

# Intraocular Pressure Changes with the Use of Difluprednate: An Observational Study

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## Abstract

**Introduction:** Steroids are the mainstay in the treatment of ocular inflammation and in post-surgical cases. While these agents effectively treat and prevent inflammation, their use is also associated with risks, including ocular hypertension. A clinically significant intraocular pressure (IOP) increase is defined as an observed value >21 mmHg and/or change from baseline  $\geq 10$  mmHg. It has been noted in a few studies that difluprednate 0.05% ophthalmic emulsion has a likelihood of increasing the IOP.

**Purpose of the study:** To study the time of onset magnitude of IOP rise and to study the response of the raised IOP to treatment using topical and oral antiglaucoma medication and withdrawal of difluprednate, on IOP changes.

**Methodology:** Total of 49 cases of post-operative cataract surgery and a case of allergic conjunctivitis treated with difluprednate 0.05% 3 times a day on monitored at weekly intervals for 6 weeks. During such monitoring patients underwent visual acuity recording and complete ophthalmic examination including evaluation of IOP.

**Results:** Out of 50 patients, the 4 of the patients from the post-operative group and a case of allergic conjunctivitis treated with difluprednate showed marked increase in IOP, associated with corneal edema, rapid loss of vision and pain.

**Conclusion:** The patients on treatment with difluprednate can show marked raise in IOP which can be the cause for acute presentations of gross fall of vision and pain, this can be an ocular emergency.

**Key words:** Corneal edema, Difluprednate, Intraocular pressure, Ocular emergency

## INTRODUCTION

Intraocular pressure (IOP) may occur with application topical ocular preparations like corticosteroid drops or ointment applied to the skin of the eyelids. The risk of IOP rise increases with duration of use and may be directly correlated to its anti-inflammatory effect.<sup>1</sup> Difluprednate is the US- Food and Drug Administration (FDA) approved for post-operative pain, and has good ocular penetration good ocular penetration. It is used as an anti-inflammatory and in post-operative cases for pain relief and to prevent

inflammatory reactions. This drug is available freely in the market as diflucor and others.

### Pharmacology of Difluprednate

Difluprednate (difluoroprednisolone butyrate acetate, or DFBA) is a synthetic difluorinated prednisolone derivative (Figure 1).<sup>1</sup> Originally developed for dermatologic applications; the molecule derives its potency from fluorination at the C6 and C9 positions. Its anti-inflammatory activity is further augmented by replacing the 17-hydroxyl group with butyrate while its lipophilicity and hence, corneal penetration is enhanced by substituting the 21-hydroxyl group with acetate.<sup>2,3</sup>

On June 24, 2008, the U.S. FDA approved difluprednate, a strong topical steroid, for the treatment of post-operative ocular inflammation and pain. The first steroid to be indicated for pain associated with ocular surgery. The approved dosing for difluprednate is one drop in the

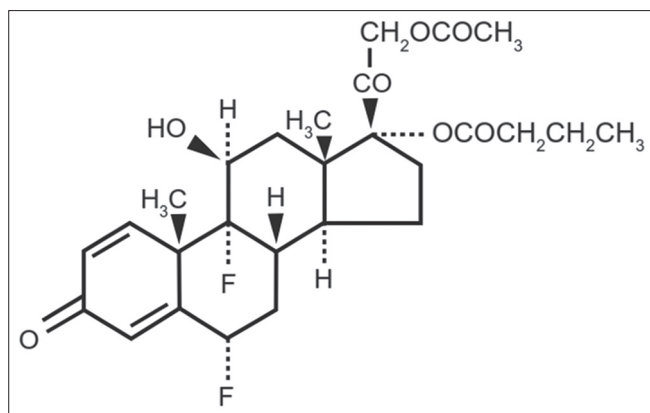
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www.ijss-sn.com

**Month of Submission :** 06-2015  
**Month of Peer Review :** 07-2015  
**Month of Acceptance :** 07-2015  
**Month of Publishing :** 08-2015

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**Figure 1: Difluprednate molecule**

affected eye(s) 4 times daily beginning 24 h after surgery and continuing for 2 weeks, followed by twice-daily dosing for a week, and then tapering based on the patient's response.<sup>4</sup>

Difluprednate ophthalmic emulsion 0.05% is also being studied in other ocular inflammatory diseases, including the U.S. Phase 3 study evaluating difluprednate for the treatment of anterior uveitis.<sup>5</sup>

This is a relatively newly developed topical anti-inflammatory steroid with high efficacy and is available as 0.05% ophthalmic emulsion. The stable oil-in-water emulsion formulation has an advantage of producing dosage consistency as the other formulations in suspension are needed to be shaken by the patient before instilling the drop for homogeneity of dosage. It has good tissue penetration and better bioavailability, along with fast local metabolism.<sup>6</sup>

