Ocular Toxicity Studies - Toxicologist Viewpoints

Introduction

Ocular toxicology is a subspecialty of toxicology. It involves evaluation of the adverse effect on ocular tissues due to drugs that are administered into the ocular drug delivery system through traditional routes, namely topical, periocular, intravitreal, and also from nonspecific systemic exposure of drugs, ocular devices, and surgical materials in the eye.

Importance of Ocular Toxicity

The eye is a unique sensory structure with many specialised sub-organs working in conjunction to make vision as we know it possible. Humans commonly obtain approximately 80% of external information from the vision in their daily life with the help of eyes.

The loss of functionality of any eyes tissue disturbs the overall function and may cause adverse effects on vision. It was reported that numerous systemic medications could induce permanent visual loss1. Humans highly relying on the vision for their lives and there will be a marked decrease in the quality of life with the loss in vision. Since, vision is arguably the most important sense organ, ocular toxicity evaluation is a key part of the preclinical development. Conducting ocular toxicology and tissue distribution studies in laboratory animals will help to ensure the safety of therapeutics applied directly to or injected into the eye to treat an ocular disease before administered to humans.

Ocular Toxicity Testing

In preclinical model, the detection and characterisation of ocular toxicity and predictions of the potential risk to humans depends on 3 preclinical testing strategy namely the availability and use of state-of-the-art ocular safety assessment techniques, the knowledge on mechanism of action of the drug, and the current regulatory needs. Therefore, the toxicologist must be aware of a different method, tool, and models that help to detect and characterise the changes in eye functions. Appropriate and relevant animal model selection for safety assessment is very critical because of the anatomical differences among laboratory animals, and it is taken into consideration while selecting models. The dog and albino rats are more common test species for toxicology testing. Rats have a susceptibility to light-induced retinal degeneration which will be complicated in case of a drug-induced ocular toxicity interpretation[2]. Ocular toxicity testing of some drugs has shown differences in albino and the pigmented rat[3], based on a hypothesis related to the melanin binding. The dog eye contains tapetum, an anatomic structure that is not present in humans making tapetal findings in dogs unlikely to be relevant to humans[4-5]. Therefore, knowing the ocular anatomy of the species of laboratory animals, commonly used for nonclinical studies, is important. The anatomy can influence how the eye will react to a drug or foreign substance, whether administered systemically or directly onto or into the eye. There are guidelines from the EU, ICH, and FDA for the conduct of ocular toxicity studies, but the description in these guidelines is concise. It does not introduce a detailed design of ocular toxicity studies. Also, for the non clinical testing of ophthalmic drug there exist a regional difference in the regulatory expectations. Many toxicologists and pathologists new to this field are responsible for testing. Therefore, the below-mentioned summarised design and techniques need to be considered by a toxicologist for the conduct of ocular toxicity study in preclinical development:

Table 1: Study design for Ocular Toxicity Studies[6-10]

Test System	Rabbit, Monkey, Dog, etc., are selected as species of choice (Need rationale for selecting species). Rabbits are the preferred species used for ocular toxicity testing, and the rabbit eye is large enough to perform accurate ocular injections or delivery by other methods
Dosing Duration	Depend upon the duration of the clinical trial to be supported
Formulations	Eyedrops, gel, ointment, particles, patch, cream, Injectables
Doses	High dose is set by the Maximum feasible Dose derived from reasons inherent to the preparation of the formulation
Route	Route of administration needs to be selected based on the clinical use and that could be Topical, Intravitreal, Subconjunctival, and Periocular routes of administration
Parameters	All endpoints of general toxicity and ocular toxicity studies are common except ophthalmological examination of ocular toxicity studies need to be performed in more detailed and includes more platform because the drug directly administered in eyes. The standard endpoints of ocular safety in preclinical ocular toxicity studies summarised in table 2
Biodistribution	Biodistribution determined for different ocular tissues, e.g., cornea, conjunctiva, the sclera, iris, ciliary body, lens, vitreous, retina, optic nerve, and aqueous humour
Conclusion	NOAEL (for focal and systemic toxicities) and target organ/tissues inside/outside the eye

Table 2: Ophthalmological Examination in Ocular Toxicity Studies[6-10]

