



2. IMMUNOMODULATING DRUGS

====
CORTICOSTEROIDS

DR SHAMS SULEMAN

LEARNING OBJECTIVES

- Describe the role of corticosteroids in General
- Describe the role of corticosteroids in particular as an immunosuppressant
- Describe clinical uses and adverse effects of corticosteroids



ADRENOCORTICAL HORMONES

Basal Secretion

Group	Hormone	Daily
Glucocorticoids	Cortisol	5 – 30 mg
	Corticosterone	2 – 5 mg
Mineralocorticoids	Aldosterone	5 – 150 mcg
	11- deoxycorticosterone	Trace
Sex Hormones		
Androgen	DHEA	15 – 30 mg
Progestogen	Progesterone	0.4 – 0.8 mg
Oestrogen	Oestradiol	Trace

ADRENAL HORMONES: SOURCES

Natural

- Glucocorticoids
 - Cortisol (Hydrocortisone)
 - Corticosterone
- Mineralocorticoids
 - 11-Desoxycorticosterone Acetate (Doca)
 - Aldosterone

Synthetic

GLUCOCORTICOIDS



Signs and Symptoms of Adrenal Crisis

- Headache / dizziness
- Low back pain
- Stomach / leg pain
- Pale skin/shivering
- Severe vomiting / diarrhea
- Lethargy / listlessness
- Loss of appetite
- Neurological deficits
- Confusion
- Low blood sugar
- Low blood pressure
- Seizures
- Cardiovascular collapse
- May present with shock-like symptoms

CLASSIFICATION

1. Short acting
2. Intermediate acting
3. Long acting
4. Inhalational

CLASSIFICATION

Short acting (8-12 hours)

- Hydrocortisone (cortisol)
- Cortisone



CLASSIFICATION

Intermediate acting (12-36 hours)

- Prednisone
- Prednisolone
- Methylprednisolone
- Fluprednisolone
- Paramethasone
- Triamcinolone



CLASSIFICATION

Long acting (36-72 hours)

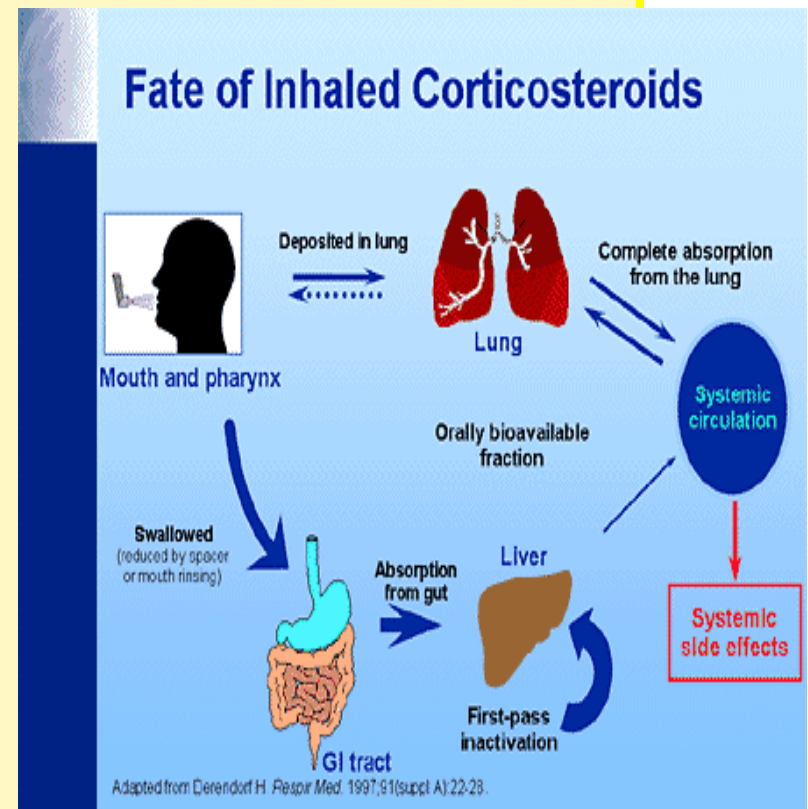
- Betamethasone
- Dexamethasone
- Beclomethasone
- Budesonide
- Fluticasone



CLASSIFICATION

Inhalational

- Triamcinolone
- Beclomethasone
- Budesonide
- Fluticasone
- Ciclesonide
- Flunisolide
- Mometasone



PHARMACOLOGICAL EFFECTS

- ▶ **Corticosteroids** are a class of **steroid hormones** that are produced in the **adrenal cortex**.
- ▶ Corticosteroids are involved in a wide range of **physiologic** systems such as
 - ▶ **stress response**,
 - ▶ **immune response** and regulation of **inflammation**,
 - ▶ **carbohydrate metabolism**,
 - ▶ **protein catabolism**,
 - ▶ **blood electrolyte** levels, and
 - ▶ **behavior**.

PHARMACOLOGICAL EFFECTS

(Extensions of physiological effects)

1. PHYSIOLOGIC EFFECTS

- Direct effects
- Permissive effects
 - ▢ Response of vascular & bronchial smooth muscle to catecholamines
 - ▢ Lipolytic response of fat cells to ACTH, catecholamines, growth hormones

PHARMACOLOGIC EFFECTS

2. METABOLIC EFFECTS

- Carbohydrate – gluconeogenesis, glycogen, decrease glucose utilization, increase blood glucose levels
- Protein (catabolic & anti-anabolic effects) – in lymphoid tissue, muscle, fat, skin
- Lipid – lipolysis, redistribution of body fat (different tissue sensitivity)

PHARMACOLOGIC EFFECTS

- 3. ANTI-INFLAMMATORY EFFECTS**
- 4. IMMUNOSUPPRESSIVE EFFECTS**
- 5. CNS** – sense of well being, insomnia, restlessness, depression, psychosis
- 6. Skeletal muscle:** required for normal function
- 7. CVS:** mineralcorticosteroid –induced changes, enhance vascular reactivity to other vasoactive substances

ANTI-INFLAMMATORY & IMMUNOSUPPRESSIVE ACTION

Reduced manifestations of inflammation

- Decreased release of vasoactive & chemoattractive factors
- Decreased secretion of lipolytic & proteolytic enzymes
- Decreased extravasation of leukocytes
(increased neutrophils in blood, decreased lymphocytes)
- Decreased fibrosis
- Decreased expression of pro-inflammatory cytokines: COX2

Immunosuppressive & anti-allergic actions

- Suppresses all types of hypersensitivity & allergic phenomenon
- At High dose: Interfere with all steps of immunological response
- Causes greater suppression of CMI (graft rejection & delayed hypersensitivity)
- Transplant rejection: ↓ antigen expression from grafted tissues, delay revascularization, ↓ sensitisation of T lymphocytes etc.

