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Research Article

In Modern Ocular Pharmacology-Dexamethasone the Top Active Corticosteroid

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Abstract

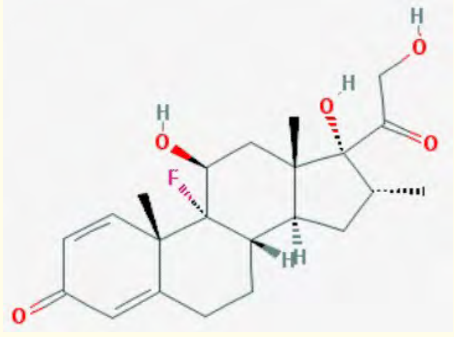
Dexamethasone has been used by ophthalmologists with increasing frequency over the 6 decades, with the concomitant development of a diverse range of drop, ointment, subconjuctival, and oral preparations. The ocular bioavailability is seriously hampered by the low aqueous solubility. Patients in the current study were with corticosteroid ocular conditions, have been treated with dexamethasone. Average initial dosages ranged from 1.5 mg. to 3.0 mg. daily. Maintenance dosages were adjusted according to individual requirements. The results obtained were similar to those generally observed with prednisone or prednisolone, in addition, dexamethasone had the highest milligram activity than any corticosteroid to date.

Keywords: *Dexamethasone; Corticosteroid; Bioavailability; Metabolic Balance; Exacerbation of Symptoms*

Introduction

Dexamethasone ($C_{22}H_{29}FO_5$), an adrenocortical steroid, has been used since May, 1958, in the treatment patients with various inflammatory intraocular conditions [1].

Dexamethasone (9-alpha-fluoro-16-alphamethyl-11-beta, 17-alpha, 21-trihydroxy-l,4-pregnadiene-3, 20-dione) is a synthetic analogue of prednisolone with the following structural formula:



Figure

Dexamethasone possesses a high degree of anti-inflammatory activity, approximately 6.5 times that of prednisone or prednisolone, and 30 to 40 times that of cortisone [2]. Its mineralocorticoid activity is much lower than that of cortisone, prednisone or prednisolone [3]. No sodium or water retention was seen with therapeutic dosages [4]. Metabolic balance studies have shown that animals on controlled and limited protein intake will exhibit nitrogen loss on exceedingly high dosage [5,6]; this has, however, not been demonstrated on dosages within the therapeutic range [7].

According to early reports, dexamethasone is said to have approximately six times the potency of prednisone or prednisolone, and 30 times that of cortisone [2]; certain of the undesirable side-effects seen with the earlier corticosteroids seem to be greatly decreased in incidence with dexamethasone [8].

Our preliminary observations in this study and in previous work [9] referred that the synthesis of dexamethasone, obtained by addition of a methyl radical at carbon 16 and a fluorine atom at carbon 9 of the prednisolone structure, constitutes a definite advance in the field of corticosteroid-responsive ocular conditions.

Methods

Clinical evaluation

Dexamethasone was given to 67 patients with corticosteroid-responsive ocular conditions. The therapeutic regimen was evenly introduced to the patients with relatively high initial dosages (up to 3.5 to 4.5 mg). However, the dosages were discontinued at the earliest possible time just in acute conditions, and gradually decreased to maintenance levels in chronic processes. So that, if the patient exhibited any sign of a flare-up, dosage was immediately increased until the exacerbation was under control.

Results and Discussion

Uveitis

Iridocyclitis: Five patients with acute iridocyclitis were treated with dexamethasone, 1.6 to 3.0 mg daily, for periods ranging from five days to six weeks. All five responded satisfactorily, with no side-effects from the corticosteroid. In one of these cases the uveitis followed trauma and there was no delay in the absorption of the accompanying hyphema.

Seven patients (34 ± 8 yrs; 74 ± 11 kg) with recurrent anterior uveitis received dexamethasone, in initial dosages of 3.0 mg. daily, given in divided doses. The response was highly satisfactory in all seven cases. The longest period of treatment was four months.

Choroiditis: The diagnosis of choroiditis activity was occurred using direct fundus examination and blue-light fundus autofluorescence. Primary outcomes were the rate of disease control and functional changes at end of follow-up. Secondary outcomes were the incidence of injection-related adverse events.

As a result, three patients with acute choroiditis responded well to essentially the same dosage regimen as given to the preceding seven cases. One patient required treatment with dexamethasone for six weeks and another for three months. The third patient has had a fluctuating response; the outcome must be considered equivocal at this time.