Categories	Methods	Testing Segment of Eyes
Required	Gross Observation (Draize method)	Conjunctiva and cornea
	The McDonald Schadduck method or the Hackett-McDonald method, using a slit lamp biomicroscopy	Eyelids, tear film, conjunctiva, cornea, lens, iris, anterior chamber, anterior vitreous
	Ophthalmoscopy (direct or indirect)	Cornea, lens vitreous body and retina
	Intraocular pressure	Iridocorneal angle (function)
Optional	Fundus Photography	Cornea, lens vitreous body and retina
	Esthesiometry	Cornea
	Electroretinography	Retina (function)
	Blinking rate count	Conjunctiva and cornea (irritation feeling)
	Schirmer test	Lacrimal gland and tear film (function)
	Confocal microscopy	Cornea
	Pachymetry	Corneal thickness
	Specular Photomicroscopy	Cornea (endothelium)
	Observation using laser flare-cell meter	Anterior chamber
	Fluorescein fundus angiography	Retina and choroid (blood vessel)
	Optical coherence tomography	Retina
	Ultrasound biomicroscopy	Conjunctiva, cornea, lens, iris, anterior chamber, anterior vitreous

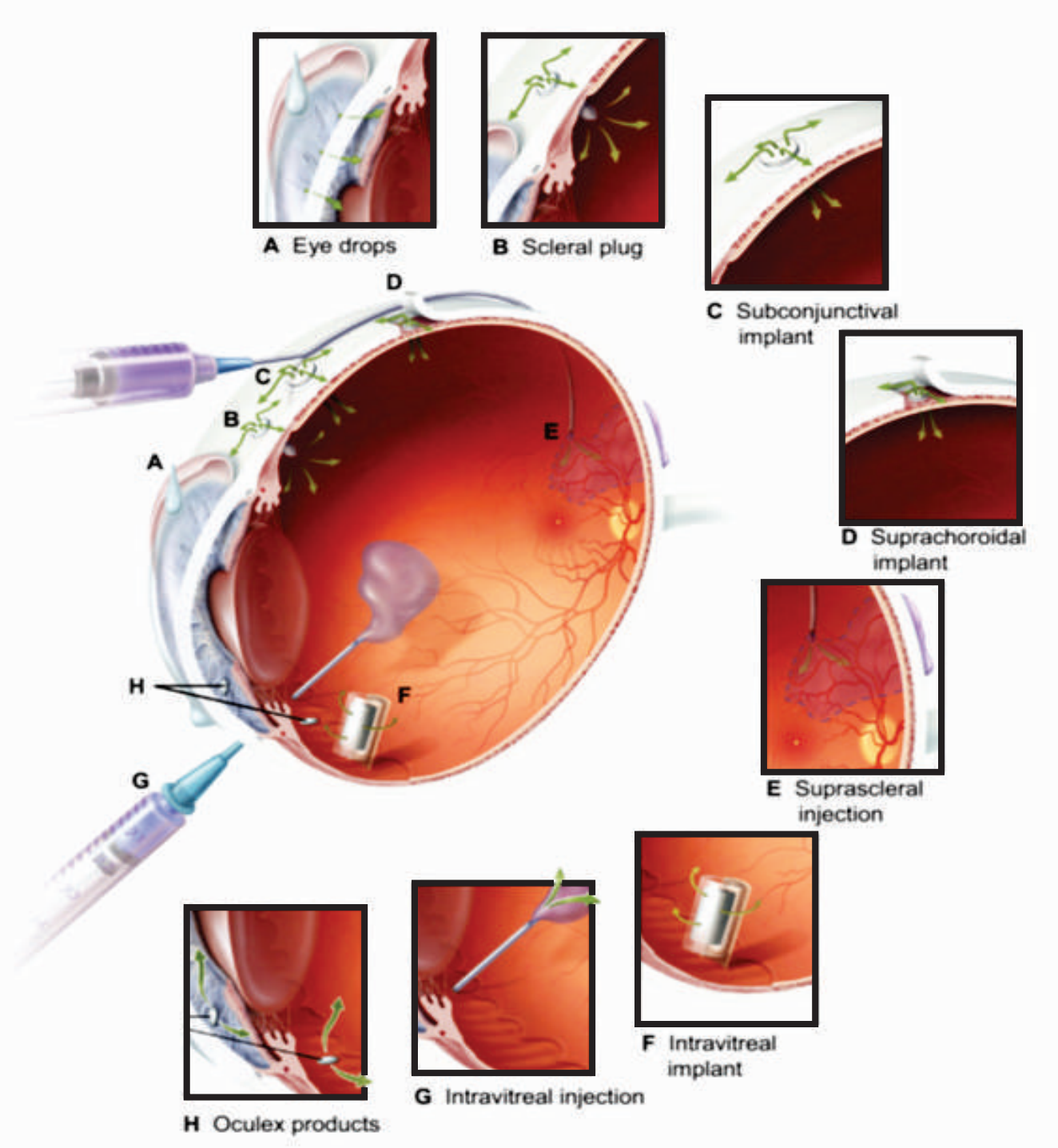

Figure: Sites and methods for ocular drug delivery to the eye[11]

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More than 8 years of experience in performing various safety pharmacology and repeated dose toxicity studies in compliance with GLP.

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