Review Article **Oral Medicine**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

CORTICOSTEROIDS- ITS ROLE IN ORAL MUCOSAL LESIONS.

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ABSTRACT

Glucocorticosteroids have a multitude of effects on many of the stages in inflammatory and immune processes. Corticosteroids are important and widely used therapies in the treatment of a large number of inflammatory and immunologically mediated diseases. However, glucocorticosteroids have proven to be the archetypal 'double-edged sword of medicine'. The risks associated with corticosteroids parallel the benefits of their therapeutic power. The price for the benefits of corticosteroid therapy may be dear indeed; the side effects are well known. In the content discussed here-long term use of moderate doses to achieve anti-immunologic and anti-inflammatory effects – the special danger is the insidious onset of infection culminating in overwhelming sepsis. Their potential to cause multiple adverse side effects presents the practitioner difficult decision on the management of patients with potentially steroid responsive disorders. The possible beneficial effects of systemic corticosteroids must be weighed against risk factors including their probability of occurrence and their degree of harm. Though the adverse effects of corticosteroids increases with the duration of drug usage based on the risk versus benefits it is used.

KEY WORDS: **Steroids, Corticosteroids, Oral Mucosal Lesions, Autoimmune diseases**.

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INTRODUCTION

Corticosteroids have been in use for almost 60 years now. In 1949, Hench was the first person to report the beneficial effects of corticosteroid. He worked with rheumatoid arthritis patients since 1929, he noticed to show improvement in patients with pregnancy and jaundice. He correlated this with and guessed that this adrenal hormone may be the reason for the improvement. In 1948 Dr. Philip.S.Hench[1] of the Mayo Clinic injected a 29 year old woman who had been bed ridden for 4 1/2 years with rheumatoid arthritis with a hormone known as Kendall's compound E. This compound was so called because E is the fifth letter and the compound was the fifth one isolated from extracts of beef adrenal glands by Edward Kendall, Mayo's famed biochemist. After Hench's injection of compound E, his patient had made miraculous recovery. He also found a relapse in the disease when the therapy is withdrawn. Further tests during 1949 established this substance as a 'Wonder Drug'. Because of the confusion of the name of compound E and Vitamin E, Hench, Kendall and their co-workers changed the name of compound E to cortisone, which is an abbreviation of its chemical name, which is, 17-hydroxy-11-dehydrocorticosterone. And now it has evolved to the level such that it is used in multiple specialties and organ systems including dermatology, rheumatology, ophthalmology, immunology and oncology. Glucocorticosteroids are pleiotropic hormones that at pharmacological doses prevent or suppress inflammation and other immunologically mediated processes. They are necessary regulators of homeostatic life processes. They are known to exhibit many important physiological and biochemical effects. Most interesting to the clinician are studies of the anti-inflammatory and anti-allergic actions. Glucocorticosteroids may intervene at several points in the immune response and appear to affect many aspects of inflammation. Of almost equal importance, however is the knowledge of biochemical actions of the corticosteroids, particularly in excessive concentration that account for the undesirable side effects in the course of corticosteroid therapy. Although substantial complications associated with glucocorticosteroids have tempered enthusiasm for their use, they have remained the cornerstone of therapy for virtually all immunologically mediated diseases. The corticosteroids allow the host to recover in self-limited conditions and to suppress some manifestations of chronic diseases that reappear when corticosteroids are withdrawn. An obvious generalization is that corticosteroid therapy is most often temporary and adjunctive. Glucocorticosteroids are nonspecific, suppressive and although useful in reducing symptoms, and are seldom curative[2.]

BIOSYNTHESIS AND REGULATION OF STEROIDS[3]

The adrenal cortex synthesizes two classes of steroids, glucorticorticoids and mineralocorticoids. They are synthesized from cholesterol. Adrenal steroidogenesis takes place under the influence of ACTH, which makes more cholesterol available for conversion to prednisolone and induces steroidogenic enzymes. Since adrenal cortex cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis.

TABLE 1
NORMAL DAILY PRODUCTION IN ADULT

Cortisol	**20 mg/ day**
Corticosterone	02 mg / day
Aldosterone	0.125 mg/day
Dehydroepiandrosterone	30 mg/day.

