The side effects of corticosteroids

Bernard Becker

Corticosteroids are of enormous value in the suppression of the ocular inflammatory reaction to various injurious agents. The administration of corticosteroids alters the metabolism of carbohydrates, proteins, and lipids, as well as affecting almost all other endocrine secretions, salt and water balance, and a large number of enzymatic reactions. Therefore, it is not at all surprising that corticosteroids have side effects.

For the intelligent use of any hormone or drug, the clinician must be familiar not only with its beneficial effects, but also with its other actions. Knowledge of the various undesirable changes permits the clinician to recognize their early occurrence in the individual patient and to alter his therapy accordingly. Such information should not lead the competent and conscientious physician to abandon the use of life-saving or sight-preserving corticosteroids when they are indicated. On the contrary, an understanding of side effects permits him to weigh carefully and continuously the relative merits against the potential risks of the prescribed therapy.

As with other potent drugs, corticosteroids should be used only when indicated, for the minimum amount of time necessary, and with competent observations for recognized side effects. It is important to re-emphasize that steroid therapy is not a cure for inflammatory disease, but is often a very important adjunct to other more specific therapies. Steroids are most valuable in the short-term treatment of self-limited inflammatory processes. In ophthalmology the alleviation of inflammatory reactions often becomes of major importance. Properly used, steroids can prevent opacification of the ocular media, avoid destruction of critical visual elements, and decrease damage to aqueous humor outflow channels.

Choice of therapy

Corticosteroids differ in their relative potency per milligram, but all available steroids are essentially the same as to their effects and side effects at the doses necessary for suppressing inflammation. The outstanding exception is the greater electrolyte-retaining effects of hydrocortisone and cortisone than of the newer and more potent anti-inflammatory corticosteroids. In Table I are presented the relative potency, size of the tablet for systemic use, and available concentrations of topical preparations for most of the currently available steroids. The clinician needs this information because some patients tolerate one steroid better than another.

Systemic side effect of steroids

In Table II are listed the common systemic side effects which may follow the
administration of any of the corticosteroids. Most of these become prominent problems only with prolonged administration and are avoided with short-term use (less than 3 to 4 weeks). When clinically feasible, ophthalmologists can avoid many of the systemic effects by the use of topical or subconjunctival medications.

The Cushingoid state with moon facies, weight gain with typical distribution, increased fat pads, striae, ecchymoses, acne, hirsutism, and hypertension is seen frequently after systemic corticosteroids and is difficult to avoid or manage. Activation of peptic ulcers, occasionally with massive hemorrhage, is a distressful and sometimes serious side effect. Although the use of antacids will partially alleviate some of the symptoms, it does not always prevent the reactivation. Another serious side effect is the precipitation or aggravation of a diabetic state. This can usually be managed by suitable regulation of diet and insulin. The retention of sodium and fluid, although somewhat less prominent with newer steroids, still remains a problem. It may be partially avoided by salt restriction or overcome by the use of diuretics. Osteoporosis, fractures, and mental and emotional symptoms are much more difficult to manage, and often require cessation of steroid therapy.

The increased susceptibility to infection and the possible dissemination of tuberculosis and fungal agents are important complications of systemic steroids. Where possible the use of specific antibiotic therapy can be most helpful. In individuals with evidence of tuberculosis, it is common practice to use isoniazid and para-amino salicylic acid when steroid therapy is undertaken. Adrenal atrophy and insufficiency are induced in all patients who are treated with systemic steroids for prolonged peri-

