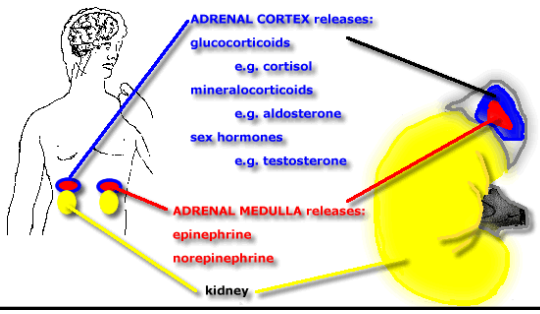
Adrenocorticoids

Adrenocorticoids

- Hormones secreted by the adrenal glands which are cap-like structures located above the kidneys.
- The inner core (medulla) of the gland secretes catecholamines, whereas the shell (cortex) of the gland synthesizes steroid hormones known as the adrenocorticoids.
- The adrenocorticoid steroids include the
  - Glucocorticoids
  - Mineralocorticoids
  - Sex hormones
    - Estrogens
    - Progestins
    - Androgens



Function

- Glucocorticoids are endogenous compounds that have an effect on
  - carbohydrate, lipid, and protein metabolism
  - exhibit **anti-inflammatory**, desensitizing, and antiallergy action.
  - **immunodepressants**,
- Mineralocorticoids are endogenous compounds that have an effect on
  - fluid and electrolytic balance in the body, mainly by promoting sodium retention in the kidney.
- Sex hormones are hormones that affect the
  - reproductive system.

Fate

- Biosynthesis
  - All the adrenocorticoids are biosynthesized mainly from cholesterol
- Metabolism or Steroid hormone catabolism take place primarily in the liver.
  - reduction of double bonds at positions 4 and 5 or 5 and 6
  - epimerization of 3α-hydroxyl groups
  - reduction of 3-keto groups to the 3α-hydroxyl function, and
  - oxidative removal of side chains
- Excretion
  - the products found in the urine and feces depend on the hormone undergoing catabolism

Classification

Sex hormones
Androsterone
Androstendion
Estrone
Progesterone

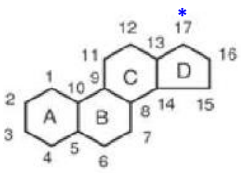
Adrenocortical Inhibitors

Glucocorticoids
Hydrocortisone, 11-dehydrocorticosterone
Corticosterone

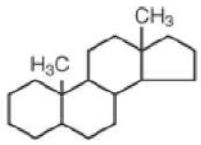
Mineralocorticoids
Aldosterone
11-deoxycorticosterone
11-deoxy-17-oxycorticosterone,

All the adrenocorticoids share a common structural backbone - the **steroid nucleus**
However, the variations in the structures provide specificity for the unique molecular targets.

Structure



Steroid template



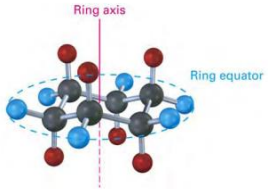
Steroid backbone

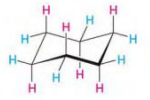
* side chain

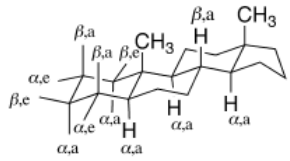
- Chemical structure
  - Four fused rings (A, B, C, and D)
  - Cyclopentano-perhydrophenanthrenes
- Numbering
  - Numbering begins in ring A at C1 and proceeds around rings A and B to C10, then into ring C beginning with C11, and snakes around rings C and D to C17.
  - The angular methyl groups are numbered 18 (attached to C13) and 19 (attached to C10).
  - The 17 side chain begins with C20, and the numbering finishes in sequential order.

Stereochemistry

- α, β
  - α- substituents (and H) which are below the plane of the rings
  - β - substituents (and H) above the plane of the rings or lying closer to the "top"
- Axial/Equatorial
  - Axial - substituents (and H) which are along the ring axis
  - Equatorial - substituents (and H) which are along the plane of the equator





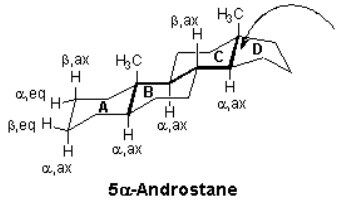


5α-Androstane

- Both α - and β -substituents may be axial or equatorial

Stereochemistry at C5

- The stereochemistry of the hydrogen at C-5 (if present) must always be included in the name of the steroid since geometry at this ring fusion determines the shape of the steroid.

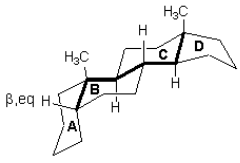


5α-Androstane

Heavy bonds are the steroid**backbone**. The *geometry* of the backbone determines the **shape** of the steroid.

A/B-*trans* (Describes the ring fusion)
B/D-*anti* (Describes the geometry for bonds connecting non-fused rings)

- When drawing steroids it is necessary to draw in all hydrogens along the steroid backbone.

