Ocular Pharmacokinetics and Pharmacodynamics of Ketorolac Tromethamine in Neonatal Sprague Dawley Rats

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Objectives: Ketorolac Tromethamine 0.45% ophthalmic solution (Acuvail) is known to be an efficacious agent to treat ocular inflammation and pain by inhibiting prostaglandin biosynthesis in ocular tissues. Retinopathy of prematurity is a disease that affects premature infants with incomplete vascularization of the retina for which Ketorolac has been hypothesized to play an important role in treatment. The objective of this analysis is to provide a quantitative understanding of the ocular and systemic disposition of ketorolac following topical instillation in healthy neonatal rats.

Methods: Ocular tissue and serum samples were collected for ketorolac and prostanoid concentrations following either a single dose or multiple dose of Acuvail to neonatal Sprague dawley rats. A naïve pooled approach was used within ADAPT5 for all modeling. The pharmacokinetic model was developed based on physiological pathways for drug disposition in the eye. An indirect response or a direct effect model was used to describe the pharmacodynamics.

Results: 1.7% of the total ocular dose is absorbed into the posterior ocular tissues. Lens received 1.3%, followed by choroid receiving 0.3%, and vitreous humor receiving 0.007%. The lens tissue may act as a reservoir for drug release into the vitreous humor, prolonging the apparent terminal half-life in this space. Ketorolac was not detected in the retina and assumed to not exhibit pharmacological activity in this space. Prostaglandin synthesis was potently inhibited in the choroid, lens and serum. Model estimated IC50s showed greater potency towards TxB2 in the serum and lens, while PGF2α was most potently inhibited in the choroid.

Conclusions: The ocular and systemic PK/PD model was able to adequately characterize the exposure and response of ketorolac in healthy rats. This model may serve as a reference to study the impact of disease on the disposition and effects of ketorolac.