CORTICOSTEROID THERAPY

Douglas Hopkins

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The purpose of this paper shall be to probe the many aspects of corticosteroid therapy, with special attention to ocular steroid therapy. Some of the general concepts of the adrenocortical system will be presented, as well as various corticosteroid preparations and routes of administration. The mechanism of ocular inflammation will be discussed, along with the systemic and ocular pharmocological actions of steroids. Also, a number of indications for corticosteroid therapy as well as contraindications will be presented. A large amount of this paper, however, will necessarily be devoted to the adverse effects of steroid therapy, both systemically and ocularly. Finally, some conclusions will be made regarding the safe use of the corticosteroids.

The adrenocortical system is composed of three basic parts: the hypothalamus, the anterior pituitary gland, and the adrenal glands. The secretion of a substance by the adrenal cortex is regulated by the blood concentration of adrenocorticotropic hormone (ACTH). The ACTH gets into the bloodstream by being secreted by the anterior pituitary. This ACTH secretion is, in turn, regulated by the blood concentration of corticotropic releasing factor (CRF), which is produced by the hypothalamus. The system has a negative feedback loop, in that as the blood level of steroids (either endogenous or exogenous) increases, the output of ACTH is decreased. This simple feedback mechanism does not completely explain regulation of ACTH, however. For example, elevated blood levels of steroids and ACTH can occur together in

situations of stress or under influence of other hormones.

When ACTH reaches the adrenal gland, it stimulates the cortex to secrete cortisol, corticosterone, aldosterone, and some weakly androgenic substances. The rate and amount of cortisol secretion is nearly entirely dependant on fluctuations in the release of ACTH by the anterior pituitary gland.

The adrenal medulla is responsible for the secretion of norepinephrine and epinephrine, subject to control by the sympathetic division of the autonomic nervous system. The adrenal cortex secretes the previously desribed substances, and can be divided into three zones, by three groups of adrenocortical hormones.

The outermost zone is called the zona glomerulosa, and is primarily responsible for the secretion of the mineralcorticoids. The mineralcorticoids are responsible for regulation of sodium and potassium metabolism. The mineralcorticoids themselves are regulated by the renin-angiotensin system and by plasma concentration of sodium and potassium. The principle mineralcorticoids in man are aldosterone and deoxycorticosterone.

The middle zone of the cortex is the zona fasciculata, and is responsible for the secretion of the glucocorticoids. The glucocorticoids exert their major effects on carbohydrate, fat, and protein metabolism. The primary glucocorticoids in man are cortisone, corticosterone, and hydrocortisone.

The innermost layer is the zona reticularis, and is responsible for the secretion of sex hormones, which supplement the actions of the androgens and estrogens. These inner two zones (fasciculata and reticularis) are the ones regulated by ACTH.

Steroid is the name given to a large group of fat-soluble

organic compounds. Corticosteroid is a steroid secreted by the adrenal cortex. If the adrenal cortex decreases its output of corticosteroids because of disease or atrophy, then that condition is known as Addison's disease. It was in this condition that the importance of the adrenocortical system was first realized in 1855. Cushing's syndrome is the name put on hypersecretion of the adrenal cortex.

Normal output is 25 mg of hydrocortisone (cortisol) and 5 mg of corticosterone per day. The rate of secretion shows diurnal fluctuations, the maximum output being from 6-8 a.m., and the lowest level of secretion occurs at about midnight.

Of the hormones secreted by the adrenal cortex, the glucocorticoids (cortisone, corticosterone, and hydrocortisone) will be the major focus of this paper. These natural steroids have strong effects on the body and are, of the three types, the most useful ophthalmologically. Unless otherwise indicated, the use of the more general terms steroid or corticosteroid will actually refer to glucocorticoids for the remainder of the paper.

After the discovery of the three glucocorticoids secreted by the adrenal cortex, cortisone was the first steroid made commercially available for topical or systemic use. Soon after, hydrocortisone was found to have greater potency, and further advances were made with the development of synthetic derivatives. The synthetic derivatives, in general, are more potent and produce fewer side effects. Table 1 shows a list of various available preparations and their relative anti-inflammatory potencies.