CELL TYPE	FACTOR	COMMENTS
Macrophages and monocytes	Arachidonic acid and its metabolites (prostaglandins and leukotrienes)	Mediated by glucocorticoid inhibition of COX-2 and PLA ₂ .
	Cytokines, including: interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α)	Production and release are blocked. The cytokines exert multiple effects on inflammation (e.g., activation of T cells, stimulation of fibroblast proliferation).
	Acute phase reactants	These include the third component of complement.
Endothelial cells	ELAM-1 and ICAM-1	ELAM-1 and ICAM-1: critical for leukocyte localization.
	Acute phase reactants Cytokines (e.g., IL-1) Arachidonic acid derivatives	Same as above, for macrophages and monocytes.
Basophils	Histamine, LTC ₄	IgE-dependent release inhibited by glucocorticoids.
Fibroblasts	Arachidonic acid metabolites	Same as above for macrophages and monocytes. Glucocorticoids also suppress growth factor-induced DNA synthesis and fibroblast proliferation.
Lymphocytes	Cytokines (IL-1, IL-2, IL-3, IL-6, TNF- α , GM-CSF, interferon- γ)	Same as above for macrophages and monocytes.

Glucocorticoids - Pharmacokinetics

- Therapeutically given by various routes – orally, IM, IV, topically
- Hydrocortisone undergoes high first pass metabolism
- Oral bioavailability of synthetic corticoids is high
- Both, endogenous and therapeutically administered GC are bound to Corticosteroid Binding Globulin (CBG)
- Synthetic steroids have to undergo reduction in liver to active compounds
- Metabolized in liver and excreted in urine
- Exogenously administered hydrocortisone has $t_{1/2}$ of 1.5 Hrs

PREPARATIONS

- **Oral:** Tablets
- **Parenteral:** Dexamethasone
 Hydrocortisone
 Pulse therapy =
 Methyl prednisolone
 1 gm IV OD * 3 days
 Depot = Triamcinolone Acetonate
- **Respiratory:**
 Nebulizers
 Revolizers
 Inhalers
- **Topical:**
 Creams/Lotions/Solutions
- **Eye, ear & nasal**
 Creams/Lotions/Solutions



PHARMACOLOGY & BIO EQUIVALENCE

- Usual dosage ===== 1 mg/kg/day
 - Preferably in a single morning dose
 - _____ Impractical !!!!!!!!!!!!!
 - Interconversions
- 1 mg Dexamethasone = 10 mg Prednisolone
- 1 mg Prednisolone = 25 mg Hydrocortisone
- Injection Hydrocortisone == 100mg/250mg/500mg
 - Tab. Prednisolone == 5 mg
 - Tab. Dexamethasone == 0.5 mg
 - Injection 1ml Dexamethasone == 4 mg
= 8 Tablets each of Prednisolone & Dexamethasone



Glucocorticoids - MOA

- Not stored:
 - rate of synthesis = rate of release
- Synthesize rhythmically and controlled by irregular pulses of ACTH, influenced by light and major pulses occur early in the morning and after meals
- Glucocorticoids act via their receptors located in nucleus (GR)
- GRs are widely distributed and located almost in all cells of the body
- They are made up of almost 800 amino acids

Glucocorticoids - MOA

- GR receptors are located in the cytoplasm
- One GR receptor has a DNA binding domain and a ligand binding domain along with stabilizing proteins (HSP 90 and HSP 70)
- This receptor is incapable of activating transcription
- Binding of free steroid molecule to GR forms an unstable compound
- Therefore HSP and other proteins get dissociated
- The S+GR complex enters the nucleus and binds to Glucocorticoids response element (GRE) on gene and regulate transcription by RNA polymerase II and others
- The resulting mRNA is transported to cytoplasm for production of protein and bring about final response

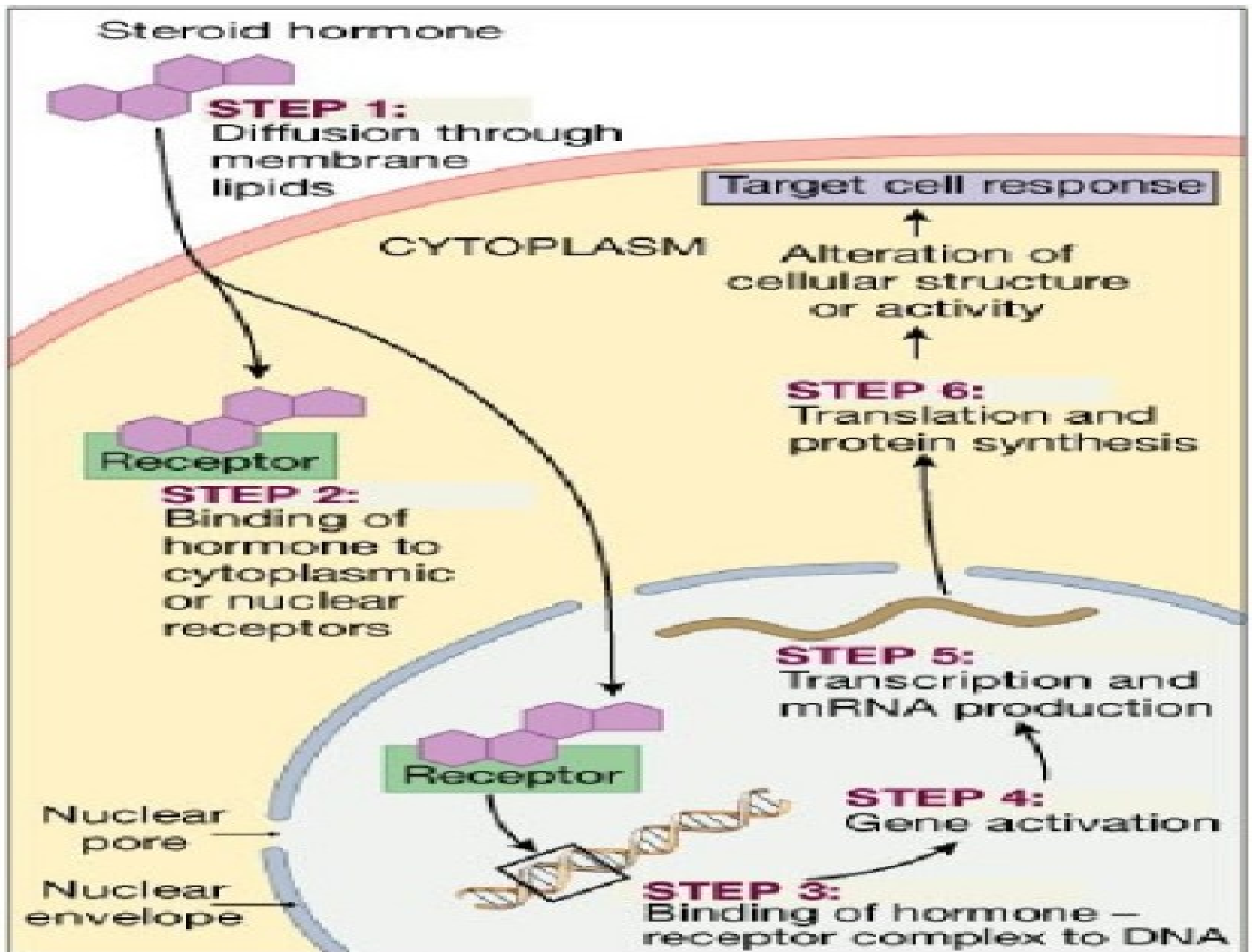
A vertical flowchart with four steps. A thick orange arrow points downwards through the center. The steps are: 1. Hormone enters cell & binds to glucocorticoid receptor (green box). 2. Conformational changes that allow it to dissociate from the Heat shock protein(HSP) (yellow box). 3. Dimerization - dimeric ligand-bound receptor complex is transported into the nucleus (orange box). 4. Interacts with DNA & nuclear proteins through GREs in the promoter of responsive genes (yellow box).

