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| **In vivo ocular pharmacokinetics and toxicity of siponimod in albino rabbits** |
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| **Background:** Diabetic retinopathy and age-related macular degeneration are leading causes of avoidable vision loss. Both conditions are characterized by pathological neovascularization, which is presently treated with anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapies. However, currently approved Anti-VEGF treatments require monthly intravitreal injection or surgical implantation, which carries a risk of increased intraocular pressure, glaucoma, endophthalmitis, and low patient adherence. Moreover, up to 40% of patients may develop resistance to anti-VEGF therapies, resulting in a significant discrepancy between their effectiveness in clinical trials and real-world scenarios. Siponimod, an S1PR1 and S1PR5 modulator is a promising agent for the inhibition of ocular neovascularization. Indeed, siponimod inhibited retinal endothelial cells’ migration and protected against TNF-α induced endothelial barrier dysfunction, both are key steps in pathological neovascularization. Additionally, the drug exhibits notable inhibition of suture-induced corneal neovascularization in albino rabbits. However, drug testing in a chronic disease model or development for ophthalmological application can be hindered by the limited information available on the drug’s ocular pharmacokinetics (PK) and toxicity. Furthermore, the limited number of ocular PK studies hampers the development of in silico models that predict the drug ocular PK. |
| **Methods:** In this study, the aqueous stability of siponimod at different temperatures and its solubility in pigs vitreous at room temperature were characterized. The ocular PK and toxicity of two different siponimod doses (1300 ng (low dose) or 6500 ng (high dose)) were established in an albino rabbit model. Rabbits were administered a siponimod dose by intravitreal injection before surgically removing the eyes and extracting the vitreous at predetermined time points (0.5, 1, 2, 4, 8, 10, and 12 hours) (n=3-5 in each time point). Siponimod concentration was quantified in the vitreous using HPLC/UV-VIS after validation of the detection method. PK parameters were calculated assuming a first-order elimination. At 24 h and 7 days after the intravitreal injections, rabbits were enucleated, and retinas were stained with H&E to evaluate potential ocular toxicity. |
| **Results:** The drug half-life was estimated as 3.3 h, with no noticeable difference between the PK parameters of both doses. For rabbits receiving 6500 ng of siponimod, the drug concentration in the vitreous remains > the IC50 of 0.39 nM (0.2 ng/ml) for 52.5 h after injection. At 24 h and 7, neither dose of siponimod caused any noticeable changes in the retinal architecture. with the treated retinas showing a normal retinal appearance with well-ordered layers, and no signs of vacuoles, inflammation, or edema. |
| **Conclusions:** Administration of siponimod solution for inhibition of neovascularization in diabetic retinopathy and age-related macular degeneration will necessitate frequent intravitreal injections (at least every 48 h) to maintain therapeutic efficacy, which would be clinically unacceptable.  Therefore, development of a sustained drug delivery system that maintains the therapeutic concentration of the drug for an extended period is crucial for future clinical use of the drug. |