

THERAPEUTIC USES OF METHYL PREDNISOLONE

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Glucocorticoids are widely used for their anti-inflammatory and immuno-suppressive effects. For some clinical situations, short course of steroid therapy alone or in combination with other drugs will control clinical symptoms without steroid induced side effects. Intravenous pulse regimes are theoretically desirable in order to obtain a rapid and prolonged therapeutic effects with fewer side effects. For this purpose, methyl prednisolone (MP) is a preferred glucocorticoid because of its high potency and low salt retaining activity(1). At present, it is the drug of choice in rapidly progressive glomerulonephritis (RPGN)(2). The drug is now being increasingly used for many other conditions, though clinical trials in India are limited.

Pharmacology

One family of proteins that mediates anti-inflammatory activity of all steroids, including methyl prednisolone is lipocortin(1). Lipocortins inhibit the synthesis of inflammatory molecules

(leukotrienes, thromboxane, platelet aggregating factor) by inhibiting phospholipase A₂. The other specific action of glucocorticoid involved in asthma include prevention and reversal of late phase reactants, reduction in mucus secretion and augmentation of adrenergic responsiveness(3).

A steroid that possesses no mineralocorticoid activity is preferred in anti-inflammatory and immunosuppressive regimes(1). Methyl prednisolone differs from prednisolone in the presence of the 6-methyl group on the B ring which prevents hydroxylation at 6th position but otherwise metabolic routes are similar to prednisolone(4). Six methyl prednisolone has greater anti-inflammatory potency and less electrolyte regulating potency than prednisolone due to its 6 methylation. All the biologically active adrenocortical steroids and their synthetic congeners undergo reduction at 4,5 double bond and 3 ketone substituent in liver and extrahepatic tissues. Their sulfate esters or glucuronides are formed mainly in liver and partly in kidney and excreted in urine within 72 hours. Neither biliary nor fecal excretion is of any clinical significance to man.

Certain anti-inflammatory and immunosuppressive effects of MP have been found only with high doses which

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include inhibition of granulocyte aggregation, inhibition of T cell interleukin II receptor and prolonged suppression of natural killer (NK) cell activity. It has been suggested to improve monocyte Fc receptor functions in SLE(1). When used in oral treatment in the range of 16-96 mg daily, it has the expected anti-inflammatory and immunomodulatory effects, such as seen with a lower dose of prednisolone(4). However, a study conducted by Andres *et al.* shows that distribution of a drug can be crucial in determining clinical performances-^n an equivalent doses, MP's increased lung permeability compared to prednisone and prednisolone should result in effective doubling of potency(5). In some other conditions also, oral MP has shown better results than prednisolone

Though the definite reason is yet unknown. Table I summarized the pharmacokinetics of methyl prednisolone(6). Table II compares the different actions of commonly used steroids. The available preparations are shown in table III.

TABLE I-Pharmacokinetics of Methyl Prednisolone.

Oral bioavailability	- (82±13)% decreases to 50-60% in higher dosage.
Plasma bound	- 60-75%
Clearance rate	- 6.2±0.9 ml/min/kg
Volume distribution	- 1.2±0.2l/kg
Plasma half life	- 2.3±0.5 h

TABLE II-Actions of Some Commonly Used Steroids.

Steroid	Anti-inflammatory	Equivalent dosage	Salt retaining capacity
Hydrocortisone	1	20	2+
Prednisolone	4	5	1+
MP	5	4	0

TABLE III-Preparation of Methyl Prednisolone.

