HHS Public Access

Author manuscript

Am J Ophthalmol. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Am J Ophthalmol. 2022 August ; 240: 232–238. doi:10.1016/j.ajo.2022.03.026.

Risk of Elevated Intraocular Pressure with Difluprednate in Patients with Non-Infectious Uveitis

Mehmet Yakin, MD[1,2], **Aman Kumar**[1,3], **Shilpa Kodati, MD**[1], **Leslie Jones, MD**[4], **H. Nida Sen, MD, MSHc**[1]

[1]National Eye Institute, National Institutes of Health, Bethesda, MD

[2]University of Health Sciences, Ankara Training and Research Hospital, Ophthalmology Department, Ankara, Turkey

[3]Albany Medical College, Albany, NY

[4]Howard University College of Medicine, Ophthalmology Department, Washington DC

Abstract

Purpose: To evaluate risk factors associated with clinically important intraocular pressure (IOP) elevation with topical difluprednate treatment in patients with non-infectious uveitis.

Design: Retrospective cohort study.

Methods: ● **Setting:** Institutional. ● **Patient Population:** 54 eyes of 54 patients with non-infectious uveitis treated with topical difluprednate. ● **Observation Procedures:** Demographics, clinical characteristics of uveitis patients were collected. ● **Main Outcome Measures**: Development of clinically important IOP elevation defined as IOP ≥21 mmHg and an increase of ≥10 mmHg from baseline.

Results: Clinically important IOP elevation was observed in 17 patients (31.5%). The mean time to clinically important IOP elevation was 7.4 ± 4.8 weeks (range, 3 – 19). Statistically significant risk factors for incident clinically important IOP elevation were being a child (adjusted hazard ratio [aHR], 7.85 [95% CI, 1.48 – 41.56], p=.02) and concurrent use of systemic steroids (aHR, 5.31 [95% CI, 1.18 – 24.00], p=.03). Patients with concurrent systemic corticosteroids developed clinically important IOP elevation earlier than patients without systemic corticosteroid (Mean; 5.7 ± 3.4 [range, 3 – 14] vs 10.4 ± 5.7 [range, 4–19] weeks, p=.05). Incident IOP ≥30mmHg occurred in 13.0% of the entire cohort. All patients responded well to the cessation of difluprednate and/or use of topical anti-glaucomatous agents and no eyes required glaucoma surgery.

Corresponding author: H. Nida Sen MD, MSHc, National Eye Institute, National Institutes of Health, 10 Center Dr, Bethesda MD 20892, senh@nei.nih.gov.

Financial Disclosures: No financial disclosures.

Conclusions: Our study demonstrates that clinically important IOP elevation is common in uveitis patients with topical difluprednate treatment. Children and patients with concurrent systemic corticosteroids are at substantial risk of developing clinically important IOP elevation.

Table of contents statement

This study suggests that clinically significant IOP elevation is common in uveitis patients with topical difluprednate treatment. Children (aHR= 7.85, p= .02) and patients with concomitant systemic corticosteroid use (aHR= 5.31, p= .03) are at substantial risk of developing clinically important IOP elevation with topical difluprednate treatment. Patients with concurrent systemic corticosteroid use develop IOP elevation earlier than patients without systemic corticosteroid use (p= .05).

INTRODUCTION

Intraocular pressure (IOP) elevation in non-infectious uveitis is multifactorial including chronic damage to trabecular meshwork, obstruction of trabecular meshwork by inflammatory material, angle closure with or without pupillary block, peripheral anterior synechiae, recovery from ciliary body shutdown with resolution of inflammation, steroid response, or combination of several of these mechanisms.[1]

Corticosteroids are essential medications in uveitis with their rapid and effective control of inflammation but have an important ocular side effect profile that includes IOP elevation.[2] Corticosteroids alter protein turnover in trabecular meshwork, increase extracellular matrix protein deposition by inhibition of matrix metalloproteinases and reorganize cytoskeletal cellular network that ultimately lead trabecular swelling and reduced trabecular outflow.[3] The degree of IOP elevation is related to a patient's individual susceptibility to corticosteroids as well as the drug's potency, ocular penetration, route, frequency and duration of administration.[2,4,5] Treating uveitis with corticosteroids results in IOP elevation in up to one-third of patients.[6] Clinically important IOP elevation usually occurs after 2 – 6 weeks of treatment and typically returns to normal limits within 2 – 4 weeks after stopping corticosteroids.[1,2]

