surface (0–12 points) or mild (13–22 points), moderate (23–32 points), or severe (33–100 points) OSD [19].

To measure the BUT, a sterile strip of fluorescein was applied to the lower eyelid fornix and was then removed. The subject was asked to blink three times and then look straight ahead without blinking. The tear film was observed under cobalt blue-filtered light from a slit lamp microscope, and the time that elapsed between the last blink and the appearance of the first break in the tear film was recorded with a stopwatch. This procedure was repeated three times for both eyes. A BUT over 10 s was considered normal.

In the Schirmer I test, a filter paper strip (Color Bar™, Eagle Vision, Memphis, TN, USA) was used to measure the level of tears produced over 5 min. The strip was placed at the junction of the middle and lateral thirds of the lower eyelid. This test was performed under ambient light. The patients were directed to look forward and blink normally during the course of the test (5 min), and the wetting of the filter paper in 5 min was recorded. The normal range for the test was 10 mm/5 min.

The cornea and conjunctiva were observed after the administration of 10 % fluorescein sodium. Fluorescein staining of the cornea and nasal and temporal conjunctiva was assessed according to the Oxford scheme, which is based on a scale from 0 to 5 [20].

Impression cytology samples were obtained using cellulose acetate paper (Millipore filter, Ireland, 0.22 μm), which was pressed to the inferior and superior bulbar conjunctiva adjacent to the corneal limbus after the application of topical anesthesia (0.5 % proparacaine hydrochloride, Alcain, Alcon, USA). The cellulose acetate paper was pressed using the rubber stopper of a 1-cc syringe for approximately 5 s (Fig. 1). The paper was then removed and kept in 95 % ethanol in 24-well plates. The cellulose acetate paper was stained with periodic acid-Schiff (PAS) to evaluate the morphology and density of the epithelial and goblet cells. Each mounted slide was examined under an optical microscope (Axiophot Zeiss microscope, Oberkochen, Germany) in a 100× high-power field (HPF) and 200× HPF. The density of the goblet cells was calculated under a 100× HPF, and images of the goblet cells were acquired using AxioVison Release 4.5.

The safety evaluations included the assessment of adverse events and ophthalmologic examinations using slit-lamp biomicroscopy during the study.

Statistical analyses were performed using the software program SPSS (ver. 20.0; SPSS Inc., Chicago, IL, USA). A paired *t*-test was used to compare the IOP, OSDI score, BUT, Schirmer I test score, Oxford scheme score, and goblet cell count at different time points. $p < 0.05$ was considered significant for all subjects.

Results

A total of 138 eyes from 138 subjects were enrolled. Twenty-two (15.9 %) eyes were dropped from the study because of adverse drug reactions, such as eye irritation, eye discharge, conjunctival hyperemia, and eye pruritus.

