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Incidence of Corneal Melt in Clinical Practice: Our Experience vs. A Meta-Analysis of the Literature

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Abstract

Purpose: To evaluate the long-term safety of NSAID drops and incidence of corneal melt including contributing factors when bromfenac, ketorolac, or nepafenac are used long-term at a dosing frequency (up to four-times daily) in patients with macular edema secondary to macular cysts, full thickness macular holes, ERM, or cystoid macular edema. A comparison of our practices safety data was compared to historically reported data to try to identify incidence rates of corneal melt as well as to identify risk factors to help predict patients at-risk.

Methods: IRB Approved retrospective review of 501 patient records, divided evenly between bromfenac, ketorolac, and nepafenac (n=167 each). Patients were on the NSAID for at least 3 months and not greater than 120 months (10 years). Data collected included the NSAID prescribed, time on the NSAID (in months), and comorbidities (focusing especially on arthritis, diabetes, dry eye, and high blood pressure).

Results: Overall, the mean duration of treatment with any NSAID was 26.1 (± 13.6) months (range: 3-120 months). Dosing was similar among the three NSAIDs, with 75.5% of patients instructed to instill the drops QID. Most patients also had at least one comorbid condition: high blood pressure and dry eye were the most common (40.9% and 33.5%, respectively). The reasons for which the NSAIDs were prescribed included macular hole (37.1%), macular cyst hole/pseudo-hole (19.2%), ERM (30.5%) and cystoid macular edema (13.2%). There were no cases of corneal melt reported.

Conclusion: Corneal melt is an extremely rare condition that likely has a multifactorial etiology, including underlying comorbidities, use of multiple medications, and surgery. Our data suggest, however, that the newer NSAIDs are safe to use over an extended period of time and at a frequency of up to four-times daily without increased risk of corneal melt.

Introduction

Topical ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in ophthalmology to prevent and treat non-infectious inflammation of the eye. In patients undergoing cataract surgery, NSAIDs are used to prevent intraoperative miosis, manage postoperative pain and inflammation, and prevent or treat cystoids macular edema (CME) after lens removal [1]. These drugs, however, are now being prescribed off-label for many retinal conditions, such as cystoid macular edema, diabetic macular edema, wet age-related macular degeneration (in combination with anti-Vascular Endothelial Growth Factor (VEGF) injections), epiretinal membrane, and macular hole and central serous retinopathy. Currently these medications are approved for only 14 days in a cataract or refractive surgical environment [2,3].

The anti-inflammatory effects of NSAIDs result from inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, blocking the synthesis of prostaglandins, which are the most critical lipid-derived mediators of tissue inflammation [3]. Additional mechanisms may also contribute to the anti-inflammatory action of NSAIDs, including the ability to suppress polymorphonuclear (PMN) cell locomotion and chemotaxis, an activity that probably occurs through a direct effect on the PMNs [4]. In experimental ocular allergy models, NSAIDs have been found to inhibit the expression of inflammatory cytokines and reduce mast cell degranulation [5]. NSAIDs have also been associated with free radical scavenger activity, which could be advantageous during inflammation [6]. Furthermore, as organic acids; NSAIDs tend to cluster at inflammation sites, a favorable attribute for anti-inflammatory drugs [6].

In recent years, the introduction of three novel ophthalmic NSAIDs, bromfenac, ketrolac tromethamine, and nepafenac, have provided clinicians a wider range of options from which to choose. Bromfenac, is indicated for the treatment of postoperative inflammation and the reduction of ocular pain following cataract surgery [7] and was approved in the United States in 2005 as bromfenac sodium ophthalmic solution 0.09% (Xibrom™), Ista Pharmaceuticals, Inc. Irvine, CA) and labeled for twice-daily use (BID). In October 2010, the Food and Drug Administration (FDA) approved bromfenac 0.09% for once-daily (QD) use (Bromday™, Ista Pharmaceuticals Inc, and Irvine, CA).

Ketorolac tromethamine was originally formulated as a 0.5% solution marketed in the United States and Europe as Acular (Allergan, Inc., Irvine, CA) and labeled for use four-times daily (QID) [1]. Since burning and stinging upon instillation were commonly reported, a new formulation, Acular LS 0.4%, was introduced in the United States in 2003.