Difluprednate is a newer synthetic corticosteroid that has a 56-times greater receptor binding affinity than prednisolone acetate, a widely accepted standard topical corticosteroid for uveitis.[7,8] Topical difluprednate has superior intraocular penetration than prednisolone acetate resulting in higher therapeutic concentrations in the posterior segment of the eye.[9–15] Although topical difluprednate (Durezol, Alcon Laboratories, Fort Worth, TX, USA) was FDA approved for the treatment of inflammation and pain associated with ocular surgery and anterior uveitis in the United States, several studies have reported clinically effective results with topical difluprednate alone for the management of uveitic, diabetic and pseudophakic macular edema and for posterior segment inflammation such as for pars planitis and Vogt-Koyanagi-Harada disease.[10–21] Also, topical difluprednate was reported to have similar efficacy compared to sub-Tenon triamcinolone injection in reducing retinal thickness in patients with refractory diabetic macular edema.[10] These data suggest that topical difluprednate may be a valuable adjunct to other treatment modalities in the management uveitis other than anterior uveitis and in uveitic macular edema.

Difluprednate 0.05% eye drop has an advantage of less frequent use over prednisolone acetate with similar efficacy;[7,22] its 4 times a day regimen has been shown to be as effective as prednisolone acetate 1% eye drop, dosed 8 times a day for the treatment of anterior uveitis, potentially increasing patient compliance to treatment.[22]

The reported incidence of clinically important IOP elevation with difluprednate varies between studies. Furthermore, there is limited information on the incidence and risk factors associated with IOP elevation following difluprednate treatment in uveitis. Thus, the aim of our study is to evaluate potential risk factors associated with clinically important IOP elevation during difluprednate treatment in patients with uveitis.

PATIENTS AND METHODS

Records of uveitis patients treated with topical difluprednate between 2014 and 2020 at the National Eye Institute were retrospectively reviewed under institutional review board-approved clinical research protocol. The study adhered to the tenets of Helsinki Declaration. All patients were seen in the uveitis clinic, provided written informed consent and underwent a comprehensive eye examination. Demographic and clinical data were recorded at the time of initiation of treatment and at follow up visits. The main outcome measure was the incidence of a clinically important IOP elevation defined as having an IOP ≥21 mmHg and ≥10 mmHg increase from baseline at the same visit. Due to retrospective nature of the study, having this clinically important IOP elevation at one visit constituted the incident event. One eye from each patient was included in the study to prevent potential correlation between eyes from the same individual. For patients who received difluprednate treatment for both eyes, one eye was randomly selected as the study eye. Eyes with a history of intravitreal dexamethasone (Ozurdex) implant in the past 1 year, fluocinolone (Retisert, Iluvien, Yutiq) implant in the past three years and/or intravitreal triamcinolone acetonide or subtenon/periocular injection of corticosteroids within the past three months were excluded. Patients who had a change in their glaucoma medications during difluprednate treatment before development of clinically important IOP elevation and patients who had a history of glaucoma surgery were also excluded from the study. The classifications of uveitis and level of inflammation were based on the Standardization of Uveitis Nomenclature criteria.[23] Retinal nerve fiber thickness (RNFL) was evaluated by optical coherence tomography (Zeiss Cirrus 5000, Carl Zeiss Meditec AG, Germany). Changes in dosing frequency of difluprednate and timing of follow up schedules were made according to clinical response and to the discretion of physician.

For statistical analyses, SPSS v.17.0 statistical software for Windows (SPSS Inc., Chicago, IL) was used. For descriptive statistics, continuous variables are presented as means ± standard deviations or medians (ranges), and categorical variables are presented as frequencies and proportions. Univariable (crude) and multivariable (adjusted) Cox proportional hazards models were used to identify statistically significant predictors of incident clinically important IOP elevation. Comparisons of continuous variables between two variables were done by student t test for normally distributed variables. If the variables were not normally distributed, Mann-Whitney U test was used for comparisons between two

independent variables and Wilcoxon signed rank test was used for two dependent variables. A two- tailed p value of < .05 was considered statistically significant.