Prednisone, prednisolone, and methyprednisolone are the shortest acting synthetic derivatives, and paramethosone and triamcinolone

Corticosterone	0.3	Triamcinolone	5.0
Cortisone	0.8	Parmetholone	10.0
Hydorcortisone	1.0	Fluprednisolone	13.5
Medrysone	2.5	Fludrocortisone	20.0
Prednisolone	4.0	Dexamethasone	25.0
Prednisone	4.0	Betamethasone	27.0
Methylprednisolone	5.0	Fluorometholone	46

Table 1

are of medium duration. The longest acting are dexamethasone, betamethasone, and metamethasone.

Topical administration of ACTH is of no practical value, since ACTH exerts its effect only through stimulation of the adrenal cortex. Oral administation of ACTH is also of no benefit, since it is destroyed in the gastro-intestinal tract.

Before the pharmacological actions of the corticalsteroids are considered, the basic process of inflammation will be discussed. Inflammation is the body's natural response to tissue injury. While defending the body against external stimuli, the inflammatory response itself may cause local tissue alteration, damage, and scarring. Ocular inflammation is especially damaging, since it may abruptly and permanently interfere with vision.

The four gerneral causative agents of inflammation are: biological (bacteria, antibodies to individual's own protein, fungus, virus), chemical (acids and alkalis), physical (heat, cold, radiation, abrasives), and allergens (pollen, smoke, dust, animal hair). Any of these agents can be classified as either toxic, in which there has been no previous exposure, or immune, which requires previous exposure. The severity of the inflammation depends on the nature of the stimulus (its potency, quantity, time of exposure) and the reaction of the host.

The ocular inflammatory response can be separated into three

phases; immeadiate, intermediate, and chronic.

The immeadiate ocular inflammatory response is initiated by various mediators from mast cells, and prolonged by the kinins. This phase consists of: brief arteriolar constriction, prolonged capillary dilation, stasis of blood, increased blood vessel permeability, and leakage of plasma proteins.

The intermediate phase shows an increase in circulating polymorphonuclear phagocytes, mononuclear phagocytes, and lysozymal enzymes. This phase is characterized by the following: migration of phagocytes, phagocytosis, enzyme release and increased capillary permeability.

The chronic or recurrent phase of ocular inflammation remains much of a mystery. The basic processes at work, however, are non-specific immunity, adaptive immunity, and autoimmunity.

The ocular inflammatory response will vary greatly depending on the specific tissue involved. For example, the cornea is avascular while ~~while~~ the choroid is highly vascular. The choroid, therefore, reacts immeadiately to an inflammatory mechanism affecting vascular permeability.

At some point during the three phases, regeneration or repair of the tissue occurs. The cell around which repair centers is the fibroblast, which lays down a collagen cicatrix which replaces destroyed or injured cells.

Now, the basic actions of the corticosteroids will be presented. There are a number of pharmacological actions, but the biological mechanisms for these has not been clearly established.

The first group of actions are anti-inflammatory. These anti-inflammatory actions are non-specific, and the basic cause of the

inflammation remains. These actions are therefore not curative, but simply suppress the inflammation that the insult caused, regardless of the cause. The following are the anit-inflammatory actions:

1. reduction of cellular and fibrinous exudation and tissue infiltration, decreased edema
2. inhibition of fibroblastic and collagen-forming activity
3. retardation of epithelial and endothelial regeneration
4. reduction of post-inflammatory neovascularization
5. restoration of normal capillary permeability
6. maintaining cell membrane permeability and minimize water transport
7. reduction of migration of phagocytes to the site of inflammation
8. stabilization of lysozymal membranes-prevent the release of proteolytic enzymes

The second group of actions caused by the corticosteroids are metabolic actions. There are four main metabolic effects. The first is an increase in blood sugar levels characterized by gluconeogenesis in the liver and decreased use of glucose in tissues. The second is protein mobilization, resulting in a decreased protein concentration in tissue and more protein readily available wherever needed. The third is fat mobilization, seen as a decrease in stored fat, resulting in a greater availability for use for energy. The final metabolic effect, which was also anti-inflammatory, is the stabilization of lysozymes.

It should also be noted that systemic steroids are metabolized in the liver. Thus, any liver problems will effect the breakdown and the total effect of the drug.