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Nepafenac 0.1% (Nevanac; Alcon Laboratories, Inc.; Fort Worth, TX) is indicated for the treatment of pain and inflammation following cataract surgery and is labeled for use as a three-times daily drug (TID) [2].

Although topical NSAIDs can be highly effective in preventing and treating inflammation of the eye, they have also been associated with various adverse events. A serious example occurred in the 1990s with the recall of a generic form of diclofenac ophthalmic solution (Falcon Pharmaceuticals, Ltd.; an affiliate of Alcon Laboratories, Inc., USA) following reports of associated corneal melts [8]. Corneal melt is still of prominent concern to clinicians today, however, very little research has been published evaluating the incidence of corneal melt with the newer NSAIDs, particularly when these agents are used long-term. Moreover, there has been no agreement as to the whether the melts are actually due to NSAID use as all reports show comorbidities and concomitant medications that confound conclusion [9-14].

The purpose of this study was to evaluate the incidence of corneal melt and contributing factors when bromfenac, ketorolac, or nepafenac are used long-term and at a high dosing frequency in clinical practice.

Methods

An IRB retrospective review of patient records was performed in our practice from 1999-2009. Patients who were on the NSAID continuously for at least 3 months duration were included in analysis.

Data collected included the NSAID prescribed, time on the NSAID (in months), whether the NSAID was dosed unilaterally or bilaterally, and comorbidities (focusing especially on arthritis, diabetes, dry eye, and high blood pressure). The reason the NSAID was prescribed was also described (for example, treatment/prevention of CME, or treatment of macular edema due to macular hole, macular cyst hole/pseudo-hole, or epiretinal membrane (ERM). Patients who had edema due to these conditions and declined surgery or were declined by insurance were placed on non steroidal drops in the hope of minimizing the cystoid component of the disease.

Results

A diagnosis of corneal melt and perforation was searched for in our billing records over the years 1999-2009. No diagnosis code was found. Since no diagnosis was found we decided to survey equal numbers of patients on different NSAID in order to examine any missed findings and describe any other comorbidities. In order to minimize bias equal numbers of charts were examined of each of the non steroidal drugs. The cases were selected randomly based on a search of each of the medications. We performed an EMR search using 3 NSAIDs over the last 10 years. One hundred sixty seven patients were selected per drug at random based on alphabetical names. Five hundred and one patient records were reviewed over this time period, with 167 patients prescribed each NSAID (bromfenac, ketorolac, or nepafenac) in order to minimize bias. Seventy-five percent of patients (374/501) were treated unilaterally. Demgraphic information for ketorolac (n=167, mean age 74, 55.7% female), nepafenac (n=167, mean age 69, 52.1% female), bromfenac (n=167, mean age 70, 57.5% female) is displayed in Figure 1.

Overall, the mean duration of treatment with any NSAID was 26.1 (± 13.6) months (range: 3-120 months). Patients were on nepafenac (36.0 ± 6.7 months), ketorolac (20.9 ± 16.8 months) and bromfenac (21.7 ± 9.0 months, Figure 2).

Dosing was similar among the three NSAIDs, with most patients

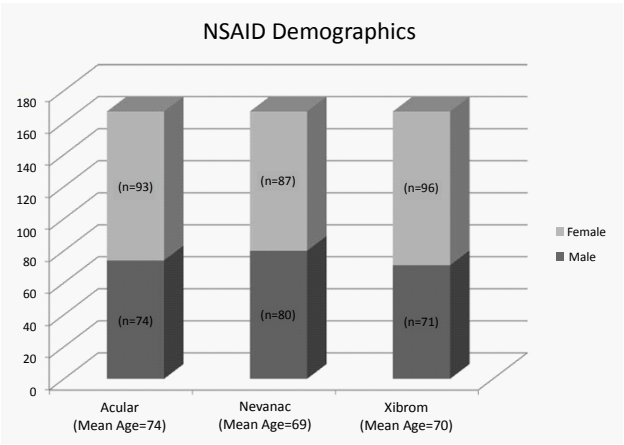

Figure 1: NSAID Demographics.