RESULTS

A total of 54 eyes of 54 patients were included in the study. The mean age of patients was 40.4 ± 18.8 years (range, 5 – 79). Nine of the patients (16.7%) were children (below age 18). Majority of patients were female (N=28; 51.9%). Uveitis was anterior in seven (13.0%), intermediate in 19 (35.2%), posterior in eight (14.8%), and panuveitis in 20 patients (37.0%). The mean duration of uveitis before difluprednate treatment was 34.0 ± 40.9 months. The indications for difluprednate treatment were active anterior uveitis in 18 patients (33.3%), active anterior uveitis with cystoid macular edema (CME) in 12 patients (22.2%), active vitritis with CME in 9 patients (16.7%), active vitritis in 7 patients (13.0%), and CME alone in 8 patients (14.8%). Difluprednate was used as monotherapy in 20 patients (37.0%), mostly in patients with anterior uveitis. In addition to topical difluprednate, 10 patients (18.5%) were on concurrent oral steroids, 9 patients (16.6%) were on other immunomodulatory therapy (IMT), and 15 patients (27.8%) received both oral steroids and other IMT. Mean dose of oral prednisone was 14.5 ± 10.5 mg; range 1 – 40).

At the time of difluprednate initiation, anterior chamber (AC) was quiet in 22 patients (40.7%). AC cell grade was 0.5+ in 11 patients (20.4%), 1+ in 14 patients (25.9%), and 2+ or worse in seven patients (13.0%). The mean baseline IOP before difluprednate treatment was 14.6 ± 3.6 mmHg (median 14, range 6 – 25). Fifteen patients (27.8%) were on topical glaucoma medications at baseline and mean number of glaucoma medications was 0.63 ± 1.1. The starting dose of difluprednate was two drops/day in 10 patients (18.5%), three drops/day in 9 patients (16.7%), four drops/day in 33 patients (61.1%), and six drops/day in two patients (3.7%). The mean duration of difluprednate treatment was 11.3 ± 9.9 weeks (range, 1 – 44). The mean peak IOP during difluprednate treatment was 22.6 ± 7.7 mmHg (median 20.5, range 10 – 48), which was significantly higher from baseline (p<.001).

Clinically important IOP elevation (defined as having IOP ≥21 mmHg together with ≥10mmHg IOP rise from baseline at the same visit) was observed in 17 patients (31.5%). All patients in our cohort who had ≥10mmHg rise in IOP from baseline also had an IOP reading ≥21 mmHg at the same visit. Three patients had an IOP of 21 – 25 mmHg at baseline. Two of them developed ≥10mmHg rise and were counted as having a clinically important IOP elevation. Among the remaining 51 patients who had an IOP <21 mmHg at baseline, 24 (47.1%) developed an IOP of ≥21 mmHg at some point during their difluprednate treatment.

The mean time to clinically important IOP elevation was 7.4 ± 4.8 weeks (median 6; range, 3 – 19). Risk factor evaluation revealed age <18 years and concurrent systemic corticosteroid use were the factors most associated with clinically important IOP elevation (Table 1). Five of 9 children (55.6%) and 12 of 45 adults (26.7%) developed clinically important IOP elevation. Children had an adjusted hazard ratio (aHR) of 7.85 (1.48 – 41.56) to develop clinically important IOP elevation compared to adults (p=.02). There was no statistically significant difference in the mean baseline IOP, duration of uveitis, duration

of difluprednate treatment and time to development of clinically important IOP elevation between children and adults (p= .65, .55, .19, and .47 respectively). Incident IOP ≥30mmHg occurred in 13.0% of the entire cohort; in 2 children (22.2%) and in 5 adults (11.1%).

Concurrent systemic corticosteroid use had an aHR of 5.31 (95% CI, 1.18 – 24.00) for developing clinically important IOP elevation (p=.03). There was no statistically significant difference in the mean baseline IOP, duration of uveitis, and duration of difluprednate treatment between patients with or without concurrent systemic steroids (p= .45, .46, and .25 respectively). However, patients with concurrent systemic corticosteroids developed clinically important IOP elevation earlier than patients without systemic corticosteroid (Mean; 5.7 ± 3.4 [range, 3 – 14] vs 10.4 ± 5.7 [range, 4 – 19] weeks, p= .05).

Cumulative dosing of difluprednate was calculated assuming compliance with the prescribed drop regimen. The mean total drop load was 228 ± 203 drops (range, 28 – 972). There was no statistically significant difference in the mean drop load between children and adult, patients with and without clinically important IOP elevation, and between patients with and without concurrent systemic steroids (p=.58, .42 and .19 consecutively).