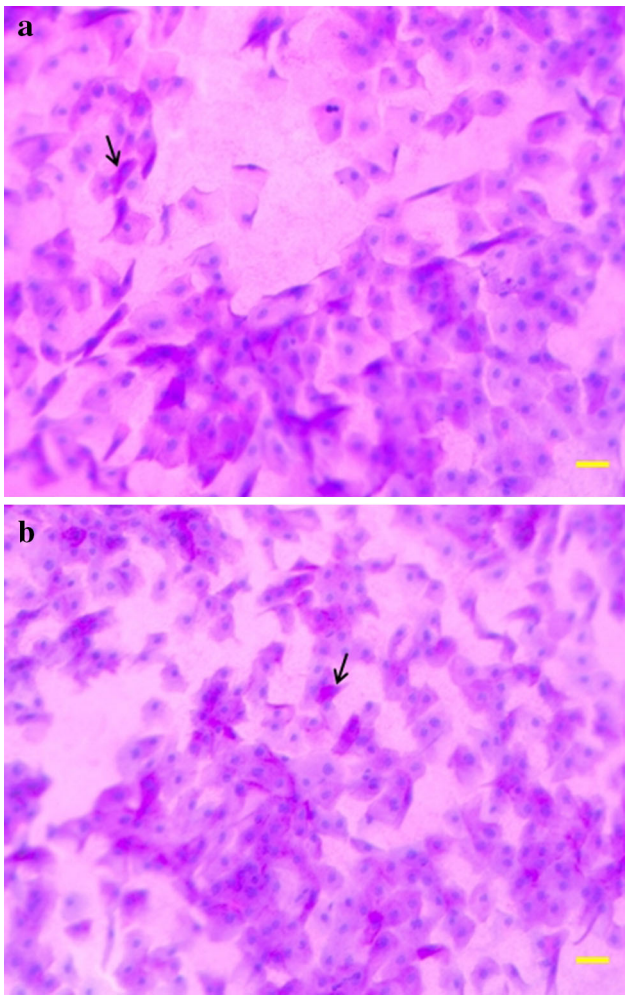

Fig. 1 Impression cytological findings (LM, periodic acid–Schiff, PAS). **a** The specimen before treatment with diquafosol exhibits a loss of goblet cells (*black arrow*). **b** The specimen after 9 weeks of treatment with diquafosol exhibits an increase in the number of PAS-positive goblet cells (*black arrow*) (*bar* = 20 μm)

As a result, 116 (84.1 %) eyes were analyzed. The mean age of the patients was 63.4 ± 13.8 years, and there were 51 men (44 %) and 65 women (56 %). All glaucoma patients exhibited open-angle glaucoma; 79 (68.1 %) had normal-tension glaucoma, and 37 (31.9 %) had primary open-angle glaucoma. The baseline IOP was 15.4 ± 2.8 mmHg, and the average number of topical glaucoma eye drops was 1.5 ± 0.5.

Throughout the treatment period, the mean IOP for all of the patients remained stable after treatment with diquafosol (15.4 ± 2.8 mmHg at baseline and 16.0 ± 2.8 mmHg at 52 weeks). Compared with the baseline levels, the IOP did not significantly change in any of the patients, and no statistically significant variations were detected.

The mean OSDI score improved significantly at 4, 12, and 52 weeks after the start of diquafosol treatment compared with the baseline values ($p = 0.003$; $p = 0.000$; $p = 0.041$). The BUT was significantly increased at 1, 4, 12, 36, and 52 weeks after the start of diquafosol treatment compared with the baseline values ($p = 0.031$; $p = 0.007$; $p = 0.006$; $p = 0.012$; $p = 0.009$). The Schirmer I test score was significantly increased 1, 12, 36, and 52 weeks after the start of diquafosol treatment ($p = 0.000$; $p = 0.003$; $p = 0.004$; $p = 0.001$, respectively). The Oxford scheme score was significantly decreased at 1, 4, 12, 36, and 52 weeks after the start of diquafosol treatment ($p = 0.000$; $p = 0.000$; $p = 0.000$; $p = 0.000$; $p = 0.000$; Table 2).

After impression cytology was performed, the goblet cell density was calculated under a light microscope. The goblet cell density increased gradually from 445.1 ± 92.2 cells/mm^2 at baseline to 511.0 ± 110.8 cells/mm^2 at 4 weeks, 520.5 ± 121.8 cells/mm^2 at 12 weeks, 504.8 ± 160.3 cells/mm^2 at 36 weeks, and 512.4 ± 177.3 cells/mm^2 at 52 weeks. A significant improvement was observed after 4 weeks of treatment with diquafosol ($p = 0.000$; $p = 0.000$; $p = 0.000$; $p = 0.000$, respectively).

Mild adverse drug reactions were reported in 22 (15.9 %) patients. All patients with adverse drug reactions were withdrawn from the study. There were no serious adverse drug reactions. Eye irritation (7 eyes, 5.1 %) occurred with the highest frequency, and additional adverse drug reactions were as follows: eye discharge (5 eyes, 3.6 %), conjunctival hyperemia (4 eyes, 2.9 %), eye pruritus (4 eyes, 2.9 %), foreign body sensation (2 eyes, 1.4 %), and ocular discomfort (2 eyes, 1.4 %).

