Steroids and the eye—indications and complications

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Summary

Corticosteroid therapy is of great value in many types of eye disease. The indications are briefly discussed, together with the choice of agent and mode of administration. The dangers of steroids are now widely recognized, and the complications are discussed, particularly cataract and glaucoma. Reference is also made to optic neuritis and thyroid ophthalmopathy, where the role of steroids is uncertain.

Particular stress is laid on the need to keep steroid dosage as low as possible, so as to avoid systemic side effects. There are unfortunately many situations where treatment of doubtful efficacy has produced severe side effects. Despite the overall benefit of steroids in ophthalmology, there is a pressing need to find alternative treatment for a variety of blinding disorders.

Introduction

Corticosteroid therapy has been applied in ocular disease from the moment it became generally available. Initial enthusiasm in trying these drugs in almost every type of eye condition soon resulted in an appreciation of their major indications (Duke-Elder, 1951), but it was a decade before the local ocular complications of their use were generally recognized.

Apart from their effect in reducing wound scarring, their major use is in the suppression of inflammation. It was very quickly realized that corticosteroids had little effect on the cause of inflammatory reactions, and that if they were withdrawn in the continuing presence of the exciting stimulus, then the inflammation would again be manifest.

Although we now know that corticosteroids are immunosuppressant in higher doses we are still largely ignorant of their mode of action in inflammatory disease.

The complications of therapy are directly related to the dosage and duration of treatment, and so the most satisfactory results are to be expected where the disease is self-limiting, and where possible potentiating effects on the underlying cause can be counteracted by specific therapy. In ophthalmology

there are many situations where these ideals do not obtain. Those of us who see a lot of chronic inflammatory eye disease are no less aware than specialists in other fields of the severe and often unacceptable side effects of these agents.

The actions of corticosteroids on ocular tissue have been widely studied. In experimental corneal wounds cortisone has been shown to inhibit the formation of the fibrinous coagulum, cellular infiltration, fibroblastic repair and endothelial regeneration (Ashton and Cook, 1951; Leopold *et al.*, 1951). Ashton and Cook (1951) were able to prevent healing completely with large enough doses. Cook and MacDonald (1951) showed that cortisone, given locally or systemically, reduced the increased permeability in ocular capillaries in inflammation, and confirmed Leopold's findings (Leopold *et al.*, 1951) that there was no effect on the permeability of normal vessels. They also observed that on withdrawal of treatment the permeability increased again, even when the ocular condition was clinically quiescent. In practice we see many cases where signs of vessel leakage persist despite inactivity of the condition.

Penetration, potency and choice of drug

Penetration obviously depends on the drug and mode of administration. For example, topical hydrocortisone penetrates the cornea better than does prednisolone, but the reverse is true if the drug is given systemically. The anti-inflammatory action is not directly associated with ease of penetration (Leopold, Kroman and Green, 1955).

Topical and subconjunctival injection produce therapeutic levels in the cornea and aqueous humour, but systemic administration or retrobulbar injection are necessary to obtain adequate levels in the vitreous, choroid and retina.

Our knowledge of penetration is mostly gained from experiments on healthy tissues, but it must be remembered that in disordered tissues, especially with breakdown of the blood-aqueous barrier, penetration will be enhanced.

Prednisolone is usually preferred to hydrocortisone, both for local and systemic use. It has been found to be effective more rapidly, and at a lower dose (King *et al.*, 1955). The depot preparation of

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methylprednisolone is also widely used for subconjunctival, intravenous or retrobulbar injection, and is well tolerated. Triamcinolone is also used for orbital injection. By this means, high concentrations of the agent are delivered in the posterior segment of the eye for at least a week after one injection (Hyndiuk and Reagan, 1968) and in practice it is rarely necessary to repeat the injection in under a fortnight.

For local use, dexamethasone is more powerful than prednisolone, but produces more problems with increased intraocular pressure.

The choice of therapy is largely determined by the part of the eye the drug has to reach, although a change from topical to depot or systemic therapy may be dictated by failure to respond to a previous method of administration. The increasing use of orbital injections for conditions otherwise requiring systemic therapy saves many patients from the burden of systemic side effects, because a much smaller overall dose is used.

Corticotrophin is not widely used because of the inconvenience of injections. It has the disadvantage of not producing such a prompt rise to high levels of circulating corticosteroid as can be achieved by giving the adrenal hormone itself.

Indications

The following summary is not intended to be exhaustive.

