Retinal toxicity of intravitreal injections

Essay Submitted For Partial Fulfillment
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Introduction

Drug delivery to the retinal tissue and the vitreous via systemic administration is constrained due to the presence of blood retinal barrier which regulates permeation of substances from blood to the retina. Although intravitreal administration overcomes this barrier, it is associated with several other problems (***Koevary et al., 2003***).

The concentration of various drugs in the vitreous after systemic administration, a percentage of concurrent serum concentrations, is poor unless the eye is inflamed. The vitreous humour drug concentration can reach as high as 10% of the serum drug concentration. Intraocular drug penetration may be enhanced by increasing the systemically administered dose. However, increased systemic doses raise the risk of extraocular toxicity and are therefore not a viable strategy for elevating intraocular drug levels (***Ogden, 1994***).

Intravitreal injection represents a promising mode of administration for the delivery of medications with potential to alleviate the burden of visual loss associated with a variety of common retinal diseases. The outcomes of treatment depend on the safety and efficacy of medications as well as the safety and efficacy of the injection procedure (***Flynn et al., 2005***).

The danger of intravitreal injection may be somewhat overstated; it is probably safe when administered carefully. Drugs must be prepared with the outmost caution and sterility. Small volume (0.05 – 0.1 ml) should be given and anterior chamber paracentesis is considered to minimize the effects on ocular hemodynamics. Patients undergoing vitreous surgery have fewer problems with delivery since drug may be instilled through a vitreous infusion (***Peyman et al., 1982***).

Numerous pharmacological agents have been tested and used for intravitreal drug therapy. These range from antibacterial, antifungal and antiviral agents used to combat endophthalmitis and retinitis, to antiproliferative and anti-inflammatory agents to prevent intraocular proliferation and fibrosis. The scope of intravitreal drug delivery is now expanding with new agents for the treatment of various posterior segment disorders (***Spaide et al., 2003***).

Intravitreal treatment carries with it a risk of the following complications: elevated intraocular pressure, intraocular haemorrhage (including hyphema), drug induced retinal toxicity and retinal detachment. In phakic eyes an added risk is that of cataract formation due to contact by the needle (***Miller et al., 2004***).

Aim of work

To evaluate the toxic effect of different intravitreal drugs on the retina and to mention the therapeutic and toxic doses of frequently used drugs.

Anatomy and physiology of Vitreous and Retina

The vitreous humour is a transparent colourless gel of a consistency somewhat firmer than egg white. The vitreous has a volume of slightly less than 3.9 ml which is approximately two-thirds the volume of the entire globe. The vitreous is bounded anteriorly by the lens, iris and ciliary body and posteriorly by the retina and the optic disc. The rigidity and viscosity of the vitreous are produced by a delicate fibrillar meshwork of collagen like protein mixed with hyaluronic acid. The fibrillar meshwork is less dense in the center than in the periphery of the vitreous body (cortical region) and is most dense at the vitreous base, where the attachment to the pars plans and vitreal periphery is strongest. The anterior condensation of peripheral vitreous forms the anterior hyaloid membrane. It extends anteriorly from the vitreous base to the posterior portion of the lens. The potential space between the lens and anterior hyaloid membrane is the space of Berger. The depressed surface of the anterior hyaloid in this area is the patellar fossa. The condensation of the posterior peripheral vitreous produces the posterior hyaloid membrane. Under normal conditions, the posterior hyaloid merges with and is indistinguishable from the inner limiting membrane of the retina. The term "posterior hyaloid face" is usually reserved for aging or pathologic states in which the condensation of the vitreous becomes visible after vitreous detachment. **(Anthony,1997)**

The posterior hyaloid is not a true basement membrane. The vitreous fibrils are oriented parallel to the retina along the posterior hyaloids. The posterior hyaloid is thickest at the vitreous base and this considerably as the optic nerve is approached. The strongest attachment of the vitreous to the retina and pars plana is in the area of vitreous base. Although the vitreous base extends 2 mm anteriorly to the ora serrata on the pars plana and 4 mm posterior to the ora serrata, attaching to

the peripheral retina, only the central 3 mm area provides firm attachment to vitreous fibrils (Fig. 1)

Fig. (1): Anatomy of vitreous base. quoted from: Vitreoretinal Disease book ,1999