No eyes required glaucoma surgery. All eyes with clinically important IOP elevation responded well to the cessation of difluprednate and/or topical anti-glaucomatous agents. The mean time to return to normal limits of IOP was 5.4 ± 3.3 weeks (range, 1 – 15.7). Mean number of topical glaucoma medications at this time was 0.81 ± 1.3 which was not significantly different from baseline (p=.06). Forty-five patients (83.3%) had no change in the number of glaucoma medications while 8 patients (14.8%) had an increase and 1 patient (1.9%) had decrease in glaucoma medications. There was no significant change in RNFL thickness at the cessation of difluprednate treatment compared to baseline in the both patients with and without clinically important IOP elevation (p=.94 and .16 respectively).

DISCUSSION

In this cohort of adult and childhood uveitis patients we found that about one-third of patients had clinically important rise in IOP with difluprednate treatment. Our study also identified several risk factors associated with clinically important IOP elevation during difluprednate treatment which are not extensively studied before in patients with uveitis (Table 1). Our results show that children with uveitis have an almost 8 times greater risk of developing clinically important IOP elevation compared to adults receiving topical difluprednate treatment (Table 1). A higher risk of corticosteroid induced IOP elevation in younger uveitis patients has been reported with other forms of corticosteroids,[5,24,25] though the risk associated with durezol among children has not been extensively studied. In a small case series, Slabaugh et al.[14] reported 50% rate of clinically important IOP elevation in patients with pediatric uveitis and Birnbaum et al.[26] also reported a higher rate of ≥10 mmHg IOP increase in children than in adults with topical difluprednate.

Unlike primary open angle glaucoma in which older age is a major risk factor, younger age is a risk factor for corticosteroid induced IOP elevation and glaucoma though the exact mechanisms of this is unclear.[3,27] Structural and functional immaturity of the trabecular

meshwork are considered important contributing factors but it isn't sufficient to explain corticosteroid related IOP elevation across the spectrum of pediatric patients since the final maturation of the angle components occur one to eight years after birth.[3,28] It is also known that trabecular meshwork cells decrease steadily throughout life and larger number of trabecular meshwork cells at a younger age, sensitive to the effects of corticosteroids, may explain higher rates of IOP elevation in younger patients.[25,27] Vitreous is more liquefied in elderly patients which may allow for more posterior segment diffusion of the drug with subsequently less corticosteroid induced IOP elevation.[25] Lastly, another hypothesis is that younger eyes may produce more aqueous than older eyes but have an equal degree of corticosteroid-induced compromise of drainage leading to greater likelihood of an IOP spike.[4] Systemic corticosteroids by themselves are known to be a risk factor for IOP elevation.[2,4,29] Our results demonstrate that concurrent topical and systemic corticosteroid use increase the risk of clinically important IOP elevation by approximately 5-fold (Table 1) and shortens the time to clinically important IOP elevation compared to topical difluprednate use alone. This may be explained by increased total cumulative exposure of the trabecular meshwork to corticosteroids with both systemic and topical therapies.

Studies suggest a gradually increased risk of IOP elevation with increased frequency of topical steroid administration both in children and adults.[29–31] In our study, we also found that patients receiving more than two drops/day of difluprednate were more likely to develop clinically important IOP elevation but the relative risk was not statistically significant (Table 1).

Previous studies on topical difluprednate treatment report variable rates of clinically important IOP elevation ranging from 1.7% to 52% (Table 2). In studies investigating the use of difluprednate in postoperative inflammation, an incidence of 1.7% – 35% of clinically important IOP elevation for variable treatment times ranging from 5 – 41.6 days has been reported.[7,32–37] Among uveitis patients incidence of IOP elevation was 6% - 52% for variable treatment duration ranging from 4 – 16.4 weeks.[14,16,22,26,38] It is challenging to compare different studies due to variabilities in study designs, study populations and treatment durations. In general, studies that included shorter periods of difluprednate treatment report lower rates of IOP elevation compared with others. For example, the incidence of clinically important IOP elevation varies from 1.7% to 16.5% for up to 1 month of difluprednate exposure, compared to 35% to 50% for longer exposure times (Table 2).

Risk factors associated with IOP elevation with topical difluprednate treatment are not well defined among uveitis patients though age and history of glaucoma have been found as risk factors among patients using difluprednate for postoperative inflammation.[37] In uveitis, it can be difficult to differentiate whether an IOP elevation is due to corticosteroid therapy, due to inflammation itself or recovery from ciliary body shutdown with resolution of inflammation. Considering the majority of our patients started with an AC cell grade of less than 2+ cells (87.9%) and developed clinically important IOP elevation at least three weeks after the start of difluprednate, we believe that drug effect is a major component of IOP elevation. Furthermore, we didn't find a significant association between AC cell grade and IOP increase in both crude and adjusted regression analyses (Table 1).