(1) *Allergic and hypersensitivity disease*

Eyelids—drug and cosmetic reactions

Conjunctiva—vernal disease

—phlyctenular disease

Cornea—interstitial keratitis and other corneal diseases where the specific antigen plays a part in eliciting a reaction. Examples are the stromal keratitis of herpes simplex and the reaction to staphylococcal antigen which respond to local steroid therapy, although effective specific therapy must be given concurrently.

(2) *Scleritis and episcleritis*

(3) *Uveal tract inflammation*

Local therapy is usually effective for anterior uveitis, but orbital or systemic therapy is usually indicated for choroiditis, retinal vasculitis, or vitreous body inflammation, and for the chronic granulomatous forms of uveitis such as sympathetic ophthalmitis.

(4) *Giant-cell arteritis*

Systemic treatment in high doses is sight-saving. The dose is reduced gradually by titration against the erythrocyte sedimentation rate, but will need to be restored to a higher level if visual symptoms return.

(5) *Trauma* (a) after injury or surgery; (b) after physical or chemical burns.

A balance must be struck between reducing scar tissue and vascularization on the one hand, and impeding healing to the extent of producing unstable wounds on the other.

(6) *Herpes zoster ophthalmicus*

The keratitis and uveitis which may occur respond well to local treatment. Scheie and McLellan (1959) reported rapid relief of pain with systemic therapy, although symptoms frequently recurred when treatment was reduced. The high doses of steroids required are hardly applicable to many of the elderly patients in whom the condition occurs, and systemic steroid therapy is not commonly employed.

Some controversial issues

(1) *Optic neuritis*

There are many reports of small groups of patients treated with steroids for acute optic neuritis. Neubauer and Karges (1959) felt that the healing process was accelerated, but Giles and Isaacson (1961) were not convinced of the superiority of steroids over other forms of therapy. Conclusions in early studies must have been at least in some degree influenced by the fact that the tendency to spontaneous recovery was not fully appreciated until the early 1960s. Rawson and Liversedge (1969) concluded that corticotrophin should be given, but their results did not show a significant difference between treated and untreated groups. In a recent series reported by McDonald (1976) no difference between treated and untreated groups was seen at 6 months, although treated patients were better than untreated patients at the end of the first and second weeks. It is McDonald's view at the present time that 'in the absence of any convincing evidence that treatment alters the outcome of acute unilateral optic neuritis, the routine use of ACTH or steroids is not indicated'.

(2) *Thyroid ophthalmopathy*

As early as 1951 reports of both success and failure in reducing exophthalmos had appeared (Olson *et al.*, 1951). (See also the discussion by Cole on p. 299 of the Olson paper.) Doses of less than 20 mg prednisolone or 100 mg hydrocortisone have been ineffective (Medical Research Council, 1955; Day and Carroll, 1961). Success has been reported with higher doses but recurrence on withdrawal of therapy is frequent, and the side effects of the doses used are severe.

Werner has reported sustained improvement with initial doses of 120–140 mg prednisolone daily in the emergency treatment of malignant exophthalmos (Werner, 1966) but he feels that 'neither prednisolone nor immunosuppressive drugs nor both together

shorten the overall course of active ocular disease' (Werner, 1972).

Corneal exposure or optic nerve involvement endangers sight and demands emergency measures. If steroids are to be used with hope of success, it would appear that initial doses of around 100 mg prednisolone daily are required, and that a response should be seen within a few days. If a rapid response is not forthcoming other therapy should be instituted. Transantral orbital decompression has proved such a relatively straightforward and successful procedure that some would consider it as primary treatment in this critical situation.

Following improvement in exophthalmos with steroids, therapy must be maintained until natural remission has occurred, or relapse may ensue (Ivy, 1972).

Exophthalmos has been treated by the retrobulbar injection of steroid, but the results are not convincing, and the wisdom of making an injection into an already tense orbit is questionable.

Complications

Systemic side effects

There are many ocular conditions requiring 20 mg prednisolone or more daily for their control, and systemic side effects are common. Ideally, systemic steroid therapy should be used only when the condition will be relatively short-lived, and then only when the local therapy (e.g. by orbital steroid injection) has failed. When treatment is begun in childhood, the problem of growth disturbance must also be faced.

Ocular side effects

Ocular side effects are seen irrespective of whether the steroid is being taken for systemic or ocular disease.

