METHYL-PREDNISOLONE TABLETS, USP

DESCRIPTION
Methylprednisolone Tablets contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in diacne, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione,11,17,21-trihydroxy-6-

PHARMACOLOGY
Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's systems.

CLINICAL PHARMACOLOGY
1. Endocrine Disorders
Prednisolone or other adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).

2. Rheumatic Disorders
A major disadvantage for short-term administration (to tide the patient over an acute episode or exacerbation) is: Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy), Ankylosing spondylitis, Acute and subacute bursitis, Synovitis of osteoarthritis, Acute nonseptic tenosynovitis, Post-traumatic osteoarthritis, Psoriatic arthritis, Epicondylitis, Acute gouty arthritis.

3. Collagen Diseases
During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus, Systemic dermatomyositis (polymyositis), Acute rheumatic fever.

4. Dermatologic Diseases
Bullous dermatitis herpetiformis, Severe erythema multiforme (Stevens-Johnson syndrome), Severe seborrheic dermatitis, Erythematous dermatitis, Mycosis fungoides, Pemphigus, Severe psoriasis.

5. Allergic States
Control of severe or incapacitating allergic conditions inadmissible to adequate trials of conventional treatment: Seasonal or perennial allergic rhinitis.
Drug hypersensitivity reactions, Serum sickness, Contact dermatitis, Bronchial asthma, Acute dermatitis.

6. Ophthalmic Diseases
Severe, acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctival conjunctival ulcerations, Herpes zoster ophthalmicus, Anterior segment inflammation, Diffuse posterior uveitis and choroiditis, Sympathetic ophthalmia, Keratitis, Optic neuritis, Allergic conjunctivitis, Conjunctivitis, Keratitis, Iritis and iridocyclitis.

7. Respiratory Diseases
Symptomatic sarcoidosis, Bronchitis, Leber's syndrome not manageable by other means.

8. Hematologic Diseases
Idiopathic thrombocytopenic purpura in adults.
Secondary thrombocytopenia in adults.
Acquired (autoimmune) hemolytic anemia (Coombs test positive), Congenital (erythropoietic) hypoplastic anemia.

9. Neoplastic Diseases

10. Edematous States
To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. Gastrointestinal Diseases
To tide the patient over a critical period of the disease in: Ulcerative colitis, Regional enteritis.

12. Nervous System
Acute exacerbations of multiple sclerosis.

13. Miscellaneous
Tuberculous meningitis with subarachnoid block or impeding block when used concurrently with appropriate anti-tuberculous chemotheraphy. Trichinosis with neurologic or myocutaneous involvement.

CONTRAINDICATIONS
Systemic fungal infections and known hypersensitivity to components.

WARNINGS
In patients on corticosteroid therapy subclinical adrenal insufficiency, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. May be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential is not recommended. The potential benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hyperadrenalinism. Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excration of potassium. These effects are less likely to occur with the synthetic derivatives when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunizing procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.

The use of Methylprednisolone Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antimicrobial therapy. If corticosteroids are indicated in patients with latent tuberculosis or tuberculous reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS
General Precautions
Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress during or after the period of hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with myxedema. Corticosteroids should be used cautiously in patients with overt or latent hyperparathyroidism. When these drugs are used in large doses, dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Aspirin should be used cautiously in conjunction with corticosteroids in hyperpigmentinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscesses or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, acute or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See dosage and administration.) Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk-benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.
Conversations have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse reactions associated with the individual use of either drug may be more apt to occur.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

Sodium retention

Congestive heart failure in susceptible patients

Hypertension

Fluid retention

Potassium loss

Hypokalemia alkalosis

Musculoskeletal

Muscle weakness

Loss of muscle mass

Steroid myopathy

Osteoporosis

Von Willebrand's disease

Aneptic necrosis of femoral and humeral heads

Pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage

Pancreatitis

Gastritis

Abdominal distention

Ulcereous esophagitis

Dermatologic

Impaired wound healing

Pettexia and eczymoses

May suppress reactions to skin tests

Thin fragile skin

Facial atrophy Increased sweating

Neurological

Increased intracranial pressure with papilledema

(headache pain) usually after treatment

Convulsions

Vomiting

Headache

Endocrine

Constitutive of Cushingoid state

Suppression of growth in children

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness

Menstrual irregularities

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism

The following additional reactions have been reported following oral or as a partial parenteral therapy:

Urticaria and other allergic, anaphylactic or hypersensitivity reactions

DOSAGE AND ADMINISTRATION

The initial dosage of Methylprednisolone Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

It should be emphasized that dosage requirements are variable and must be individualized in the basis of the disease under treatment. The response of the patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Methylprednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be discontinued, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis: In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of Methylprednisolone is equivalent to 5 mg of prednisolone). ADT (Alternative Day Therapy): Alternative day therapy is a corticosteroid dosing regimen in which the twice the usual daily dose of corticosteroid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose corticosteroid therapy with the beneficial effects of corticosteroids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, Corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effects of prednisolone persists longer than their physical presence and metabolic effects and (b) the administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the other day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH). Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenocortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 am and 6 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma cortisol during the day with the lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing’s disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruising, muscle weakness with eating, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hypercortisolism may be noted during conventional long-term daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated cortisol values during the night may play a significant role in the development of undesirable corticosteroid escape. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every six hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days after a single dose and are thus recommended for alternate day therapy.

The following should be kept in mind in considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.

2) ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic therapy is anticipated.

In less severe disease states in which corticosteroid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for control of the disease process. The initial suppressive daily dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended.

Once control has been established, two courses are available: (a) change to ADT and then gradually reduce the amount of oral corticosteroids every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

4) Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been treated with long periods of time (eg, patients with rheumatoid arthritis).

Since these patients may already have a suppressed HPA axis, establishing them on ADT may be difficult and not always successful. However, accompanying other control of the disease process should reduce the daily dose of corticoid to the lowest effective level as rapidly as possible.

5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (eg, dexamethasone and betamethasone).

6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

7) In using ADT it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off corticoid period. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be reinstituted.

9) Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticosteroid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets are available in the following strengths and package sizes:

4 mg (White, oval shaped tablets debossed with “TL 001” on one side and quadradrated on the other side.)

8 mg (White, oval shaped tablets debossed with “TL 002”, scored on one side and plain on the other side.)

16 mg (White, oval shaped tablets, debossed with “TL 003” on one side and quadradrated on the other side.)

32 mg (White, oval shaped tablets, debossed with “TL 015” on one side and biasected on the other side.)

Bottles of 100 NDC 59746-001-00

Unit of use pack (21 tablets) NDC 59746-001-03

Bottles of 50 NDC 59746-002-04

Bottles of 100 NDC 59746-002-04

Bottles of 100 NDC 59746-002-06

Bottles of 50 NDC 59746-002-06

Bottles of 25 NDC 59746-001-03

Bottles of 100 NDC 59746-001-06

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