

SAFETY, PHARMACOKINETICS, AND EFFICACY OF INTRAOCULAR CELECOXIB

Stephen Kim, Vanderbilt Eye Institute

Jinsong Sheng, Vanderbilt University

Roban Shab, Vanderbilt

Sunil Vooturi, University of Colorado Denver

Uday Kompella, University of Colorado Denver

Purpose: To determine the safety, pharmacokinetics, and anti-inflammatory effects of intraocular celecoxib in rabbits.

Methods: The right eye of animals received a single 0.1 ml injection of celecoxib (1.5mg, 3mg, or 6mg) prepared in dimethyl sulfoxide (DMSO). Left eyes served as controls and received 0.1ml DMSO. Dark- and light-adapted electroretinograms (ERG) were obtained at baseline and at 1, 4, and 12 weeks after injection. After 12 weeks, eyes were enucleated for histopathological analysis. For intraocular pharmacokinetics, 3mg of celecoxib was injected into both eyes of each animal. Drug levels in vitreous and retina/choroid were analyzed by high-performance liquid chromatography and tandem mass spectrometry at the following time points after injection: 0.25hr (15 min), 1, 4, 24, and 72 hours and at 1, 2, 4, and 8 weeks. For efficacy experiments, 1µg lipopolysaccharide (LPS) in 50µl saline was injected into the vitreous of both eyes to induce inflammation. The right eye of each animal was then injected immediately afterwards with either 3mg celecoxib (6 eyes) or 2mg triamcinolone acetonide (6 eyes). The left eye served as a control and was injected with equal volume (50µl) saline. Twenty-four hours later, 200 µl of aqueous fluid was removed and total leukocyte concentration was determined by a masked observer using a hemocytometer. Remaining aqueous fluid was immediately diluted 1:1 in chilled stabilization buffer and prostaglandin E2 (PGE2) concentration was later determined by enzyme-linked immunoassay.

Results: Serial ophthalmic examinations showed no signs of intraocular inflammation or increased intraocular pressure in celecoxib-injected eyes, but cataract formation was observed at higher concentrations. Histologic and ERG studies demonstrated no signs of retinal or optic nerve toxicity. After a single injection of 3mg celecoxib, both vitreous (28.5 ng/ml) and retina/choroid (26.1 µg/ml) drug concentration at 8 weeks exceeded the minimum inhibitory concentration 50 (MIC50) of its target enzyme cyclooxygenase-2. Treatment with celecoxib and triamcinolone significantly reduced total leukocyte count by 40% (P = 0.02) and 31% (P= 0.01) respectively. Mean leukocyte count was 13,400 ± 7052 cells/µl in control eyes (LPS and saline) and 8094 ± 6400 cells/µl and 9222 ± 5100 cells/µl in celecoxib- and triamcinolone-treated eyes respectively. Reduction in PGE2 levels paralleled reduction in leukocyte counts. Mean PGE2 was 7140 pg/ml in control eyes and 2769 pg/ml (P = 0.04) and 1209 pg/ml (P < 0.01) in celecoxib- and triamcinolone-treated eyes respectively.

Conclusions: Intraocular injection of celecoxib was nontoxic to the retina and optic nerve. Pharmacokinetic analysis demonstrated excellent penetration into the retina/choroid and maintenance of drug levels that exceeded the MIC50 out to 8 weeks. Celecoxib demonstrated potent anti-inflammatory effects after intraocular injection but there was an association with cataract formation at higher concentrations.