Six patients with recurrent choroiditis, including two cases of choroiditis juxtapapillaris, responded dramatically to dexamethasone. In our experience choroiditis juxtapapillaris is usually a difficult disease to manage. The duration of therapy is generally longer than that required in lesions of similar appearance located in other areas of the choroid.

Four patients with long-standing chronic choroiditis received dexamethasone. In one of these cases vision was 8/200 at the initial examination, and the density of the vitreous membranes prevented examination of fundus detail. This patient failed to respond after a trial period of two months on dexamethasone, 4.0 mg daily. Another patient (male, 39 yrs; 84 kg) with myopia (7 dioptres) in both eyes

sought medical attention for a 1-month history of paracental scotomas in his left eye. In addition, the patient had previously been on triamcinolone with a similar response, and then developed marked muscle weakness. However, under the specified treatment in this work, the patient responded initially with improvement of vision from 20/80 to 20/50, and then fluctuated irregularly. After approximately one month on dexamethasone, he again complained of muscle weakness, in milder degree. However, this reaction disappeared gradually. When the patient appeared to be responding satisfactorily, he developed new lesions and, despite all efforts, lost vision in the affected eye.

A difficult case

The following case illustrates the management of an unusually difficult problem. M. O., a woman aged 71 years, was first seen on August 28, 2016, as a referral. She had had choroiditis in the left eye since April; she had been on prednisolone, 10 mg., since that time. Her vision in the affected eye was 20/80 with glasses. She exhibited considerable anterior and posterior uveitic reaction. There was a vague yellow area occupying most of the superior quadrant, and a similar area just above the macula. She was placed on prednisone, 40 mg daily; this dosage was slowly tapered down. Six weeks later she returned with vision of 20/200 and an exacerbation of symptoms. She had abruptly discontinued medication 48 hours before. The patient was hospitalized for three and one half weeks and placed on intravenous adrenocorticotropic hormone (ACTH) stimulation; vision improved to 20/70. She was discharged on prednisolone, 60 mg. daily; this dosage again was gradually tapered down to 25 mg daily. Five weeks later her vision was 20/80. She had a marked cushingoid syndrome and was given chlorothiazide orally and mercuhydrin sodium intramuscularly. She was instructed to keep her usage of salt to a minimum. This regimen controlled her water retention. Several subconjunctival injections of hydrocortisone were given at various times.

The patient returned after a month with deteriorated vision reached 20/200. She was then placed on 6-methyl-prednisolone, 24 mg daily. Seven weeks later her vision had improved to 20/60, and the lesions started to harden. When she complained of weakness, the dosage was slowly decreased. Six weeks later her vision was 20/70. She had lost 12 pounds but did not feel as weak as on the occasion of the last visit.

Two months later vision regressed to 20/200, with exacerbation of all findings. Therefore, the patient was introduced dexamethasone, 4.0 mg daily for one week. After that, the dosage was reduced by decrements of 0.5 mg weekly. Three weeks later vision had improved to 20/60, with the lesions again hardening.

On July 28, 2017, after three weeks of treatment though patient vision improved to 20/50, but, was complaining of chest pain. Dosage was then decreased to 1.0 mg. daily, by decrements of 0.5 mg, every two weeks. On September 16, 2017, vision still was 20/50, and the lesions were hard. On October 20th, dosage was reduced to 0.5 mg daily. On November 17th she was corrected to 20/40; it was felt that 20/40 was the maximum possible vision, since the lesion had affected the macula. In view of the improvement all medication was discontinued.

Generalized uveitis: A patient with severe, acute retinal periarteritis and generalized uveitis, and 20/80 vision, presented a hazy vitreous. He had been placed on prednisone, 30 mg daily, when first seen. The patient was transferred to dexamethasone, 3.0 mg daily, with excellent response within one week. The period of treatment was 10 weeks, and vision has improved to 20/20.

Twenty patients with chronic generalized uveitis were treated with dexamethasone. The uveitis was brought under excellent control in 18 of these cases; one patient developed marked edema, requiring transfer to an alternate corticoid, and another must be considered a failure at this time. Five patients developed edema in varying degrees. Water retention was controlled in most cases by administration of chlorothiazide, 500 mg once or twice daily or every other day. In the more severe reactions, intramuscular injection of mercury, 2.0 cc. every week or every other week, proved of great value.