Elevated IOP caused by corticosteroids is usually more controllable than those arising from other causes in uveitis patients.[39] Indeed, in our study, all cases with clinically important IOP elevation responded well to the cessation of the drug and/or anti-glaucomatous medications and none of the patients required surgery.

Our study is limited by its retrospective design, limited sample size, especially for children, variability in patient characteristics and uveitis etiologies, non-standardized difluprednate dosing, variability in systemic prednisone dosing during difluprednate treatment, treatment and follow up times, lack of multiple IOP timepoints and by a potential bias due to the tertiary care setting which may have resulted in the inclusion of more refractory uveitis patients. Also, due to variability in study designs, study populations and treatment durations, comparisons across studies including with our own are difficult to make. On the other hand, our study has the strength of incorporating risk factor evaluation by regression analyses while adjusting for multiple clinical factors and thus provides an important contribution to the knowledge gap on the association between IOP elevation and topical difluprednate treatment in non-infectious uveitis patients.

In conclusion, our study demonstrates that clinically important IOP elevation is common in uveitis patients with difluprednate treatment. Children and patients with concurrent systemic corticosteroids are at substantial risk of developing clinically important IOP elevation. Thus, our results emphasize the importance of careful management of inflammation with difluprednate and surveillance for IOP elevation at each visit especially for children and patients with concurrent systemic corticosteroid use. Prospective, comparative studies in uveitis population are needed to better understand the relationship between IOP and difluprednate use which would be a better guidance about timing, dosing and monitoring of difluprednate treatment in uveitis.

ACKNOWLEDGMENTS/DISCLOSURE

Funding/Support: This work was supported by the National Eye Institute Intramural Research Program, National Institutes of Health.

REFERENCES

1. Kesav N, Palestine AG, Kahook MY, Pantcheva MB. Current management of uveitis-associated ocular hypertension and glaucoma. Surv Ophthalmol. 2020;65(4):397–407. [PubMed: 31816329]
2. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol. 2000;11(6):478–483. [PubMed: 11141645]
3. Roberti G, Oddone F, Agnifili L, et al. Steroid-induced glaucoma: Epidemiology,pathophysiology, and clinical management. Surv Ophthalmol. 2020;65(4):458–472. [PubMed: 32057761]
4. Friedman DS, Holbrook JT, Ansari H, et al. Risk of elevated intraocular pressure and glaucoma in patients with uveitis: results of the multicenter uveitis steroid treatment trial. Ophthalmology. 2013;120(8):1571–1579. [PubMed: 23601801]
5. Musleh MG, Bokre D, Dahlmann-Noor AH. Risk of intraocular pressure elevation after topical steroids in children and adults: A systematic review. Eur J Ophthalmol. 2020;30(5):856–866. [PubMed: 31668084]
6. Baneke AJ, Lim KS, Stanford M. The pathogenesis of raised intraocular pressure in uveitis. Curr Eye Res. 2016;41(2):137–149. [PubMed: 25974243]