The basic mechanism of inflammation and the effect of corticosteroids on such inflammation has been described. What, then, are

some of the uses of corticosteroid therapy? First, the systemic indications for corticosteroid therapy will be considered. The following is a rather exhaustive list of systemic uses of steroids;

1. Endocrine disorders-substitution therapy
   a. acute adrenal insufficiency
   b. chronic adrenal insufficiency
   c. congenital adrenal hyperplasia
   d. adrenal insufficiency secondary to pituitary insufficiency
2. Rheumatic disorders
   a. rheumatoid arthritis
   b. osteoarthritis
   rheumatic carditis
3. Collagen diseases
   a. scleroderma
   b. polymyositis
   c. polyarteritis nodosa
   d. granulomatous-polyarteritis group
4. Dermatologic disease
5. Allergic states
   a. hay fever
   b. serum sickness
   c. urticaria
   d. contact dermatitis
   e. drug reactions
   f. bee stings
   g. anaphylaxis
6. Respiratory diseases
   a. severe bronchial asthma
7. Hematologic disorders
   a. thrombocytopenia
   b. hemolytic anemia
8. Neoplastic diseases
   a. acute lymphocytic leukemia
   b. lymphomas
   c. breast carcinoma
9. Edematous states
   a. brain trauma
   b. cerebrovascular accident
   c. nephrotic syndrome
10. Gastro-intestinal diseases
   a. celiac sprue
   b. chronic ulcerative colitis
11. Liver diseases
   a. subacute hepatic necrosis
   b. chronic active hepatitis
   c. alcoholic hepatitis
   d. nonalcoholic cirrhosis
12. Some renal diseases
13. Sarcoidosis
14. Organ transplants
15. Ocular diseases

The ocular use of corticosteroid therapy shows an enormous value in the treatment of ocular inflammatory disease. The reason for this is that by prompt control of inflammation and swelling of the external eye, corneal scarring may be arrested or prevented. If ocular inflammation is not promptly treated, it can be uncomfortable, painful, and potentially damaging to vision. Even a slight inflammation can destroy ocular function.

The general indications for ocular steroid therapy are: all allergic ocular diseases, most non-pyogenic inflammations, and the reduction of scarring from certain types of severe injury. Corticosteroids have been found to be useful in the following specific ocular diseases:

allergic blepharitis and conjunctivitis
vernal conjunctivitis
contact dermatitis
immune graft reaction
herpes zoster
herpes simplex (disciform stage)
marginal corneal ulcers
adenovirus
APC virus type 3
superficial puctate keratitis
sclerosing keratitis
non-specific keratitis
chemical burns of the cornea and conjunctiva
juvenile xanthogranuloma
thyrotropic exophthalmos
Boeck's sarcoid uveitis
acne rosacea keratitis
stromal and uveal viral infections
infiltrative corneal disease
ocular pemphigus
anterior and posterior uveitis
retinitis
endophthalmitis
iritis, iridocyclitis
scleritis, episcleritis
phlyctenular keratoconjunctivitis
optic neuritis
sympathetic ophthalmia
temporal arteritis
hemorrhagic glaucoma
retinal vasculitis

Ocular steroid tharapy is administered via three basic routes: topically, local injection, or systemically (orally). The route of administration is very important in determining the result of therapy. Local routes are favored whenever possible because of the decreased incidence of side effects.

Topical therapy, in the form of drops or ointment, are generally used in inflammation of the anterior segment. High doses are reserved for sight-threatening conditions. As the inflammation improves, the dosage should be adjusted to the lowest amount to maintain regression of the condition. If it worsens, the dosage should be increased. The topical route is easy, costs less, the most common route utilized, and produces a minimal number of systemic effects. A continuous delivery devise for corticosteroid therapy has been used under experimental conditions.

Local injection may be required for adequate control if topical or systemic administrtion alone is ineffective. They are also useful if systemic therapy can't be used because of systemic complications, or if the patient can't be trusted to take the medication. The advantages of this route are that it is more potent, produces a longer-lasting effect, and results in fewer systemic effects. These injections, however, are uncomfortable, and once they are injected, are hard to reverse without surgical removal.

The three local injection routes are sub-conjunctival, sub-tenon's, and retrobulbar.

Sub-tenon injections are made immeadiately adjacent to the sclera, and penetrate the sclera by direct diffusion. The greatest concentration of the drug is found adjacent to the position of the injection. This method is more efficient than oral or IM administration,

and can be used as a supplement to topical or systemic therapy.

A sub-conjunctival or sub-tenon injection over a diseased sclera could lead to thinning and possible rupture at the site of injection. Extreme care must also be employed so that no accidental intraocular injection occurs.