Cortisol secretion is regulated by hormonal interactions among the hypothalamus, pituitary gland and adrenal cortex. The hypothalamus produces corticotropin releasing hormone (CRH), which is released in small pulses into the pituitary portal circulation. The anterior pituitary responds to CRH with ACTH synthesis and its subsequent

pulsatile secretion into the peripheral circulation. The inner adrenal cortex, in turn responds to plasma ACTH with generation and secretion of cortisol. There are three main endogenous controls for cortisol secretion. First is the negative feedback effect that plasma cortisol has on inhibiting the secretion of CRH and ACTH by the hypothalamus and pituitary. Second is the pulsatile secretion of ACTH based on a cicardian rhythm. Third control comes from neural effects on the hypothalamic-pituitary adrenal (HPA) axis as a result of various emotional or physical stresses.

TABLE 2
RELATIVE ACTIVITY OF CORTICOSTEROIDS [2,4]

Duration of action	Compound	Gluco-Corticoid Potency	Mineralo-Corticoid Potency.	Equivalent Dosage. (Mg)	Protein Binding	Plasma half Life (hours)
Short acting	Hydrocortisone	1	1	20	100	1.5-2
T1/2 (8-12 hrs).	Cortisone	0.8	0.8	25	1	0.5
Intermediate acting	Prednisolone	4	0.8	5	220	2.1-3.5
T1/2	Methyl -prednisolone	5	0.5	4	1350	>3.5
(12-36 hrs).	Triamcinolone	5	0	4	-	2-5
Long acting	Paramethasone	10	0	2		
T1/2	Dexamethasone	25	0	0.75	540	3-4.5
(36-54 hrs).	Betamethasone	25	0	0.75	400	3-5

ROLE OF CORTICOSTEROIDS IN ORAL MUCOSAL LESIONS

Glucocorticosteroids are used in oral medicine for their anti-inflammatory and immunosuppressive effects. Most of the diseases for which steroids are used are characterized by inflammation, which appears secondary to a hypersensitivity reaction against auto components. Glucocorticosteroids do not interfere with the primary disease mechanisms. But it is concluded from the literature, that because of anti-inflammatory and immunosuppressive effects of the hormones, it seems reasonable to profit from steroids as palliatives in acute phases of the diseases and / or as long-term suppressors of the general host defense[6]. Its action in various mucosal disorders is as follows.

RECURRENT APHTHOUS STOMATITIS [6,7]

Steroids inhibit effector B and T cells and T helper cells. A suppressor cell deficiency is consistent with the high antibody titres seen in RAU and the lowered lymphocyte reactivity found in some invitro tests could be a reflection of the same phenomenon. Glucocorticosteroids have no effect on the primary disease mechanisms but they are able to interfere with the inflammatory reactions as well as T & B lymphocyte functions. Therefore steroids can be used as palliatives in acute phases of the diseases or as longtime suppressors of general host defense. The use of topical and systemic steroids in an attempt to manage aphthous stomatitis is based on the presumption that the aphthae are the result of a noninfectious inflammatory process. Corticosteroid limits the inflammatory process associated with the formation of aphthae. It may act directly on T-lymphocytes and alter the response of effector cells to precipitants of immunopathogenesis (e.g. food allergies, trauma, and microorganisms).Topical glucocorticosteroids that have demonstrated efficacy for recurrent aphthous stomatitis is fluocinonide, triamcinolone and clobetasol.

BEHCET'S DISEASE

Immunosuppressive therapy is the mainstay of treatment for Behcet's disease. Successful treatment consists of anti-inflammatory agents that modify neutrophil activity. In the acute phase, prednisone, at doses of 40-60 mg/day, may be helpful, used alone or in combination with other immunosuppressive agents[8]

ORAL SUBMUCOUS FIBROSIS[9,10]

Steroids act as an immunosuppressive agent by opposing the action of soluble factors released by sensitized lymphocytes following activation by specific antigens. They also prevent or suppress inflammatory reactions thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of

collagen. The initial symptomatic relief could be due to the anti-inflammatory action of the steroids, which helps in clearing the juxta epithelial inflammatory reaction.

ORAL LICHEN PLANUS [6,8,11,12]

The benefit of steroids to some extent can be explained by the anti-immunologic properties with suppressed T cell functions and decreased IgG synthesis. The anti-inflammatory properties however seem to be most important. With the suppressed inflammation, tissue destruction is lowered and a minimum of antigen released. Steroids thereby, interrupt a vicious cycle. Steroids have no effect on hyperkeratotic lesions while the atrophic and erosive types respond to local and/or systemic corticosteroid administration with quick relief of symptoms.

