Acta Veterinaria-Beograd 2025, 75 (4), 437-447
UDK: 615.457.06(497.11)"2012/2020"
617.77-002(497.11)"2012/2020"
DOI: 10.2478/acve-2025-0034

Research article

SUSPECTED DORZOLAMIDE–INDUCED DELAYED HYPERSENSITIVITY BLEPHARITIS IN DOGS

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(Received 18 May, Accepted 15 October 2025)

The aim was to investigate the incidence, clinical presentation, and potential risk factors for suspected dorzolamide-induced blepharitis (DIB), in dogs diagnosed with glaucoma or hereditary glaucoma predisposition. A retrospective review was conducted using clinical records of 286 dogs with primary or secondary glaucoma, or a hereditary predisposition to glaucoma (goniodysgenesis), that received dorzolamide eye drops between October 1, 2012, and January 1, 2020. Cases of suspected DIB were identified based on resolution of blepharitis following drug withdrawal. Statistical analysis, including odds ratio calculations, was performed to assess the potential risk factors. Eighteen dogs (6.2%) developed DIB after dorzolamide use. The median time before the development of DIB was 60 days. A significant association was identified between dogs with a history of seasonal skin allergies and the development of blepharitis (odds ratio: 12.4, 95% CI: 4.04–35.3, $p < 0.001$). However, no significant association was found with prior intraocular surgery ($p = 0.26$) or dry eye disease ($p = 0.19$). Clinical symptoms resolved within a median of 60 days after discontinuing dorzolamide, and most dogs were successfully switched to brinzolamide without recurrence of symptoms. Seasonal allergies seem to be a significant risk factor for development of DIB. Dorzolamide is one of the most frequently used drugs for treatment of glaucoma, with relatively high prevalence of suspected delayed hypersensitivity reaction (blepharitis). Brinzolamide may be the safer option for the treatment of glaucoma in dogs.

Keywords: dorzolamide, dog glaucoma, blepharitis, atopy

INTRODUCTION

Dorzolamide, a topical carbonic anhydrase inhibitor, is commonly prescribed to lower intraocular pressure in dogs with glaucoma. As a sulfonamide derivative, a range of hypersensitivity reactions may occur, particularly among patients sensitive to sulfa-based medications as previously reported [1,2]. While local ocular side effects of

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dorzolamide in dogs such as keratitis have been previously documented, less common manifestations of allergic responses, such as periocular skin reactions, can also arise [3-5]. These cutaneous changes, including erythema, pruritus, and eyelid margin skin depigmentation, can significantly impact patient comfort, and can result in the abnormal function of the eyelids and tear film, potentially increasing the risk for corneal pathology [6-15]. In this manuscript, we present a retrospective analysis of suspected periocular skin reaction to dorzolamide eye drops and discuss the clinical presentation and management strategies. Our findings highlight the importance of recognizing adverse reactions to dorzolamide to ensure timely intervention and optimize the best possible clinical outcomes.

MATERIAL AND METHODS

A retrospective analysis of clinical records from a single veterinary ophthalmology specialist hospital was conducted for the period between October 1, 2012, and January 1, 2020, to identify dogs receiving dorzolamide eye drops. Additional analyses were performed to identify patients with suspected dorzolamide-induced blepharitis (DIB), where resolution of clinical symptoms was observed upon withdrawal of dorzolamide eye drops.

Data collected for each of the cases included patient history of previous and current diseases, current medications, signalment (age, sex, breed), presenting clinical signs, vital parameters, and results of laboratory analysis.

Statistical Methodology

Results are presented as counts (%), means ± standard deviation, or medians (25th–75th percentile), depending on data type and distribution. All data were analyzed using R 3.4.2 (R Core Team, 2017). Risk odds ratios were calculated using GraphPad Prism 10 (Dotmatics, Boston, MA, USA).