Retrobulbar injection provides a high local concentration of the drug without systemic complications. There is a problem, however, in getting immeadiately adjacent to the retrobulbar structure without damage to some other structure.

The oral route is preferred by most patients and is easy to use. This route, however, causes the greatest incidence of systemic complications. Systemic therapy may be required in certain ocular conditions, however.

While the corticosteroids are useful in a very large number of disorders, there are certain conditions in which they should be used with caution or in which their use is contraindicated.

Steroids should be avoided in systemic fungal infections, or if the individual is hypersensitive to the steroid or any component of the drug. Precautions chould be taken in using steroids on patients with diabetes, congestive heart failure, peptic ulcer, hypertension, glaucoma, tuberculosis, or multiple sclerosis.

Ocularly, steroids are of no benefit in degenerative diseases (senile macular degeneration, cataract, primary glaucoma, corneal dystrophies, old chorioretinal scars), or in infections unless an appropriate antibiotic is used before and simultaneously with the steroid for the infection. Steroids should not be used prophyactically in minor corneal abrasions since no benefit can be expected and the susceptibility of secondary infection is increased. Other

ocular contraindications to corticosteroid use include herpes simplex keratitis, fugal infections, and most viral infections.

The failure of an ocular inflammation to respond to local or systemic steroid therapy may occur for the following reasons: the disease is of microbial origin, therapy was started too late, variable patient response to the drug, inadequate dosage, or inappropriate route.

Most of the remainder of this paper will concern itself with the adverse effects of corticosteroid therapy. The following is a list of adverse systemic effects which may occur with local or systemic therapy. The effects are much more common with systemic therapy.

1. Fluid and electrolyte disturbances
   a. sodium retention
   b. fluid retention
   c. congestive heart failure in susceptible patients
   d. potassium loss
   e. hypokalemic alkalosis
   f. hypertension
2. Musculoskeletal
   a. muscle weakness
   b. steroid myopathy
   c. osteoporosis
   d. vertebral compression fractures
   e. pathologis fracture of long bones
3. Gastrointestinal
   a. peptic ulcer-possibly perforation and hemorrhage
   b. pancreatitis
   c. abdominal distention
4. Dermatologic
   a. impaired wound healing
   b. thin fragile skin
   c. petechiae and ecchymosis
   d. erythema
   e. increased sweating
   f. allergic dermatitis
5. Nerologic
   a. convulsions
   b. increased intracranial pressure with papilledema(psuedotumor cerel
   c. vertigo
   d. headache
   e. mental changes from euphoria to psychoses
6. Metabolic
   a. negative nitrogen balance

7. Endocrine
   a. menstrual irregularity
   b. development of cushingoid state
   c. suppressed growth in children
   d. decreased carbhydrate tolerance
   e. manifestations of latent diabetes
   f. increased insulin requirement
   g. secondary adrenocortical and pituitary unresponsiveness
8. Other
   a. hypersensitivity
   b. thromboembolism
   c. weight gain
   d. increased appetite
   e. nausea
   f. malaise

It has been advocated that alternate-day systemic therapy reduces the side effects. This has been modified to a single two-day dose at every other breakfast. As has been pointed out, the diurnal fluctuation of plasma cortisol levels shows the greatest concentration around breakfast time and the lowest levels near midnight. Any disturbance in this diurnal rhythm may play a significant role in predisposing a person to side effects. The breakfast-time dose permits metabolic recovery and prevents toxic effects from being cumulative. There is less of a need to taper therapy slowly (too rapid withdrawal is more likely to result in adrenal insufficiency), and the effect is especially noticeable in children. Alternate-day therapy cannot be used, however, when suppression of an acute inflammatory process is required.

The ocular adverse reactions to steroid therapy are numerous. In approximately one-third of all patients treated with steroids, there is a significant rise in intraocular pressure (IOP). If the pressure is not reduced, it is accompanied by cupping of the optic nerve head and by field loss. The increase is usually reversible on cessation of treatment, but in a certain number of cases, the increase is irreversible. It is possible to get an increased

pressure even after discontinuation which is not effected by pilocarpine, epinephrine, or diamox. The effect is probably not actually irreversible, but rather is a long-term effect. The increased pressures are found with both topical and systemic administration, but more often and more severe in topical therapy. The effect may be quite rapid, and may possibly be seen within one week. Patient's with Krukenberg's spindle, diabetes mellitis, or myopia of more than five diopters seem to be more susceptible to this response.