7. Donnenfeld ED. Difluprednate for the prevention of ocular inflammation postsurgery: an update. Clin Ophthalmol. 2011;5:811–816. [PubMed: 21750615]
8. Tajika T, Waki M, Tsuzuki M, Kida T, Sakaki H. Pharmacokinetic features ofdifluprednate ophthalmic emulsion in rabbits as determined by glucocorticoid receptor-binding bioassay. J Ocul Pharmacol Ther. 2011;27(1):29–34. [PubMed: 21182429]
9. Tajika T, Isowaki A, Sakaki H. Ocular distribution of difluprednate ophthalmicemulsion 0.05% in rabbits. J Ocul Pharmacol Ther. 2011;27(1):43–49. [PubMed: 21118027]
10. Nakano S, Yamamoto T, Kirii E, Abe S, Yamashita H. Steroid eye drop treatment (difluprednate ophthalmic emulsion) is effective in reducing refractory diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2010;248(6):805–810. [PubMed: 20180131]
11. Nakano Goto S, Yamamoto T, Kirii E, Abe S, Yamashita H. Treatment of diffusediabetic macular oedema using steroid eye drops. Acta Ophthalmol. 2012;90(7):628632.
12. Lu S, Taban M. Topical difluprednate for treatment of serous retinal detachment andpanuveitis associated with Vogt-Koyanagi-Harada disease. Digit J Ophthalmol. 2016; 22(2): 54–57. [PubMed: 27582676]
13. Kurz PA, Chheda LV, Kurz DE. Effects of twice-daily topical difluprednate 0.05%emulsion in a child with pars planitis. Ocul Immunol Inflamm. 2011;19(1):84–85. [PubMed: 21034305]
14. Slabaugh MA, Herlihy E, Ongchin S, van Gelder RN. Efficacy and potentialcomplications of difluprednate use for pediatric uveitis. Am J Ophthalmol. 2012;153(5):932–938. [PubMed: 22265149]
15. Onishi SM, Asahi MG, Chou C, Gallemore RP. Topical difluprednate for thetreatment of Harada's disease. Clin Ophthalmol. 2015; 9:157–167. [PubMed: 25653498]
16. Schallhorn JM, Niemeyer KM, Browne EN, Chhetri P, Acharya NR. Dfluprednate forthe treatment of uveitic cystoid macular edema. Am J Ophthalmol. 2018;191:14–22. [PubMed: 29580977]
17. Feiler D, Lowder CY. Resolution of uveitic cystoid macular edema with topicaldifluprednate. Invest Ophthalmol Vis Sci. 2015;56(7):6175.
18. Feiler DL, Srivastava SK, Pichi F, Bena J, Lowder CY. Resolution of noninfectiousuveitic cystoid macular edema with topical difluprednate. Retina. 2017;37(5):844–850. [PubMed: 27529841]
19. Symes RJ, Forooghian F. Topical difluprednate monotherapy for uveitic macularedema. Can J Ophthalmol. 2016;51(1):47–49. [PubMed: 26874159]
20. Chalam K, Khetpal V, Patel CJ. Spectral domain optical coherence tomographydocumented rapid resolution of pseudophakic cystoid macular edema with topical difluprednate. Clin Ophthalmol. 2012;6:155–158. [PubMed: 22291458]
21. Kaur S, Yangzes S, Singh S, Sachdev N. Efficacy and safety of topical difluprednatein persistent diabetic macular edema. Int Ophthalmol. 2016;36(3):335–340. [PubMed: 26296375]
22. Foster CS, Davanzo R, Flynn TE, McLeod K, Vogel R, Crockett RS. Durezol(Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. J Ocul Pharmacol Ther. 2010;26(5):475–483. [PubMed: 20809807]
23. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature(SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–516. [PubMed: 16196117]
24. Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitrealtriamcinolone in uveitis. Ophthalmology. 2005;112(11):1916.e1–7.
25. Parekh A, Srivastava S, Bena J, Albini T, Nguyen QD, Goldstein DA. Risk factorsassociated with intraocular pressure increase in patients with uveitis treated with the fluocinolone acetonide implant. JAMA Ophthalmol. 2015;133(5):568–573. [PubMed: 25719937]
26. Birnbaum AD, Jiang Y, Tessler HH, Goldstein DA. Elevation of intraocular pressurein patients with uveitis treated with topical difluprednate. Arch Ophthalmol. 2011;129(5):667–668. [PubMed: 21555625]
27. Tektas OY, Lütjen-Drecoll E. Structural changes of the trabecular meshwork indifferent kinds of glaucoma. Exp Eye Res. 2009;88(4):769–775. [PubMed: 19114037]
28. Reme C, d'Epinay SL. Periods of development of the normal human chamber angle. Doc Ophthalmol. 1981;51(3):241–268. [PubMed: 7285772]

29. Daniel E, Pistilli M, Kothari S, et al. Risk of ocular hypertension in adults with noninfectious uveitis. Ophthalmology. 2017;124(8):1196–1208. [PubMed: 28433444]

30. Kothari S, Foster CS, Pistilli M, et al. The Risk of Intraocular Pressure Elevation inPediatric Noninfectious Uveitis. Ophthalmology. 2015;122(10):1987–2001. [PubMed: 26233626]

31. Ng JS, Fan DS, Young AL, et al. Ocular hypertensive response to topicaldexamethasone in children: a dose-dependent phenomenon. Ophthalmology. 2000;107(11):2097–2100. [PubMed: 11054340]

32. Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS. Difluprednateophthalmic emulsion 0.05% for postoperative inflammation and pain. J Cataract Refract Surg. 2009;35(1):26–34. [PubMed: 19101421]

33. Smith S, Lorenz D, Peace J, McLeod K, Crockett RS, Vogel R. Difluprednateophthalmic emulsion 0.05% (Durezol) administered two times daily for managing ocular inflammation and pain following cataract surgery. Clin Ophthalmol. 2010;4:983–991. [PubMed: 20856594]

34. Donnenfeld ED, Holland EJ, Solomon KD, et al. A multicenter randomized controlledfellow eye trial of pulse-dosed difluprednate 0.05% versus prednisolone acetate 1% in cataract surgery. American J Ophthalmol. 2011;152(4):609–617.e1.