It should be pointed out that the intensity and duration of treatment in chronic uveitis exceed those seen in most medical diseases, and that the probability of eliciting side effects is thus greatly increased.

Neuritis

A patient with an acute generalized uveitis and bilateral optic neuritis responded extremely well to dexamethasone, given for one month.

A woman patient with retrobulbar neuritis, whose vision had been reduced to hand movements, responded to dexamethasone within 48 hours. Treatment was continued for approximately two weeks when vision became normal. After discontinuation of treatment at the patient's request, there was a prompt relapse of vision to approximately 20/50. When dexamethasone was reinstituted there was again immediate and continued improvement to 20/15. Treatment was continued for an additional six weeks at lower dosage.

A patient with a chronic optic neuritis of one year's duration in one eye and of several months' duration in the other eye is responding quite well to dexamethasone, with marked improvement in vision and reduction of edema within the nerve.

Corneal transplant

A patient, who underwent a 9-mm corneal transplant, had an intense postoperative reaction, including a severe uveitis; he was successfully managed on dexamethasone, given for a period of over two months.

Coat's disease

A patient with Coats' disease was treated for six weeks with dexamethasone. There was no improvement in his condition; none had been expected. Two other patients with burned out chronic uveitis were treated for approximately three months, with no improvement in vision.

Behçet's syndrome

A male patient with Behcet's syndrome, who shared in our published articles [9,10] had failed previously on prednisone and had been managed only on massive doses of ACTH (120 to 200 units daily), responded to dexamethasone, 4.0 mg daily in the same degree as to ACTH.

Macular degeneration

A patient with macular degeneration, consisting of white plaques and edema with marked loss of vision, had sudden diminution of vision with marked distortion and macular edema in his other eye. He responded dramatically to dexamethasone, 3.0 mg. daily, for one week. Improvement was reflected in disappearance of distortion and edema, and return of vision to 20/15. Treatment was continued at lower dosage for another two weeks. A similar improvement from 20/80 to 20/30 was obtained in a high myope's only seeing eye. The patient had a history of loss of vision over a period of three months, and had previously been given up as hopeless. It is assumed that macular edema was absorbed in both these cases. Since the underlying pathology is not influenced, the possibility of a future relapse cannot be ruled out. Three other cases with macular changes and edema failed to respond to several weeks of dexamethasone therapy.

Herpes zoster

A case of herpes zoster with keratitis and severe uveitis responded dramatically to dexamethasone in initial doses of 3.0 mg. daily. Systemic treatment was continued for only three weeks. Topical dexamethasone was applied to the eye and skin concomitantly and after cessation of systemic therapy.

Glaucoma

A woman patient with a quiescent chronic uveitis, who developed a wide-angle glaucoma which required filtering surgery, was managed successfully with dexamethasone, 3.0 mg. daily, during the period of surgical treatment.

Central serous retinopathy

Three patients with central serous retinopathy were treated with dexamethasone. Duration of therapy was seven months in one, and four months in another. One of these patients had an excellent response, while the patient who had been under treatment for the longer period of time is, at this writing, only starting to respond. Because of the length of time involved, the question arises whether the response can be attributed to the therapy. The third patient failed to respond.

Disciform keratitis

Two patients with disciform keratitis were treated successfully with dexamethasone. The initial dosage was 3.0 mg. daily. Topical dexamethasone was employed concomitantly.

Conclusions

Dexamethasone proved to have the highest milligram activity of any corticosteroid which has been studied to date. Effective dosages are approximately one-tenth those of prednisone, prednisolone, 6-methylprednisolone, or triamcinolone, and one thirtieth those of cortisone. The only side-effects observed with dexamethasone in this series were edema in varying degrees and four cases of acne; this is particularly gratifying since, in ophthalmology, one is more likely to elicit side effects in view of the prolonged treatment at high dosage levels frequently required in chronic intraocular inflammations. However, there were no gastrointestinal ulcers or other significant gastrointestinal reactions; two patients complained of bloating. Consequently, dexamethasone proved to be an effective corticosteroid in the majority of cases. As is true with any steroid, its effect in some patients was no greater than that of previous corticoids, while in others the change to dexamethasone resulted in dramatic improvement. Consequently, dexamethasone is not the ultimate adrenocortical steroid, but in sharp, it represents a major step in ocular anti-inflammatory therapy.

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