### Pharmacokinetics

Once instilled, difluprednate emulsion is rapidly deacetylated in the aqueous humor to difluoroprednisolone butyrate (DFB), the drug's active metabolite, which has a similar corticosteroid activity profile. Endogenous tissue esterases then metabolize DFB to the inert metabolite hydroxyfluoroprednisolone butyrate, which limits systemic exposure to the active compound.<sup>7,8</sup>

Two multicenter, randomized, placebo-controlled phase 3 (registration) trials in 438 subjects with significant postoperative ocular inflammation (defined as more than 11 AC cells) demonstrated that both 4-times-daily and 2-times-daily difluprednate, beginning 24 h after surgery, effectively reduced inflammation and pain compared with placebo.<sup>9</sup>

### Purpose of the Study

Difluprednate ophthalmic emulsion has been shown to be associated with raised IOP when used for durations less than for other steroids, in this study we aim to study the

time of onset, magnitude of IOP rise. And response to treatment using topical and oral antiglaucoma medication and withdrawal of difluprednate on IOP changes.

## METHODOLOGY

A sample of 49 patients who had undergone small incision cataract surgery operated at a tertiary care hospital - KIMS Hospital and Research Centre, a case of allergic conjunctivitis who came to the ophthalmology outpatient department of KIMS Hospital. All the cases were operated and were started on medication after written consent. Helsinki Guidelines were followed for treatment of all patients. All patients were given difluprednate 0.05% ophthalmic emulsion (DIFLUCOR) manufactured by Ajantha Pharma, the patients were followed up over 6 weeks.

IOP was within normal limits before starting the drug and on further visits. The IOP was recorded using a rebound tonometer (icare) and a Perkins applanation tonometer. All patients underwent slit lamp examination, visual acuity testing at each visit.

## RESULTS

Out of 50 patients treated with difluprednate 0.05% 3 times a day, 5 patients showed significant increase in IOP from 2 days to 4 weeks, the range of IOP rise was 35-67 mmHg which is a clinically significant IOP increase, The earliest presentation was 2nd day and other case was 5<sup>th</sup> day, remaining 3 cases presented with raised pressures between 2<sup>nd</sup> and 4<sup>th</sup> week, as the IOP rise was marked, and was associated pain, loss of vision and corneal edema patients presented early. This helped to treat glaucoma and do the follow-up with concomitant medication.

All cases responded to the withdrawal of difluprednate and topical anti-glaucoma medication. Around 1% of cases are found to have a rapid rise in IOP.

### Case 1

Female aged 55 years underwent cataract surgery without complications. Recovered 6/9 vision by the end of 4 weeks, anterior segment was normal. The patient was started on topical difluprednate (0.05%) three times daily post-operatively.

Early in the 5<sup>th</sup> week, patient presented with a headache and inability to see with the operated eye. On examination we found ground glass cornea (oedematous), IOP measured 67 mm of Hg, vision was PL, the other eye showed IOP of 35 mm of Hg.

The patient was treated with anti-glaucoma drugs, timolol maleate (0.5%) and brimonidine. IOP became normal within 2 days in both the eyes.

Difluprednate (0.05%) was then restarted and the subject developed rise in IOP up to 60 mm of hg within 1-week in the operated eye and 25 mm of Hg in the other eye.

A provisional diagnosis of steroid-induced glaucoma was made, and the difluprednate (0.05%) was withdrawn and anti-glaucoma drugs (brimonidine and timolol) continued for another 2 weeks when the IOP normalized all anti-glaucoma drugs are withdrawn and patient's follow-up was uneventful.

#### Case 2

Female aged 65 years underwent cataract surgery without complications. Vision recovered to 6/24 by 2<sup>nd</sup> week, but by 3<sup>rd</sup> week subject developed corneal edema and gross drop in the vision to PL, IOP measured 48 mm of Hg and the other eye had IOP of 25 mm of hg.

The patient was continued with difluprednate (0.05%) and topical anti-glaucoma drugs timolol maleate (0.5%) and brimonidine (0.2%) combination, hyperosmotic agents, and cycloplegic therapy. Patient did not respond to the management the possibility of endothelial decompensation was thought of as the eye was not showing any inflammatory reactions, all the treatment withdrawn except anti-glaucoma drugs (timolol maleate 0.5% + brimonidine 0.2%) 2 times daily.

On follow-up after 2 months the cornea had become clear, uncorrected vision was 6/24 IOP measured 13 mm of hg in both the eyes. The timolol maleate + brimonidine 0.2% was withdrawn and the case was followed up weekly for 3 months and showed no recurrence of corneal edema and rise in IOP.

#### Case 3

Male aged 48 years underwent uneventful cataract surgery. Post-operative unaided vision acuity was 6/6 distant and  $n = 12$  near acuity on the 2<sup>nd</sup> week.

In 4<sup>th</sup> week, patient presented with total blurring of the vision. On examination IOP was 44 mm of hg and the other eye 22 mmHg.

