METHYLPREDNISOLONE

Introduction

Methylprednisolone is a highly potent synthetic corticosteroid.

Methylprednisolone sodium succinate is especially well suited for **intravenous** use in situations in which high blood levels of methylprednisolone are required rapidly.

There is also a preparation available for *intramuscular* or *intra-articular joint* use, (trade name **Depo-medrol**), which is primarily used by rheumatologists and sports medicine physicians.

Methylprednisolone has:

- About 5 times the anti-inflammatory effect of hydrocortisone.
- Greater anti-inflammatory potency than prednisolone
- Less tendency than prednisolone to induce sodium and water retention.

In the Emergency Department, the **IV** form, methylprednisolone **sodium succinate**, is used primarily for:

- Acute exacerbations of **asthma in children**
- Acute exacerbations of autoimmune neurological conditions such as **multiple sclerosis**
- Acute exacerbations of autoimmune rheumatological conditions

History

Cortisone was first identified by the American chemists **Edward Calvin Kendall** (1886 - 1972) and **Harold L. Mason** while researching at the Mayo Clinic.

Kendall was awarded the **1950 Nobel Prize for Physiology or Medicine** along with **Philip S. Hench** and **Tadeus Reichstein** for the discovery of the adrenal cortex hormones as well as their structures and functions.

Harold Mason's contributions to the crystallization and characterization of cortisol have generally been forgotten outside of the Mayo Clinic.

Prednisone and prednisolone were introduced into clinical practice in 1955.

Chemistry

Methylprednisolone is a methylated form of prednisolone.

The methyl group is attached to the carbon 6 atom of the B ring.

Physiology

The principle physiological roles of the corticosteroids are widespread and complex, but essentially fall into three groups:

1. Enhancing the effects of circulating catecholamines

2. Metabolic effects

3. Global suppression of anti-inflammatory and immune responses

At the highest level, the corticosteroids are said to enable and enhance the complex cardiovascular and metabolic "fight or flight" survival responses of the organism to the presence of "stressors"

Classification

Naturally occurring adrenocortical steroids:

The **naturally occurring** adrenocortical steroids are:

- **Hydrocortisone (or cortisol)**

- **Cortisone**

These have both anti-inflammatory (glucocorticoid) and salt retaining (mineralocorticoid) properties.

They are principally used as replacement therapy in adrenocortical deficiency states.

Synthetic corticosteroids:

The **synthetic** corticosteroid compounds include:

- **Prednisolone**

- **Prednisone**

- **Dexamethasone**

- **Methylprednisolone**
- **Fludrocortisone**

These are mainly used for their anti-inflammatory properties.

Classification according to predominant activity:

1. Synthetic agents with *marked glucocorticoid* activity and an *absence* of significant salt-retaining activity:

   - **Dexamethasone**
   - **Prednisolone**
   - **Methylprednisolone**
   - **Betamethasone**

   These drugs are primarily used for their potent anti-inflammatory effects.

2. Synthetic agents with predominant mineralocorticoid activity:

   - **Fludrocortisone**

   It is used as a mineralocorticoid replacement for patients with primary adrenal insufficiency and as a treatment for orthostatic hypotension.

3. Agents with a combination of both *glucocorticoid* activity and mineralocorticoid activity.

   - **Hydrocortisone**

Preparations

Available preparations include:

Ampoules:

- **Methylprednisolone sodium succinate** for **IV** use:

  Methylprednisolone sodium succinate is extremely soluble in water so that it may be administered in a small volume of diluent and is especially well suited for intravenous use in situations in which high blood levels of methylprednisolone are required rapidly.

  Ampoules containing powder for reconstitution are available in a wide range of doses, including:

- ♥ 40 mg, 125 mg, 500mg, 1 gram, 2 grams.

- **Methylprednisolone acetate** for **IM** use and **intra-articular joint** use.
  - ♥ 40 mg/mL, 1 mL
  - ♥ Note that this preparation **cannot** be used IV (serious adverse events reported).

Topical:

Methylprednisolone aceponate as a 0.1% ointment/cream can applied topically for dermatological conditions

Mechanism of Action

The corticosteroids **regulate gene expression**.