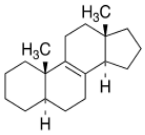


5β-Androstane

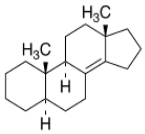
A/B-*cis* (Describes the geometry of the A/B ring fusion)

Double bond

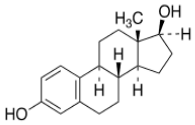
- Double bonds are specified with the number of the position from which the bond originates followed by -ene.
- Both carbons are indicated in the name if the double bond is not between sequentially numbered carbons (e.g., 5-androst-8(14)-ene or 5-8(14)-androstene
  - Eg. Double bonds from C8 may go toward C9 or C14,



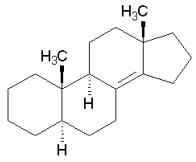
5α-Androst-8-ene or
5α-Δ^{8}-Androstene



5α-Androst-8(14)-ene
5α-$\Delta^{8(14)}$-Androstene



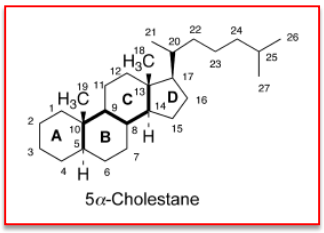
17β-estradiol
(Estra-1,3,5(10)-triene-3,17β-diol)



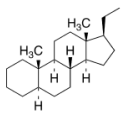
5α-$\Delta^{8(14)}$-Androstene
or 5a-Androst-8(14)-ene

- The symbol Δ is often is used to designate a C-C double bond in a steroid.
- If the C=C is between positions 4 and 5, the compound is referred to as a C4-steroid.
  If the C=C is between positions 5 and 10, the compound is designated a C5(10)-steroid.

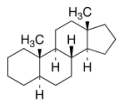
Nomenclature



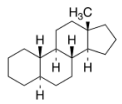
5α-Cholestane



5α-Pregnane

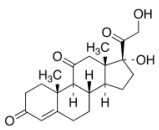


5α-Androstane

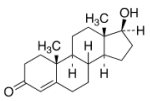


5α-Estrane

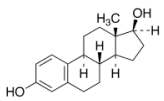
Examples of Common and Systematic Names



Cortisone
(17,21-Dihydroxypregn-4-ene-3,11,20-trione)



Testosterone
(17β-Hydroxyandrost-4-en-3-one)



17β-estradiol
(Estra-1,3,5(10)-triene-3,17β-diol)

Nearly all steroids are named as derivatives of cholestane, androstane, pregnane, or estrane. The standard system of numbering is illustrated with 5-cholestane (the H8 and H9 protons have been omitted here for clarity).

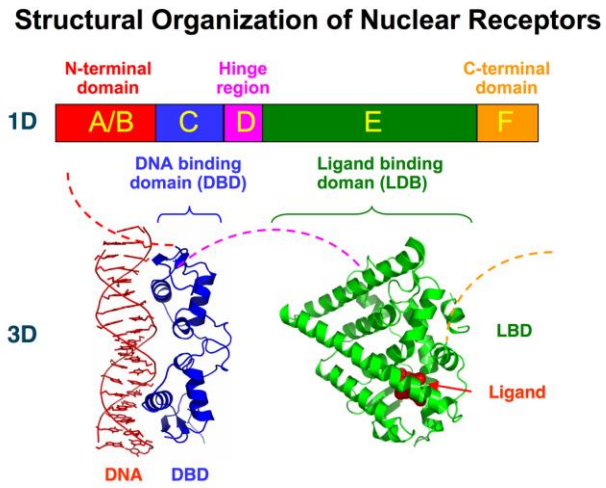
Pharmacokinetics

- Steroids reversibly bind with two proteins in the plasma:
  - corticosteroid-binding globulin, which is a specific α2-globulin;
  - albumin, which has nonspecific activity and a weakly expressed affinity to steroids.
- Free steroids that do not bind with plasma proteins enter target cells by passive diffusion and bind with cytoplasmic soluble-binding proteins (acceptor region), forming a steroid–protein complex.
- This enters the nucleus, where it interacts with steroid receptors on chromatin.

Steroid receptor

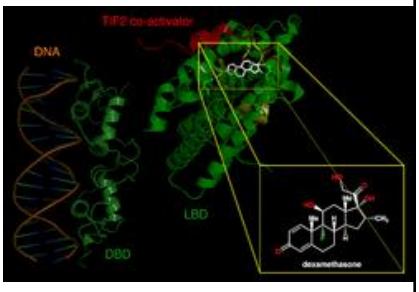
- Steroid receptors belong to the family of nuclear receptors.
- Nuclear receptors have the ability to directly bind to DNA and regulate the expression of adjacent genes, hence these receptors are classified as transcription factors
- The regulation of gene expression by nuclear receptors generally only happens when a specific ligand is present.
- More specifically, ligand binding to a nuclear receptor results in a conformational change in the receptor, which, in turn, activates the receptor, resulting in up-regulation or down-regulation of gene expression.

Nuclear receptors



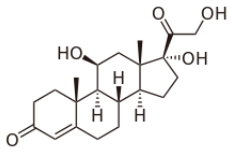
Steroid receptors

- The GR is expressed in almost every cell in the body and regulates genes controlling the development, metabolism, and immune response.
- The unbound receptor resides in the cytosol of the cell complexed with a variety of proteins including heat shock proteins.
- The endogenous glucocorticoid hormone cortisol diffuses through the cell membrane into the cytoplasm and binds to the glucocorticoid receptor (GR) resulting in release of the heat shock proteins.
- After the receptor is bound to glucocorticoid, the receptor-glucorticoid complex can take either of two paths.
- The activated GR complex
  - up-regulates the expression of anti-inflammatory proteins (lipocortin) in the nucleus or
  - represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus).