### Table I. Corticosteroid preparations and potency

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Relative potency</th>
<th>Dose form</th>
<th>Systemic (mg.)</th>
<th>Topical (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (Cortef, Hydrocortone)</td>
<td>1</td>
<td>20</td>
<td>0.5 and 2.5</td>
<td></td>
</tr>
<tr>
<td>Cortisone (Cortone)</td>
<td>0.8</td>
<td>25</td>
<td>0.5 and 2.5</td>
<td></td>
</tr>
<tr>
<td>Prednisone (Meticorten, Deltasone)</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone (Meticortelone, Sterone)</td>
<td>4</td>
<td>5</td>
<td>0.12, 0.2, 0.5, and 1.0</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone (Medrol)</td>
<td>5</td>
<td>4</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone (Aristocort, Kenacort)</td>
<td>5</td>
<td>4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Paramethasone (Haldron)</td>
<td>10</td>
<td>2</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Fluprednisolone (Alphadrol)</td>
<td>13</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone (Florinef)</td>
<td>20</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (Decadron, Maxidex, Hexadrol, Gambacorten)</td>
<td>28</td>
<td>0.75</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Betamethasone (Celestone)</td>
<td>33</td>
<td>0.6</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

*Depo Medrol, 20 mg. and 40 mg. per milliliter for injection.

†Marked mineralocorticoid effects.
Table II. Systemic side effects of corticosteroids

1. Cushingoid state  
2. Activation of peptic ulcer  
3. Precipitation of diabetes  
4. Retention of sodium and fluid  
5. Osteoporosis  
6. Acute interstitial pancreatitis  
7. Mental and emotional symptoms  
8. Increased susceptibility to infection  
9. Iatrogenic adrenal insufficiency

Table III. Ocular side effects of corticosteroids

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataracts</td>
<td>Keratitis: viral, bacterial, fungal</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>

The major ocular side effect of systemic steroid therapy is the development of posterior subcapsular cataracts (Table III). Without steroids posterior subcapsular cataracts are described in 0 to 5 per cent of individuals with rheumatoid arthritis, and in 0 to 4 per cent of normal individuals. In patients with rheumatoid arthritis subjected to steroids, after long-term use (over 2 years) at moderate doses (10 mg. of prednisone or equivalent), 30 to 40 per cent are found to have posterior subcapsular cataracts. With high doses (over 15 mg. of prednisone) and long-term therapy (over 4 years), the incidence of cataracts approaches 80 to 100 per cent. Steroid-induced cataracts are also described in patients with lupus erythematosus, nephrotic syndromes, sarcoid, scleroderma, asthma, pemphigus, and lymphoma. The fact that the lens changes relate to the dose and time of administration, as well as their occurrence in very young individuals, lends credence to the belief that the cataracts are steroid induced. The failure of some observers to note lens changes suggests variations in different populations. Such marked differences in individual susceptibility to lens opacification may reflect genetic factors.

Fortunately, most of the lens changes that follow steroid therapy do not markedly impair visual acuity. Thus, in various series, less than 10 per cent of patients on long-term steroids had vision reduced to less than 20/60. The management of patients with cataracts induced by systemic steroids must depend on the early observation of the lens alterations, re-evaluation of the needs of the patient for steroids, and the degree of visual impairment. If steroids can be given for short periods of time, cataracts are not a significant problem. If long-term steroids are necessary for the maintenance of life or for permitting the patient to continue as a productive individual, then they may be continued in spite of increasing lens changes. If lens changes occur which are of sufficient magnitude to impair visual acuity, cataract surgery may be necessary. The question as to whether the less frequent (e.g., weekly) administration of steroids in very large doses will reduce the incidence of cataracts is not yet resolved.

Papilledema is a rare complication that occurs after prolonged systemic administration of triamcinolone or prednisone to children. Unless a careful history is taken and due consideration given to this cause...
of papilledema, the patient, parents, and physician may suffer unnecessarily. There are also reports of keratitis or impaired outflow facility after systemic corticosteroids, but of lesser magnitude than follow topical administration.