35. Jeng KW, Fine HF, Wheatley HM, Roth D, Connors DB, Prenner JL. Incidence ofsteroid-induced ocular hypertension after vitreoretinal surgery with difluprednate versus prednisolone acetate. Retina. 2014;34(10):1990–1996. [PubMed: 25121927]

36. Wilson ME, O'Halloran H, VanderVeen D et al. . Difluprednate versus prednisoloneacetate for inflammation following cataract surgery in pediatric patients: a randomized safety and efficacy study. Eye (Lond). 2016;30(9):1187–1194. [PubMed: 27367745]

37. Kusne Y, Kang P, Fintelmann RE. A retrospective analysis of intraocular pressurechanges after cataract surgery with the use of prednisolone acetate 1% versus difluprednate 0.05%. Clin Ophthalmol. 2016;10:2329–2336. [PubMed: 27920493]

38. Sheppard JD, Toyos MM, Kempen JH, Kaur P, Foster CS. Difluprednate 0.05%versus prednisolone acetate 1% for endogenous anterior uveitis: a phase III, multicenter, randomized study. Invest Ophthalmol Vis Sci. 2014;55(5):2993–3002. [PubMed: 24677110]

39. Sallam A, Sheth HG, Habot-Wilner Z, Lightman S. Outcome of raised intraocularpressure in uveitic eyes with and without a corticosteroid-induced hypertensive response. Am J Ophthalmol. 2009;148(2):207–213.e1. [PubMed: 19403113]

HIGHLIGHTS

- IOP elevation is common among uveitis patients treated with difluprednate drops
- Children are more sensitive to difluprednate associated IOP elevation than adults
- Concurrent systemic steroid use increases likelihood of IOP elevation
- Concurrent systemic steroids cause earlier IOP elevation than difluprednate alone

Table 1.

Risk factors of clinically important IOP elevation with difluprednate in patients with non-infectious uveitis.*

Variable		Crude			Adjusted**	
		Events/At Risk	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age group	Adult	12/45 (26.7%)	1		1	
	Children	5/9 (55.6%)	1.98 (0.69 – 5.65)	.21	7.85 (1.48 – 41.56)	.02
Gender	Male	8/26 (30.8%)	1		1	
	Female	9/28 (32.1%)	1.04 (0.40 – 2.69)	.94	1.32 (0.33 – 5.40)	.70
Uveitis category	Anterior	1/7 (14.3%)	1		1	
	Intermediate	4/19 (21.1%)	1.26 (0.14 – 11.33)	.84	6.66 (0.21 – 216.44)	.29
	Posterior	3/8 (37.5%)	2.05 (0.21 – 19.76)	.54	5.74 (0.25 – 134.08)	.28
	Panuveitis	9/20 (45.0%)	2.42 (0.31 – 19.22)	.40	23.85 (0.82 – 692.45)	.07
Duration of uveitis history	<6 Months	7/20 (35.0%)	1		1	
	6 Months to <2 Years	5/14 (35.7%)	0.94 (0.30 – 2.98)	.92	5.76 (0.36 – 91.76)	.22
	2 to <5 Years	2/8 (25.0%)	0.71 (0.15 – 3.41)	.66	3.58 (0.38 – 33.95)	.27
	5+ years	3/12 (25.0%)	0.46 (0.12 – 1.77)	.26	3.49 (0.18 – 68.42)	.41
Anterior chamber cell grade at baseline	Quiet	7/22 (31.8%)	1		1	
	0.5+	4/11 (36.4%)	1.21 (0.35 – 4.16)	.76	3.24 (0.43 – 24.54)	.26
	1+	3/14 (21.4%)	0.85 (0.22 – 3.28)	.81	2.45 (0.30 – 19.78)	.40
	2+ or worse	3/7 (42.9%)	1.87 (0.48 – 7.28)	.36	1.09 (0.12 – 9.94)	.94
History of glaucoma/OHT	No	11/38 (28.9%)	1		1	
	Yes	6/16 (37.5%)	1.23 (0.45 – 3.35)	.69	1.98 (0.55 – 7.12)	.30
Prior cataract surgery	No	15/42 (35.7%)	1		1	
	Yes	2/12 (16.7%)	0.35 (0.08 – 1.52)	.16	0.10 (0.005 – 2.18)	.14
Difluprednate drops/day at baseline	2	2/10 (20.0%)	1		1	
	3	3/9 (33.3%)	1.69 (0.28 – 10.18)	.57	0.48 (0.04 – 5.73)	.56
	4 or more***	12/35 (34.3%)	2.50 (0.56 – 11.23)	.23	1.81 (0.29 – 11.33)	.52