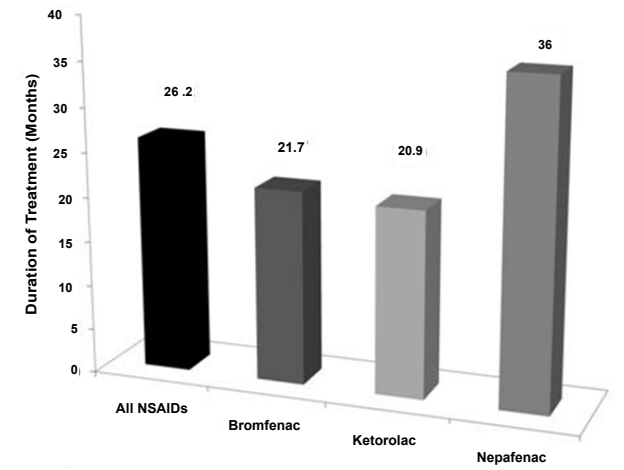

Figure 2: Mean duration of treatment (in months) for all patients and by each NSAID.

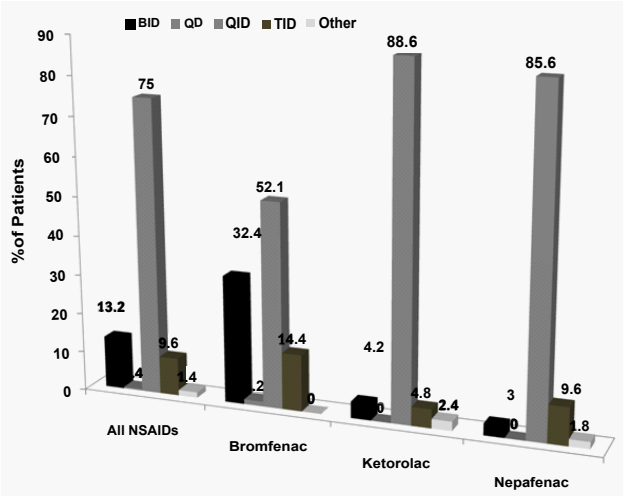

Figure 3: Dosing frequency of NSAIDs in all patients and by each NSAID.

instructed to instill the drops QID (Figure 3). Most patients also had at least one comorbid condition, with high blood pressure the most common, at 40.9% (Figure 4) followed by dry eye (34.5%), diabetes (31.1%) and arthritis (25.4%).

The most common reasons for which the NSAIDs were prescribed included full thickness macular hole (37.1%) macular cyst hole/pseudohole (19.2%), ERM (30.5%) and cystoid macular edema (13.2%). The three NSAIDs were all prescribed for each condition but their distributions varied by the etiology being treated (Figure 5).

No corneal melts were found during a query of all the patients on non-steroidals in our practice over the last 10 years. All three NSAIDS were safe and there was a 0.0% incidence of corneal melting or corneal thinning in this cohort. Corneal melt was defined as any persistent defect or thinning of the cornea other than superficial pinctate keratitis. In addition, there was no difference in the development of new corneal diagnoses (dry eyes, Keratitis) between the different drugs.

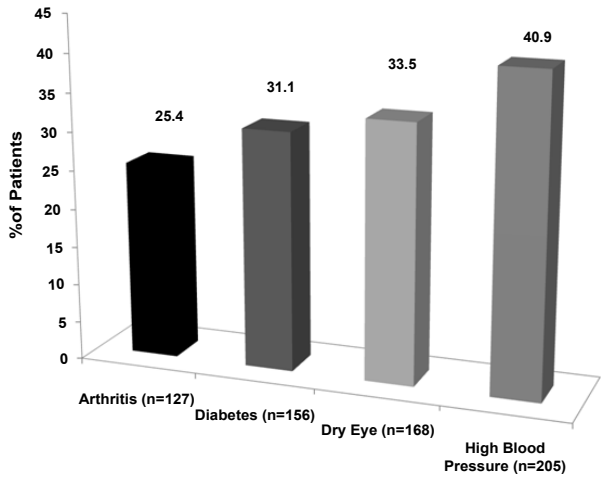

Figure 4: Distribution of comorbid conditions.