The attachment is so strong that any attempts to separate the vitreous base will result in detachment of the pars plana, pigmented epithelial cells and retina. The attachments of the vitreous fibrils are almost perpendicular to the retina at the vitreous base. Strong areas of physiological adherence behind the vitreous base can occur over retinal blood vessels. The vitreous is also firmly attached in the peripapillary region and less firmly adherent at the macula. It is also fixed anteriorly at the posterior peripheral surface of the lens (the ligament of Weigert) this ring like attachment is weaker in older individuals. Normally, the cortical layer of vitreous contains a small number of cells termed hyalocytes

which are concentrated mostly around the vitreous base. Hyalocytes may produce hyaluronic acid or may have phagocytic activity **(Anthony,1997)**

In the young eye the vitreous appears to be relatively optically transparent on slit-lamp biomicroscopy. With increasing age a veil-like scattering of light may be seen which undulates with movements of the eye. This is due to an alteration of the gel structure, but the fibriller appearance is not caused by a visibility of collagen fibrils, which are of molecular dimensions. In older age or in the younger myopic eye breakdown in structure occurs indicated by increased scattering properties and the appearance of optically empty spaces (syneresis) and the altered gel may collapse, so that its outer surface pulls away from internal coats of the eye (vitreous detachment). This detachment of vitreous is facilitated by the weakening of the adhesion between vitreous and structures external to it, which occurs with age. Detachment may merely split the internal limiting membrane of the retina at the points of attachment of the vitreous, may separate vitreous from the internal limiting membrane, may split the cortical vitreous or may at times tear the retina itself leading to retinal detachment (**Anthony, 1997**).

Vitreous Barriers:

Blood-vitreous or vitreoretinal barriers are functional terms describing the inability of the vitreous constituents to equilibrate with blood and with surrounding fluids. A variety of mechanisms cause this imbalance, including:

(1) Tight junctional complexes inhibiting passage of high molecular weight constituents at the level of the retinal vascular

endothelium (fig.2a) pigment epithelium of the retina(fig.2b), and non-pigmented epithelium of the ciliary body.

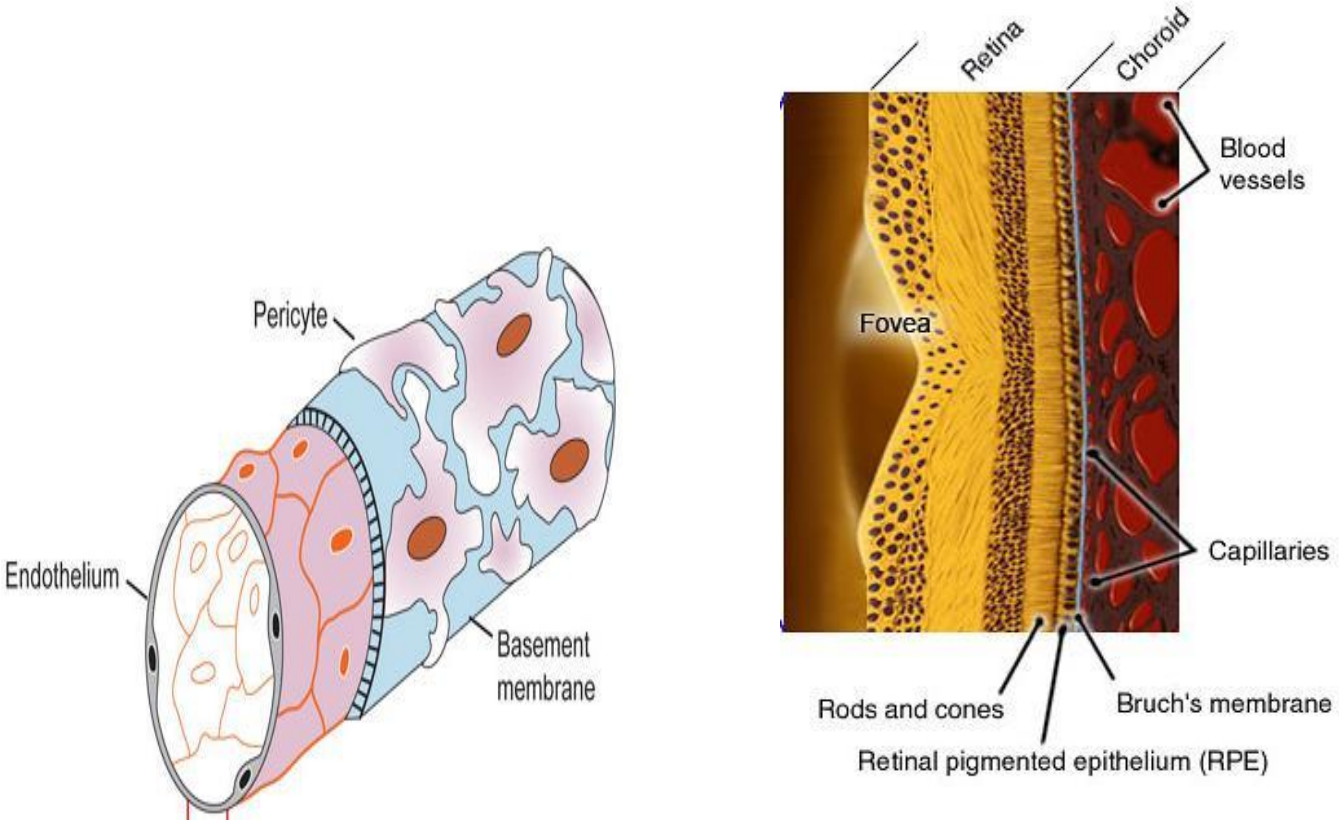
(2) Active transport pumping mechanisms at these same sites.