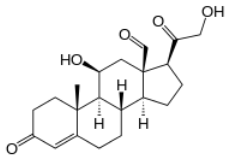


Specificity

- The binding pockets of different nuclear receptors differ in key residues leading to specificity in binding
- The structures of the Glucocorticoid receptor (GR) and MR LBDs also reveal the features that provide the specificities for these two receptors.
- In the LBD of the GR, a key glutamine residue is replaced by a leucine in the MR.
  - the glutamine side chain can hydrogen bond with the 17-hydroxyl, which is seen in GRs, but is absent in aldosterone.



Cortisol
(GR)



Aldosterone
(MR)

Therapeutics

- Corticosteroids do not heal illnesses, but they are widely used in various conditions when it is necessary to utilize their anti-inflammatory, immunosuppressant, and mineralocorticoid properties.
  - Corticosteroids can be used in vital situations for asthma, severe allergic reactions, and transplant rejections.
  - They are effective in noninfectious granulomatous diseases such as sarcoidosis, collagen vascular disease, rheumatoid arthritis and leukemia.
  - Steroids are used as lotions, ointments, etc. in treating a number of dermatological and ophthalmologic diseases.
- In addition, they are used in replacement therapy for patients who have adrenal insufficiency.
- Corticosteroids are very powerful drugs whose side effects are practically impossible to avoid. Therefore, they should be used in the smallest effective doses, and for a very short time.

Properties

Chemical/Physical properties

- Because the steroids have 17 or more carbon atoms, it is not surprising that they tend to be water insoluble.
- Addition of hydroxyls or other polar groups (or decreasing carbons) increases water solubility slightly, as expected.
- Salts are the most water soluble.

Changes to modify pharmacokinetics

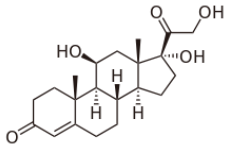
- Steroids can be made more lipid soluble or more water soluble by making suitable ester derivatives of hydroxyl (OH) groups.
  - More lipophilicity desired
    - Derivatives with increased lipid solubility are often made to decrease the release rate of the drug from intramuscular (IM) injection sites (i.e., in depot preparations).
    - More lipid-soluble derivatives also have improved skin absorption properties and thus, are preferred for dermatological preparations.
  - More hydrophilicity desired
    - Derivatives with increased water solubility are needed for intravenous preparations.
- Since hydrolyzing enzymes are found throughout mammalian cells especially in the liver, converting OH groups to esters does not significantly modify the activity of most compounds.

Glucocorticosteroids

- **Metabolism**
  - Glucocorticoids are compounds that act first and foremost on the metabolism of carbohydrates, proteins, and fats, and to some degree on the electrolytic and water balance in the body.
- **Immunomodulator**
  - They have effects on practically all tissues and organs, and can change the immune response of the body to various types of influences. They have an effect on the cardiovascular system, the gastrointestinal tract, the skeletal musculature, skin, connective tissue, blood, and the endocrine system.
- **Inflammation, Allergy**
  - The direct indication for using them is severe and chronic adrenal insufficiency. They are used for collagenosis, rheumatoid arthritis, rheumatism, eczema, neurodermatitis, and other skin diseases, allergies, tissue transplants, bronchial asthma, and many other diseases.

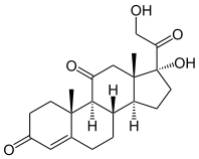
Systemic Glucocorticoids

Hydrocortisone (Cortisol)



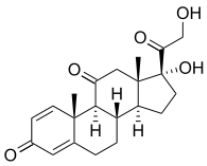
11β,17α,21-trihydroxy pregn-4-en-3,20-dione

Cortisone



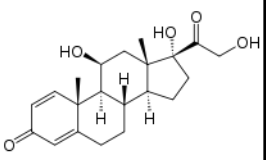
17α,21-dihydroxy pregn-4-en-3,11,20-trione

Prednisone



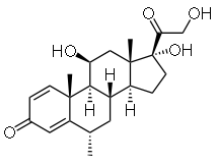
17α,21-dihydroxy pregna-1,4-dien-3,11-20-trione

Prednisolone



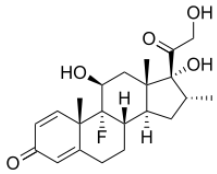
11β,17α,21-trihydroxy pregna-1,4-dien-3,20-dione

Methyl Prednisolone



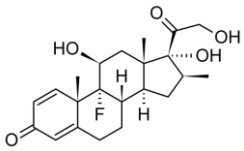
11β,17α,21-trihydroxy-6α-methyl pregna-1, 4-dien-3,20-dione

Dexamethasone



9α-fluoro-16α-methyl-11β,17,21-trihydroxy pregna-1,4-dien-3,20-dione

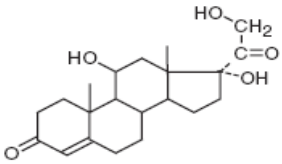
Betamethasone

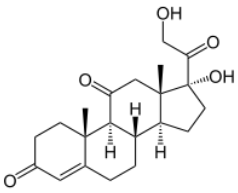


9α-fluoro-16β-methyl-11 β,17,21-trihydroxypregna-1,4-dien-3,20-dione

SAR

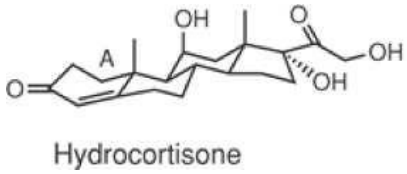
- Minimum structural features for superior glucocorticoid activity
  - a carbonyl group at C3,
  - a double bond between carbons 4 and 5,
  - an oxygen (C=O or β-OH) at carbon 11, and
  - a β-ketol side chain at position 17
  - a α-OH group at position 17