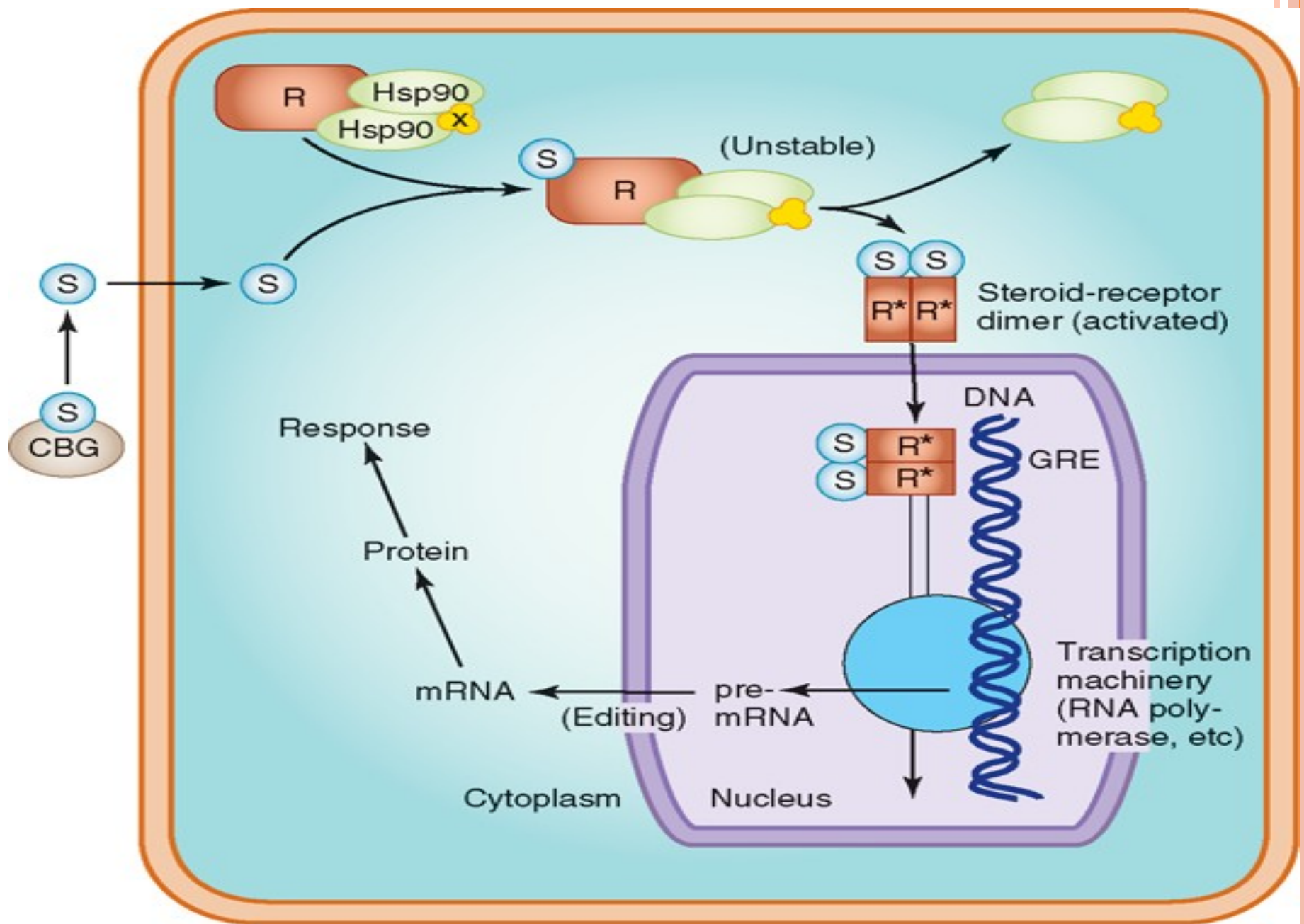
Hormone enters cell & binds to glucocorticoid receptor