(3) Physical blockage of large molecules at the basal lamina of the vitreoretinal junction.

(4) The physicochemical characteristics of the vitreous collagen-hyaluronic acid network that effectively block or retard movement of cells, macromolecules and cations.

In addition to these barriers, equilibrium of the vitreous with its surrounding structure is slow because of its small surface area/ volume ratio.

These barriers can be overcome by loss of retinal vascular integrity such as that occurs with inflammation **.(Anthony,1997)**



(a)Inner blood retinal barrier **(b)outer blood retinal barrier**

Fig. (2): Blood retinal barriers .quoted from :Wolff s Anatomy of the eye and orbit ,eighth edition,1997

The retina is an area of the eye responsible for receptive light and converting the patterns of light and shadow to neural impulses for interpretation by the cerebral cortex .It is derived from ,and is part of, the central nervous system . The sensory retina is transparent , except for the blood vessels , so the apparent color of the fundus is derived from the retinal pigment epithelial melanin , the melanin of the choroidal melanocytes , and the choroidal vessels.

The retinal pigment epithelium (RPE) is derived embryologically from the same neural tube tissue as the neurosensory retina , RPE cells differentiate into a monolayer epithelium that behaves functionally

more like the lining of the gallbladder than like central nervous system tissue . The cells are linked by tight junctions and show anatomic and physiologic membrane specialization on the apical and basal surface These enable the RPE to control water and nutrient access to the subretinal space ,which is critical to the viability of the photoreceptors.

The choroidal vessels ,which provide nutrition to the outer retina , are leaky , and the other part of the blood –retinal barrier is provided by tight junctions of the RPE The apical and basal RPE membranes contains a variety of selective ion channels and a variety of active and facilitative transport systems that control the movement of ions and water and the transport of metabolites , such as glucose and amino acids. **(Carl et al.,1999)**

Technique of intravitreal injection

- Principles: Intravitreal injections can be given at the outpatient department or minor operation theatre set up. Use of sterile surgical gloves and sterile (plastic) sheets are a must.

- Visual acuity and intraocular pressure are measured and an indirect examination is performed.

- Topical proparacaine hydrochloride 0.5% is applied to the affected eye for a total of two applications, 5 minutes apart.

- A betadine swab is applied to the bular and palpebral conjunctiva of the affected eye.

- Using a 27-gauge needle, 0.5 ml of 2% xylocaine without epinephrine is injected subconjunctivally temporal to the limbus, ensuring adequate bleb formation.

- After 5 minutes, the hub of a sterile syringe (not a tuberculin syringe) is used to produce a circular indentation with a diameter of 4 mm marking the pars plana needle entry site. The injectable drug is injected into the eye 4 mm from the limbus temporally or slightly inferotemporally. The needle is aimed toward the center of the globe. (fig.3)

- An attempt may be made to aspirate by gentle suction some vitreous fluid through pars plana for bacteriological analysis. Often one is likely to fail to get fluid. The needle must be withdrawn slowly letting the vitreous collagen clogging the needle to escape back without causing traction retinal tears.

- The conjunctiva is irrigated with sterile saline (though it is possible to mix an antibiotic and dexamethasone, it is not advisable to mix two antibiotics in the syringe).

- In order that concentrated drugs do not settle on the macula, one may use a pillow during the procedure and turn the head to the opposite side immediately after the injection or the patient may maintain a face down position for 10 to 15 minutes for the drugs to move towards the anterior segment.