RESULTS

The analysis of medical records identified 286 primary and secondary glaucoma patients, patients with hereditary glaucoma predisposition (goniodysgenesis) who received dorzolamide eye drops during the study period. Among these, 18 patients (6.2%) of both genders developed suspected dorzolamide-induced blepharitis (DIB) in one or both eyes (Figure 1). The age of affected dogs ranged from 1 to 11.5 years. The distribution of patients based on basic clinical characteristics is presented in Table 1. As shown, the gender distribution was male-dominant. Breed distribution was as following: Poodle and poodle mix (3/18, 22.2%), Siberian Husky (3/18, 16.6%), Labrador Retriever (3/18, 16.6%), Australian Shepherd (3/18, 16.6%), Shih Tzu

(1/18, 5.5%), Shih Tzu mix (1/18, 5.5%), Havanese (1/18, 5.5%), Australian Blue Heeler (1/18, 5.5%), Cocker Spaniel (1/18, 5.5%), and Yorkie (1/18, 5.5%).

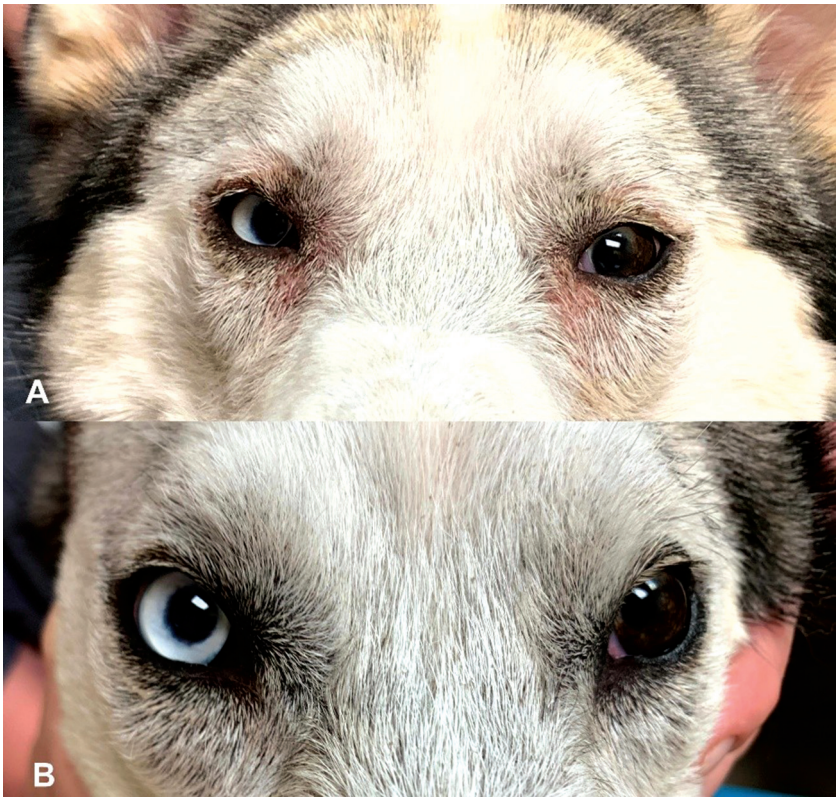

Figure 1. A) Development of the periocular erythema and blepharitis 28 days after initiation of dorzolamide eye drops. **B)** Resolution of periocular changes was achieved with the discontinuation of dorzolamide eye drops and initiation of brinzolamide eye drops (resolution of periocular symptoms was observed 90 days post dorzolamide discontinuation)

The majority of patients with suspected DIB were receiving dorzolamide therapy in both eyes, all had blepharitis, and one-third had keratitis. The skin reaction was detected between 35 and 300 days after the start of topical dorzolamide application with a median time of 60 days (Table 1).

The distribution of patients regarding concurrent medications, comorbidities, and laboratory abnormalities is summarized in Table 2.

Table 1. Basic Clinical Characteristics of Patients.
OD (oculus dexter, right eye), **OS** (oculus sinister – left eye)

Characteristic	N (%), Mean ± SD, Median (25th–75th percentile)
Age (years)	6.6 ± 3.3
Sex	
Male/Castrated Male	11 (61.1%)
Female/Spayed female	7 (39.9%)
Dorzolamide Administration	
OD	1 (5.6%)
OS	4 (22.2%)
OU	13 (72.2%)
Clinical Symptoms	
Blepharitis	18 (100%)
Keratitis	6 (33.6%)
Time Until Diagnosis (days)	60 (35–300)

Table 2. Concurrent Medications, Diseases, and Laboratory Abnormalities.
Some patients were treated with multiple systemic and ophthalmic medications.
ALP – alkaline phosphatase; **ALT** – alanine aminotransferase