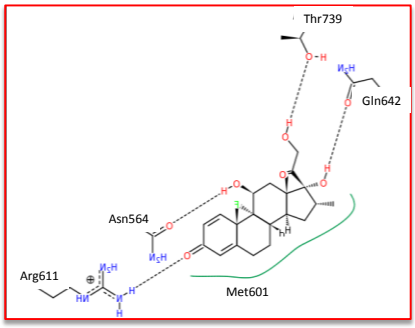


SAR

- Generally, insertion of bulky substituents on the β-side of the molecule abolishes glycogenic activity, whereas insertion on the α-side does not.
- It has been suggested that association of these steroids with receptors involves β-surfaces of rings C and D and the 17β-ketol side chain
- It is possible, however, that association with the α-surface of rings A, C, and D, as well as with the ketol side chain, is essential for sodium-retaining activity.



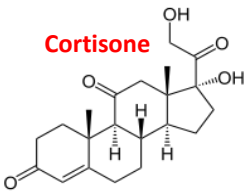
Hydrocortisone



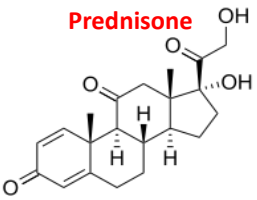
SAR

- Insertion of a double bond between positions 1 and 2 in hydrocortisone
  - increases glucocorticoid activity.
  - The C1-corticoids have a much longer half-life in the blood than hydrocortisone as ring A is much more slowly metabolized,
  - A double bond between positions 1 and 2 (C1-corticoids) also reduces the sodium retention activity of the parent drug (mineralocorticoid activity).
- If, however, a double bond is inserted between positions 9 and 11 (no oxygen function at 11), a decrease in glucocorticoid activity is observed.

Cortisone

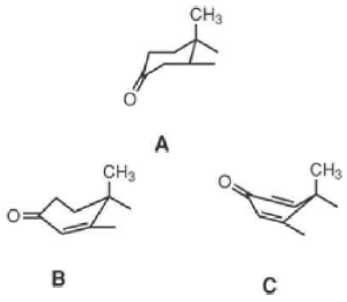


Prednisone



Ring A geometry

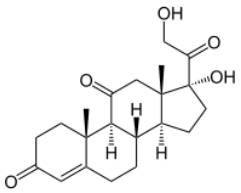
- The increased potency reflects the effect in the change in geometry of ring A caused by the introduction of C1=C2 function on glucocorticoid receptor (GR) affinity and altered pharmacokinetics (primarily metabolism).
- Although the remaining portions of the steroid are essentially unchanged (except for less easily visualized molecular perturbations), the conformation of ring A changes from a chair, as in 5α-pregnan-3-one, to a half-chair (pregn-4-en-3-one) and to a flattened boat (pregna-1,4-dien-3-one) on introduction of unsaturation



The order of GR affinity is

dexamethasone > triamcinolone > methylprednisolone > prednisolone > hydrocortisone
(10X) (5X) (4X) (2X) (1X)

SAR



- Methylcorticoids
  - 2α-methyl derivatives are found to be inactive, whereas the 2α-methyl-9α-fluoro analogues have potent mineralocorticoid activity.
  - A 6α–methyl group increases the duration of action of the steroid eg. methylprednisolone
  - A 16α–methyl group decreases the mineralocorticoid activity of the steroid eg. dexamethasone
  - A 16β–methyl group decreases the mineralocorticoid activity of the steroid eg. betamethasone
- Halo-corticoids
  - A 9α–halo group increases the potency of the steroid with F being the best substituent in this position eg. Dexamethasone, betamethasone, fludrocortisone
  - 9α-fluoro group increases the anti -inflammatory potency, but it also markedly increases the mineralocorticoid potency.
- Hydroxy-corticoids
  - 16α-hydroxy group decreases the mineralocorticoid activity.
- Acetonide (ketal) derivatives at the 16,17-position enhance lipophilicity to provide potent topical anti-inflammatory agents

Glucocorticoids

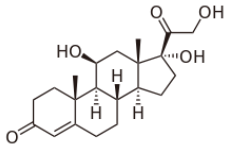
- The primary endogenic glucocorticoids are hydrocortisone and cortisone.
- Numerous synthetic analogs of natural glucocorticoids have been made and used, and they have turned out to be more effective, and currently they have almost completely replaced cortisone
  - Longer duration
  - More potent
  - More glucocorticoid activity
  - Less mineralocorticoid activity
- Glucocorticoids are used orally, intravenously, intramuscularly, as inhalants, and in the form of ointments, creams, and so on.