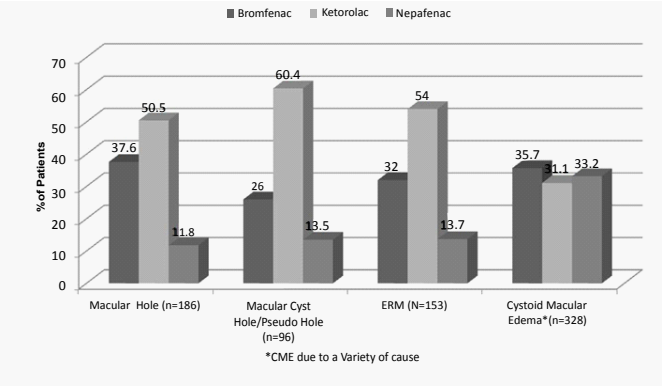

Figure 5. Distribution of each NSAID prescribed for each etiology

Discussion

Our intention is not to establish efficacy but to document safety. In the present study, there were no corneal melts reported, despite the extended duration of use (over 26.2 months) and dosing frequencies that were typically greater than the labeled instructions (75.5% were dosed QID, which is more frequent than the BID or QD label for bromfenac and than TID for nepafenac).

In 1999, reports of corneal melts prompted the recall of a generic form of diclofenac ophthalmic solution. Flach examined 11 cases involving patients who experienced corneal melt after using topical diclofenac [8]. After pointing out the inconsistent and variable dose-toxicity relationships in these cases, Flach noted the likelihood that coexisting factors other than drug toxicity may be involved in corneal melting associated with topical ophthalmic NSAID use. All 11 cases involved coexistent diseases and medical treatments. Moreover, potentially important conditions appear to have been largely ignored. Two patients required punctal plugs, for example, but were categorized as "healthy, asymptomatic patients" despite the fact that dry eye can predispose patients to corneal melts with or without coexistent surgery or medical treatment [8]. These findings suggest that any number of factors could have contributed to the development of corneal melts in these patients.

The difficulty in characterizing risk factors associated with the development of corneal melts is highlighted in the present study. For instance, dry eye is suggested to be a risk factor for the development of corneal complications associated with NSAID use as evidenced by warnings in the package insert for currently available NSAIDs [1,2,7]. In the cohort in the present study, however, 33.6% (n=168) had a concomitant dry eye diagnosis but none developed corneal complication or melts. Similarly, a survey conducted by the American Society of Cataract and Refractive Surgery found that severe corneal melts were associated with a history of diabetes[15] but none of the 156 diabetic patients in our cohort had any signs of corneal melt.

In a recent evaluation of bromfenac ophthalmic solution 0.09%, Jones et al noted that four reports in the medical literature describe serious corneal damage that developed in patients after using bromfenac ophthalmic solution [9]. These events consisted of corneal perforation, corneal melt, and epithelial defect with corneal thinning. In all four cases, however, the cornea undergoing treatment had a significant preexisting condition (eg, Stevens-Johnson syndrome, culture-proven bacterial ulcer) that likely affected these outcomes. Also, bromfenac was one of multiple agents these patients were taking at the same time, which further obscures the situation. In the two U.S. Phase III clinical trials, no cases of corneal melt were reported for the 356 patients who used bromfenac as prescribed [16]. Additionally, a post-market surveillance study of bromfenac ophthalmic solution 0.1% in Japan yielded no reports of corneal melt among 3,425 reported cases [17].

Numerous other case reports also suggest that the incidence of corneal melt is increased by the presence of underlying comorbidites, use of multiple ophthalmic agents, or by surgery. Wolf and associates described a case a patient experiencing corneal ulcerations and melting with both ketorolac and nepafenac in a patient with graft versus host disease [10]. Di Pascuale reported a case of corneal melt in a patient with chronic CME after five months of nepafenac [12]. Another case study detailed an incident of corneal melt after vitroretinal surgery and use of ketorolac 0.4% in a patient with an uncomplicated systemic history who was also prescribed tobradex and ciprofloxacin. The melt occurred 10 days postoperatively [18]. Khalifa et al reported a case of keratitis and corneal melt after conductive keratoplasty (CK) enhancement in a patient prescribed ketorolac [14].