The susceptibility to IOP rise from the use of steroids is genetically determined. If it is assumed that there is one gene determining this response, then the combination of two different alleles would predict three types of responses (N-allele for no response, G-allele for glaucomatous response).

1. NN-those who have no allele for the response and do not respond to steroid therapy with a rise in IOP
2. NG-those who are heterozygous for the response and show a moderate increase in IOP
3. GG-those who are homozygous for the response and show a marked increase in IOP

It should be noted that while the mode of inheritance of glaucoma is believed to be autosomal recessive, the IOP response to corticosteroids is a dominant trait.

Potential IOP responders may be correlated with an ability to taste the chemical phenylthiourea.

A corticosteroid provocative test for the predicting of the development of open-angle glaucoma was devised by Becker, and was based on the above-mentioned theory. Subjects were administered betamethasone 1.0% four times a day for three weeks and the rise in

IOP noted. It was found that this was far more sensitive than the water-drinking tonography test, but whether or not the homozygous responders will actually subsequently develop glaucoma cannot be predicted with great accuracy.

A number of various theiries have been proposed for the reason behind the intraocular pressure rise.

One theory says that, in the case of a cyclitis, aqueous production is decreased. Corticosteroid therapy, then, allows the aqueous production to return to the normal level, inducing temporary over-production of aqueous.

Another theory notes that the increased permeability of the iris vessels in inflammation destroys the blood-aqueous-barrier. This eliminates the osmotic differential responsible for maintaining normal IOP. Corticosteroid therapy, however blockes their abnormal leakage.

A third theory holds that corticosteroids potentiate the vasoconstricting effects of norepinephrine. This may result in some narrowing of the outflow venous channels, with a subsequent decreased outflow of aqueous.

Still another theory is based on a study and also based on the normal diurnal rythum of plasma cortisol levels, which were checked at 8am and 8pm. The study found that:

1. Plasma cortisol levels were higher in glaucomtous eyes at both times.
2. The diurnal variation of plasma cortisol paralled the diurnal variation of IOP in normal and glaucomatous eyes.
3. The diurnal variation of plasma cortisol was greater in glaucomatous eyes.

The study concluded that in the morning, the increased cortisol value may cause an increased inflow. In normals the outflow also increases

to compensate, but in glaucoma the outflow can't keep up.

Electron microscope studies have revealed the following mechanism. The outer part of the trabecular meshwork apjacent to the canal of Schlemm was found to be swollen and the trabecular lamellae were enlarged and thickened. The intertrabecular spaces were filled with amorphous and fibrinous material, mostly glycosaminohlycan (a mycopolysaccaride (MPS)). MPS is normally deposited in the angle, and a catabolic enzyme depolymerizes the MPS. Corticosteroids strengthen the lysosomal membranes and therefor prevent the liberation of the catalytic enzyme. The corticosteroids not only prevent the depolymerization of the MPS, but also increases the water-binding capacity of the MPS, causing it to swell and obstruct the angle further. The variable rate at which corticosteroid-induced glaucoma wears off has been attributed to the rate at which different individuals remove the deposited MPS. There is also an enlargement of the basement membrane of the trabecular lamellal and of the endothelial cells. The deposition of materials in the meshwork decreases the intertrabecular space, narrows the aqueous pathway, and consequently increases the resistance to aqueous outflow.

The majority of evidence seems to favor a combination of the last two mechanisms. It is thought that systemic corticosteroid therapy produces an increased aqueous production in accordance with plasma cortisol levels, and has little or no effect on outflow. It is believed that topical corticosteroids, on the other hand, decrease your outflow as just described, with little or no effect on aqueous production. Additionally, the reaction to systemic therapy tends to be a quicker increase and decrease, since the change is mediated by the hormone itself. The reaction to topical therapy, however, is much slower because it is a structural alteration that takes time to build up.

The amount of the pressure rise, of course, varies greatly with the individual response. In one study of a general population, dexamethasone 0.1% was administered topically three times a day for six weeks. The NN group responded with an average rise of 1.6 mm Hg and represented 66.2% of the population. The NG group increased an average of 10 mm Hg and comprised 28.8%, while the GG group increased 16mm Hg and reprsented 5%.