Routes	Available preparations	Cost.
Oral	2-32 mg tablets	4 mg tablet-Rs. 9.10
Injectable	20-80 mg/ml (Suppression)	500 mg injectable-Rs.510/-
	40-200 mg/ml (Powder)	
Topical	0.25% -1%	
Rectal suppository	40 mg/bottle	

Therapeutic Indications

I. Renal

(i) Rapidly Progressive Glomerulonephritis (RPGN)

In the treatment of idiopathic RPGN at present, MP pulse therapy is the drug of choice(2). After taking necessary precautions for relative contraindications like peptic ulcer, overt psychosis, uncontrolled infections, 30 mg/kg dose is given three times on alternate days followed by oral prednisolone 2 mg/kg/day on alternate days for 2 months. About 75% patients including some oliguric and on dialysis have shown dramatic response with a return of renal functions to normal or near normal levels. Responses have generally been evident within 5-10 days and have continued for 4-6 weeks(2,7). Success rates approaching 75% have been reported in patients treated also with plasma exchange but MP is cheaper and safer. The clinical responses indicated by improvement in renal functions has also been confirmed by repeated biopsies.

(ii) Lupus Nephritis

MP has been used in lupus nephritis in a dose of 1 g/m²/day intravenously for 3 days alongwith oral prednisolone 0.5 mg/kg/d x 4 days. A repeat dose of MP may be given monthly upto 6 months, if active nephritis persists. There have been no comparative trials of pulse MP therapy versus conventional high dose oral prednisolone. The current use of pulse MP is primarily based on the consensus that it is at least as effective as oral prednisolone but has fewer side effects(2).

(iii) In kidney transplantation, MP is

the current first line treatment for acute rejection(2,8). The dose is 30 mg/kg/day x 3 days given in 4 divided doses. The previous oral prednisolone dose prior to IV MP therapy is then continued. If the patient does not respond to the first set of 3 days therapy after a skip day, another set of 3 days can be given with continuous evaluation of patient's condition. The chance of reversing a first rejection with a 2-3 sets of therapy is about 85%(2). It is better to administer MP only twice in 3 months span since the risks may outweigh the benefits.

2. Hematological

(i) Aplastic Anemia

Early marrow transplant is the treatment of choice when an HLA matched sibling donor is available(9). However, due to its astronomical cost which remains prohibitive even in developed countries, a combination of antithymocytic globulin (ATG) with MP remains the practical treatment of choice(9). Again, nonavailability and relatively higher cost of ATG led researchers to have clinical trials with only MP and results are encouraging(10). Marmont *et al.*(1) observed 38% response with MP alone. Two other studies show definite improvement in most of the patients after receiving methyl prednisolone; a modest improvement was found in other patients(12,13).

(ii) TTP

Several pilot studies have found W pulse methyl prednisolone (30 mg/kg/d intravenously over 20 minutes for 2 days) to be effective in increasing the platelet count to a safe level. A randomized trial in adults with FTP has found

that intravenous pulse methylprednisolone leads to a more rapid rise in platelet count than oral prednisolone. The rate of response is equivalent to intravenous immunoglobulin and the cost is considerably less(14).

3. Bronchial Asthma

The role of glucocorticoids in the long term treatment and suppression of bronchial asthma is well recognized(15). Prompt use of MP intravenously in the emergency treatment of severe asthma can prevent significant morbidity, reduce the period of hospitalization and effect substantial savings in health care costs(14). The early beneficial effects of MP may result from prompt potentiation of the catecholamines in bronchial smooth muscles, probably by inhibiting the breakdown of epinephrine by catechol -O- methyl transferase(12). MP has significant effect within an average period of 4 hours(15). The dose used is 1 mg/kg every 6 hours.

4. Ophthalmological Conditions

Oral prednisolone is the recommended drug for treatment of optic neuritis. However, in a recent trial with intravenous methyl prednisolone in patients with optic neuritis, recovery of visual functions was faster than oral prednisolone group. At 6 months, MP group had similar visual acuity but visual fields, contrast sensitivity and color vision were better as compared to oral prednisolone group. The rate of new episodes of optic neuritis was higher in oral prednisolone group(16).

In other ophthalmologic diseases also, MP has been used. In an uncon-

trolled trial of 17 patients with severe inflammatory eye diseases, improvement occurred in 88% of patients on an average follow up of 10 months. Diagnosis included SLE, Bechet syndrome, juvenile rheumatoid arthritis; several cases were idiopathic(17).