Characteristic	N (%)
Concurrent Eye Medications	
Latanoprost	14 (77.8%)
Neopolydex	8 (44.4%)
Tacrolimus	9 (50%)
Dexamethasone	8 (44.4%)
Ketorolac	1 (5.6%)
Cyclosporine	1 (5.6%)
Systemic Medications	
ISM (prednisolone, cyclosporine, leflunomide)	4 (22.2%)
Oclacitinib	8 (44.4%)
Hydroxyzine	6 (33.3%)
Other	4 (22.2%)
Suspected Autoimmune/Immune-Mediated Diseases	
Seasonal allergies	14 (77.8%)
KCS (dry eye disease)	9 (50%)
Other	3 (16.7%)
Additional Systemic Diseases	
Systemic Hypertension (SH)	3 (16.7%)
Sudden Acquired Retinal Degeneration Syndrome (SARDS)	2 (11.1%)
Pancreatitis	3 (16.7%)
Other	4 (22.2%)
Laboratory Abnormalities	
Elevated ALP	7 (38.9%)
Elevated ALT	4 (22.2%)
Other Abnormalities	3 (16.7%)

Most patients were also receiving latanoprost, while nearly 50% were prescribed neopolydex, tacrolimus, and dexamethasone topical eye drops. The majority were also receiving systemic medications for different systemic health problems, with immunosuppressive medications (ISM) being the most common (oclacitinib, prednisolone, leflunomide, cyclosporine). Nearly half of the patients were on oclacitinib for seasonal skin allergies. Seasonal skin allergies were the most prevalent systemic health problem, while keratoconjunctivitis sicca (KCS) was present in half of the affected patients. Laboratory abnormalities were detected in 50% of the cases, with elevated alkaline phosphatase (ALP) being the most common finding.

The distribution of patients based on ocular abnormalities and outcomes is presented in Table 3.

Table 3. Concurrent ocular pathology and clinical outcome post dorzolamide withdrawal

Characteristic	N (%)
Ocular Abnormalities	
Primary glaucoma	13 (72.2%)
Goniodysgenesis with ocular hypertension post cataract surgery	3 (16.7%)
Goniodysgenesis w/o active glaucoma	2 (11.1%)
KCS	9 (50.0%)
Cataract	5 (27.8%)
Uveitis	3 (16.7%)
Other Ocular Immune Diseases	2 (11.1%)
Corneal Stromal Abscess	1 (5.6%)
Other Non-Immune Ocular Diseases	1 (5.6%)
Resolution of Blepharitis After Stopping Dorzolamide (days)	60 (22–90)
Brinzolamide Switch	14 (77.8%)
Brinzolamide Duration Post-Switch (months, n=14)	9 (6–20)

Primary glaucoma was the predominant form of ocular disease (67% of patients). The median time to the DIB resolution after discontinuing dorzolamide was 60 days. The majority of patients were switched to brinzolamide 1%, with a median treatment duration of 9 months after the switch.

Since the history of seasonal allergies was prevalent among patients who exhibited a reaction to dorzolamide (Table 2), we evaluated whether this could be a potential risk factor. A total of 14 out of 18 patients in the DIB group had a current or past history of seasonal allergies. The calculation of the odds ratio revealed a statistically significant value of 12.4 when compared to all patients in the study (95% CI: 4.04–35.3, $p < 0.001$, Fisher's exact test).

We also assessed whether previous intraocular surgery was a risk factor for developing a dorzolamide-induced reaction. A total of 7 out of 18 patients in the DIB group had a history of intraocular surgery (38.89%). However, the calculated odds ratio was 1.9, which was not statistically significant when compared to all patients in the study (95% CI: 0.75–5.23, $p = 0.26$, Fisher's exact test).

Additionally, we investigated whether a history of dry eye disease was associated with an increased risk of a dorzolamide-induced reaction. A total of 8 out of 18 patients in the DIB group had a history of dry eye disease. However, the calculated odds ratio was 1.9, which was not statistically significant when compared to all patients in the study (95% CI: 0.73–5.2, $p = 0.19$, Fisher's exact test).