When a corticosteroid enters a cell, it combines with corticosteroid receptors in the cytoplasm.

This drug-receptor complex enters the nucleus where it controls synthesis of protein, including enzymes that regulate cell activity such as inflammation.

Pharmacodynamics

Effects of the corticosteroids in general include:

1. Glucocorticoid effects including:
   - **Enhancing the vascular sensitivity to circulating catecholamines.**
   - Metabolic effects:
     - ♥ Gluconeogenesis:
       - ♥♥ This is the generation of glucose from *non-carbohydrate* carbon substrates such as pyruvate, lactate, glycerol, and glucogenic amino acids.
     - ♥ Proteolysis
     - ♥ Lipolysis
     - ♥ All corticosteroids can increase calcium excretion
   - Suppression of inflammation and immune responses.

2. Mineralocorticoid effects including:

- Hypertension
- Sodium and water retention
- Potassium loss.

The corticosteroids as a group may have predominantly glucocorticoid effects (e.g. dexamethasone), mineralocorticoid effects (fludrocortisone), or a combination of both (e.g. **hydrocortisone**).

Note that *systemic effects* may result from all of oral, intramuscular, intravenous, inhaled, intra-articular and topical administration.

In regard to methylprednisolone:

- This has a potent anti-inflammatory effect, about 4 times more so than hydrocortisone.
- It has a greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention.

Pharmacokinetics

Absorption:

- Methylprednisolone can be formulated to be given IV or IM or topically.

  Methylprednisolone sodium succinate can be given IV (or IM, but IV is the preferred route of administration.

  Methylprednisolone acetate is for **IM** use and **intra-articular joint** use. It must **not** be given IV

  Methylprednisolone aceponate is for topical use.

- In vivo, cholinesterases rapidly hydrolyse methylprednisolone sodium succinate to free methylprednisolone.

Distribution:

- In humans, methylprednisolone forms a weak dissociable bond with albumin and transcortin; approximately 40 to 90% of the drug is bound.

Metabolism and excretion:

- Metabolism of methylprednisolone occurs via the liver and is qualitatively similar to metabolism of cortisol.

  The major metabolites are 20-beta-hydroxymethylprednisolone and 20-beta-hydroxy-6-alpha-methylprednisolone.

  The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds.
- The plasma half-life of methylprednisolone is 2.3 to 4 hours and appears to be independent of the route/ pattern of administration. The biological half-life is 12 to 38 hours.

  The intracellular activity of glucocorticoids results in the marked variation in the plasma and pharmacological half-lives. Pharmacological activity persists after plasma levels are no longer measurable.

Indications

In the Emergency Department, the **IV** form, methylprednisolone **sodium succinate**, is used primarily for:

- Acute exacerbations of **asthma in children**

- Acute exacerbations of autoimmune neurological conditions such as **multiple sclerosis**

- Acute exacerbations of autoimmune rheumatological conditions

Contra-indications/precautions

These include:

1. Infections (caution):

   Immunosuppression can increase the risk and severity of infection and so caution is advised when prescribing hydrocortisone in a patient with active or latent infection.

   Some conditions require *both* corticosteroid and control of infection, (e.g. infective exacerbation of COPD or asthma) and this is usually safe so long as the infection can be effectively treated at the same time.

   In general terms, the decision to start or continue corticosteroids in a patient with infection depends on a number of factors including:

   - The type of infection:

- ♥ Including whether active or latent
- ♥ **Systemic fungal** infections generally contraindicate the use of corticosteroids.

- Its severity
- Whether the infection can be treated or controlled at the same time.
- The specific indication for hydrocortisone.

2. Live vaccines:

   - Administration of live or live attenuated vaccines is contraindicated in patients receiving **immunosuppressive doses** of corticosteroids.

     Killed or **inactivated** vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids, however the response to such vaccines may be diminished.

3. Known hypersensitivity to the excipients of methylprednisolone

4. Intra-articular injection (corticosteroids in general):

   - Corticosteroids are contraindicated in patients with infective arthritis, skin or soft tissue infections near joint (risk of introducing bacteria into joint) or a prosthetic joint.

