Systemic steroids and Pulse therapy in Dermatology

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Systemic glucocorticoids

- Potent immunosuppressive and anti-inflammatory agents
- Knowledge of basic pharmacology - essential to maximize their efficacy and safety as therapeutic agents

- Major naturally occurring glucocorticoid – Cortisol (hydrocortisone)
- Synthesized from *cholesterol* by the adrenal cortex
- Normally, <5% of circulating cortisol is unbound → the active therapeutic form
- Remainder - inactive

Mechanism of glucocorticoids action

- Passive diffusion of the glucocorticoids through the cell membrane
- F/b binding to soluble receptor proteins in the cytoplasm
- The hormone-receptor complex then moves to the nucleus
- Regulates the transcription of its target genes

Cellular effects of glucocorticoids

- Affect the replication and movement of cells
- Induce monocytopenia, eosinopenia, and lymphocytopenia
- Lymphocytopenia - a redistribution of cells - migration from the circulation to other lymphoid tissues
- Increase in circulating PMN leukocytes - movement of cells from the bone marrow, diminished rate of removal from circulation and possibly inhibition of neutrophil apoptosis
- Macrophage functions, including phagocytosis, antigen processing and cell killing - decreased by cortisol
- This affects immediate and delayed hypersensitivity
- Granulomatous infectious diseases (e.g. tuberculosis) - prone to exacerbation/ relapse during prolonged glucocorticoid therapy
- Antibody-forming cells, B lymphocytes and plasma cells - relatively resistant to effects of glucocorticoids

Most Common Indications of Systemic Steroids

- Serious blistering diseases (pemphigus, bullous pemphigoid, cicatricial pemphigoid, linear immunoglobulin A bullous dermatoses, epidermolysis bullosa acquisita, herpes gestationis, erythema multiforme, toxic epidermal necrolysis)
- Connective tissue diseases (dermatomyositis, systemic lupus erythematosus, mixed connective tissue disease, eosinophilic fasciitis, relapsing polychondritis)
- Vasculitis
- Neutrophilic dermatoses (pyoderma gangrenosum, acute febrile neutrophilic dermatosis, Behçet disease)
- Sarcoidosis
- Type I reactive leprosy
- Hemangioma of infancy
- Panniculitis
- Urticaria/angioedema

Short courses of glucocorticoids

Have been used for

- Severe dermatitis
- Contact dermatitis
- Atopic dermatitis
- Photodermatitis
- Exfoliative dermatitis & Erythrodermas

Fundamental principles of glucocorticoids therapy

- Before glucocorticoids therapy with is begun - the benefit
- Alternative/ adjunctive therapies (azathioprine, cyclophosphamide)
- Especially if long term treatment
- Coexisting illnesses such as diabetes, hypertension and osteoporosis need consideration

Glucocorticoid Equivalencies

	EQUIVALENT DOSE (mg)	GLUCOCORTICOID POTENCY	HPA SUPPRESSION	MINERALOCORTICOID POTENCY
Short-acting Glucocorticoids				
Cortisol	20	1.0	1.0	1.0
Cortisone	25	0.8		0.8
Intermediate-acting Glucocorticoids				
Prednisone	5	4.0	4.0	0.3
Prednisolone	5	5.0		0.3
Triamcinolone	4	5.0	4.0	0
Methylprednisolone	4	5.0	4.0	0
Long-acting Glucocorticoids				
Dexamethasone	0.75	30	17	0
Betamethasone	0.6	25-40		0
Mineralocorticoids				
Fludrocortisone	2	10	12.0	250
Desoxycorticosterone acetate		0		20

Diet during glucocorticoids therapy

- Low in calories, fat and sodium
- High in protein, potassium and calcium as tolerated
- Also consider associated comorbidities
- Protein intake - to reduce steroid-induced nitrogen/ muscle wasting
- Minimize alcohol, coffee and nicotine/ smoking
- Encourage exercise

- Basic preventative measures – to be followed

Potential adverse effects

- A plethora of variety of side effects, when used in high (supra-*physiological*) doses and in long term regimens
- Short courses (2–3 weeks) of GCs - relatively safe

Side effects due to *mineralocorticoids* action

- Hypernatraemia and water retention
- Hypertension and weight gain
- Hypokalaemia, hypocalcaemia

Side effects due to *glucocorticoids* action

- Hyperglycaemia, development of diabetes
- Deterioration of diabetic control
- Dyslipidaemia – hypertriglyceridaemia, hypercholesterolaemia
- Increased appetite, weight gain
- Menstrual irregularities
- Cushingoid features (lipodystrophy) – moon face, ‘buffalo hump’, central obesity (thin limbs, plump trunk)