DISCUSSION

A recent case report described a periorbital delayed allergic skin reaction to dorzolamide and dorzolamide-timolol eye drops in two dogs, while a case series published by Beckwith-Cohen et al. (2015) reported the development of keratitis in six dogs, suspected to be an allergic reaction to topical carbonic anhydrase inhibitors (CAIs)[3, 5]. However, this is the first large-scale study investigating the incidence of topical CAI-induced ocular reactions in dogs, with the goal of identifying potential risk factors. A previous study on dorzolamide/timolol-induced periorbital dermatitis (PD) in human patients reported an incidence of 2.2%, which is lower than the 6.2% observed in this study[16]. However, a large-scale study conducted in Canada, which examined 128,942 human patients receiving oral or topical CAIs over a 25-year period, reported a dramatically lower incidence of CAI-induced allergic reactions, with a rate of 2.08 adverse reactions per 1,000 patients [1]. This study demonstrated that the presence of seasonal skin allergies was a significant factor that may have contributed to the development of dorzolamide-induced blepharitis in dogs. This finding aligns with previously published studies in human patients population [2]. While the study by Kim et al. identified prior ocular surgery as a significant risk factor for the development of dorzolamide-induced ocular allergic reactions in human patients, our data did not confirm this observation in dogs [16]. Consistent with previous reports in dogs, the suspected allergic reaction to dorzolamide in this study was delayed, with a median onset of 60 days, and clinical symptoms resolved in a similarly delayed manner (median resolution time of 60 days) [5]. Previous studies have proposed several potential mechanisms for CAI hypersensitivity:

1. **Type IV Hypersensitivity (Delayed-Type Hypersensitivity)** – a drug may induce a delayed immune reaction mediated by T cells. In this case, dorzolamide or its metabolites bind to proteins, forming larger antigenic complexes that, when recognized by sensitized T cells, trigger a localized inflammation [17,18].
2. **Non-Immune Mechanisms** – a drug may cause local irritation and allergy-like symptoms due to its chemical properties or as a reaction to the preservative in the eye drops (benzalkonium chloride, BAK), resulting in a localized inflammatory response [19,20].

Considering the delayed onset and resolution of clinical symptoms following dorzolamide withdrawal, we speculate that the observed dorzolamide-induced

blepharitis is most likely a result of Type IV (delayed-type) hypersensitivity. A non-immune mechanism due to chemical properties or preservatives was excluded, as all affected patients continued using other ophthalmic medications containing preservatives without adverse effects.

Dorzolamide and brinzolamide have nearly identical sulfa-ring–based chemical structures. However, brinzolamide possesses an additional side carbon chain that improves its liposolubility and enhances corneal and tissue penetration (Figure 2) [21].

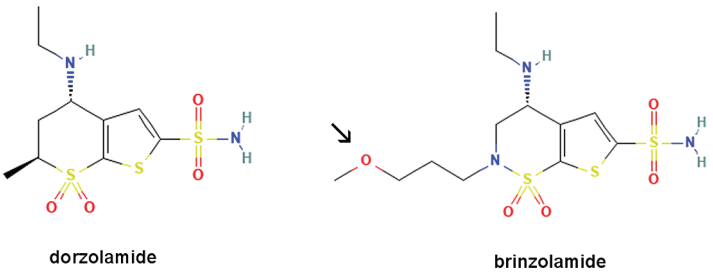

Figure 2. Comparison of dorzolamide and brinzolamide chemical structure. The arrow point to the carbon chain in brinzolamide structure which improved liposolubility and tissue penetration of brinzolamide. Image is a modification of the original images from the US National Library of Medicine – PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/)

Limited data exists regarding the relationship between drug solubility and drug-induced allergic reactions. Liposoluble drugs tend to achieve better tissue penetration and generally have a shorter half-life in the blood, resulting in a reduced exposure to immune cells [22,23]. However, their prolonged presence in tissues, particularly in the skin, may lead to extended exposure to antigen-presenting cells, potentially increasing the risk of allergic reactions [23]. In contrast, hydrophilic drugs have a greater capacity to form immunogenic hapten (drug-protein) complexes, which can trigger delayed hypersensitivity reactions. Penicillin and sulfonamide drug-induced allergies are among the most frequently recognized examples [24-26]. Several studies established a strong correlation between specific human leukocyte antigen (HLA) alleles and genetic susceptibility to CAI adverse reactions [27]. It will be interesting to evaluate whether similar findings can be replicated in dogs with adverse reactions to CAIs.