MELKERSON ROSENTHAL SYNDROME[13]

Corticosteroids are the single most effective drug in the treatment of Melkerson Rosenthal syndrome. Systemic corticosteroids are effective in reducing swelling and preventing persistent tissue edema. Treatment of a single episode, however, apparently does not change the natural history of the disease. Intralesional corticosteroids have also been beneficial but multiple injections for months or years may be necessary. The placement of anesthetic lip block before the intralesional injection of corticosteroids increased the patient's acceptance to this form of therapy.

FACIAL PALSY (BELL'S PALSY)[14,15]

There is some evidence however that steroid use may prevent denervation, autonomic synkinesis and progression of paresis to palsy. Some studies suggest that recovery time is improved with the use of corticosteroids.

Fagan recommends the following regimen

Steroid tapering regimen with prednisone as the reference,

60 mg x 3 days
40 mg x 3 days
20 mg x 3 days
10 mg x 3 days
5 mg x 3 days

This is for patients presenting with in the first 10 days of onset.

POST HERPETIC NEURALGIA[16]

Although the cause of post herpetic neuralgia remains obscure, the pain in the acute phase of the disease is presumed to be due to abnormal pain discharges in the dorsal gray matter of the cord, secondary to inflammation of the segmental dorsal root ganglia. The persistence of pain may be associated with post inflammatory fibrosis in the root ganglia or sensory roots, but is perpetuated by central mechanisms, it seems logical to try to inhibit the inflammatory process in the acute phase by the use of corticosteroids, since this may avoid the late development of intractable central pain.

PEMPHIGUS VULGARIS AND PEMPHIGUS VEGETANS[17,19,19,20,21]

The clinical improvement after steroid treatment is followed by a fall in autoantibody titer. Steroids do not seem to prevent the binding of pemphigus antibodies in the target tissue but through interference with lymphocyte subpopulations they supposedly lower the autoantibody production. An immediate reduction of vascular permeability may prevent the leakage of antibodies, complement and inflammatory cells to the focus and stabilization of epithelial cell membranes inhibits the release of proteolytic enzymes. Before the advent of immunosuppressive therapy, pemphigus vulgaris was frequently a fatal disease. Most deaths were due to electrolyte loss and wound infection. Since the use of corticosteroids to treat pemphigus vulgaris, the mortality has dropped to below 10% with most deaths due to treatment complications. Lever and Schaumberg-Lever, recommend a two-tiered regimen for patients with severe disease. Patients with mild disease are given 40 mg of prednisone every other day, along with a daily immunosuppressive agent, usually azathioprine, for at least 1 year. For more severe cases, patients are given 200-400 mg of prednisone per day for 5-10 weeks. This is then reduced to 40 mg/day for 1 week then 30-mg/ day for 1 week, and then 25 mg/day for 1 week, at which time patients are started on the combined therapy schedule used for mild cases. Bystryn and Steinman recommend a treatment schedule that is adjusted for the needs of the patient. If the disease is mild, the patient is started with an initial dose of 20

mg/day for 2 weeks. If the patient does not respond or rapidly progresses, the dose is increased to 80-90 mg/day. This dose is increased every 4-7 days in 50% increments until there are no new lesions or itching, which signifies that the disease is under control. The dose is maintained until 80-90 % of the lesions have resolved at which time the dose is tapered by 50% every 2 weeks. Dumas et al. described 7 pemphigus patients, 3 of whom were treated with clobetasol propionate 0.05% cream as monotherapy for their mild PV. PV was defined as "mild" if fewer than 10 new bullae appeared per week and if the circulating pemphigus antibody titer was 1:320. The cream was applied twice a day for at least 15 days, and then tapered. Lesions were controlled in only 1 of the 3 PV patients. Triamcinolone acetonide, diluted to 5 – 10 mg/mL, may be used for intralesional injections of cutaneous lesions. A higher concentration, 10 – 20 mg/mL, is recommended for intraoral lesions. Multiple injections may be necessary for large lesions. The injections should be administered at weekly or biweekly intervals until complete resolution of the lesions is achieved.