Systemic glucocorticoids

- Only few corticosteroids are used clinically by the oral route, including
  - hydrocortisone
  - Prednisone
  - prednisolone
  - methylprednisolone
  - dexamethasone
- They are well-absorbed, undergo little first-pass metabolism in the liver, and demonstrate oral bioavailabilities of 70 to 80

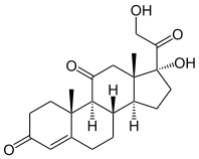
Systemic Glucocorticoids

Hydrocortisone (Cortisol)



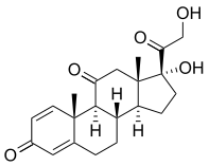
11β,17α,21-trihydroxy pregn-4-en-3,20-dione

Cortisone



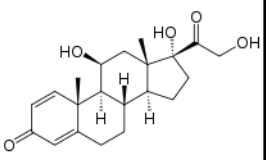
17α,21-dihydroxy pregn-4-en-3,11,20-trione

Prednisone



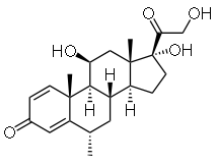
17α,21-dihydroxy pregna-1,4-dien-3,11-20-trione

Prednisolone



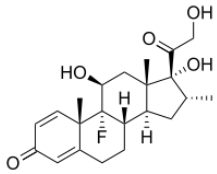
11β,17α,21-trihydroxy pregna-1,4-dien-3,20-dione

Methyl Prednisolone



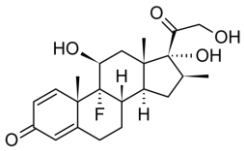
11β,17α,21-trihydroxy-6α-methyl pregna-1, 4-dien-3,20-dione

Dexamethasone



9α-fluoro-16α-methyl-11β,17,21-trihydroxy pregna-1,4-dien-3,20-dione

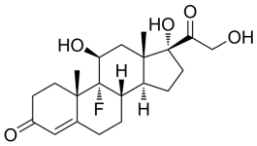
Betamethasone



9α-fluoro-16β-methyl-11 β,17,21-trihydroxypregna-1,4-dien-3,20-dione

Glucocorticoids

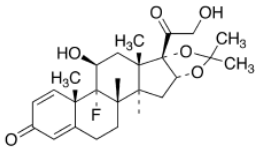
Fludrocortisone acetate



Orally effective

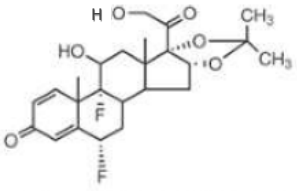
Increase in both **glucocorticoid**- (11 times) and **mineralocorticoid**- (300 to 800 times)

triamcinolone



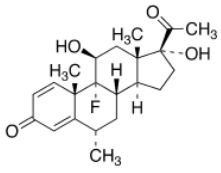
Inhaled and nasal corticosteroid

fluocinolone



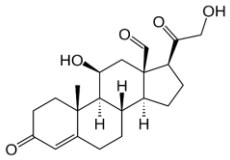
Topical corticosteroid

Flurometholone

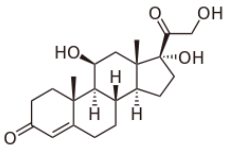


Topical corticosteroid

Aldosterone



Hydrocortisone



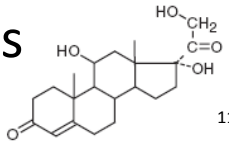
Systemic corticosteroid
- **Oral**
- **Parenteral (salts are given by iv, im route)**

Topical corticosteroid- ophthalmic

11β,17α,21-trihydroxypregn-4-en-3,20-dione

- Also known as Cortisol
- Cyclopentanophenanthrene with
  - Hydroxy groups at C11 and C17α
  - keto-groups at C3 and C20 and
  - an unsaturated bond between C4 and C5 (indicated as Δ^4)
  - presence of an axial β-CO-CH2OH side chain at C17
- Hydrocortisone is used in the form of a free alcohol (speaking of the hydroxyl group at C21), as well as in the form of an acetate, succinate, or phosphate

Therapeutic uses

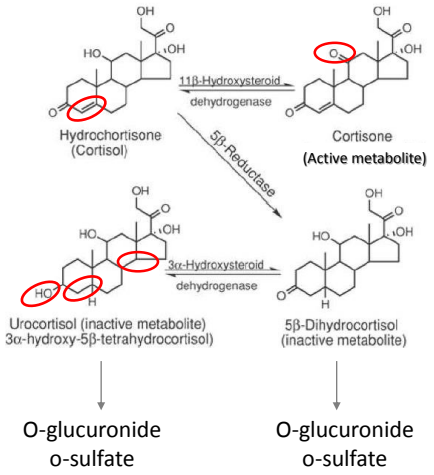


11β,17α,21-trihydroxypregn-4-en-3,20-dione

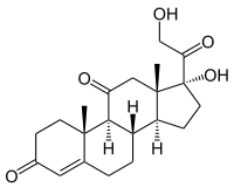
- It raises sugar content in the blood, increases potassium secretion, and lowers sodium excretion from the body.
- Hydrocortisone exhibits anti-allergy, and anti-inflammatory action.
- It exhibits anti-metabolic action and reduces histamine synthesis in the body.
- Hydrocortisone drugs are used for severe inflammation
  - ulcerative colitis
  - rheumatoid, gouty, and psoriatic arthritis
  - collagen and dermatological diseases
  - allergic conditions
  - ophthalmologic
  - gastrointestinal diseases
  - respiratory tract diseases

Metabolism

- Hydrocortisone is metabolized by the liver following administration by any route, with a half-life of approximately l.0 to 1.5 hours.
- Hydrocortisone is mainly excreted in the urine as inactive O-glucuronide conjugates and minor O-sulfate conjugates of urocortisol, 5β-dihydrocortisol, and urocortisone
- The formation of 5β-metabolites from hydrocortisone is characterized by reduction of the 4,5-double bond to a 5β geometry for rings A and B (a *cis* configuration) by 5β-reductase or reduction of the 3-ketone by 3α-hydroxysteroid dehydrogenase (3α-hydroxyl configuration) or 3β-hydroxysteroid dehydrogenase (3β-hydroxyl configuration).
- These reactions represent the major pathways of metabolism for the glucocorticoids and their endogenous counterparts.