Cutaneous side effects

- Purpura, bruising, striae, dermal and epidermal atrophy, telangiectasia
- ‘Steroid acne’, rosacea-like syndrome
- Impaired wound healing
- Hirsutism
- Fat atrophy with injected GCs
- Cutaneous infections – staphylococcal and herpetic
- Hyperhidrosis

- Osteoporosis.
  - ➢Osteonecrosis (avascular necrosis).
  - ➢ Growth impairment in children.
- Gastrointestinal
  - ➢Peptic ulceration.
  - ➢Bowel perforation (particular risk with active diverticulitis and recent bowel anastomosis).
  - ➢Pancreatitis.
  - ➢Fatty liver.
  - ➢Gastro-oesophageal reflux.
  - ➢Candidiasis.

- Psychiatric - occur in approximately 6% of patients

➢Psychosis.

➢Euphoria, depression, agitation.

➢Suicidal ideation.

➢Insomnia, nightmares.

➢Irritability, mood lability.

- Ocular

➢Ocular hypertension and glaucoma.

➢Cataracts – *posterior subcapsular*.

➢Central serous chorioretinopathy.

➢Ocular infections, including herpes simplex.

- Neuromuscular

➢ Muscle weakness (*proximal* myopathy).

➢Intracranial hypertension (pseudotumor cerebri).

➢Spinal epidural lipomatosis.

- Infections
  - ➢Tuberculosis reactivation.
  - ➢Opportunistic infections (consider *Pneumocystis jiroveci* pneumonia prophylaxis)

- Prior to initiating GC therapy
- The patient and family members → provided adequate counselling
- Information about the potential adverse effects
- A steroid treatment card - to be provided

Dosage regimens

- Oral administration - Depends on:
  - ➢Clinical diagnosis
  - ➢Severity
  - ➢Presence of other factors
- Prednisolone (or equivalent) at a starting dose of *up to* 1 mg/kg bw/d, ideally given as a single morning dose
- Less likely to cause adverse effects
- Less likely to result in HPA axis suppression

Pulse therapy

- *Oral*
- *IV Pulse therapy* (DCP, DP, methylprednisolone)
- Administration of supra-*pharmacologic* doses of drugs in an intermittent manner - “pulse therapy”
- In pemphigus, pulse therapy refers to intravenous (IV) infusion of high doses of steroids for quicker, better efficacy and to decrease the side effects of long-term steroids

- Feduska et al. first used pulse therapy in 1972 for reversal of renal allograft rejection

- In India, JS Pasricha & Ramji Gupta, 1984

Oral minipulse therapy (OMP)

- Corticosteroids therapy i.e., dexamethasone/betamethasone
- On 2 consecutive days in a week
- Can be continued for up to 3-6 months
- MC Indications – vitiligo, alopecia areata

DCP / DP Pulse therapy

- DCP
- DP
- Methylprednisolone - also used

- *Most common* indication - Pemphigus

Medications

- Dexamethasone (100 mg) – economic option
- or methylprednisolone (20-30 mg/kg)
- With cyclophosphamide 500 mg on 2nd day of pulse

Steps of pulse therapy

Day of pulse	Drug administered
Day 1	Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 h
Day 2	Dexamethasone 100 mg + 500 mg cyclophosphamide in 500 ml of 5% dextrose IV over 2 h
Day 3	Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 h

IV: Intravenous

Phases of pulse therapy

Phase	Lesions	DCP	Oral cyclophosphamide 50 mg daily in between DCP	End point
1	Present	+	+	Till no new lesions
2	Absent	+	+	9 months (original pulse therapy was 6 months)
3	Absent	–	+	9 months (original pulse therapy was 12 months)
4	Absent	–	–	Follow-up once a year for at least 10 years[6]

Modifications

- Dexamethasone‑azathioprine pulse (DAP):
- Cyclophosphamide is replaced by daily oral azathioprine.
- No bolus dose of azathioprine is given during the pulse
- DAP is recommended for unmarried patients
- Who have not completed their family (Cyclophosphamide not given-gonadal failure at a cumulative dose of 30 g and 12 g in women and men)

Common side effects

- Mood and behavior alteration, hyperactivity, psychosis, disorientation and sleep disturbances - 10% patients
- Hyperglycemia, hypokalemia
- Infections
- Hiccups, facial flushing, diarrhea, weakness,
- Generalized swelling, myalgia
- Arrhythmias and shock