Side Effects Associated with Prostaglandin Analogue Therapy

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The introduction of Prostaglandin analogues (PGA) in the mid 1990’s was received with great enthusiasm because of its superior intraocular pressure (IOP) lowering efficacy and a near absence of systemic side effects. Almost two decades after its introduction however, a number of trivial and serious ocular effects are being reported.

Mechanism of Action
Immunohistochemical data have shown that the IOP reduction with topical PGF2-alpha is associated with a reduction of collagens within the uveoscleral outflow pathway. The ciliary body contains several prostaglandin receptors whose activation seems to stimulate a second messenger cascade for metalloproteinases synthesis which alter extracellular matrix modelling.¹

Common Side Effects
Conjunctival Hyperaemia
Eyelash changes
Iris hyperpigmentation
Periocular skin-pigmentation

Less Common Side Effects
Iris cysts
Cystoid macular edema
Anterior uveitis
Reactivation of herpes simplex keratitis
Prostaglandin induced periorbitopathy (PIP)

Common Side Effects
Conjunctival hyperaemia
Mild conjunctival hyperaemia is a common side effect of PGA’s and is seen least frequently with latanoprost when compared to other PGA’s. It usually occurs within the first 2 days of initiating treatment and declines over time.² ³

Conjunctival changes associated with prolonged use of Prostaglandin analogues
Chronic administration of topical PGA’s has been shown to cause inflammation, scarring, keratinization and neovascularisation. Many studies show an increase in the number of fibroblasts and inflammatory cells in the conjunctival substantia propria and epithelial metaplasia. However, there is no conclusive evidence as to whether these changes are due to the prostaglandins or preservatives like BAK in these formulations.

Eyelash changes
Main changes in eyelash appearance include increased number, length, thickness, curvature and pigmentation. An increased pigmentation of the eyelid and periocular skin has also been reported. Eyelash lengthening is a fairly common side effect with between 45%-57% eyes affected after treatment for 6-12 months. Average increase in length of 0.7-0.8mm have been reported in various studies.⁴
Iris hyperpigmentation
It usually develops within first 8 months of initiating topical treatment. Possible mechanisms suggested for iris pigmentation are stimulation of melanogenesis in iridial melanocytes, upregulation of transcription of the tyrosinase gene and migration of iris stromal melanocytes to thicken the anterior border region with no net gain in melanocyte numbers. Uniformly brown irises appear to be at low risk for induced pigmentation. Uniformly blue/gray irises carry little or no risk for iris pigmentation, whereas heterogeneous hazel eyes especially golden brown or green brown are highly likely to develop iris pigmentation. Iris pigmentation is a permanent change and does not disappear on stopping treatment.

Less Common Side Effects

Iris cysts
A rare event that may or may not have a direct association with PGA therapy is development of iris cysts. Cessation of medication was followed by decrease in size of the cyst with complete reversal over few months. Krohn and Hove have proposed that iris cyst formation might be related to flow pressures caused by increased uveoscleral drainage.

Periocular skin pigmentation
Darkening of the skin of the lids or other sites around the eye is an occasional side effect. PGA induced pigmentation is most prominent in the eyelids and becomes apparent in few months though it can occur up to after 3 years. The prostanoid effects of melanogenesis and melanocyte proliferation have been suggested as possible mechanisms for skin pigmentation. Skin pigmentation is reversible with normal coloration returning over a period of 7-8 weeks.

Cystoid macular edema
Cystoid macular edema (CME) has been reported in few patients receiving topical PGA’s but a causal relationship has not yet been proved or disproved. In most cases CME appears weeks to months after initiating PGA therapy. Furthermore the CME is reversible with early discontinuation of PGA and it has been shown that CME can be prevented with a NSAID. However, the risk increases if a PC rent occurs during cataract surgery.

Anterior uveitis
Prostaglandin induced uveitis seems to be due to a breakdown of blood-aqueous barrier and not really an inflammatory process (Arjomand et al). A comparative study of flare in patients on PGA’s showed that after 3 months travoprost and bimatoprost had less flare than latanoprost which reflects a slightly superior break of the blood aqueous barrier by Latanoprost. Uveitis usually resolves after discontinuation of PGA’s.

Reactivation of Herpes simplex keratitis
There have been a few case reports of reactivation of Herpes simplex keratitis (HSK) after initiating PGA therapy. Discontinuation of PGA is usually followed by resolution of keratitis in most of these cases. Zimmerman et al analysed the data of 93,869 glaucoma patients for reactivation of HSK following administration of PGA’s. The study revealed a rate similar to that found in the general population and did not correlate with any antiglaucoma therapy. It appears, therefore that the risk of activating an ocular herpes simplex infection through initiation of PGA is low.

Corneal toxicity
Dendritiform epitheliopathy has been reported after latanoprost treatment. Few studies have shown episodes of mild punctuate epithelial erosions.

Prostaglandin Associated Periorbitopathy

Deepening of upper eyelid sulcus
Upper eyelid ptosis
Involution of Dermatochalasis
Periorbital fat atrophy
Mild enophthalmos
Inferior scleral show
Increased prominence of lid vessels
Tight eyelids
In a study, periorbital fat loss was the most frequent finding and was observed in nearly all PAP patients. Frequency of PAP was most with bimatoprost group and least with latanoprost group. The frequency of milder changes (the presence of either only periorbital fat loss or dermatochalasis involution or the presence of both) was higher in the latanoprost group than with travoprost and bimatoprost.\textsuperscript{14}

**Systemic Side Effects**

Occasional systemic side effects have been reported. These include gastrointestinal disturbances similar to those caused by aspirin or other nonsteroidal anti-inflammatory agents, chest pain, palpitations and upper respiratory tract infections.

**References**