It has been shown that the newer synthetic derivatives produce less of an ocular hypertensive response. While fluorometholone, medrysone, and tetrahydrotriamcinolone prevent the increased IOP well, they are also less effective in other areas. It has been reported that triamcinolone produces significantly more glaucoma than some others, and that dexamethasone provides the highest incidence of increased pressures. It should be pointed out that no corticosteroid is entirely free of this effect.

The effect of steroids on intraocular pressure also varies with the dose, concentration, and duration of treatment. The dose, concentration, and frequency of administration are all directly related to the pressure rise. An increase in any of these will cause an increased response. The relationship of duration seems to be paradoxical, however. That is, the longer the duration of treatment, the less likely the development of secondary glaucoma.

In general, the systemic route increases pressure about sixty percent of the amount of the topical route.

If a large pressure rise is feared in a patient, a logical starting point would be a water-soluable compound, if local injection is used. The less water soluable the compound, the longer the effect, and the more likely the development of adverse effects.

Any patient with an increased IOP and open angles should be questioned about the use of steroids, and any patient on steroid therapy should be followed periodically. Steroid therapy should be discontinued for at least a month before the diagnosis of glaucoma is made. Also, just because a patient has an increased IOP, this is not necessarily an indication to discontinue steroid therapy. Changes in dose, drug, or route should be made first. Also, the potential visual loss from the primary condition must be weighed against the possible visual loss from the secondary glaucoma.

A second widely reported adverse ocular effect of corticosteroid therapy is the development of a cataract. This was first reported in 1960, and is in the posterior subcapsular location. Fortunately, visual impairment is rare with subjective symptoms either transient, minimal or absent.

The cataract has been associated with long-term systemic therapy. Although it has been reported with topical therapy, the incidence is much lower. The cataract is also more common in children than adults. Again, individual response varies, and it seems to vary even more to the topical route.

Fifteen year statistics on posterior subcapsular cataracts (PSC) show that 25% of those on systemic steroid therapy for rheumatoid disease had them. Their incidence is related to both dose and duration of treatment, but more closely to dose (higher dose- higher incidence).

The PSC is slow in developing. None have been reported with less than one year of steroid therapy. All have taken more than one year, and most have taken two or more years to begin. It may continue to develop even with a lower dose, but halts when the steroid is discontinued. Reversal of the PSC is rare after systemic use, but some

authors have reported regression following cessation of topical therapy. The individual response, again, is quite variable.

It is interesting to note that cushingoid changes are more common in individuals who develop PSC. These persons may be more sensitive to the effects of the steroid. Also, almost two-thirds of the reported cases of steroid-induced cataract have been in patients who are receiving steroids for rheumatoid arthritis.

The cause for the development of the PSC is unknown. Some theorize that the steroid itself directly induces the effect. Others feel that the basic inflammatory disease may be the underlying cause. It has also beem reported that long-term topical steroid use in rabbit eyes resulted in markedly lower ascorbic acid content of the lens, and that this may induce cataract.

The anti-inflammatory effects of the corticosteroids have been very useful in ocular therapy because the delicate ocular structures are very susceptible to damage by inflammation and scarring. Properly used, steroids may make the difference between usefle vision and its loss. A third ocular side effect, however, is a decresed resistance to infection or enhancement of an existing infection.

Since the inflammatory response is suppressed but the cause remains, steroids may induce a false security in an infection. The condition may look better, while the organism is actually multiplying. The steroid itself has no antibacterial effect (or antiviral or antifungal), but rather increases susceptibility to a secondary infection by lowering host resistance.

The practical value of this is that it is very hazardous to discontinue medication while there is any evidence of active inflammation. The steroid treatment must also be continued after the

apparent cure, and the dose must be gradually tapered off over about a week's time to avoid a relapse. The reason for the decreased resistance to infection is that any amount of the steroid above the anti-inflammatory dose is an immunosuppresive dose, which causes a loss of control of the cell-mediated defense system.

A special risk is incurred in herpes simplex keratitis. Steroid therapy may cause this viral infection to become much worse, or even reactivate an inactive herpes. When used on a dendritic ulcer, steroids cause a more prolonged course, and a higher incidence of deeper, more extensive ulceration. They should never be used on the dendritic ulcer, and in other stages (disciform) only in conjunction with idoxuridine. If they are used in the appropriate manner, secondary infection must be closely minitored, and the therapy must not be discontinued abruptly.

