CLINICAL PHARMACOLOGY | St George's University of London

Is there a safe and effective way to wean patients off long-term corticosteroids?

Professor Emma Baker

Professor of Clinical Pharmacology

Overview

- Approach to corticosteroid therapy
- Definition of ‘long term use’
- Challenges of deprescribing
  - HPA suppression
  - Psychological dependence
  - Physical dependence without HPA suppression
- Topical corticosteroids

Corticosteroid therapy

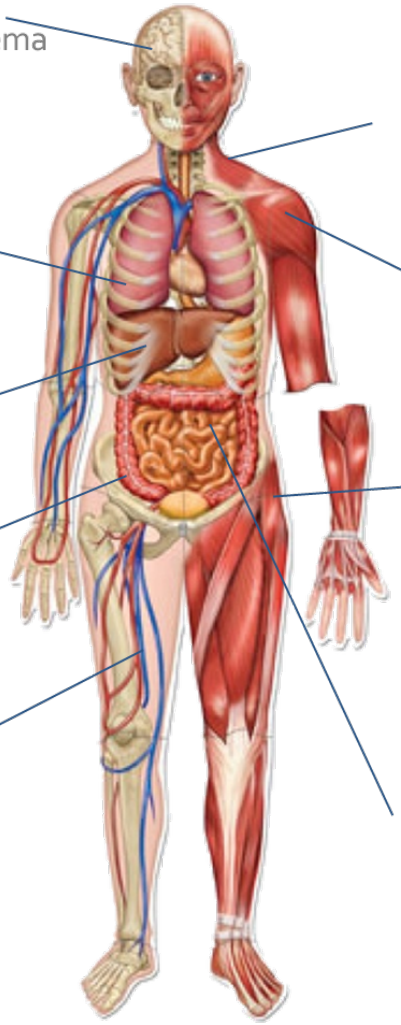
Aim:

- Maximum possible therapeutic benefit with least possible cumulative dosage to minimise adverse effects

Approach:

- Treat until disease is controlled (or not despite adequate trial)
- Withdraw steroids without reactivating disease or causing withdrawal reactions

Indications



Brain
- Cerebral oedema

Skin
- Dermatitis
- Pemphigus

Pulmonary
- Asthma/COPD
- Sarcoid
- Pneumonitis

Musculoskeletal
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Myositis
- Polyarteritis
- Polymyalgia rheumatica

Gastrointestinal
- Inflammatory bowel disease
- Chronic active hepatitis

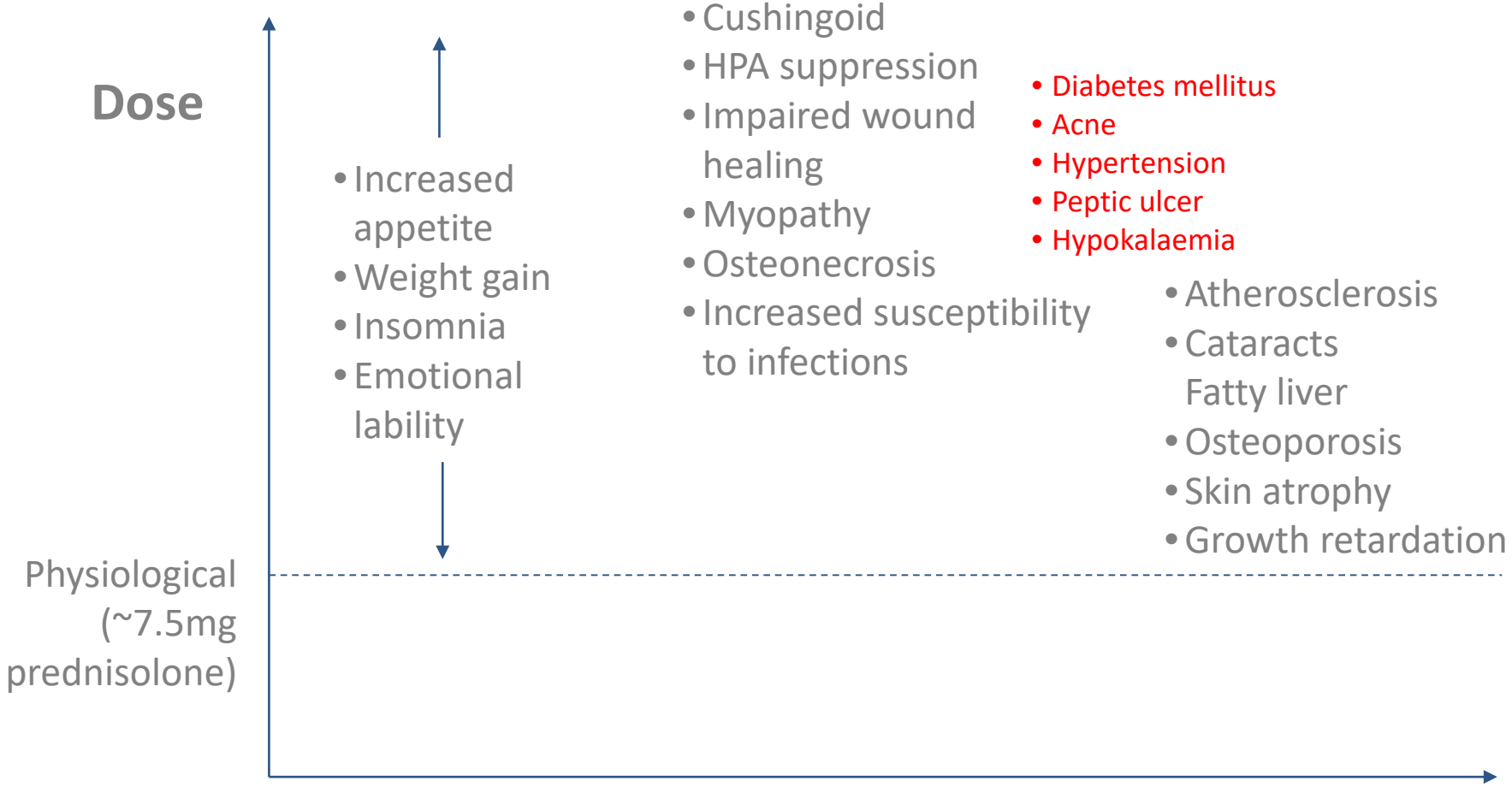
Blood
- Haemolytic anaemias
- Immune thrombocytopaenic purpura
- Leukaemia, lymphoma (with chemotherapy)