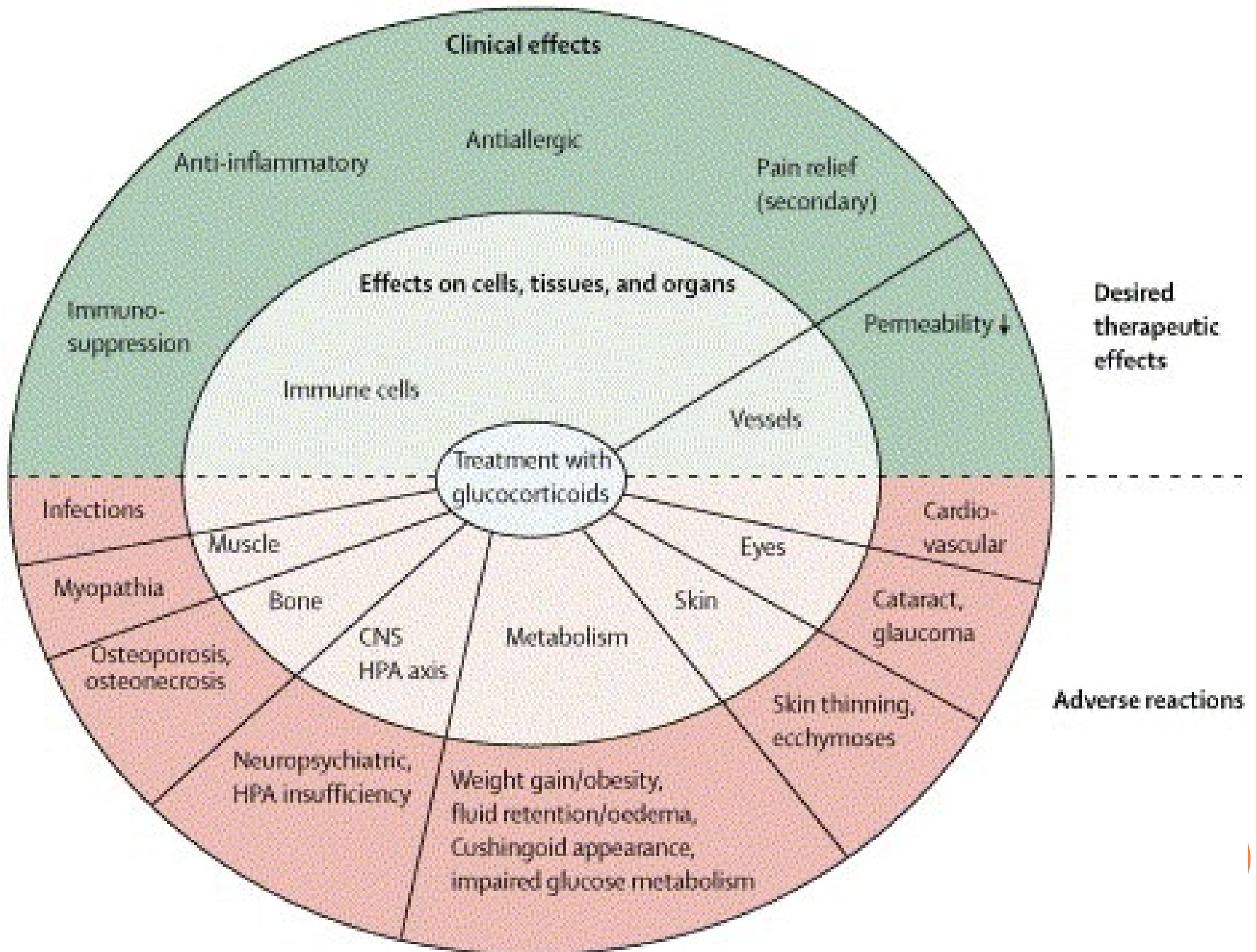
Conformational changes that allow it to dissociate from the Heat shock protein(HSP)

Dimerization - dimeric ligand-bound receptor complex is transported into the nucleus

Interacts with DNA & nuclear proteins through GREs in the promoter of responsive genes







THERAPEUTIC USES

1. Diagnosis & treatment of disturbed adrenal function
2. Prevention of infant respiratory distress syndrome
3. Non-adrenal disorders

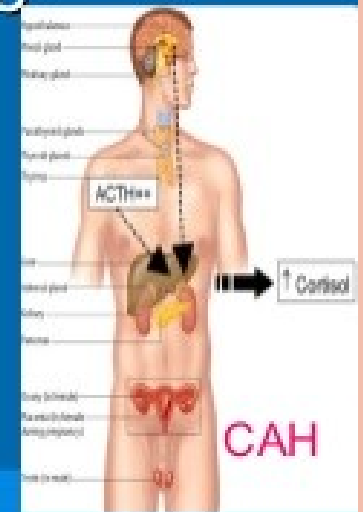
Replacement Therapy

➤ Adrenal insufficiency – acute/chronic

- Abrupt withdrawal of steroid therapy
- Chronic infections – Tuberculosis
- Autoimmune adrenal disease
- Surgery, Hemorrhage and AIDS

➤ Congenital adrenal hyperplasia

- Congenital disorder due to deficiency of 21-hydroxylase enzyme – no cortisol but ACTH – increased androgen production



Addisonian Crisis



Features:

- Severe shock – hypotension, tachycardia
- Fever, abdominal pain, nausea & vomiting
- Hyponatraemia/hyperkalaemia
± hypercalcaemia, hypoglycaemia

Management:

ABCDE assessment

- Correct volume depletion
- Replace glucocorticoids
- Correct metabolic abnormalities
- Treat underlying cause

**100mg
hydrocortisone
I/V every 8hrs**

Replacement Therapy

- Acute adrenal insufficiency
 - IV replacement of sodium chloride and fluid
 - IV hydrocortisone 100 mg stat followed by 100 mg every 8 Hrs – maximal daily rate of secretion(alternatively, dexamethasone can be used)
- Chronic adrenal insufficiency
 - Hydrocortisone
 - Prednisolone or dexamethasone – long acting
 - Fludrocortisone for mineralocorticoid effects
- Congenital adrenal hyperplasia
 - Hydrocortisone 0.6 mg/kg in divided doses – to maintain feedback suppression

EMERGENCY USES

- ❖ Acute severe asthma
- ❖ Raised intracranial pressure
- ❖ Septic shock
- ❖ Acute adrenal insufficiency
- ❖ Anaphylactic shock – 2nd choice

NON-ADRENAL DISORDERS

1. Allergic reactions:

- Urticaria
- Angio -neurotic edema
- Contact dermatitis
- Bee stings
- Serum sickness,
- Drug reactions