Yet another factor that may contribute to the incidence of corneal melt is inappropriate dosing. Flach has described examples of corneal melting that were associated with the unapproved use of bromfenac

Ref #	Case #	NSAID Drops Indicated Post..	Days of Use	Complications	Medical History	Age
1	1	Surgery	10	Scleral melt, conjuctival defect, culture negative	None reported	77
1	2	Surgery	18	Corneal melt at wound, ulceration at sideport, culture negative	Diabetes, coronary heart disease	86
1	3	Surgery	30	Scleral melt, culture negative	None reported	82
1	4	Surgery	105	Corneal melt at cataract wound	Diabetes, rheumatoid arthritis	70
1	5	Not reported	19	Central corneal melt both eyes	Diabetes, sarcoidosis	43
1	6	Surgery	21	Corneal melt, ulceration and infiltrate, culture negative	None reported	67
2	7	Surgery	15	Corneal melt with infiltrate, ulceration, 80% thinning	None reported	58
2	8	Surgery	40	Corneal melt with 60% thinning	None reported	71
2	9	Surgery	5	Corneal melt with perforation	Anemia	76
3	10	Surgery	10	Corneal melt, 80% thinning, eventual perforation	Coronary heart disease, hypertension, hyperlipidemia, hiatal hernia	76
3	11	Cataract Surgery	29	Corneal melt with 50% thinning	Hypothyroid	66
3	12	Cataract Surgery	18	Corneal melt with perforation	Arrhythmia	77
3	13	Cataract Surgery	11	Corneal melt, 90% thinning, eventual perforation	Coronary heart disease, hypertension, diabetes, gastritis	71
3	14	Surgery	17	Corneal melt, 99% thinning, eventual perforation	Hypothyroid	79
4	15	Surgery	10	Corneal ulcer with melt, 80% thinning, eventual perforation	None reported	76
4	16	Cataract surgery	29	Corneal melt with 50% thinning	None reported	66
4	17	Cataract surgery	18	Corneal melt with perforation	None reported	77
4	18	Cataract surgery	11	Corneal melt with perforation	Diabetes, hypertension	71
4	19	Surgery	17	Corneal melt with descmetocele	None reported	79
4	20	Surgery	5	Corneal melt with perforation	None reported	27
4	21	Surgery	4	Corneal melt with descmetocele	None reported	47
4	22	Surgery	300 (drug1), 120 (drug2)	Corneal melt with descmetocele	None reported	80
4	23	Surgery	150	Corneal melt with descmetocele	None reported	65
4	24	Surgery	14	Corneal melt with eventual perforation	None reported	77
5	25	PRK	5	Corneal melt with perforation	None reported, including negative serologies	31
6	26	Surgery	10	Corneal melt with central perforation	Hypertension	79
7	27	Surgery	14	Corneal melt	None reported	62
8	28	Surgery	14	Central corneal melt with perforation	Graft vs host disease, post allogeneic stem cell transplant for leukemia	56
9	29	Surgery	60	Central corneal melt with perforation, cultures negative	None reported	50
10	30	PRK	5	Corneal melt with perforation, cultures negative	None reported	27
10	31	PRK	3	Central corneal melt with descmetocele	None reported	49
10	32	Surgery	300	Central corneal melt with descmetocele, eventual perforation	Diabetes	80
11	33	LASIK	6	Dislodged flap, corneal melt, descmetocele, ring infiltrate	None reported	42
11	34	LASIK	3	Dislodged flap, corneal melt, descmetocele, ring infiltrate	Leukemia, status post bone marrow transplant	41
11	35	Surgery	14	Dislodged flap, corneal melt perforation, descmetocele, ring infiltrate	None reported	44
12	36	Cataract surgery	21	Melt with perforation	None reported	83
13	37	Vitrectomy	25	Melts	Asthma, gastroesophageal reflux, prematurity	38
13	38	Vitrectomy	25	Melts	None reported	77

Table 1: Synopsis of published and reported cases.

sodium 0.09% [9]. Similarly, Mian and associates reported a case of corneal ulceration and perforation in a patient presenting five days post-PRK [20]. When questioned, the patient admitted to using ketorolac every hour, ciprofloxacin every hour, and prednisolone 1% QID. Feiz and associates reported a case of bilateral corneal melt three days after PRK in a patient that was instilling nepafenac every two hours [13]. The authors concluded that the frequent dosing was associated with the melt.