Ocular side effects of topical or subconjunctival corticosteroids

**Herpetic keratitis.** The incidence of herpetic keratitis induced by topical steroids appears to be very low. The administration of topical steroids for periods of 6 to 16 weeks to over a thousand individuals with normal eyes, with primary open-angle glaucoma, or with suspected glaucoma, failed to induce a single instance of herpetic keratitis in spite of weekly tonometry and tonography. On the other hand, there is reasonable clinical and experimental evidence that herpetic keratitis can be reactivated or made very much worse by the use of topical or subconjunctival corticosteroids. It is the experience of many ophthalmologists that individuals with herpetic keratitis too frequently have been continued on topical steroids to the point of descemetocele and perforation. In spite of considerable publicity and attempts to disseminate this information, most large clinics continue to see herpetic keratitis mismanaged in this fashion.

Although it is generally agreed that steroids are contraindicated in superficial dendritic keratitis, there are many who feel that steroids can be of great help in the stromal and anterior uveal involvement which may follow herpetic keratitis. In these instances some investigators believe that iodo-deoxyuridine (IDU) may be of help in attacking the virus while steroids are reducing the inflammatory reaction in the cornea. In individual instances it does prove possible to avoid recurrence of herpetic figures by the use of IDU and suitable reduction of corticosteroid dose. However, the question of whether IDU and corticosteroids used together may potentiate the deleterious effects of each on wound repair and healing of corneal stromal lesions requires further study. The occurrence of herpetic keratitis in a patient who is taking topical steroids for other purposes is best managed by discontinuing the steroids and probably instituting IDU therapy.

**Other viral and bacterial infections.** It is not yet clear as to how many other viral diseases of the cornea are aggravated by topical steroids. There is suggestive evidence that this may be true for vaccinia. There are also reports of systemic spread of herpes zoster following steroid administration. Trachoma and bacterial infections may also be enhanced by topical steroids even when the clinical picture seems deceptively improved. The use of specific antibiotics is most important in the management of these conditions, and may even permit the continuation of corticosteroids if necessary. It is much better to treat these infections if and when they occur rather than to use routine combinations of corticosteroids and antibacterial or antiviral agents. Such admixtures involve unnecessary expense, arbitrary dosage, increased risk of sensitization to the antibiotic, potentiation of development of resistant organisms, and increased risk of superinfections with fungi and low-grade pathogens.

**Fungal keratitis.** Fungal keratitis is another potential danger of the use of topical or subconjunctival corticosteroids. The characteristic picture here is of a trivial farm injury to the cornea, especially with vegetable matter. Treatment with corticosteroids and antibiotics is followed by the development of a mycotic abscess of the cornea. As with herpetic lesions, the aggravation of fungal keratitis can be demonstrated in experimental rabbits as well as in patients. Management consists of avoiding steroids in certain types of injury, discontinuing steroids promptly, and the possible use of such agents as nystatin or amphotericin. Many of these eyes require corneal transplantation and too many are lost.

**Corticosteroid glaucoma.** Isolated cases of corticosteroid glaucoma have been
described in the literature for many years, but it is only in the past two or three years that it has been generally appreciated how frequently topical or subconjunctival steroids induce elevations of intraocular pressure in human eyes. Although the detailed mechanism of this elevation is not yet known, it is clear that the pressure elevation simulates that of primary open-angle glaucoma. Thus, one sees impaired outflow facility, elevated intraocular pressure and, if sustained long enough, characteristic glaucomatous cupping of the optic nerve and field loss. The more marked pressure elevations after topical steroids appear to be genetically determined. They are the rule in patients with primary open-angle glaucoma and occur in a large percentage of the close relatives of such patients. In addition, significant pressure elevations are noted in some 30 to 50 per cent of the adult population. In the secondary and angle-closure glaucomas, the prevalence of pressure elevation more closely resembles that of the normal population rather than the primary open-angle glaucoma group.

In addition to genetic determinants, a number of other factors contribute to the pressure rise induced by topical steroids. The rise in pressure occurs more frequently in older people. It appears to be related to the potency and dose of the agent used, the frequency of its administration, and the duration of therapy. The less potent agents take longer to produce pressure elevation, and the elevation is not as high as those induced by more potent agents. Another important factor in determining the degree of elevation of intraocular pressure is the ease with which the steroid penetrates into the anterior chamber. There is evidence that only those steroids that get into the anterior chamber influence outflow facility. Poor penetration as well as plasma dilution undoubtedly account for the much lesser effect of systemic steroids on intraocular pressure. It should therefore be possible to find anti-inflammatory steroids that fail to penetrate into the anterior chamber when applied topically, but which can be very effective in the treatment of external diseases involving the lids and conjunctiva.