Cortisone



17α,21-dihydroxypregn-4-en-3,11,20-trione

Systemic corticosteroid

- **Oral**
- **Parenteral (salts are given by im route)**

- Closely related to Cortisol and differs only in having a 11-keto instead of a 11-hydroxy group
- Cortisone suppresses the immune system, thus reducing inflammation and attendant pain and swelling at the site of the injury.
- Cortisone is used for treatment of inflammatory processes and allergies
- Risks exist, in particular in the long-term use of cortisone causing suppression of immune system.
- Oral use of cortisone has a number of potential systemic side-effects: hyperglycemia, insulin resistance, diabetes mellitus
- It can be administered intravenously, orally, intraarticularly (into a joint), or transcutaneously.

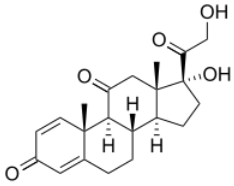
Therapeutic indications

- A cortisone injection is used to give short-term pain relief and reduce the swelling from inflammation of a joint, tendon, or bursa in, for example, the joints of the knee, elbow, and shoulder.
- Cortisone may also be used to deliberately suppress immune response in persons with autoimmune diseases or following an organ transplant to prevent transplant rejection.
- Cortisone is a common treatment for a severe sore throat that occurs commonly with EBV infectious mononucleosis. Cortisone does not decrease the duration of the viral infection, but is used purely to increase the comfort of a patient with trouble speaking or swallowing as a result of the mononucleosis-induced swollen throat.
- Cortisone is also used by dermatologists to relieve the symptoms of eczema and atopic dermatitis

Prednisone, prednisolone and derivatives

- These compounds are known as Δ^1-corticoids, because they contain an additional double bond between positions 1 and 2
- 1-dehydro derivatives of cortisone and hydrocortisone—namely, prednisone and prednisolone—are more potent antirheumatic and antiallergenic agents than the parent compounds and produced fewer undesirable side effects.

Prednisone



Systemic corticosteroid
- **Oral**

Topical corticosteroid

17α,21-dihydroxypregna-1,4-dien-3,11-20-trione

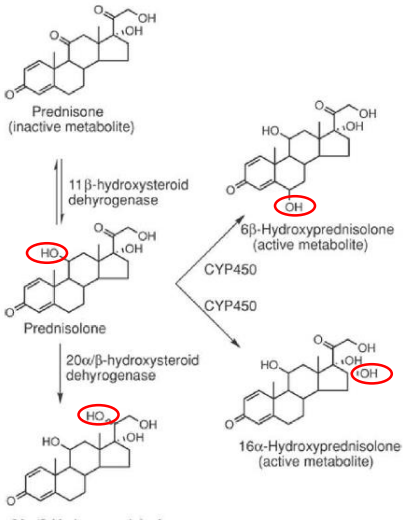
- Prednisone differs from cortisone in the presence of an additional double bond between C1and C2.
- Prednisone is a synthetic corticosteroid drug that is particularly effective as an immunosuppressant drug.
- It is used to treat certain inflammatory diseases (such as moderate allergic reactions) and (at higher doses) some types of cancer, but has significant adverse effects.

Therapeutic indications

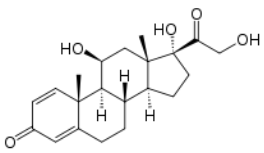
- Prednisone is used for many different autoimmune and inflammatory indications
  - asthma, COPD, rheumatic disorders, allergic disorders, ulcerative colitis and Crohn's disease, adrenocortical insufficiency, hypercalcemia due to cancer, thyroiditis, laryngitis, severe tuberculosis, urticaria (hives), lipid pneumonitis, pericarditis, multiple sclerosis, nephrotic syndrome, lupus, myasthenia gravis, poison oak exposure, Meniere's disease
- Because it suppresses the immune system, it leaves patients more susceptible to infections.
- Prednisone is also used as part of a drug regimen to prevent rejection post organ transplant

Metabolism

- Prednisone and prednisolone are interconvertible by 11β-hydroxysteroid dehydrogenase in the liver.
- For practical purposes, prednisone and prednisolone are equally potent and may be used interchangeably.
- When prednisone or prednisolone is used in the treatment of rheumatoid arthritis, smaller doses are required than with hydrocortisone.
- Prednisolone is metabolized into a number of hydrophilic and less active metabolites except there is no reduction of ring A as with hydrocortisone.
- The major metabolites are primarily excreted as glucuronide conjugates in the urine.