Allergic Disorders

- Exhibit a delayed response in allergies (1-2 hrs even in IV injection)
- In anaphylaxis, angioneurotic oedema and serum sickness etc. – adrenaline is the choice
- Seasonal allergies, bee sting, drug allergies –
 - Allergic reactions can be suppressed by corticosteroids as supplements
- Intranasal administration in allergic rhinitis - budesonide and flunisolide

NON-ADRENAL DISORDERS

2. Anti-Inflammatory & Immunosuppression:

- ❑ Inflammatory Arthritides; RA, SLE, Gout, Reactive Arthritis
- ❑ Bronchial Asthma
- ❑ Inflammatory Bowel Disease
- ❑ Bechet's syndrome
- ❑ Nephrotic syndrome
- ❑ Organ transplant
- ❑ Subacute thyroiditis
- ❑ Sarcoidosis, asthma



Anti-inflammatory Uses

- For suppression of inflammatory components in
 - - Rheumatoid arthritis – as adjuvant with NSAIDs in severe cases
 - Osteoarthritis – NSAIDs, intra-articular injection
 - Rheumatic fever – severe cases with carditis and CHF
 - Gout – NSAID failed cases and colchicine failed cases – intra-articular injection
 - Vasculitic disorders: Polyarteritis nodosa

Intra-articular Steroids

Can be used in inflammatory
Non-inflammatory diseases

- Knee joint
- Shoulder joint
- Tennis elbow
- Carpal tunnel syndrome



Bronchial Asthma

- The increased recognition of the immunological and inflammatory nature of Bronchial asthma has led to the use of corticosteroids
- In severe asthma attacks
 - IV hydrocortisone Methylprednisolone
 - Oral prednisolone
- Acute attacks:
 - *Inhaled beclmethasone, budesonide, flunisolide
alone or combined with beta-2 agonists/ipratropium
 - *Oral steroids



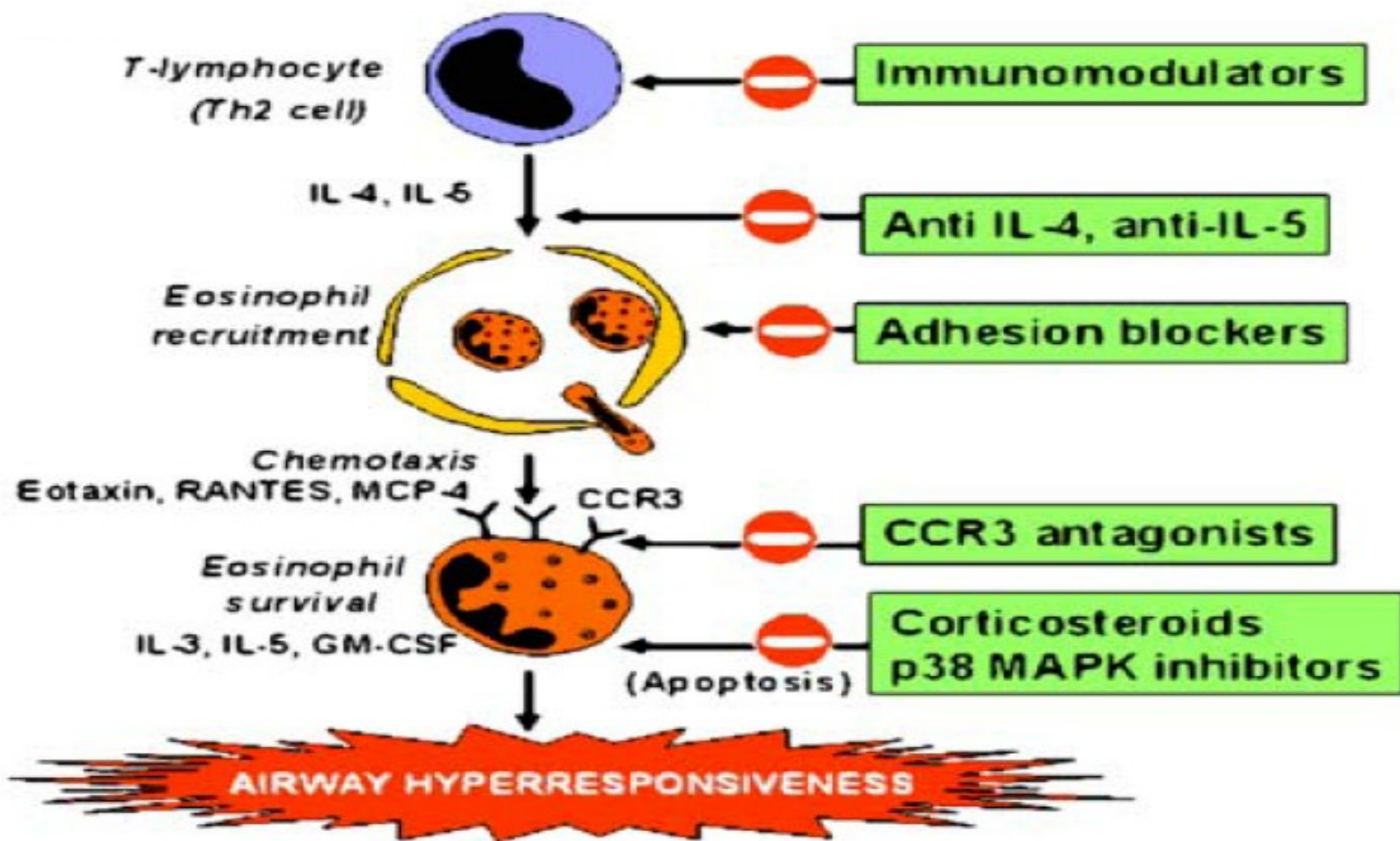
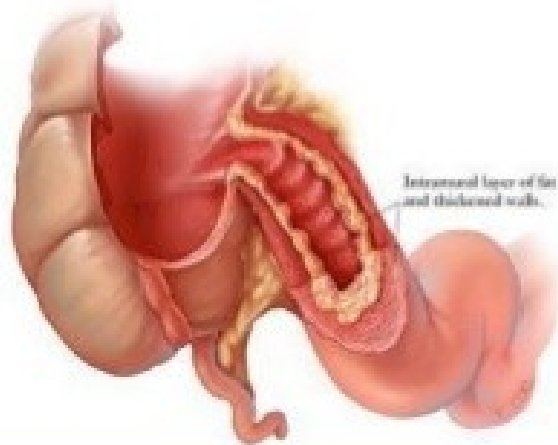


Figure 1. Inhibition of eosinophilic inflammation. Several strategies are possible to inhibit eosinophil inflammation in tissues, including immunomodulators (e.g., cyclosporin), inhibitors of proinflammatory cytokines (e.g., IL-4 and IL-5), inhibition of critical adhesion molecules (e.g., VLA4), blockade of chemokine receptors on eosinophils (e.g., CCR3) and induction of apoptosis (e.g., by corticosteroids and p38 MAP kinase inhibitors).



