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Steroid response – a guide for clinicians

Stephen A Vernon - Nottingham

Important learning points

Steroid response:

- is of variable magnitude which may vary between the eyes
- is more common in children
- is related to the potency of the steroid
- may commence within a few days or be delayed by months
- can occur in a functioning trabeculectomy
- may occur following depot injections when drops induced no response

The effect of steroids on eye pressure

The first use of glucocorticoids to treat disease occurred in 1948 and by the 1950s topical glucocorticoids were beginning to be used to suppress ocular inflammation. By the early 1960s the link between raised IOP and glucocorticoid treatment, both systemic and topical, was well established. Although recognised by most ophthalmologists, "steroid response", a phenomenon where some individuals suffer an increase in IOP following exposure to glucocorticoids, may still cause confusion. This article attempts to resolve many common misconceptions and serve as a timely reminder to those who may induce steroid induced glaucoma (SIG), exacerbate a pre-existing glaucoma, have to interpret IOP post ophthalmic surgery, or need to consider the possible adverse effects of a significantly raised IOP, albeit short-lived.

Mechanism and degrees of steroid response

The mechanism of the response may be different in individual cases involving both intra and extracellular changes in the trabecular meshwork which are usually reversible but may lead to trabecular sclerosis. Recent genomic research has identified a number of polymorphisms associated with the response[1].

Steroid response is considered to be predominantly genetically determined with three patterns of response identified in the 1960s. Considering a response to topical steroids as defined following a four week course of 0.1% dexamethasone drops used qds, a minimal response (IOP rise of <6mmHg) occurs in 60% of the normal population, an intermediate response (a rise of IOP of 6-15mmHg) in 35% of normals, and a high response (>15mmHg) in 5% of normal adults. In those with POAG (as diagnosed in the 1960s i.e. with a much higher mean presenting pressure than a modern cohort) the rate of high level steroid response was estimated at 90%. This is certainly an overestimate. In general, the lower the anti-inflammatory potency of the topical agent the lower the rate and magnitude of response.

Steroid response in practice

An over secretion of cortisol, as occurs in Cushing's disease, in a susceptible individual, may cause raised IOP and simulate POAG, with the ophthalmologist occasionally having the opportunity to diagnose the systemic condition! However it is exogenous glucocorticoids that dominate the domain of steroid response issues that ophthalmologists encounter. In the UK, glucocorticoids, either systemic or topical, are almost always prescribed under the supervision of a doctor. Elsewhere in the world this may not be the case and self medication may induce blindness secondary to unidentified SIG.

Systemic exposure to steroids

Although any dose of systemically ingested glucocorticoid may increase IOP, chronic use of oral steroids at relatively low doses (<10mg prednisolone or equivalent) seems to be a rare cause of significantly raised IOP[2], although when it does occur the response cannot be linked to dosage or duration of ingestion[3].

Inhaled steroids have in the past been identified as a potentially potent cause of raised IOP in steroid responders[4]; however the more modern steroids used in inhalers appear not to increase the incidence of glaucoma in long-term users[5], although inhaled steroids may significantly worsen IOP control in those with glaucoma. If their use is seasonal, secondary raised IOP may not be detected and the mechanism of glaucoma progression not appreciated by the ophthalmologist. The use of nasal steroids does not appear to be a significant risk factor for raised IOP[6].

Ocular steroids and the steroid response

It is when ophthalmic disease is treated where ophthalmologists and optometrists are likely to encounter the majority of steroid responders. Knowledge of the variety of response possible, its time of onset and resolution, and the degree of response, even in situations where a response may not be anticipated such as with a functioning trabeculectomy bleb, is valuable in the management of patients under routine care. Such knowledge may prevent unnecessary intervention, or prevent iatrogenic visual loss from inadvertent persistence of raised IOP.

As a general rule, children, particularly under the age of 10 years, are more susceptible than adults to exposure to ocular steroids. A study on post squint surgery eyes found that 56% of children exhibited a high response and 38% an intermediate response following one month of qds 0.1% dexamethasone whereas only 6% of fellow eyes treated with FML for a similar time responded at the high level.

It is therefore not surprising that about 5% of paediatric glaucoma cases in a tertiary centre were found to be from iatrogenic steroid use[7] with 87% being associated with Vernal Keratoconjunctivitis (VKC) treatment. In another tertiary centre, a recent report indicated that the rate of SIG in VKC was 2.24% with a third bilaterally blind from glaucoma following a mean duration of steroid use of 24 months[8]. In paediatric cases, a permanent effect on IOP is more common than in adults.

Steroid response following ocular surgery

The commonest scenario for encountering a steroid response is following cataract surgery. With around 400,000 operations annually in the UK and a 5% chance of a high response (with qds dexamethasone), significantly raised IOPs in otherwise normal eyes are relatively common. However as the time of onset of the

IOP rise varies from a few days to four weeks and the subsequent fall in IOP following a short course of treatment may be complete at a week following cessation, fewer are identified than would be expected. So which eyes might be at particular risk of what is likely to be a very temporary "high" IOP? Patients with advanced glaucoma where fixation is threatened may be at risk of acuity reduction from such an IOP spike. This can occur before steroids are commenced, despite careful post-surgery prophylaxis[9] or soon after exposure making frequent careful IOP monitoring mandatory in such cases if steroids are used in the postoperative phase. Remember nonsteroidals as an alternative to steroid drops can have an equal anti-inflammatory effect and may result in less cystoid macula oedema[10] . Patients in whom non-arteritic AION has occurred are also probably at risk if they are steroid responders and the author has seen three cases where such an event occurred in association with raised IOP post routine cataract surgery.

A functioning trabeculectomy might intrinsically be thought to protect from a steroid response post cataract surgery. The chronic failure of bleb function following such surgery is a well known phenomenon, but a temporary increase in IOP that resolves following steroid cessation is less well appreciated[11]. A rise in IOP up to the high teens in an eye with a pre-cataract surgery IOP or around 12mmHg is not uncommon and, in the presence of a good looking drainage bleb, should not be a reason to induce additional bleb-related treatment. Observation or a change to non-steroidal drops should be the initial management in such circumstances.

Glaucoma is a relative contraindication to corneal refractive surgery but in those who do undergo such treatment, the potential for a masking of a steroid response by the biomechanical changes that occur in the cornea should be considered with a measured IOP (with GAT or similar) being lower post treatment than the real IOP[12].

Depot injections of steroids

Depot injections of steroids increase the risk of a significantly raised IOP in responders, with intravitreal steroids being at greater risk than subconjunctival or subtenon's delivery. In routine cataract patients without glaucoma or a family history of the same, significant rises in IOP following a single dose of triamcinolone 40 mg are rare[13] but a response can be delayed occurring many months following exposure. Rates of IOP elevation of >10mg above baseline following 4mg of triamcinolone delivered intravitreally occur in 38% of retinal vein occlusion patients and 44% of patients with diabetic maculopathy. IOP control can require glaucoma surgery in such cases, with the long acting fluocinolone acetate depot injection having a 4.8% rate of incisional surgery at 36 months post insertion in one study[14] and unfortunately a history of non-response to topical steroids does not eliminate a severe response with depot therapy[15].

Conclusions

The clinician, usually an ophthalmologist, prescribing/delivering steroids is responsible for warning a patient of a potential steroid response and organizing monitoring for the same. Being aware that a response may be unilateral, may occur when previous similar steroids have not induced an effect and may be delayed in long-term topical use or following depot injections will reduce the chance of adverse events for the patient and litigation for the clinician.

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Andrew Tatham
Editor, Focus