Conduta nas Uveítes

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General Guidelines for Immunosuppresive Therapy with Sterolds and Cytotoic Agents in Uveitis

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INTRODUCTION

The therapy for intraocular inflammatory disease is undergoing constant refinement. Eye care physicians that practiced before the steroid era will attest to the problems associated with patients being treated with either paracentesis or fever therapy. The administration of corticosteroids has become relatively easy, and they have been found to work with great efficacy. They are, though, potentially dangerous drugs, and must be administered with clear guidelines in mind.

Indications: In all cases of therapy, the primary indication for therapy is an attempt to reduce inflamatory activity in the eye because of the possibility of complications due to uveitis. A second consideration is the comfort of the patient, which should be directly related to the main goal. Therapy should take account of: 1. the anatomic position of the inflammation and 2. the extent or seriousness of the inflammatory condition. It must be stressed that an attempt to identify a specific etiology for each case of uveitis is mandatory. What are described here are non-specific therapeutic modalities that should be used only in cases of non-infectious inflammations.

CORTICOSTEROID THERAPY

Mechanisms: The mechanism by which corticosteroids mediate their anti-inflammatory and immunosuppresive actions probably vary from species to species. Man is considered as "corticosteroid-resistant", and the lysis of immune cells by steroids probably plays a small, if any, role. Rather, some of the mechanisms in man may be: 1. Stabilization of the vascular bed, thus preventing "leakage" of cells and fluid into an inflammatory area 2. Altering the functional capabilities of granulocytes and monocytes, 3. Decreasing the circulating lymphocyte subsets, 4. Decreasing immunoglobulin and complement levels, and 5. Stabilizing lysosomal membranes.

1. Topical Therapy

Indications: Steroid drops are an effective mode of therapy for many inflammatory problems of the anterior segment. Their therapy should fit the severity of the entity being treated. Besides rendering the patient considerably more comfortable, the rationale for therapy is to prevent the secondary sight threatening problems of an anterior uveitis or iridocyclitis. These would include secondary glaucoma, corneal decompensation, anterior vitreal opacities, and cataract. In general, this therapy is complemented with mydriasis.

Contra-indications: Active herpetic corneal disease with an epithelial defect can be aggravated by the application of steroid drops. Relative contraindications would include a history of 1. glaucoma secondary to steroids 2. an advancing posterior subcapsular cataract and 3. patients with a systemic disease that leaves them in an immunologically compromised situation, i.e. diabetes, chronic granulomatous disease, leukemia,

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Hodgkin's disease, patients being immunosupressed for non-ophthalmic reasons.

Dosages: Therapeutic concentrations of steroid can be found in the aqueous two hours and longer after topical applications. The schedule of administration should be tailored to the degree of inflammation, i.e., from every hour to every other day. In our experience the prednisolone acetate and dexamethasone phosphate preparations have been effective with this regimen. It is advisable to treat most new cases with frequent applications of steroid. It is imperative not to abruptly stop therapy, since this may likely re-activate the disease process. In cases where a steroid induced glaucoma is seen or expected, fluoromethalone can be used, though its anti-inflammatory capabilities are less than that of the most effective topical steroid preparations.

Complications: It is known that topically administered steroids are taken up systemically. Though unlikely, it is possible that adrenal suppression could occur. Steroid induced glaucoma must be monitored for, and long term use is cataractogenic. There is debate whether old, healed herpes epithelial disease of the cornea can be reactivated with steroid drops. The appearance of unusual fungal and bacterial lesions must be monitored. All patients treated with topical steroids should have a fundus examination so that a posterior uveitic condition with an anterior chamber reaction can be ruled out.

2. Periocular Steroid Injections

Indications: This method of therapy is useful in treating moderate to severe disease, particularly if it is uniocular. It has been found to be effective in the treatment of pars planitis and chronic iridocyclitis. The methodology permits the treating physician to place the steroid close to the site of inflammation, and also assures him that therapy has been administered, which may be important in a patient whose reliability is questionable. It is a plausible approach to anti-inflammatory therapy in patients in whom systemic steroid side effects are to be avoided. For uveitis patients in need of ocular surgery, it is also a valuable method of steroid administration.

Contra-indications: The injection of peri-ocular steroids in an eye with scleritis could lead to perforation of the globe. This mode of therapy is contra-indicated in ocular toxoplasmosis.

Dosage: We have generally used soluble steroid preparations. We have found that 2-4 mg of dexamethasone phosphate or 40-60 mg of hydrocortisone injected periocularly has been effective. The injections can be repeated frequently, i.e., once a day, or infrequently i.e., once every 1 to 2 months, depending on the condition and the response to therapy. Depo-steroid injections will give a longer therapeutic effect.

Complications: There is systemic uptake of steroid administered in this fashion, though permanent adrenal suppression would be unusual. The activation of a previously unsuspected ocular toxoplasmosis lesion must always be considered. Repeated peri-ocular injections can cause extra-ocular muscle fibrosis and granuloma formation with limitation of gaze, proptosis, and choroidal folds. Penetration of the globe with the needle and subsequent injection of the steroid into the eye must always be guarded against. An intractable glaucoma due to this method of steroid administration, which persisted months after the major therapeutic effects of the drug had dissipated, has been reported. If depot steroid preparations are injected into a blood vessel, retinal artery occlusions due to emboli can ensue, resulting in blindness. When used in conjunction with surgery, slow or poor wound healing must be expected. Infections are also a possible side effect.