5. Miscellaneous

(i) Acute Spinal Cord Injury

MP when given in the first few hours after injury improved the neurological outcome in a dosage of 30 mg/kg bolus followed by an infusion of 5.4 mg/kg/h for 23 hours(10). It may act by suppressing breakdown of membrane through inhibition of lipid peroxidation and hydrolysis at injury site. When lipid peroxide is inhibited, products of arachidonic acid is reduced thus improving the blood flow at the injury site(18). In a multicentric study, patients given MP within 8 hours of injury improved significantly within 6 months as compared to those given placebo(18).

(ii) Graft vs Host Disease (GVH)

In GVH, intravenous MP is a common first choice in a dosage of 2-20 mg/kg/d 6th hourly. Response is apparent within 3-5 days. Once the disease is controlled, it can be tapered off in 5-7 days(19).

(iii) Rheumatoid Arthritis

It may be used as a method of sparing oral steroids. It also overcomes lag period while the other slowly acting antirheumatoid drugs become effective. For longer control, MP may be repeated at 4-6 weeks interval. Some clinicians prefer MP in life threatening complication and as adjuvant to other drugs to

minimize side effects and better ambulatory life(20).

(iv) *Ulcerative Colitis*

In severe ulcerative colitis, MP finds its use as intravenous 2-10 mg/kg/d for 10 days. MP enema can be used alone or in combination of sulfasalazine(21).

(v) In *Goodpasture syndrome*, pulmonary hemorrhage commonly responds to intravenous MP therapy.

(vi) Severe nausea and vomiting caused by cancer chemotherapy may compromise compliance with treatment and conventional antiemetics are frequently ineffective or cause excessive drowsiness. MP appears to be an effective antiemetic(22) in this situation.

MP has also been found beneficial in crescentic glomerulonephritis, polyarteritis nodosa, and mesangioproliferative glomerulonephritis. In several other conditions like myasthenia gravis(23), multiple sclerosis, ankylosing spondylitis(24), polymyositis, severe idiopathic childhood nephrotic syndrome (MCNS), cadaveric transplant(25), erythema multiforme (in those patients where steroid is indicated), angioneurotic edema, anaphylaxis, cerebral edema secondary to cerebral tumor, endocrine disorders requiring treatment with a glucocorticoid, MP has been used with encouraging results but comparative studies are lacking to recommend routine use in clinical practice.

Major Side Effects

Side effects like peptic ulcer, susceptibility to infection, suppression of pituitary adrenal axis are like other steroids

only. However, some side effects are unique to MP especially when used in pulse form of therapy such as hiccups, muscle weakness, a metallic taste, and painful joints-leading gradually to non-inflammatory effusion. There is some evidence that there are fewer infections associated with pulse therapy(26).

Rarer side effects include seizure, severe hypertension, arrhythmias, sudden death but no increased incidence of arrhythmia in myocardial infarction patients. Also sudden death is related only to hypovolemia or K⁺ disturbances(2).

To minimize side effects, patients should be normovolemic, should not have received diuretic in previous 48 hours and have normal K⁺ levels. Intravenous infusion should be given very slowly diluted in 50-100 ml of 5% dextrose /normal saline over 1 hour to avoid K⁺ and fluid shifts which can lead to acute cardiac dysfunction.

Contraindications

MP should not be used in the following groups of patients:

(i) Preterm babies—benzyl alcohol used as diluent can cause fatal gasping syndrome(4).

(ii) Nursing mothers, as the drug is secreted in breastmilk(4).

The relative contraindications are given in *Table IV*.

Drug Interaction

MP increases cyclosporin level through some unknown mechanism. Ketoconazole decreases hepatic metabolism of MP by inhibiting 6B hydroxylase therapy prolonging adrenal suppression

TABLE IV—Relative Contraindications of MP.

Systemic fungal infection
Varicella and vaccinia infection
Herpes simplex keratitis
Cerebral edema
Acute psychosis Peptic ulcer
Major surgery within last 2 weeks
Hypersensitivity to the drug

of MP. Erythromycin reduces elimination of MP. The efficacy of cyclophosphamide is reduced by MP.

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