Prednisolone



Systemic corticosteroid
- **Oral**
- **Parenteral (salts are given by im route)**

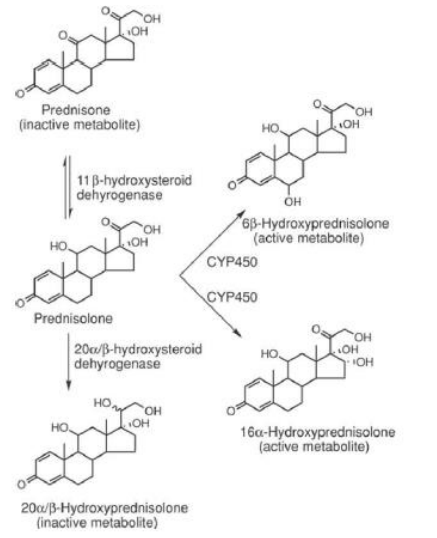
Topical corticosteroid

11β,17α,21-trihydroxypregna-1,4-dien-3,20-dione

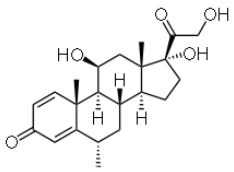
- It is the active metabolite (11-keto to 11-hydroxy) of the drug prednisone and is used especially in patients with hepatic failure, as these individuals are unable to metabolise prednisone into prednisolone.
- It is a synthetic glucocorticoid which is used to treat a variety of inflammatory and auto-immune conditions.

Prednisolone metabolism

- Prednisolone is metabolized into a number of hydrophilic and less active metabolites, except there is no reduction of ring A as with hydrocortisone. The major metabolites (6β- and 16β-hydroxy) are primarily excreted as glucuronide conjugates in the urine.



Methylprednisolone



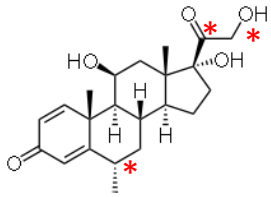
Systemic corticosteroid
- **Oral**
- **Parenteral (salts are given by iv, im route)**

Topical corticosteroid

11β,17α,21-trihydroxy-6α-methylpregna-1, 4-dien-3,20-dione

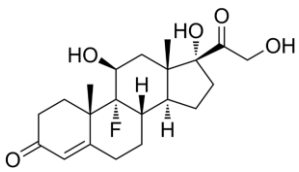
- It differs from prednisolone in the presence of a methyl group at position C6 of the steroid skeleton of the molecule.
- Methylprednisolone is an analog of prednisolone that exhibits a more prolonged effect than prednisolone and cortisone;
- The larger volume of distribution for methylprednisolone compared to prednisolone is thought to result from a combination of increased lipophilicity, decrease in metabolism to 6α-hydroxy, and better tissue penetration.
- In addition, it has practically no mineralocorticosteroid activity and is better tolerated.

Metabolism



- The metabolic pathways include
  - reduction of C20 ketone,
  - oxidation of 17β-ketol group to C21-COOH and C20-COOH
  - 6β-hydroxylation (CYP3A4).

Fludrocortisone



Systemic corticosteroid

- **Oral**

- Glucocorticoid activity is inversely proportional to the size of the halogen at carbon 9 with best activity coming from F
- The 9α-fluoro analogue (fludrocortisone) is approximately 11 times as potent as cortisone acetate
- Glucocorticoid activity is increased 11 times by insertion of the 9α-fluoro substituent, mineralocorticoid activity is increased 300 to 800 times
- Because of its intense sodium-retaining activity, fludrocortisone is contraindicated in all conditions except those that require a high degree of mineralocorticoid activity, because it leads to edema.
- Fludrocortisone acetate is used orally for mineralocorticoid replacement therapy in patients with adrenocortical insufficiency, such as Addison's disease.

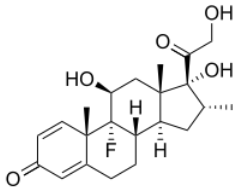
Selective glucocorticoids

- **High glucocorticoid and High mineralocorticoid activity**
  - Cortisone acetate or hydrocortisone usually is the corticosteroid of choice for replacement therapy in patients with adrenocortical insufficiency, because these drugs have both glucocorticoid and mineralocorticoid properties.
  - When used only for anti-inflammatory effect (glucocorticoid) for eg. In treating rheumatoid arthritis, these drugs show mineralocorticoid side effects such as excessive sodium retention and potassium excretion, negative nitrogen balance, increased gastric acidity, edema, and psychosis, are exaggerated manifestations of the normal metabolic functions of the hormones.
- It was hoped that a compound with **high glucocorticoid and low mineralocorticoid activity** could be synthesized.

High glucocorticoid, Low mineralocorticoid activity

- Minimum structural features for superior glucocorticoid activity were retained
  - a carbonyl group at C3,
  - a double bond between carbons 4 and 5,
  - an oxygen (C=O or β-OH) at carbon 11, and
  - a β-ketol side chain at position 17
- Additional groups were inserted into other positions of the basic steroid structure, with the expectation that these new substituents might modify the glucocorticoid and mineralocorticoid activities of the parent drugs.

Dexamethasone



Systemic corticosteroid
- **Oral**

Topical corticosteroid- ophthalmic

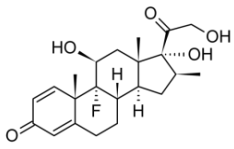
9α-fluoro-16α-methyl-11β,17,21-trihydroxypregna-1,4-dien-3,20-dione

- The distinctive characteristic of dexamethasone is the presence of a fluorine atom at C9 of the steroid ring and a methyl substituent at the C16 alpha position.
- It is 25 times more potent than cortisol (due to 9 fluoro substituent) in its glucocorticoid effect, while having minimal mineralocorticoid effect (due to 16 methyl substituent).