3. Systemic Corticosteroids

Indications: In general, this mode of therapy is reserved for a severe, bilateral, sight threatening uveitis, of a non-infectious etiology. Knowledge of the health status of the patient is important. One should know if there is a history of or if the patient has 1. diabetes, 2. peptic ulcer, 3. hypertension or 4. osteoporosis, and 5. tuberculosis,

Contra-indications: The above conditions that have been screened for are relative contraindications. One must weigh the beneficial effects of therapy with the potential hazards. Though they may be used as an adjunct to specific therapy, systemic steroids alone are not the treatment of ocular toxoplasmosis.

Dosages: We generally use prednisone, either 5 mg or 20 mg tablets. Other preparations, such as dexamethasone, are certainly effective. It is wise to use effective doses initially. For prednisone, this usually ranges from 60-80 mg per day p.o. for the average adult. It has been well shown that initial therapy for severe disease should be given daily until the disease activity comes under control. One can taper once a beneficial response is seen. For longer therapy, every other day therapy is a reasonable goal. One way to convert a patient from every day to every other day therapy is to double the daily steroid dosage, and slowly decrease the steroid dose every second or third cycle. Steroid therapy should never be abruptly discontinued. For patients on a daily steroid schedule modest decreases of 21/2-5 mg every 2-3 days (or even every week) should be attempted,

all the while monitoring the ocular inflammatory activity. The importance of patience in stopping or decreasing a steroid regimen cannot be overemphasized. Patients should not be taking aspirin products when on oral steroids.

Complications: The administration of daily exogenous steroids can seriously alter the body's homeostatic balance. Systemic steroids can induce diabetes, peptic ulcer, hypertension, osteoporosis, myopathy, psychosis and Cushing's disease. Cataractogenesis is a well known side effect. Infections due to opportunistic organisms such as candida and cytomegalovirus can occur. Easy bruisability due to increased capillary fragility is seen. Slow or poor wound healing will be seen. If long-term therapy is abruptly halted, the patient could have a reactivation of ocular disease, or go into adrenal crisis, a medical emergency. Neoplasms, such as lymphoma and reticulum cell sarcoma, could masquerade as a uveitis, with an initial good response to the steroid therapy.

IMMUNOSUPPRESSIVE THERAPY WITH CYTOTOXIC AGENTS

Several clinical trials have demonstrated the beneficial aspects of immunosuppressive therapy with cytotoxic agents in well selected patients. Cytotoxic agents are a class of drugs that interfere with the multiplication of cells, particularly rapidly dividing ones, as the immune system's components generally are. Agents in this group either block pyrimidine or purine synthesis or cross-link DNA, thereby preventing cell proliferation. Three of the more commonly used medications will be mentioned in this discussion: cyclophosphamide, chlorambucil, and azothioprine. These drugs are potentially dangerous. If they are used for ophthalmic indications, it is wise for an internist with experience in using these medications to follow the patient with the ophthalmologist. Patients should be aware of the risks of this therapy and should give their consent for this therapy.

Indications: The only well defined uveitic entity in which cytotoxic therapy appears superior to corticosteroid therapy is Behcet's disease. Most reports have supported the effectiveness of chlorambucil in this disease. In the case of other ocular inflammatory conditions, immunosuppresive agents should be utilized in a bilateral, severe non-infectious uveitis that is responding poorly to systemic corticosteroids. Another indication to use these drugs would be in patients who have severe steroid side effects, and are unable to continue with their therapy because of them.

Contra-indications: Evidence of acute or chronic infection, or an underlying hematologic abnormality in a patient would not permit the use of these agents. A major complicating factor as well would be an underlyng neoplasm. Though some of these medications have been used in pregnancy, the teratogenecity of these drugs is a real possibility.

Dosages: Chlorambucil is usually given at a dose of 0.1 - 0.2 mg/kg. An effective dose is usually reached between 6-8 mg per day p.o., and only after several weeks. A lower dose is initially administered to be sure that idiosyncratic effects will not be seen. Daily doses above 8 mg may be needed, but must be given very cautiously. The initial therapeutic dose of cyclophosphamide (cytoxan) is 1-2 mg/kg/day. This is decreased as an immunosuppresive effect is seen i.e. a drop in the peripheral white count. A response to the cytoxan regimen is usually seen somewhat more rapidly than to chlorambucil. Azothioprine (Imuran) is usually given in the dosage of 2.0 - 2.5 mg/kg/day. All of these drugs can be given in conjunction with steroids. Often patients will need both steroids and one of these agents to fully suppress their ocular inflammatory disease.

Complications: Frequent complete blood counts with special attention to the white count and differential are mandatory. Though a moderate leukopenia is a goal of this therapy, all these medications can cause severe bone marrow depression. Infections due to opportunistic organisms (fungus, virus) can be seen. The possibility of a secondary neoplasm must be discussed with the patient before the initiation of therapy. More specifically, 1. Chlorambucil has been associated with pulmonary fibrosis, liver toxicity, rash, and male sterility. 2. Cytoxan has been associated with alopecia, male and female sterility, pulmonary fibrosis, and hemorrhagic cystitis. and 3. Azothioprine has been associated with liver and gastrointestinal toxicity, rash, and fever.

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