*The following **precautions** do not apply when used at **physiological doses for adrenal insufficiency**:* [2]

5. Latent TB:

   - May be reactivated; consider treatment with isoniazid.

6. Peptic ulcer disease:

   - Corticosteroids may increase the risk of peptic ulcers.

7. Diabetes:

   - Corticosteroids (including intra-articular injections) may cause hyperglycaemia and worsen diabetes control.

8. Hypertension/ heart failure:

- May be worsened due to sodium and water retention (mineralocorticoid effect).

9. Psychiatric disorders:

   - May be exacerbated.

10. Glaucoma:

    - Intraocular pressure may increase.

11. Osteoporosis:

    - Long-term corticosteroid use increases the risk of osteoporotic fractures and accelerates bone loss.

12. Myasthenia gravis:

    - Increased muscle weakness may occur during the first few weeks of treatment with corticosteroids; (seek specialist advice).

Pregnancy

Methylprednisolone **sodium succinate** is a category A drug with respect to pregnancy.

Drugs A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Breast feeding

Compatible, but caution with high pulse doses.

Adverse Effects

Adverse effects are an inevitable result of **systemic** corticosteroid treatment if the **dose and/ or duration** of treatment are sufficient, because most are dose-related biological effects of the hormone.

Short courses of high dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

For **methylprednisolone** adverse affects of **acute** administration can include:

1. CVS:

   Methylprednisolone must be infused **slowly**

Excessively rapid IV administration can cause:

- Bradyarrhythmias
- Ventricular arrhythmias/ cardiac arrest

Doses should be given over 1 hour.

For patients at possible cardiac risk (especially arrhythmias, IHD), methylprednisolone should be given over 2 - 3 hours. [1]

2. Effects related to inappropriate routes of administration:

Administration of the different formulations by **other than their intended routes** has been associated with reports of serious medical events including:

- Chemical arachnoiditis, meningitis
- Paraparesis/ paraplegia
- Sensory disturbances
- Headache
- Functional gastrointestinal disorder/ bladder dysfunction
- Seizures
- Visual impairment including blindness, ocular and periocular inflammation

The **longer - term** adverse effects of corticosteroids **in general** include:

Adverse glucocorticoid effects:

1. Adrenal suppression

Manifests with longer term exogenous administration when:

- Therapy is **abruptly ceased**

Or

- When a **stressor occurs**; due to secondary adrenocortical and pituitary unresponsiveness, particularly in trauma, surgery, infection or illness

Adrenal hypofunction can lead to Shock/ increased risk of shock states.

The hypothalamic-pituitary-adrenal axis is suppressed by glucocorticoid therapy.

The dose, duration of treatment and individual patient characteristics affect the onset and extent of this effect.

Treatment with **prednisolone** at doses **greater than 10 mg** (or equivalent dose of glucocorticoid) **daily for more than three weeks** can be considered sufficient to cause clinically significant adrenal suppression that requires glucocorticoid replacement at a time of intercurrent illness, trauma or surgical stress. [1]

Therefore, in this situation, tapering of the glucocorticoid dose is required to avoid both adrenal insufficiency and the rebound in symptoms that may occur with sudden cessation.

After long-term use (more than 2 weeks), dose reduction must be slow to enable the hypothalamic-adrenal feedback system to re-equilibrate.

2. Immunosuppression:

- Increased risk of infection.
- Infections are more common in people treated with supraphysiological doses of corticosteroids, due to immunosuppressive effects.
- **Corticosteroids may also mask the early symptoms and signs (by suppressing the inflammatory repose) of infection, resulting in later diagnosis, delay in treatment, and more severe clinical consequences.**
- Reactivation of *Mycobacterium tuberculosis* infection occurs with such frequency that before commencing immunosuppressant treatment with corticosteroids, screening for active or latent tuberculosis (TB) should be considered.
- Prophylaxis for *Pneumocystis jiroveci (carinii)* infection should be considered in patients who are at risk and taking high dose oral corticosteroids long term.