GIT

Features of Inflammatory Bowel Disease

Colon - Crohn's and Ulcerative Colitis

Toxic Disease

High fever
Distension
Pain

Diffuse Disease

Diarrhea
Bleeding
Fever
Malaise

Rectal Disease

Urgency
Pain
Bleeding

Stricture

Distension
Pain/Cramps
Loud bowel sounds
Changes in bowel habits



CCFA

➤ Inflammatory conditions of intestine like

- Ulcerative colitis
- Crohn`s disease
- Coeliac disease

(oral therapy or retention enema with hydrocortisone)

➤ May mask the major complications like perforation and peritonitis

Autoimmune diseases



- Autoimmune haemolytic anaemia
- Idiopathic thrombocytopenic purpura
- Active chronic hepatitis, alcoholic hepatitis

(Prednisolone 1-2 mg/kg/day given till remission followed by gradual withdrawal or low dose maintenance)

Renal diseases



- Nephrotic syndrome in children
 - Renal disease secondary to SLE
 - Renal sarcoidosis
 - Glomerulonephritis – membranous type
- (Life saving importance – usually given in large doses followed by tapering to maintenance dose)

Ocular Diseases



- Important drug therapy for suppressing inflammation in eye and preservation of sight
- Topical instillations are used for conditions of the anterior chamber – allergic conjunctivitis, iritis, iridocyclitis and keratitis etc.
- Systemic steroids for the posterior chamber
- Dexamethasone topical 0.1%
- Prednisolone oral
- Contraindicated in viral, fulminant bacterial infections, fungal infections and injuries

NON-ADRENAL USES

3. Stimulation of fetal lung maturation (RESPIRATORY DISTRESS SYNDROME)

- Treatment of mother with large dose of glucocorticoids
- BETAMETHASONE I/M to mother

NON-ADRENAL USES

4. Infections: Gram negative septicemia
5. Leukemia, lymphoma
6. Pemphigus and other skin diseases
7. Use in raised intracranial pressure
8. Mountain sickness
9. Hypercalcemia
10. Multiple sclerosis

Infectious Diseases

- Indicated only in severe infective diseases to tide over crisis or prevent complications
 - AIDS and pneumocystis carinii pneumonia
 - In haemophilus influenza meningitis to reduce neurological complications
 - Tubercular meningitis
 - Lepra reaction
 - Scepticaemia

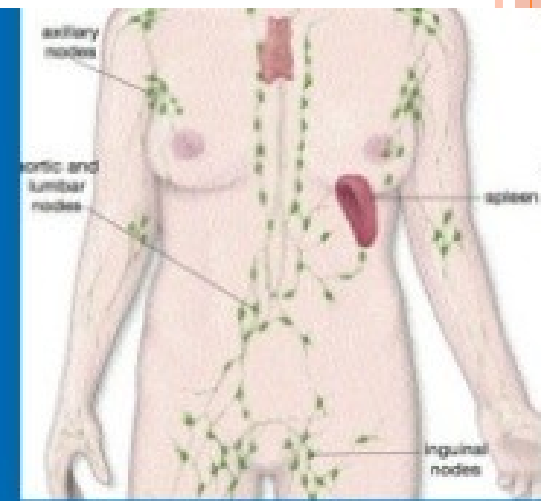
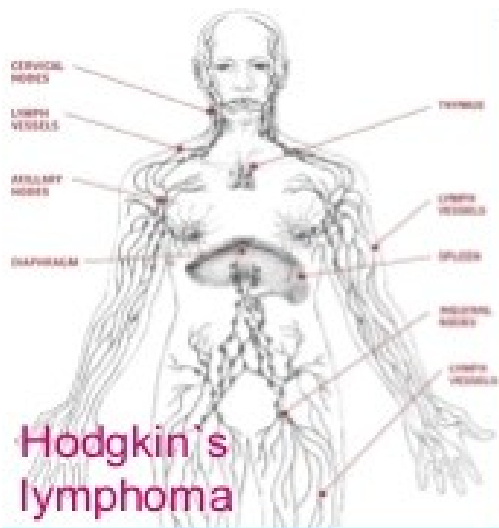


Lepra reaction

INDICATIONS OF CORTICOSTEROIDS (ALONG WITH ATT) IN T.B

- Massive T.B pleural effusion
- Massive T.B pericardial effusion
- T.B ascites (massive)
- T.B meningitis
- T.B choroiditis