Corticosteroids also increase the susceptibility to fungal infection, and have been shown to enhance viral replication, worsening the conditions of vaccinia and trachoma.

The combination of an antibiotic and a steroid for "red eye" must be frowned upon. The steroid increases the chance of a secondary infection, may worsen the primary condition, and obscures the effect of the antibiotic. The steroid may decrease the effectiveness of the antibiotic even if it is the appropriate one. If the antibiotic is inappropriate, the steroid may allow for rapid destruction of the globe.

Another adverse ocular effect of corticosteroid therapy is delayed wound healing. This effect is a direct result of some of the previously described pharmacological actions. Steroids inhibit the formation of fibroblasts in the corneal stroma, retard epithelial and endothelial regeneration, and inhibit granulation tissue formation

in the eye. The total effect is a modification of the duration of the cell's mitotic cycle and therefore a slower rate of healing.

Other side effects of steroid therapy include ptosis and mydriasis. The ptosis is bilateral and reversible. The mydriasis is about 1.0 mm on the average and is reversible. There is an increase in the tonus of the iris dilator muscle and a decrease in the tonus of the sphincter muscle.

In one experiment, it was found that dexamethasone and a vehicle produced both mydriasis and ptosis. Dexamethasone and saline, however, failed to produce either mydriasis or ptosis. The vehicle alone did produce these effects. The mydriasis and ptosis, therefore, is probably due to the vehicle, but the mechanism is not known.

Other reported ocular side effects include:

exophthalmous- as great as 25 mm
subjective visual complaints
epithelial puntate keratitis
corneal and scleromalacia
decreased corneal tensile strength
psuedotumor cerebri with secondary papilledema
uveitis
diplopia
paresis or paralysis of extraocular muscles
dyschromatopsia
visual field changes- scotoma or enlarged blind spot
retinal edema
subconjunctival or retinal hemorrhages
paralysis of accomodation
irritation- photophobia, lacrimation, pain
blindness
optic atrophy
granulomas

In conclusion, the use of corticosteroid therapy has many advantages and disadvantages in systemic and topical disorders. The prescribing of the corticosteroids can be a tricky business and the clinician would be well-advised to question the patient in certain areas before commencing steroid therapy. Relevant

questioning might include the prescence of any history of diabetes, open angle glaucoma, recurrent herpes, cardiovascular disorders, tuberculosis, peptic ulcer, renal disease, chronic infection, osteoporosis, or psychological disturbances.

Additionally, a number of guidelines for the use of steroids can be followed. These are intended to reduce the risk of serious side effects, and are as follows:

1. Use steroid therapy only after the diagnosis is established and other less potentially harmful measures have been tried.
2. Use the minimum dose needed to suppress inflammation and to keep it suppressed.
3. Use soon enough, often enough, and long enough to obtain the desired results.
4. Do not abruptly discontinue high dose, long term steroid therapy.
5. A single dose (even large) is virtually without harmful effects.
6. A few days of therapy (without specific contraindications) is unlikely to produce harmful effects.
7. As length of therapy increases, potential for side effects increases.
8. Systemic side effects are limited with topical administration, but prolonged use may result in systemic effects.
9. The specific type of ocular disease and its response to steroid therapy may determine what route of administration to use.
10. Use is not curative or etiological (except in adrenal insufficiency).
11. Start with a high dose and decrease dose as the disease responds.
12. Too low a dose may be worse than no steroid therapy at all.
13. If one steroid fails, try another.
14. Do not decrease dosage by a predetermined amount, but rather by the individual response of the patient.

In routine care, the patient on corticosteroid therapy should be minitored for possible manifestations of side effects of the medication. Such follow-up examinations should include:

1. repeated tonometry.
2. careful slit-lamp examination for early signs of fungal or herpetic keratitis and for changes in the posterior subcapsular portion of the crystalline lens.
3. staining of the cornea for possible punctate keratitis.
4. examination of pupil size and lid position.

A periodic glucose tolerance test for checking blood glucose levels is also indicated.

The corticosteroids have a very great potential in both ocular and systemic disorders, but this potential goes in both directions, positively and negitavely. With the previously mentioned guidelines, the safe use of the corticosteroids for both ocular and systemic disorders can be continued. Each patient must be considered individually and frequently monitered if steroid therapy is to be prescribed.

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