3. Metabolic effects:

- Hyperglycaemia:
  - ♥ Hyperglycaemia may accompany treatment with corticosteroids, particularly when higher doses are used, and blood glucose concentrations may require monitoring.
- Hypertriglyceridaemia

- Weight gain/ redistribution of fat centripetally, leading to the development of a “Cushingoid” state.

- All corticosteroids increase calcium excretion

4. Dermatological effects:

    - Skin atrophy leading to thin fragile skin.

    - Purpura/ ecchymoses

    - **Poor wound healing**

    - Striae

    - Hirsutism

5. Gastrointestinal effects:

    - Dyspepsia

    - Peptic ulceration

    - Gastrointestinal bleeding

6. Myopathy:

    - Steroid myopathy with muscle weakness/ loss of muscle mass.

    - Tendon rupture can also occur, particularly of the Achilles tendon

7. Bone effects:

    - Osteoporosis:

        - ♥ **Bone density loss** leading to osteoporosis is a risk for patients on continuous (> one month) corticosteroid therapy in doses greater than the equivalent of prednisolone **5 to 7.5 mg per day** or who are receiving frequent pulses of corticosteroid.

        - ♥ It can occur in men as well as women.

        - ♥ The risk of osteoporosis becomes greater at higher glucocorticoid doses.

        - ♥ Loss of bone mineral density occurs rapidly after corticosteroids are commenced and may exacerbate the osteoporosis associated

with some rheumatological diseases, such as ankylosing spondylitis, and inflammatory bowel disease.

- Avascular (ischaemic) necrosis:
  - ♥ Most typically of the of the proximal femoral and humeral head
  - ♥ It is infrequent
  - ♥ It is idiosyncratic (ie unpredictable).
  - ♥ It occurs more commonly following exposure to doses in excess of **20 mg** per day prednisolone (or equivalent dose of other corticosteroid).
  - ♥ The time between corticosteroid exposure and the development of avascular necrosis is variable, and can be up to *many years*, which makes diagnosis difficult.
  - ♥ Avascular necrosis should be considered in the differential diagnosis of hip and groin pain especially in patients who have been on high-dose and/or long-term corticosteroids at any time.
  - ♥ Both the pathogenesis and treatment of this condition remain controversial.

8. Ocular effects:
   - Increased intraocular pressure
   - Cataracts
9. Growth retardation in children:
   - Chronic use of corticosteroids (at pharmacological doses) may retard growth in children.
   - Follow growth and development carefully
   - Catch-up growth may occur after corticosteroid withdrawal.
10. Menstrual irregularities:
    - Principally amenorrhoea
11. Psychiatric disturbances:
    - Euphoria

- Depression
- Paranoid psychosis

Note that preexisting emotional instability or psychotic tendencies may also be *aggravated* by corticosteroids.

Adverse mineralocorticoid effects:

1. Sodium retaining effects:
   - Oedema
   - Hypertension
2. Hypokalaemic alkalosis.

Note that most of the adverse effects relate to long term treatment and do not preclude *short* term use.

Dosing

Exact dosing and the duration of dosing depend on the condition being treated as well as the severity of the condition and illness.

Methylprednisolone must be infused **slowly.**

Doses should be given over 1 hour.

For patients at possible cardiac risk (especially arrhythmias, IHD), methylprednisolone should be given over 2 - 3 hours.

See individual conditions and latest Therapeutic Guidelines for full prescribing details.

Multiple sclerosis:

For significant exacerbation of MS, under the direction of a neurologist, give

- **Methylprednisolone 1 gram IV over 1 hour, daily for 3 days.** [1]

For moderate - severe asthma in children:

- Give **methylprednisolone 1 mg/kg IV** daily, or up to 6 hourly, depending on severity

Appendix 1

Approximate relative potencies and half-lives of the glucocorticoids:

Glucocorticoid	Relative glucocorticoid potency	Equivalent dose for glucocorticoid effect	Estimated biological half-life
Hydrocortisone	1	20 mg	8 to 12 hours
Cortisone acetate	0.8	25 mg	8 to 12 hours
Dexamethasone	25 to 50	400 to 800 micrograms	36 to 54 hours
Prednis(ol)one	4	5 mg	18 to 36 hours
Methylprednisolone	5	4 mg	12 to 36 hours

