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The effects of corticosteroid drugs on the visual function of zebrafish

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Introduction: Glaucoma, a leading cause of blindness, is a heterogenous eye condition characterized by gradual loss of visual acuity due to degeneration of retinal ganglion cells (1). Glaucoma is an off-target effect of corticosteroids when administered intraocularly for treatment of some ocular indications (2). This study uses zebrafish to study whether a glaucoma-type disease is induced by treatment with corticosteroids by assessing the effects on retinal histology and visual function.

Methods: 3 days post-fertilization (dpf) transgenic Tg[*fli1*:EGFP] zebrafish larvae (3), expressing enhanced green fluorescent protein in their vasculature, were treated with 10 µM, 20 µM, 50 µM and 80 µM of corticosteroids dexamethasone and prednisolone (n = 15 larvae/experiment). At 5 dpf larvae were examined by light microscopy to evaluate overall morphological development. Visual behaviour was assessed by optokinetic response (OKR) and visual motor response (VMR) assays. Retinal differentiation and optic nerve morphology were examined in semi-thin plastic sections. RNA was extracted from pooled 5 dpf larvae to study the effect of corticosteroids on myocilin (*myoc*) and nyctalopin (*nyx*) gene expression. Statistics: one-way ANOVA with Dunnett's correction for multiple comparisons.

Results: While drug treatment had no effects on gross morphology of zebrafish, corticosteroid treatment impacted visual behaviour, reducing the OKR from 23 saccades/minute in control to 14 and 9 for 30 µM dexamethasone and prednisolone respectively (p-value <0.05). Treatment with 80 µM dexamethasone and prednisolone caused a severe visual impairment (< 5 saccades/minute; p-value <0.001). 80 µM prednisolone increased overall locomotor (VMR) activity by ~50% compared to control, while 80 µM dexamethasone did not affect locomotion. In histological examination, retinal lamination and cell number appeared normal in corticosteroid-treated samples compared to control, however eye diameter appeared marginally increased. Preliminary results examining gene expression suggest an upregulation of *myoc* gene expression, while *nyx* gene expression was unaffected in 80 µM dexamethasone-treated larvae.

Conclusion: This study provides an ocular safety assessment for corticosteroids dexamethasone and prednisolone in zebrafish. Both drugs show concentration-dependent effects on visual behaviour, without exhibiting off-target effects on gross morphology. Additional work needs to be done to identify the mechanism of how corticosteroids affect visual function and upregulation of *myoc* gene expression. This study is the first step towards developing a corticosteroid-induced model of glaucoma in zebrafish.

References:

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3. Lawson ND and Weinstein BM (2002). *Dev Biol*. **248**: 307-18.