In order to get a better understanding of incidence and risk factors, we surveyed the literature as well as keranet to obtain as many cases of corneal melt as we could. The results are summarized in Table 1. When one considers the literature as a whole, the mean onset of corneal melting from the initiation of use is approximately 44 days ranging from 3 to 450 days, with most cases occurring between 4-6 weeks [8,10-14]. Most commonly, topical steroids and topical antibiotic drops were being co-administered at the time of corneal melt. Treatments varied from discontinuation of the drop without significant sequelae to corneal transplant with a large range of final best corrected visual acuity. The most commonly reported associated ocular and systemic conditions were dry eye and diabetes mellitus respectively. Many patients also had a history of an autoimmune disease or positive autoimmune serologies (Table 1).

In the population from our practice, there were no corneal melts. Possible explanations may be that the incidence was extremely low, and the vast majority of our patients treated with NSIAD drops were not post surgical. In terms of trying to estimate incidence, we have surveyed the 3 largest manufacturers of ocular NSAID drops (Allergan, ISTA, and Alcon) to ascertain the number of units sold since each has been on the market. There have been approximately 65 million doses of non-steroidal drops prescribed. If we assume that the results of our search (56 cases) accounts only for 5% of the reported cases of corneal melts, we estimate that the total melts may be around 1180 cases. Assuming 65 million doses of NSAID drops (from Alcon, Allergan, ISTA) have been prescribed, and the total number of melts in the US to date is 1120 then the incidence rate can be estimated as 1120 divided by 65,000,000 or 0.00172%. This is an extremely rare event and probably not related to the type frequency or duration of drop used. To give perspective, the incidence of endophthalmitis in cataract surgery is approximately 125 times higher [21]. The literature review suggests that this extremely rare adverse event is not related to the type, frequency or duration of dosing of any NSAID, rather is it typically a post surgical complication confounded by an existing co-morbidity [8,10,22-24].

Our review of the literature shows this condition has an extremely rare incidence as well as an association with multiple comoborbidities, none of which is at all predictive of who is at risk to develop a corneal melt. In addition in our practice in which patients were given high doses of NSAID drops over long periods of time and did not develop a corneal melts, we believe that corneal melts are idiosyncratic reactions, probably related to an underlying medical condition that may be exacerbated by surgery. However due to the extreme nature of this complication, we believe it is prudent to have patients who will be on long tern NSAID drops to have a safety check at 4-6 weeks (the mean time of presentation of corneal melt in our review of the literature) to insure that this devastating processes is not occurring.

Due to the retrospective nature of the study, one cannot assure whether the patient follow-up and data collection were done in a standardized manner throughout 10 years of study period. Comorbidities were established through patient history on every single visit and a diagnostic criterion was based on patient reported history and medication questionnaires.

Conclusion

In conclusion, the entirety of the evidence suggests that corneal melts are idiosyncratic reactions, probably related to an underlying medical condition that is complicated by surgery, use of multiple medications, and excessively frequent dosing. Our data suggest that the newer NSAIDs are safe to use over an extended period of time and at a frequency of up to four-times daily without increased risk of corneal melt. Almost all cases of corneal melts in the literature were related to surgery along with an underlying disease process in over 80% of cases. Our results provide evidence that the newer NSAIDs, bromfenac, ketorolac, and nepafenac may be dosed safely over an extended period of time and at increased daily doses (up to four-times daily) in patients with retinal conditions including CME, macular hole, macular cyst or ERM. However due to the extreme nature of this complication, we believe it is prudent to have patients who will be on long tern NSAID drops to have a safety check at 4-6 weeks (the mean time of presentation was 44 days) to ensure that this devastating process is not occurring.

Financial Disclosures

The authors have no conflicting financial interests to disclose.

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