Malignancy

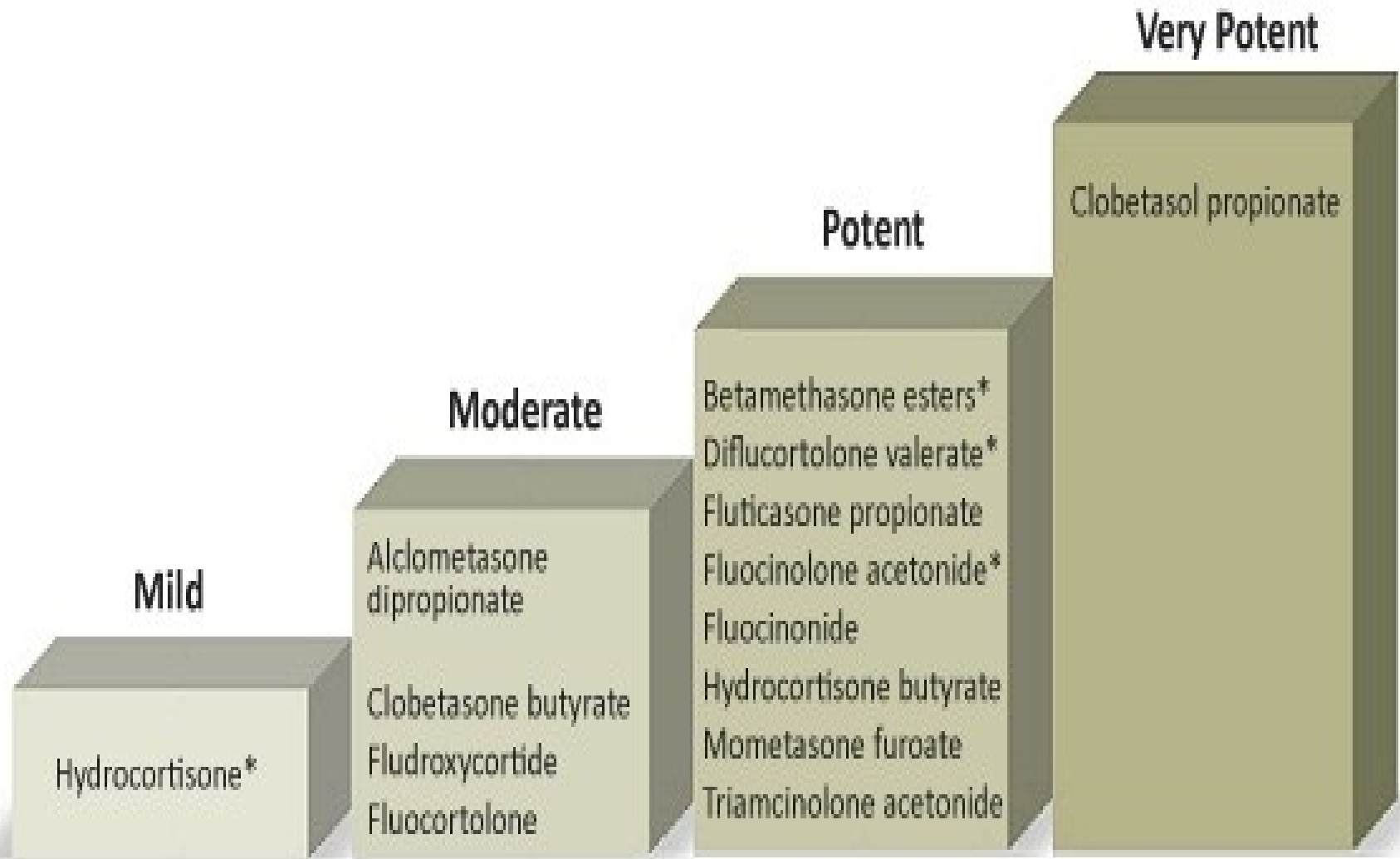


- Essential for combined chemotherapy of
 - Acute lymphatic leukemia
 - Hodgkin's and other lymphomas
 - Hormone responsive breast carcinoma
- Symptomatic relief in other advance malignancies by improving appetite and controlling secondary hypercalcaemia

Skin Diseases



- The largest application of steroid therapy
- Topical forms are widely used in many eczematous skin diseases
- Systemic therapy are also required and may be life saving in
 - Pemphigus vulgaris
 - Exfoliative dermatitis
 - Stevens-Johnson syndrome

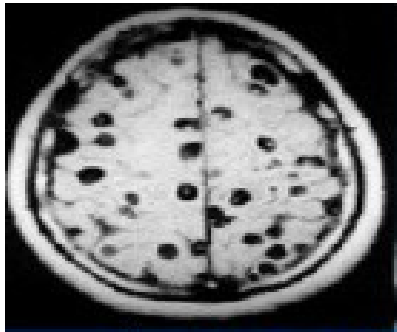


Potency of steroid creams

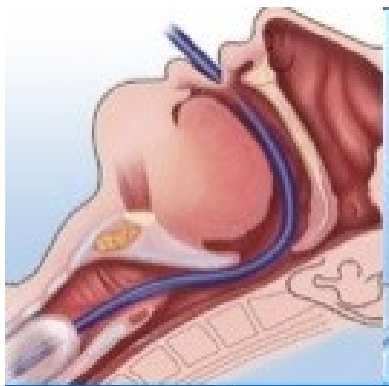
Potency	Generic name	Delivery vehicle and trade name
Class 1: Weak	Hydrocortisone acetate 1%	cream (Biocort ^f ; Stopitch ^g)
	Hydrocortisone acetate 0,5%	cream, ointment (Dilucort ^h)
	Hydrocortisone 1%	cream (Procutan ^c ; Vari-Hydrocortisone ^b)
	Hydrocortisone 0.5%	cream (Skincalm ^h)
Class 2: Moderately Potent	Betamethasone valerate 0.05%	cream (Betnovate Half Strength ^l)
Class 3: Potent	Fluticasone propionate 0.05%	Cream (Cutivate ^k)
	Fluticasone propionate 0.005%	Ointment (Cutivate ^k)
	Hydrocortisone butyrate 0.1%	cream, ointment, lotion (Locoid ^l) topical (Locoid Crelo ^l)
	Betametasone valerate 0.1%	cream (Betnovate ^l ; Repivate ^e ; Adco-Betamethasone ^g ; Vari-Betamethasone ^b) ointment, lotion (Betnovate ^l ; Lenovate ^h ; Persivate ^h)
	Fluocinolone acetonide 0,025%	ointment, gel, cream (Synalar ^l) cream, ointment (Cortoderm ^h)
	Beclomethasone dipropionate 0.025%	cream (Beclate ^e)
	Diflucortolone valerate 0.1%	ointment, cream (Nerisone ^d)
	Methylprednisolone aceponate 0.1%	cream, ointment, milk (Advantan ^d)
	Betamethasone dipropionate 0.05%	cream, ointment (Diprosone ^c)
	Mometasone furoate 0.1%	cream, ointment, lotion (Elocon ^c) cream (Aspen Mometasone ^h ; Mometagen ^p)
Class 4: Very Potent	Clobetasol propionate 0.05%	cream, ointment (Dermovate ⁱ ; Dovate ^h ; Xenovate ^h)

^fAkacia HealthCare, Isando, South Africa; ^gAdcock Ingram, Bryanston, South Africa; ^hAspen Pharmacare, Woodmead, South Africa; ^bSpecpharm Holdings, Halfway House, South Africa; ^cMSD/Schering-Plough South Africa, Midrand, South Africa; ^lSekpharma, Sandton, South Africa; ^kGlaxoSmithKline South Africa, Bryanston, South Africa; ^lAstellas Pharma, Bedfordview South Africa; ^eCipla SA, Bellville, South Africa; ⁱGlenmark Pharmaceuticals South Africa, Midrand, South Africa; ^dBayer, Isando, South Africa; ^pMylan South Africa, Modderfontein, South Africa