(1) *Posterior subcapsular cataracts*

These were first reported by Black *et al.* (1960) in seventeen of forty-four patients with rheumatoid arthritis on prolonged corticosteroid treatment. A further follow-up of the same patients (Oglesby *et al.*, 1961) revealed that no patient developed cataract in less than 1 year after beginning treatment, and it occurred in only one patient on less than 10 mg prednisolone daily. All twelve patients who had taken 15 mg daily for more than 1 year developed cataract. Serious visual impairment was uncommon, although one patient required cataract extraction.

This experience is general. Lens opacities have developed in five of eleven renal transplant patients being followed by the author, but in no case with any great visual effect. In this condition it is a small price to pay for survival.

When steroids are used for ocular conditions similar opacities develop at similar dose levels.

However, opacities may also be produced by the ocular inflammation itself, and are not uncommon in chronic uveitis. Steroid therapy will add to this tendency.

The mechanism of the lens damage is not understood.

(2) *Glaucoma*

In 1951, McLean, Gordon and Koteen reported seven cases of anterior or generalized uveitis developing a raised intra-ocular pressure after systemic treatment with ACTH or cortisone, and one after local therapy. François (1954) reported eight cases of intra-ocular pressure elevation after 15 days–15 months of treatment. Goldman (1962) suggested an individual predisposition to this effect, and Armaly has concluded that the response to steroids has a genetic foundation (Armaly, 1966). Armaly found a significant elevation of intra-ocular pressure after 0.1% dexamethasone drops three times daily for 4 weeks in 30–40% of eyes sampled at random (Armaly, 1963). He suggested that the effect is due to alterations in the mucopolysaccharides in the intertrabecular spaces of the pore area of the trabecular meshwork, interfering with aqueous drainage. Becker and Hahn (1964) suggested that a high pressure response to topical steroid is transmitted as a monogenetic dominant with a gene prevalence of 0.2 which in the homozygous state is associated with a primary open angle glaucoma. The greatest elevations in intraocular pressure are seen in patients with this condition and, recently, evidence has been presented for generalized hypersensitivity to glucocorticoids in these patients (Becker and Podos, 1974).

Dexamethasone more commonly causes a serious rise than do prednisolone or hydrocortisone, and this complication is seen much more frequently with topical than with systemic treatment. The lesson is not to give steroids for long periods without supervision, especially for minor irritations where less harmful preparations, or simple reassurance are more appropriate.

On withdrawal of the drug the intra-ocular pressure falls to normal. Where steroids must be maintained, changing to a different compound may suffice, but treatment to control the intra-ocular pressure is often necessary as well, and may prove difficult to achieve.

(3) *Enhancement of infective disease*

Thygeson, Hogan and Kimura (1953) reviewed the results of cortisone and hydrocortisone in ocular infection, and pointed out the danger of depressing tissue defences and masking the progress of the infecting agent. Fungus infections are particularly liable to enhancement. Of the greatest practical importance is the disastrous effect of steroids on herpetic epithelial keratitis. The above authors also

drew attention to this (Thygeson *et al.*, 1960), but one still sees cases of enhanced herpes simplex keratitis produced by unsupervised use of local steroids. The mixed antibiotic plus steroid preparations are the usual offenders.

Conclusion

In concluding it would be well to summarize the aims of therapy—to control the disorder within acceptable limits with a dose of steroid which is tolerable from the point of view of side effects. Once control is established attempts should be made to find the lowest effective dose, but reduction should be gradual. Attempted reduction in patients who have become used to a certain dose over many months or years often produces a flare-up, even though the disease may have been quiescent for a long time.

In most cases of anterior uveitis it is possible to achieve control with local treatment, thus avoiding systemic side effects. At the other end of the spectrum are conditions such as sympathetic ophthalmitis and Behçet's disease where high-dose systemic therapy commonly produces severe side effects and still does not control the disease. It is important in these cases to realize that a perfect solution does not exist. Some patients regret that they were ever treated with steroids when they find themselves incapacitated by enormous doses which have been continually increased in the pursuit of an evasive clinical cure. This dilemma has led some workers to try other forms of treatment in these severe sight-threatening disorders. Immunosuppressive drugs have been used, and the author himself has experience along these lines at the Institute of Ophthalmology (Dinning and Perkins, 1975).

Nonetheless, one must not let these gloomy considerations cloud the fact that thousands of patients have enjoyed great relief of symptoms and prevention of long-term complications in a wide variety of eye disease. The benefits of corticosteroids to ophthalmology far outweigh their disadvantages.

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