Therapeutic indications

- Dexamethasone is used for the same indications as all corticosteroids; however, it exhibits a significantly more powerful anti-inflammatory and anti-allergic action.
- It is used for circulatory collapse—shock during or after surgical operations, trauma, blood loss, myocardial infarction, and burns.
- It is also used in severe infections—toxemia, vascular collapse in meningococcosis, septicemia, diphtheria, typhoid fever, and peritonitis.
- It is used in severe allergic conditions—asthmatic status, laryngeal edema, severe anaphylactic reactions to medicinal drugs, and pyrogenic reactions.

Betamethasone



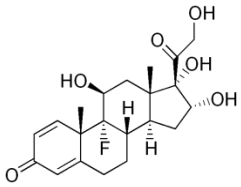
Systemic corticosteroid
- **Oral**
- **Parenteral (salts are given by im route)**

Topical corticosteroid

9α-fluoro-16β-methyl-11 β,17,21-trihydroxypregna-1,4-dien-3,20-dione

- Betamethasone only differs from dexamethasone in the orientation of the methyl group at C16.
- Potent glucocorticoid steroid with anti-inflammatory and immuno-suppressive properties.
- Unlike other drugs with these effects, betamethasone does not cause water retention.
- It is applied as a topical cream, ointment, foam, lotion or gel to treat itching. Betamethasone sodium phosphate is sometimes prescribed as anintramuscular injection (I.M) for itching from various ailments, including allergic reactions to poison ivy and similar plants.

Triamcinolone



Systemic corticosteroid
- **Oral**
- **Parenteral (salts are given by iv, im route)**

Topical corticosteroid - ophthalmic

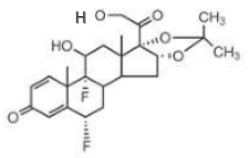
(11β,16α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione

- A natural extension of corticoid research involved examination of compounds containing both a 9α-fluoro group and a double bond between positions 1 and 2.
- Triamcinolone (9-fluoro-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3,20-dione), introduced in 1958, combines the structural features of a C1-corticoid and a 9α-fluoro corticoid
- As mentioned previously, the 9α-fluoro group increases the anti -inflammatory potency, but it also markedly increases the mineralocorticoid potency.
- This is undesirable if the drug is to be used internally for the treatment of rheumatoid arthritis.
- By inserting a 16α-hydroxy group into the molecule, one can decrease the mineralocorticoid activity.

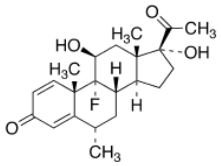
Topical corticosteroids

- Topically applied glucocorticoids are also capable of being systemically absorbed, although to a much smaller extent.
- Once absorbed through the skin, topical corticosteroids are handled through metabolic pathways similar to the systemically administered corticosteroids.
- Circulating levels of the topical glucocorticoids often are well below those after systemic administration but this does not reduce the risk for potential adverse effects from systemic exposure of topical corticosteroids.

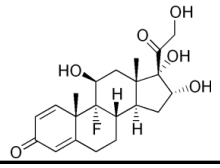
Fluocinolone



Flurometholone



Triamcinolone



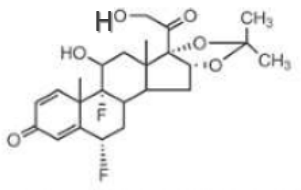
Therapeutic applications

- Inflammation of the eye, mucous membrane
- Chronic hand eczema
- atopic eczema
- Severe eczema
- Psoriasis
- Treatment of thick, chronic lesions caused by psoriasis, lichen simplex chronicus, and discoid lupus erythematosus.

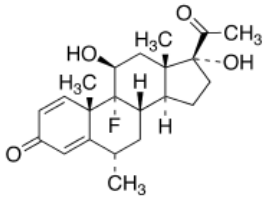
Topical corticosteroids

- Mono- and difluorinated analogues for topical application include fluorometholone (6α-methyl-9α-fluoro; ophthalmic use), fluocinolone acetonide (a 6α, 9α-difluoro-16α,17α-acetonide), and fluocinonide (21-acetate ester of fluocinolone acetonide)
- The acetonide (ketal) derivatives at the 16,17-position enhance lipophilicity to provide potent topical anti-inflammatory agents

Fluocinolone



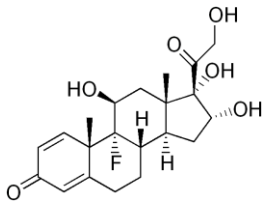
Flurometholone



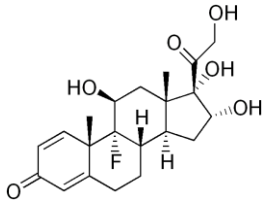
Topical corticosteroids

- Triamcinolone to be used topically is generally dispensed as its more potent and lipophilic acetonide, a 16α,17α-methylenedioxy cyclic ketal or isopropylidene derivative
- It is effective in the treatment of psoriasis and other corticoid-sensitive dermatologic conditions.
- The side effects of the drug, however, have occurred with sufficient frequency to discourage its routine use for rheumatoid patients requiring steroid therapy.
- The drug may be employed advantageously as a special-purpose steroid for instances in which salt and water retention (from other corticoids, hypertension, or cardiac compensation) or excessive appetite and weight gain are problems in management.

Triamcinolone



Inhaled and nasal corticosteroid



Triamcinolone

- Triamcinolone acetonide is also used by inhalation for the treatment of lung diseases (e.g., asthma).