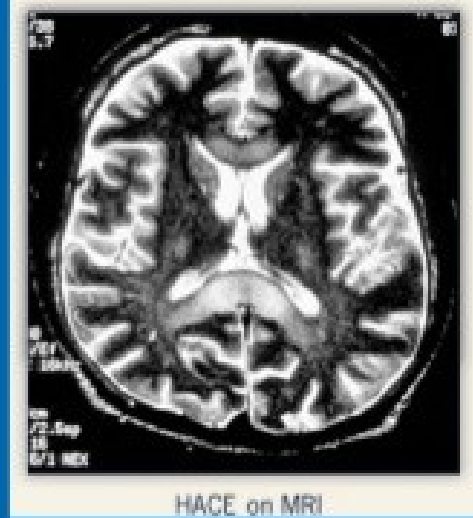
Cerebral Oedema



- Cerebral oedema due to tumors (neoplasms)
- Traumatic and poststroke oedema (?)
(Dexamethasone or betamethasone is preferred because no Na⁺ retaining activity)
- Other CNS conditions - spinal chord injury, Bell`s palsy and neurocysticercosis
- (Oral Prednisolone is the preferred drug)



Other Uses



- Antiemetic – with ondansetron
- Acute mountain sickness
- Aspiration pneumonia, pulmonary oedema from drowning
- Hyperthyroidism – thyroid storm

Adverse Effects

- Two types:
 - From abrupt withdrawal
 - Chronic therapeutic use of high dose
- Withdrawal
 - Flare up of underlying disease
 - Suppression of HPA axis and acute adrenal insufficiency
 - Increased ICT and papilloedema

WITHDRAWAL

- ❑ Not to be stopped abruptly if patient is on hydrocortisone [>25 mg/day] or for $> 2-3$ weeks
- ❑ Severe adrenal crisis & death of patient due to suppression of HPA axis
- ❑ Use short acting steroids with lowest possible doses form
- ❑ Prescribe the whole daily dose of the drugs at once in the morning
- ❑ Switch to alternate day therapy if possible
- ❑ After the long term use intermediate acting steroids allow for more flexible withdrawal

ADVERSE EFFECTS

- ❖ Long term therapy – immunosuppression
- ❖ HPA axis suppression
- ❖ Addison-like symptoms
- Tapering the dose
- Physiological daily replacement (5mg prednisone) until adrenal function is restored

Adverse Effects



Cushing's habitus

- High blood sugar
- High blood pressure
- Vertigo
- Blurred vision
- Female balding
- Menstrual irregularities
- Hirsutism
- Severe depression
- Cognitive impairment
- Emotional instability
- Easy fatiguability



Major Side Effects Associated with Corticosteroid Therapy

Dermatologic and soft tissue

- Skin thinning and purpura
- Cushingoid appearance
- Alopecia
- Acne
- Hirsutism
- Striae
- Hypertrichosis

Eye

- Posterior subcapsular cataract
- Elevated intraocular pressure/glaucoma
- Exophthalmos

Cardiovascular

- Hypertension
- Perturbations of serum lipoproteins
- Premature atherosclerotic disease
- Arrhythmias with pulse infusions

Gastrointestinal

- Gastritis
- Peptic ulcer disease
- Pancreatitis
- Steatohepatitis
- Visceral perforation

Renal

- Hypokalemia
- Fluid volume shifts

Genitourinary and reproductive

- Amenorrhea/infertility
- Intrauterine growth retardation

Bone

- Osteoporosis
- Avascular necrosis

Muscle

- Myopathy

Neuropsychiatric

- Euphoria
- Dysphoria/depression
- Insomnia/akathisia
- Psychosis
- Pseudo tumor cerebri

Endocrine

- Diabetes mellitus
- Hypothalamic-pituitary-adrenal insufficiency

Infectious disease

- Heightened risk of typical infections
- Opportunistic infections
- Herpes zoster

ADVERSE EFFECTS

- ❖ Supraphysiological doses for > 2-3 wks
- ✓ Extensions of pharmacological effects
 - Metabolic
 - Cushing's syndrome
 - GIT
 - Muscle
 - Bone
 - Eye
 - Electrolytes
 - Water retention
 - CNS
 - Growth
- ❖ Withdrawal of therapy
 - HPA axis suppression

ADVERSE EFFECTS

- ❖ Metabolic
 - Hyperglycemia, glycosuria
 - Moon facies, obesity, hyperlipidemia
 - Increased appetite
- ❖ Skin – Increases growth of fine hair, thinning of skin, with striae & bruising, punctate acne
- ❖ GIT – peptic ulcer, pancreatitis, NV
- ❖ Muscle - muscle wasting, myopathy, growth retardation in children

ADVERSE EFFECTS

- ❖ CNS - insomnia, depression, acute psychosis
- ❖ Eye - cataract, raised IOP
- ❖ Bone - Osteoporosis, aseptic necrosis of hip
- ❖ Fluid & electrolytes - Water retention, hypokalemia, alkalosis, hypertension
- ❖ BLOOD – Lymphopenia, leukocytosis

CONTRAINDICATIONS

- Diabetes mellitus
- Peptic ulcer
- Hypertension
- Pregnancy
- Osteoporosis
- Tuberculosis & other infection
- Epilepsy
- Renal failure
- CCF

- Glaucoma
- Cushing's syndrome
- Herpes simplex keratitis
- Psychosis

MISUSE IN SPORTS

- ▢ Normal dose ___ relaxation effects on the respiratory tract
- ▢ In larger dose ___ analgesic effects.
- ▢ Enables athletes for better training and sporting performance.
- ▢ Glucocorticoids are catabolic steroids.
- ▢ **VS** ___ anabolic steroids = increase muscle mass and strength.

CLINICAL PHARMACOLOGY

Adrenocorticosteroid Inhibitors

- **Metyrapone:** 11 beta-hydroxylase enzyme inhibitor – used in Cushing's syndrome and test of pituitary efficiency
- **Aminoglutethimide:** Stops conversion of cholesterol to pregnelone (**Medical adrenalectomy**) – Breast cancers
- **Mifepristone:** Progesterone antagonist
- **Spirolactone:** Aldosterone antagonist
- **Ketoconazole:** Inhibits synthesis of all hormones in testes and adrenal cortex – used in Cushing's syndrome and also in hirsutism in female

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Email address for queries on the topic

drshams11@hotmail.com