Am J Ophthalmol. Author manuscript; available in PMC 2023 August 01.

Variable		Crude			Adjusted**	
		Events/At Risk	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Concurrent systemic steroid use	No	6/29 (20.7%)	1		1	
	Yes	11/25 (44.0%)	2.56 (0.94 – 6.99)	.07	5.31 (1.18 – 24.00)	.03
Concurrent systemic immunosuppressive therapy/Biologics	No	10/30 (33.3%)	1		1	
	Yes	7/24 (29.2%)	0.61 (0.23 – 1.60)	.31	0.30 (0.06 – 1.56)	.15

*Clinically important IOP elevation defined as having an IOP ≥21 mmHg and ≥10 mmHg increase from baseline at the same visit.

**Adjusted by age group, gender, uveitis category, duration of prior uveitis, anterior chamber cell grading, history of glaucoma/OHT, prior cataract surgery, difluprednate dosage, concurrent systemic steroid use, concurrent immunosuppressive use.

***Only 2 eyes received 6 drops/day regimen. The rest of the eyes received 4 drops/day regimen.

IOP; Intraocular pressure, OHT; Ocular hypertension, 95% CI; 95% confidence interval.

Table 2.

Studies about difluprednate treatment for the management of uveitis or postoperative inflammation control.

Study and year	Study population	No. of patients	Mean age in years ± SD (range)	Difluprednate time	Clinically important IOP elevation*	Risk factors identified
Our study	Uveitis	54	40.4 ± 18.8 (5 – 79)	Mean 11.3 ± 9.9 weeks (1 – 44)	31.5%	Children Concurrent systemic steroid
Schallhorn et al. 2018	Uveitic macular edema	58 (72 eyes)	Median 45 (7 –92)	1 month	8 eyes (11%)	
Kusne et al. 2016	Post-cataract surgery in adults	1337	70.6 ± 8.5	Range 5 – 10 days	4.4%	Older age (>75 years) Glaucoma history
Wilson et al. 2016	Post-cataract surgery in children	39	Range 0 – 3	4 weeks	5.1% (IOP >21 mmHg)	
Jeng et al. 2014	Post-vitreoretinal surgery	100	64.9	Mean 41.6 days	35%	
Sheppard et al. 2014	Endogenous anterior uveitis	56	49.9 ± 15.3 (11 – 87)	Mean 27.0 ± 7.1 days	16.1%	
Slabaugh et al. 2012	Pediatric non-infectious uveitis	14	12 ± 3 (7 – 18)	Median 27 weeks (4 – 63)	50% **	
Birnbaum et al. 2011	Uveitis	27	34 (6 – 63)	Mean 16.4 weeks (1 – 46)	52% (≥10 mmHg IOP increase)	Children
Donnenfeld et al. 2011	Post-cataract surgery in adults	59	70.5 (51 – 105)	2 weeks	1.7%	
Foster et al. 2010	Endogenous anterior uveitis	50	46.5 ± 15.1	4 weeks	6%	
Smith et al. 2010	Post-cataract surgery	81	69.4 ± 9.44 (44 – 86)	1 month	3.7%	
Korenfeld et al. 2009	Post-ocular surgery in adults	218	Median 70 (24 – 88)	4 weeks	3%	

*Clinically important IOP elevation defined as having an IOP ≥21 mmHg and ≥10 mmHg increase from baseline at the same visit.

**Clinically important IOP elevation defined as having an IOP ≥24 mmHg and ≥10 mmHg increase from baseline in this study.

IOP; Intraocular pressure, SD; Standard deviation.