The suspicion of steroid-induced glaucoma was made; difluprednate was withdrawn and started on timolol maleate 0.5% + brimonidine 0.2% 2 times daily.

By the end of 1-week, cornea became clear, and IOP measured 14 mmHg in both the eyes. Further follow-up

of patients without anti-glaucoma drugs showed normal IOP of 16 mmHg and uncorrected vision 6/6.

#### Case 4

Female patient aged 52 years underwent an uneventful cataract surgery in her left eye. The patient was started on difluprednate and moxifloxacin eye drop combination on 1<sup>st</sup> post-operative day.

The patient came back on the second post-operative day with pain, watering and blurring of vision in the operated eye. On examination cornea was hazy, descemets folds were seen. IOP was 40 mmHg measured with I care tonometer.

The patient was started on tab acetazolamide 250 mg tid and timolol maleate (0.5%) bd. Difluprednate eye drops was stopped, and patient was started on fluorometholone (0.1%) e/d and moxifloxacin e/d 6 times/day. The patient was followed up after 2 days with pressure down to 18 mmHg. The patient was continued on fluorometholone (0.1%) and tapered till 6 weeks later surgery.

#### Case 5

Male aged 26 years came with severe allergic conjunctivitis with visual acuity of 6/6 vision on both the eyes and was started on difluprednate eye drops 3 times a day.

The patient came back after 5 days with history of cloudy vision, and allergy symptom had disappeared. On examination cornea was hazy with IOP of 35 and 38 mmHg on the right and left eye respectively. Visual acuity was dropped to 6/12 vision in both the eyes.

Difluprednate eye drops were stopped and timolol maleate 0.5% twice a day started along with olopatadine 0.1% eye drops twice a day.

Patient was followed up after 1-week and the pressure was 18 and 19 mmHg in right and left eye, respectively, and the vision had improved to 6/6 in both the eyes and timolol maleate stopped after 3 weeks.

These observations were recorded within 6 months period among 60 patients treated with difluprednate (0.05%). This shows the possibility of incidence of steroid-induced glaucoma in patients receiving difluprednate (0.05%). This may probably be due to higher bioavailability of the drug in the eye as proven by studies and literature. These observations need to be substantiated by comparative studies with other steroid drugs and close monitoring of all cases on difluprednate (0.05%) for glaucoma and corneal changes at frequent intervals and if so proven the dosage and strength,

frequency and safety of difluprednate drug needs to be re-evaluated.

## DISCUSSION

There are several reports of difluprednate induced raised IOP.

The IOP-increasing potential of difluprednate investigated by Cable<sup>10</sup> in a retrospective chart review. Data from 100 consecutive, uncomplicated phacoemulsification patients treated with difluprednate ophthalmic emulsion 0.05% twice daily post-operatively were analyzed. Five percent of patients, all with a history of open-angle glaucoma, responded with ocular hypertension. The average increase in IOP among responders was 17.8 mmHg, considerably higher than the accepted value for a clinically significant increase ( $\geq 10$  mmHg). Moreover, 60% of IOP elevations were noted on post-operative day 1 and a further 40% on post-operative day 7. The authors concluded that difluprednate administered twice daily could cause significant and early elevations in IOP.

The present study showed marked IOP change probably because the cases were treated with difluprednate thrice daily as this product particulate can clog the trabecular meshwork. The incidence is low in our study as all the cases who showed raised IOP were normotensives before treatment. All patients who had raised IOP presented with acute manifestations. These patients may be strong steroid responders and treatment with difluprednate was stopped. They were started on loteprednol etabonate 0.5% eye drops and anti-glaucoma medications.

Meehan has reported raising of IOP within 2 weeks of initiating difluprednate treatment, resulting in an IOP increase from 9 mmHg to 48 mmHg with subsequent micro cystic edema.<sup>11</sup>

A significant IOP response (IOP increase of  $\geq 10$  mmHg from baseline and IOP  $\geq 24$  mmHg) was seen in 50% of eyes (13/26) and in 50% of patients (7/14) in patients treated with difluprednate in paediatric uveitis; 3 eyes of 2 patients required glaucoma surgery.<sup>12</sup>

## CONCLUSION

All patients are receiving topical ocular steroids, especially difluprednate have to be followed regularly and should be cautioned of acute raised of IOP causing pain and drop in vision. Once raise in IOP is observed, the drugs should be withdrawn and treated as early as possible with adjuvant medications. These cases may be high steroids responders. They should be branded as difluprednate responders. Future use should be prevented and if steroid use is necessary, safer steroids should or other alternatives should be preferred.

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**How to cite this article:** Sowbhagya HN, Manjunath N, Shetty S, Kumar LK. Intraocular Pressure Changes with the Use of Difluprednate: An Observational Study. *Int J Sci Stud* 2015;3(5):54-57.

**Source of Support:** Nil, **Conflict of Interest:** None declared.