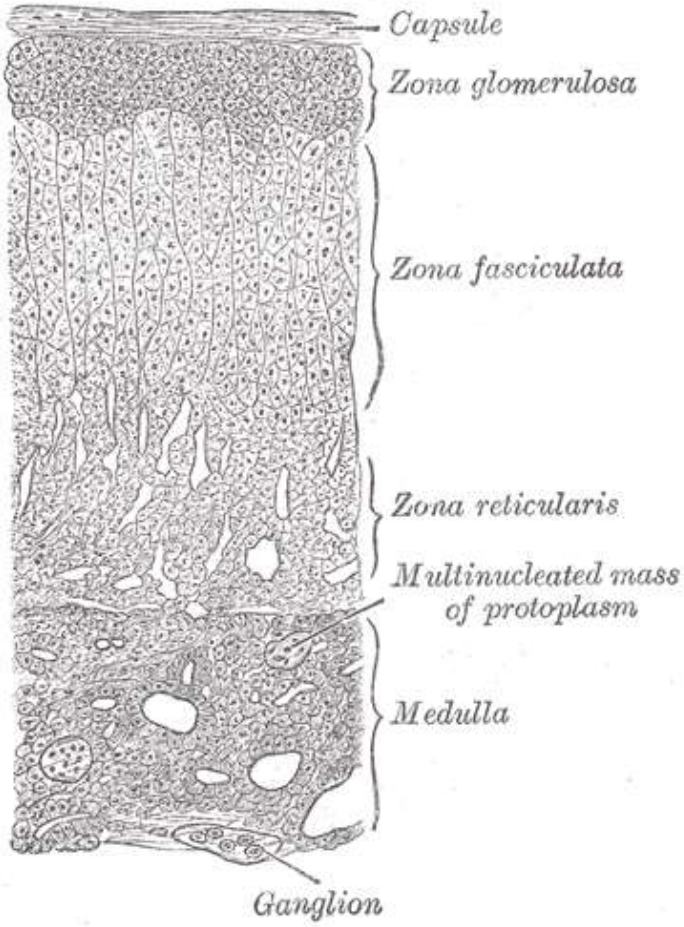
Appendix 2

Relative potencies of the topical preparations of the corticosteroids:

Mild	
Desonide	0.05%
Hydrocortisone	0.5%, 1%
Hydrocortisone acetate	0.5%, 1%
Moderate	
Betamethasone valerate	0.02%, 0.05%
Clobetasone butyrate	0.05%
Methylprednisolone aceponate	0.1%
Triamcinolone acetonide	0.02%
Potent	
Betamethasone dipropionate	0.05%
Betamethasone valerate	0.1%
Mometasone furoate	0.1%
Triamcinolone acetonide	0.1%
Very potent	
Betamethasone dipropionate	0.05% in optimised vehicle
Clobetasol propionate	0.05%

Appendix 3

Physiology of the Adrenal Gland:



Cross sectional anatomy of the adrenal gland, (Gray's Anatomy 1918).

The Adrenal Cortex:

This consists of **3 zones**:

- Zona glomerulosa:
  - ♥ This layer is the main site for production of the **mineralocorticoid** hormone, **aldosterone.**
- Zona fasciculata:
  - ♥ This layer is the main site for production of the **glucocorticoids** (mainly **cortisol**).

- Zona reticularis:
    - ♥ This layer is the main site for production of **androgens**; mainly dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione (the precursor to testosterone) in humans.

The Adrenal Medulla:

- The chromaffin cells of the medulla are the body's main source of the circulating catecholamines; **adrenaline** (80 %) and **noradrenaline** (20 %).

References

1 eTG - March 2015

2. Methylprednisolone in Australian Medicines Handbook, Accessed February 2015

3. Methylprednisolone in MIMs 1 May 2011.

4. RCH Clinical Guidelines - Asthma March 2014.

Dr J. Hayes
April 2015.