CANINE KERATITIS ASSOCIATED WITH BRINZOLAMIDE AND DORZOLAMIDE: CLINICAL AND HISTOLOGICAL DIAGNOSIS AND TREATMENT
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To describe a topical CAI induced immune-mediated keratitis in six dogs

Clinical cases: 4 dogs, 7 eyes
- Treated with Brinzolamide or Dorzolamide
- Non-responsive to steroids
- Responsive to drug cessation

Histopathological cases: 3 dogs, 4 globes
- Treated with Brinzolamide
- Non-responsive to steroids
- Enucleated
Nonantibacterial sulfonamide agents- brinzolamide, dorzolamide

- Approved by the FDA in 1994 and 1998, respectively
- Reduce the production of aqueous humor
- When compared with systemic CAI
  - Associated with fewer side effects (e.g. gastrointestinal)
  - Improved quality of life
  - Improved compliance to therapy
TOPICAL CAI SIDE EFFECTS IN DOGS AND CATS

- **Systemic**
  - Metabolic acidosis (Thiessen, *JECC*, in press) - also reported in one neonate, Morris et al. 2003

- **Local**
  - Blepharitis (anecdotal)
  - Local irritation (professional forums) - possibly pH associated
  - Reversible KCS in dogs (professional forums)
  - Punctate keratopathy (personal communications)
| 1 | FS, Welsh terrier 5-10yrs | Dorzolamide Brinzolamide | Goniodysgenesis |  | Resolved (later enucleated) |
| 2 | MN, Beagle 10-14yrs | Dorzolamide | Cataract ➔ phaco ➔ glaucoma | Diabetes | Resolved |
| 3 | MN, Border Collie X, 9-12yrs | Dorzolamide | Cataract ➔ phaco ➔ glaucoma | Diabetes | Resolved |
| 4 | F, Norwich terrier, 4yrs | Brinzolamide | Cataract OD ➔ phaco OD ➔ glaucoma OU |  | Enucleated Euthanasia |
| 5 | FS, Aussie Shepherd X, 10-11yrs | Brinzolamide | Uveitis ➔ glaucoma + HM cataract |  | Enucleated |
| 6 | FS, Leonberger 3.5-6yrs | Dorzolamide Methimazole Brinzolamide | Goniodysgenesis OU |  | Enucleated OS Resolved OD Euthanasia |
CLINICAL SIGNS- CASE 1

- FS, Welsh terrier, 5 y/o at presentation
- Primary glaucoma
- Dorzolamide ➔ Brinzolamide
- Initial signs within 1 week
- Severe signs within 133 days
- MN, Beagle 10 y/o at presentation
- Diabetes
- Cataract → phaco → glaucoma
- Dorzolamide
- Initial signs within 3 months
- Severe signs within 8 months
CLINICAL SIGNS- CASE 5

- FS, Australian Shepherd cross, 10 y/o at presentation
- Uveitis → glaucoma + HM cataract
- Brinzolamide
- Initial signs within 1 month
- Severe end stage corneal disease within 275 days
- This eye was enucleated

Courtesy Dr. Elizabeth Adkins
## DISEASE COURSE (DAYS)

<table>
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<tr>
<th></th>
<th>Days to initial CS</th>
<th>Days to severe CS</th>
<th>Days to D/C</th>
<th>Days to Enucleation</th>
<th>Days to improve</th>
<th>Days to resolve</th>
<th>Follow-up w/o CS **</th>
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</table>

* Switched to Brinzolamide on day 58

** Follow-up appears in months
TOPICAL CAI SIDE EFFECTS IN PEOPLE

- **Local**
  - Ocular discomfort and stinging - common
  - Blurred vision - common
  - Drug induced ectropion *(Hegde et al. Ophth 2007)*
  - Contact dermatitis *(Kalavala et al. Cont. Derm. 2006)*
  - Marginal punctate keratitis *(Abdel et al., AJO, 2000)*
  - Irreversible corneal decompensation/edema *(Konowal et al., AJO, 1999)*

- **Systemic**
  - Stevens Johnson syndrome/Erythema Multiforme *(Munshi et al., JOPT, 2007)*
  - Severe thrombocytopenia and skin eruption *(Santos et al., WIMJ, 2010)*
  - Systemic contact dermatitis *(Kluger et al. Cont. Derm. 2008)*

- **Non-ocular related**
  - Dysgeusia - common
PERIORBITAL DERMATITIS AS A SIDE EFFECT OF TOPICAL DORZOLAMIDE

Figure 1  Case 14. Marked dermatitis of the left lower lid and periorbital area, which resolved on discontinuing topical dorzolamide.

Figure 2  Case 2. Bilateral periorbital dermatitis with erythema and scaling involving the upper and lower lids.

MARGINAL KERATITIS

FIGURE 1. Photograph of the right eye shows conjunctival hyperemia and marginal corneal infiltrates (black arrows).

FIGURE 2. Photograph of the right eye 1 week after discontinuation of topical dorzolamide hydrochloride shows complete resolution of the conjunctival hyperemia and marginal corneal infiltrates.

Canine corneal immunology is poorly described

- Avascular

- Studies in humans:
  - Corneal immune privilege
  - Peripheral cornea differs from central
    - Proximity to vessels
    - Abundance of Langerhans cells and inflammatory cells
    - C1 and IgM (d/t high molecular weight)
Specimens were stained with H&E
Further stains included
  - Gram stain- negative
  - GMS stain- negative
IHC
  - CD-20 (B-cell)
  - CD-79a (B-cell)
  - CD-3 (T-cell)
  - Ig-G (Rabbit anti dog)
B-CELL CD20/CD79A

Case 4

Case 5
T-CELL CD3

Case 4

Case 5
This is the first report of CAI related ocular lesions in dogs
Time to onset of severe signs was prolonged
Cases were unresponsive to steroids ± immune modulators
Clinical cases rapidly resolved following drug discontinuation
One case that resolved was treated again after a few months, and then redness and discomfort occurred within 48 hours
The distribution of inflammatory cells and their nature are suggestive of hypersensitivity
Alternative CAIs may be a valid option
DISCUSSION

- Diabetes or ocular surgery may complicate the immune response in these cases.
- It is possible that the severity of case 5 is related to the uveitis, that impaired the blood aqueous barrier.
- The long lag until clinical signs is unusual, also for delayed type hypersensitivity- this could be to unique corneal immunology, or the fact that some patients were treated with NSAIDs or steroids.
- Biopsy specimens prior to d/c CAI would be useful in proving pathogenesis.
CONCLUSION

- Topical carbonic anhydrase inhibitors can cause a non-steroid responsive immune-mediated keratitis that is rapidly responsive to drug cessation.
- If drug administration is continued, disease can progress to end stage corneal disease
RECENT CASE- KERATOCONJUNCTIVITIS

- 7 y/o FS Staffordshire cross dog
- Uveitis, glaucoma
- Dorzolamide
- 2.5 month hx of ocular surface dz
FUTURE THOUGHTS

- Dorzolamide LTT test for drug-specific lymphocytes targeted at the parent drug, dorzolamide capture lymphocytes reactive with dorzolamide metabolites (generated by canine liver microsomes)
- Patch testing
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QUESTIONS?