- A repeat indirect examination is performed, checking for vascular pulsations and adequate perfusion of the optic disc.

- Repeat intraocular pressure measurement is performed every ten minutes. Put a pad and bandage for at least an hour. A pain killer and a tablet of Diamox 250 mg is optional , paracentesis also may be needed.(**Peyman and Schulman 1994)**

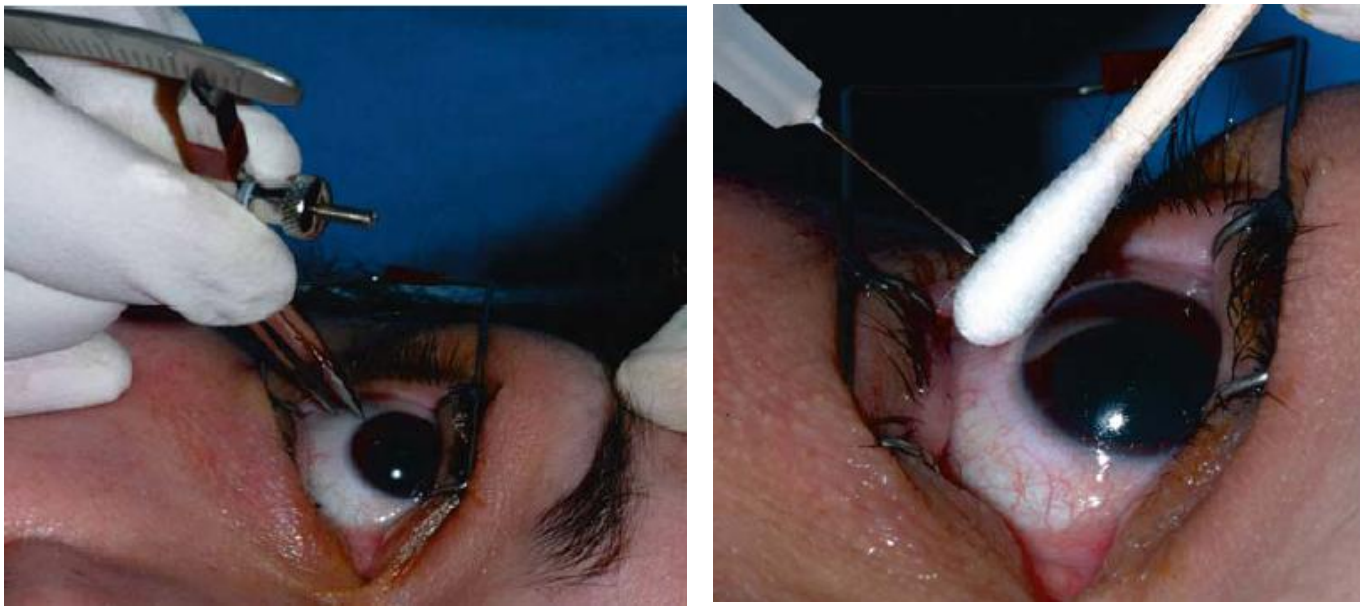


Fig.(3) :Technique of injection. quoted from: Retinal Vascular Diseases textbook, 2007

A-Steroidal Anti-inflammatory Drugs

1-Triamcinolone Acetonide

Triamcinolone Acetonide (TA) is a synthetic steroid with marked anti-inflammatory action. It is a minimally water soluble steroid injected in a suspension form. The decreased water solubility contributes to its prolonged duration of action. It is considered as an effective and safe agent for intravitreal injection in conditions requiring long-term steroid administration (**Beer et al., 2003**).

Triamcinolone is a potent synthetic glucocorticoid that is used to treat number of autoimmune and allergic conditions. Triamcinolone Acetonide (TA) was the first halogenated corticosteroid to be widely used topically and when first introduced was found to be dramatically more effective than any previous topical corticosteroid (**Beer et al., 2003**).

Because dexamethasone is washed out of the eye within 24 hours after a single intravitreal injection, **Machemer** suggested using the crystalline form of cortisone, which because of an absorption time of about 2 months, provides intraocularly available cortisone for a considerably longer period than the single injection of soluble cortisone (**Jonas, 2002**).

Intravitreal Triamcinolone has increasingly been used in pilot studies for treatment of intraocular proliferative, oedematous and neovascular diseases, such as long standing macular oedema due to central retinal vein occlusion, diffuse diabetic macular oedema, proliferative diabetic retinopathy, neovascular glaucoma,