The finding that intraocular pressure can be elevated by the administration of topical steroids leads many ophthalmologists to give up the use of topical steroids completely. This is indeed unfortunate, for these agents are extremely valuable components of the pharmacologic armamentarium of the eye physician. It is important to know that glaucoma can follow the use of topical corticosteroids and this offers a strong argument against the indiscriminate administration of these agents for a large variety of minor ills. However, since intraocular pressure can be measured readily, and when corticosteroids are discontinued the pressure effects appear to be entirely reversible, there is every reason for using topical steroids when they are needed. It can be demonstrated that even the early changes in visual fields that follow the intraocular pressure elevation induced by corticosteroids are also reversible after the pressure is normalized. However, the prolonged use of topical steroids can produce extensive cupping and irreversible field loss which persist even after intraocular pressure and outflow facility return to normal.

It is important to remember that the degree of pressure elevation as well as the time to return to normal after steroids are discontinued relate to the duration of administration as well as to the dose and potency of the steroid. For most external diseases the problem may be resolved when corticosteroids become available which are effective anti-inflammatory agents but do not induce elevations of intraocular pressure (because of their poor penetration or pharmacologic properties). As a reasonable rule until then, one should use short-term administration of an agent just potent enough and sufficiently frequent to overcome the inflammatory process. Intraocular pressure should be measured and elevations anticipated. If there are pressure elevations and it is felt to be essential to con-
continue the topical steroid administration, antiglaucoma medications, such as miotics, topical epinephrine, and systemic carbonic anhydrase inhibitors, should be used as needed. It has been demonstrated repeatedly that these antiglaucoma agents act in steroid-induced glaucoma very much as they do in primary open-angle glaucoma. Ultimately, the effectiveness of the antiglaucoma medication can be evaluated by measurements of intraocular pressure and outflow facility. It often proves necessary to continue such antiglaucoma medication for considerable periods of time (months) after long-term topical corticosteroids are discontinued. So far as the side effects of elevated intraocular pressure are concerned, therefore, the crux of the use of topical steroids depends upon the measurement of intraocular pressure, the continuous re-evaluation of need for steroid therapy, and the careful follow-up of the individual patient.

Other side effects. Other ocular side effects that have been noted following topical corticosteroid administration include slight dilatation of the pupil, unexplained blurring of vision, occasional refractive changes, rare posterior subcapsular lens opacities, and variable ptosis. All of these are confined to the eye receiving steroids and have been better delineated in controlled series of "normal" individuals in whom topical steroids have been applied to one eye. The mechanisms of these changes are unknown but may provide important clues to the pathogenesis of these ocular conditions as well as to the effects of topical steroids. However, except for the lens changes, these side effects are entirely reversible and rarely prove of sufficient magnitude to alter therapy.

Conclusion

The administration of corticosteroids induces a multiplicity of interrelated alterations in metabolic processes. As with other drugs, only a small per cent of such changes are beneficial. The remainder is either meaningless or undesirable. The clinician must determine and continue to re-evaluate the needs of the individual patient for corticosteroids, the choice of dose, route, agent, duration of therapy, and the relative therapeutic benefits as compared to the possible harmful effects. In the individual patient this may depend on hereditary factors, the disease process itself, the presence of other diseases, the nutritional and endocrine status of the patient, and many other factors. The ophthalmologist determines the nature and severity of the patient's eye disease and knows the prognosis without therapy. It is most important that he have an awareness of the complications as well as the benefits of the potent agents that are placed at his disposal.

Summary

The systemic and ocular complications of the use of corticosteroids are reviewed and suggestions made for their management.