Limitations of this study

There are several limitations to this study. The number of affected dogs is very small, and considering variability in breeds and age, it is difficult to discern any predictability pertinent to these parameters. Future studies with much larger patient population may reveal potential breed and age influence on DIB in dogs. None of the evaluated patients underwent skin testing with dorzolamide, as has been previously reported for

CAI allergy patients [18]. Multiple medications were used in all patients with suspected drug-induced blepharitis (DIB), so we cannot exclude the possibility that other drugs contributed to the observed blepharitis [28,29]. Biopsy and histopathological evaluation were not performed in any of the patients to rule out other forms of skin disease responsible for the observed changes. Considering the high prevalence of seasonal allergies in the DIB group, we also cannot exclude the possibility that dorzolamide-induced topical irritation triggered a flare-up of seasonal allergies. Finally, this study did not evaluate the possible influence of HLA allele phenotype, which appears to be an extremely important factor in the development of drug hypersensitivity in humans [30].

CONCLUSION

Dorzolamide is one of the most frequently used drugs for treatment of glaucoma, with relatively high prevalence of suspected delayed hypersensitivity reaction (blepharitis). Seasonal allergies seem to be a significant risk factor for development of DIB. Brinzolamide may be the safer option for the treatment of glaucoma in dogs.

Acknowledgements

We would like to thank Dr Ivana Lakic (Oculus) for the provided help with data collection. We would like to thank Ivan Soldatovic MD, PhD from Department of Biostatistics, College of Medicine, University of Belgrade, Belgrade, Serbia for the help and suggestions with statistical analysis.

Authors' contributions

SG devised the study, performed evaluation of data and wrote the manuscript. SL performed electronic medical record data analysis. TL and NM performed control of data analysis and statistical analysis and helped with manuscript writing..

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

Funding

This study was supported by the internal research funding provided by Animal Eye Consultants of Iowa.

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SUMNJA NA DORZOLAMIDOM IZAZVAN BLEFARITIS PASA POVEZAN SA ODLOŽENOM HIPERSENZITIVNOM REAKCIJOM

Sinisa GROZDANIĆ, Sergei LUZHETSKII, Tatjana LAZIĆ,
Natalija MILČIĆ–MATIĆ

Cilj istraživanja bio je da se ispita učestalost, klinička slika i mogući faktori rizika za sumnju na dorzolamidom izazvan blefaritis (DIB) kod pasa sa dijagnostikovanim glaukomom ili naslednom predispozicijom za glaukom. Sproveden je retrospektivni pregled kliničke dokumentacije 286 pasa sa primarnim ili sekundarnim glaukomom, kao i onih sa naslednom predispozicijom (goniodisgeneza), kojima su aplikovane kapi za oči sa dorzolamidom u periodu od 1. oktobra 2012. do 1. januara 2020. godine. Suspektni slučajevi na DIB su identifikovani na osnovu povlačenja blefaritisa nakon prekida primene kapi. Statistička analiza, uključujući proračune odnosa šansi, sprovedena je radi procene potencijalnih faktora rizika. Osamnaest pasa (6,2%) razvilo je DIB nakon upotrebe dorzolamida. Prosečno vreme do pojave DIB bilo je 60 dana. Uočena je značajna povezanost između pasa sa sezonskim kožnim alergijama i razvoja blefaritisa (odnos šansi: 12,4; 95% CI: 4,04–35,3; $p < 0,001$). Medjutim, nije utvrđena značajna korelacija kod pasa sa prethodnim intraokularnim hirurškim zahvatima ($p = 0,26$), kao ni kod pasa sa sindromom suvog oka ($p = 0,19$). Klinički simptomi su se povukli u proseku za 60 dana nakon prekida primene dorzolamida, a većina pasa je uspešno prebačena na kapi sa brinzolamidom, bez ponovne pojave simptoma. Sezonske alergije predstavljaju značajan faktor rizika za razvoj DIB. Dorzolamid je jedan od najčešće korišćenih lekova u terapiji glaukoma kod pasa, ali se kod manjeg procenta životinja može javiti odložena reakcija preosetljivosti u vidu blefaritisa. Brinzolamid se pokazao kao potencijalno bezbednija alternativa u lečenju glaukoma kod pasa.