BENIGN MUCOUS MEMBRANE PEMPHIGOID[6,8,18]

The serum autoantibody titres remain very high after the disappearance of clinical lesions. Therefore the benefit of steroids in bullous pemhigoid and benign mucous membrane pemphigoid might be due to anti-inflammatory actions, including lowered enzyme release, reduced cell migration and decreased leakage of humoral factors .

BULLOUS PEMPIGHOID[18,19]

Patients with localized lesions of bullous pemphigoid may be treated with high potency topical steroids; whereas patients with severe diseases require use of systemic corticosteroids alone or combined with immunosuppressive drugs.Potent topical steroids should be considered and favored in the management of localized or limited disease, since this variant responds to such therapy.

ERYTHEMA MULTIFORME[6,8,18]

So far little is known about immunopathologic changes after steroid therapy. However, most of the features seen in erythema multiforme are sensitive to steroid actions, i.e. the emigration of the mononuclear cells, the production of antibodies and consequently the formation of immune complexes and activation of complement. although the etiology of erythema multiforme is unknown, the use of corticosteroids in controlling the disease is in accordance with immunopathologic findings.

LUPUS ERYTHEMATOSUS[6,8,18]

Administration of steroids has been found to induce reconstitution of T suppressor cell function, disappearance of n-DNA antibodies from serum and fall in the ANA titre. The sub epidermal deposits of Igs partly resolve after several months of therapy. They diminish phagocytic activity, T-cell number and function-features that are already part of the disease. The immune complexes deposited in the vessel walls initiate an inflammatory process. So the anti-inflammatory properties of steroids might also be of importance for benefit in SLE. Steroids lessen the tissue destruction followed by minimal release of antigenic components and induce vessel wall stability, which prevents antigens from reaching the blood circulation. In conclusion the benefit of steroids in SLE is probably due to both suppressed inflammation and reduced Ig synthesis. The main alleviating effect of steroids is probably due to their anti-inflammatory properties, as the immune system of SLE patients appears intact. As in SLE, however reduced local antigen release could lead to less tissue destruction. Oral ulcerations of systemic lupus erythematosus are transient, occurring with acute lupus flares. Symptomatic lesions can be treated with high potency topical corticoids or intralesional steroid injections.

PSORIASIS[8,18]

Oral lesions have been treated with intralesional steroid injections. Topical or intralesional injection of corticosteroids has an anti-inflammatory effect and retard the increased epidermal proliferation.

MUCOCELE[18]

Intralesional injections of corticosteroids have been used successfully to treat mucoceles.

CENTRAL GIANT CELL GRANULOMA[22]

Intralesional steroids are used to treat. In one of the study, equal parts of triamcinolone acetonide (10mg) and lidocaine (0.5 %) were mixed.

INFECTIOUS MONONUCLEOSIS[23]

Corticosteroids have shown to significantly shorten the febrile course and alleviate malaise and lassitude. Prednisone in doses of 60 –80 mg /day should be used initially with rapid reduction as clinical and biochemical improvement occurs.

ADVERSE EFFECTS [24]

These are extension of pharmacological actions occurring with prolonged therapy and are a great limitation to use glucocorticosteroids in chronic diseases. Hypokalemic alkalosis, edema and hypertension[5] particularly in patients with primary hyper-aldosteronism secondary to an adrenal adenoma or in patients treated with potent mineralocorticoids. Cushing's habitus[6], skin atrophy, precipitation of diabetes. myopathy, susceptibility to infection delayed healing of wounds [3], peptic ulceration, osteoporosis, osteonecrosis, opthalmic complications, growth retardation, fetal abnormalities[4], CNS complications, suppression of HPA axis, reproductive system, hyperlipidemia, weight gain, atherosclerosis, hypertension, malignancy.

TOPICAL CORTICOSTEROIDS[5]

Topical corticosteroids represent a major chemotherapeutic class in dermatology and have been used for decades to treat skin diseases; there efficacy/ toxicity is related to their potency and percutaneous penetration. Shortly after the synthesis of hydrocortisone in 1951, topical steroids were recognized as effective agents for the treatment of skin disease. The first major advance in topical glucocorticosteroid therapy came with the introduction of triamcinolone acetonide in the late 1950's, followed shortly by floucinolone acetonide. Betamethasone -17- Valerate was introduced in the late 1960's and was found to be more active than triamcinolone acetonide and fluocinolone acetonide. The early 1970's saw the introduction of the 21-acetate derivative of fluocinolone acetonide, which had more biological activity than others. Since the late 1970's, many more potent topically active glucocorticosteroids have been introduced, including desoximethasone, clobetasol propionate and betamethasone-17-diproprionate.