Discussion

In this study, we found no significant differences in IOP levels in glaucoma patients who were treated with diquafosol during the 52-week follow-up period. Unlike the animal studies, we did not observe an increasing IOP effect from diquafosol in human eyes. Unlike normal eyes, there are some changes in the ciliary body in glaucomatous eyes. According to two studies, the primary open-angle glaucoma-related ciliary body changes were as follows: (1) the ciliary muscle contained an increased level of plaque material, the anterior tendons of the ciliary muscle appeared to be glued together, and the fiber sheaths of neighboring tendons tended to merge [21]; and (2) the ciliary muscle exhibited hyalinization and atrophy [22]. These changes interfere with the muscle function and outflow facility via the uveoscleral route, which may result in decreased outflow of the aqueous humor without interfering with the aqueous humor production function of the ciliary body. Therefore, we hypothesized that diquafosol may minimally exert its effect on $P2Y_2$ receptors or may

Table 2 Changes in the OSDI score, BUT, Schirmer I test value, and Oxford scheme score after 1, 4, 12, 36, and 52 weeks of treatment with diquafosol

	OSDI (score) (*p* value*)	BUT (s) (*p* value*)	Schirmer I test (mm) (*p* value*)	Oxford scheme (score) (*p* value*)
Baseline	52.17 ± 13.02	3.79 ± 1.94	4.52 ± 2.11	2.84 ± 1.01
Week 1	51.32 ± 13.14 (0.653)	4.30 ± 2.15 (0.031)	6.10 ± 2.75 (0.000)	2.30 ± 0.84 (0.000)
Week 4	47.34 ± 12.62 (0.002)	4.56 ± 2.50 (0.007)	4.86 ± 2.44 (0.223)	2.12 ± 0.88 (0.000)
Week 12	45.61 ± 12.48 (0.000)	4.72 ± 2.69 (0.006)	5.39 ± 2.47 (0.003)	1.93 ± 0.89 (0.000)
Week 36	49.71 ± 13.20 (0.164)	4.53 ± 2.65 (0.012)	5.44 ± 2.43 (0.004)	1.90 ± 0.76 (0.000)
Week 52	48.77 ± 13.27 (0.041)	4.70 ± 2.81 (0.009)	5.64 ± 2.79 (0.001)	1.89 ± 0.75 (0.000)

Expressed as the mean ± standard deviation

OSDI ocular surface disease index, *BUT* tear film break-up time

* Paired *t*-test statistical significance: $p < 0.05$ vs baseline

have another pharmacological effect on aqueous humor production and outflow in human eyes. Further studies are needed to determine the pharmacological effect of diquafosol in human glaucomatous eyes.

An improvement in the subjective symptoms (OSDI questionnaire) was observed 4, 12, and 52 weeks after administering diquafosol. The BUT, Schirmer I test, and Oxford scheme scores steadily improved over time during diquafosol therapy, which represented an improvement in the ocular surface properties of the treated eyes. As OSD progresses in severity, the number of goblet cells decreases, which may result in squamous metaplasia, enlargement of the epithelial area, and occasional keratinization of the ocular surface [23]. The goblet cell density was obtained using impression cytology in this study. A significant improvement in the goblet cell density was detected after 4 weeks of treatment with diquafosol compared with the baseline density, and this difference was statistically significant after 4 weeks of treatment. This secondary effect of diquafosol on goblet cells may be explained by the ability of diquafosol to promote calcium release from the endoplasmic reticulum of conjunctival epithelial and goblet cells, which promotes mucin and aqueous humor secretion from goblet cells and the conjunctival epithelium, respectively [7, 8]. The results of our study indicate that diquafosol is effective for OSD as well as for treating glaucomatous eyes with OSD.

Our study had the following limitations: (1) the study lacked a control group, and (2) our results do not reflect the type of glaucoma diagnosis or the number or type of anti-glaucoma medications used. A randomized, parallel group comparison study may be necessary to determine the usefulness of diquafosol. Additionally, the pharmacological mechanism of the effects of diquafosol on the ciliary body is needed to clarify the differences between previous animal studies [24–26] and our clinical study.

In conclusion, diquafosol was effective in improving objective and subjective symptoms and maintained a stable IOP in glaucoma patients with DES. Therefore, the addition of diquafosol treatment for glaucoma patients with DES or ocular surface side effects using anti-glaucoma medication may be beneficial.

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Conflicts of interest S. W. Jin, None; J. S. Min, None.

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