CONTRAINDICATIONSTO GLUCOCORTICOSTEROID THERAPY[6]

The following are aggravated by corticosteroids. Since steroids may have to be used as a life saving measure, all these are relative contraindications:

- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Pregnancy
- Tuberculosis and other infections
- Osteoporosis
- Herpes simplex infections
- Psychosis
- Epilepsy
- Congestive heart failure
- Renal failure.

TABLE 3
CORTICOSTEROIDS IN ORAL MUCOSAL LESIONS

LESION	DRUG	ROUTE OF ADMINSTRATION	DOSAGE
Recurrent aphthous stomatitis	Clobetasol	Topical	0.05%, 3 times daily
	Fluocinonide,	Topical	0.05%, 6 times daily
	Dexamethasone elixir	Topical	0.5 mg / 5 ml held over the area, 4 times a day for 15 minutes.
	Prednisolone	Systemic (oral)	40mg / day for one week and then gradually tapered.
Major aphthous ulcer			
Behcet's disease	Prednisone	Systemic (oral)	40-60 mg/day for one week and then tapered
Oral submucous	Dexamethasone	Intralesional	4mg/ml (in combination with 2 parts of hyaluronidase

fibrosis			and 1ml of 2% lignocaine)
	Triamcinolone	Intralesional	10mg/ml (with 1ml of 2% lignocaine)
Oral Lichen Planus	Clobetasol proprionate	Topical	0.05% , 3 times a day
	Betamethasone valerate	Topical	0.1-0.05%, 3 -5 times a day
	Fluocinonide	Topical	0.05%, 6 times a day
	Clobetasol butyrate	Topical	0.05%, 3-5 times a day
	Triamcinolone acetonide	Topical, intralesional or elixir	0.1%, 3-5 times a day and 0.2-0.4 ml of 10 mg /ml solution, 1.0 mg acqueous solution to gargle for 2minutes respectively.
	Dexamethasone elixir	Topical	0.1 mg / ml, instructed to gargle with 5 ml of the solution for 2 minutes after meals and at night
	Prednisolone	Sysetemic (Oral)	10-20 mg/day for moderately severe cases to as high as 35 mg/day (0.5 mg/kg/daily) for severe for 2 weeks and then the dosage is altered.
Melkerson rosenthal syndrome	Prednisolone	Systemic (Oral)	1 to 1.5 mg /kg/day, tapering over 3-6 weeks
Facial palsy	Prednisone	Systemic (Oral)	1 mg/kg/day over 10-14 days followed by a tapering dose.
Post Herpetic neuralgia	Prednisone	Systemic (Oral)	40 mg daily for 10 days, which is gradually tailed off over the following 3 weeks
Pemphigus	Prednisone	Systemic (Oral)	1mg/kg/day in 2 or 3 divided doses for 6 to 10 weeks and tapered every 2 weeks by 5 or 10 mg followed by maintenanace dose of 5mg/day for months to years.
	Triamcinolone acetonide	Intralesional	Triamcinolone acetonide diluted to 10-20 mg/ ml with epinephrine for 1 to 2 weeks
	Methylprednisolone	Pulse Therapy	1 g/day i.v over 1-3 hrs for a few (usually 3) consecutive days
Paraneoplastic Pemphigus	Prednisone	Systemic	1mg/kg/day in 2 or 3 divided doses
Pemphigoid	Triamcinolone, fluocinonide and clobetasol propionate	Topical	
	Prednisone	Systemic	
Erythema Multiforme	Prednisone	Systemic	1mg/kg/day in 2 or 3 divided doses and then tapered gradually
Lupus erythematosus	Prednisone	Systemic	1mg/kg/day in 2 or 3 divided doses and then tapered gradually
Psoriasis	Triamcinolone acetonide	Intralesional	
	Prednisone	Systemic	

CONCLUSION

It is evident that these drugs should not be used for trivial reasons and careful consideration must be given to each individual patient before administering these hormones. However if the physician maintains the proper guidelines of care, patients on glucocorticosteroids have the highest benefits and lowest risk possible. Current advances in understanding of these agents should allow their more rational and effective use in clinical settings.

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