Renal
- Nephrotic syndrome
- Graft versus host disease

(~1-3% adults)

Adverse effects

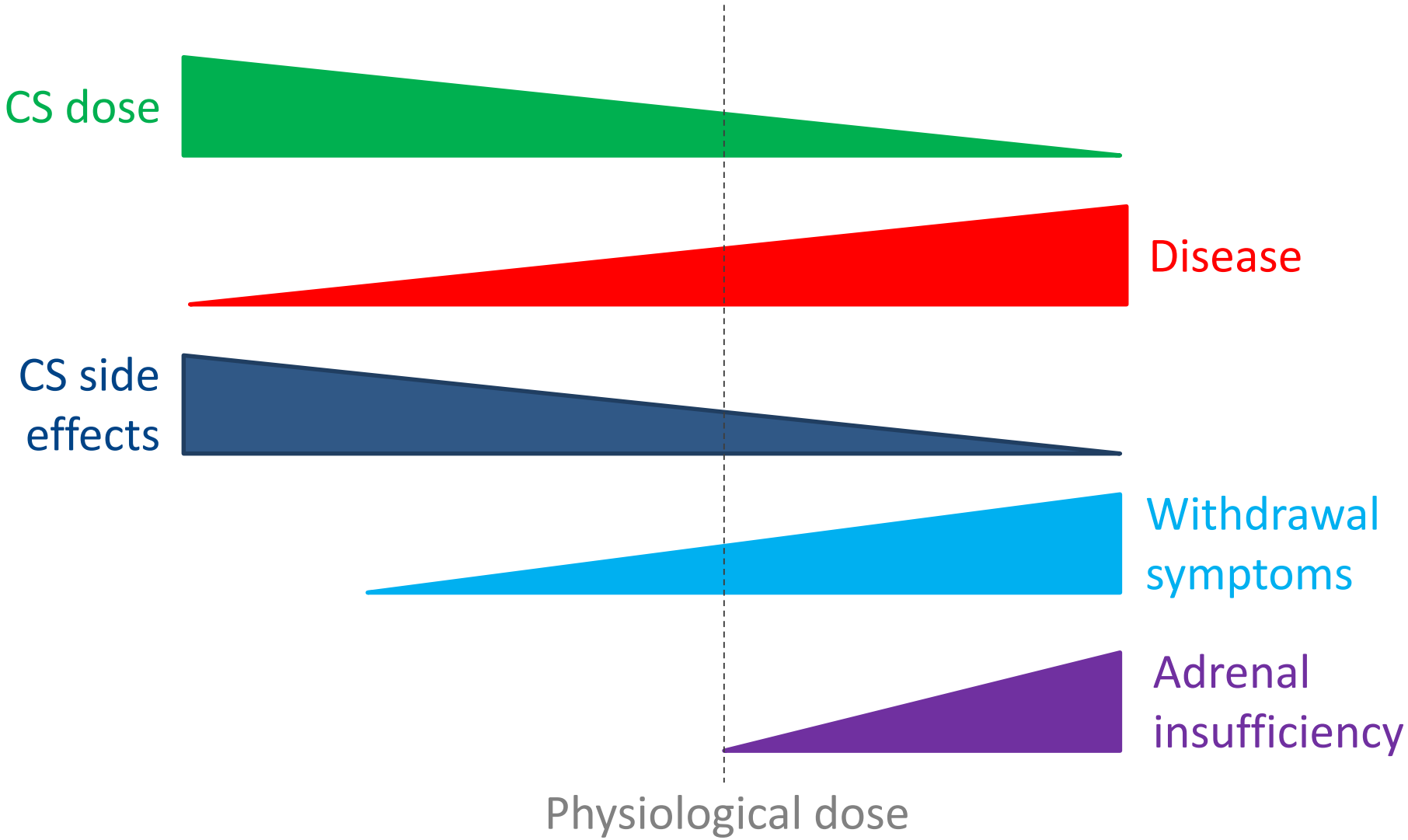
Nicolaides et al https://www.ncbi.nlm.nih.gov/books/NBK279156/



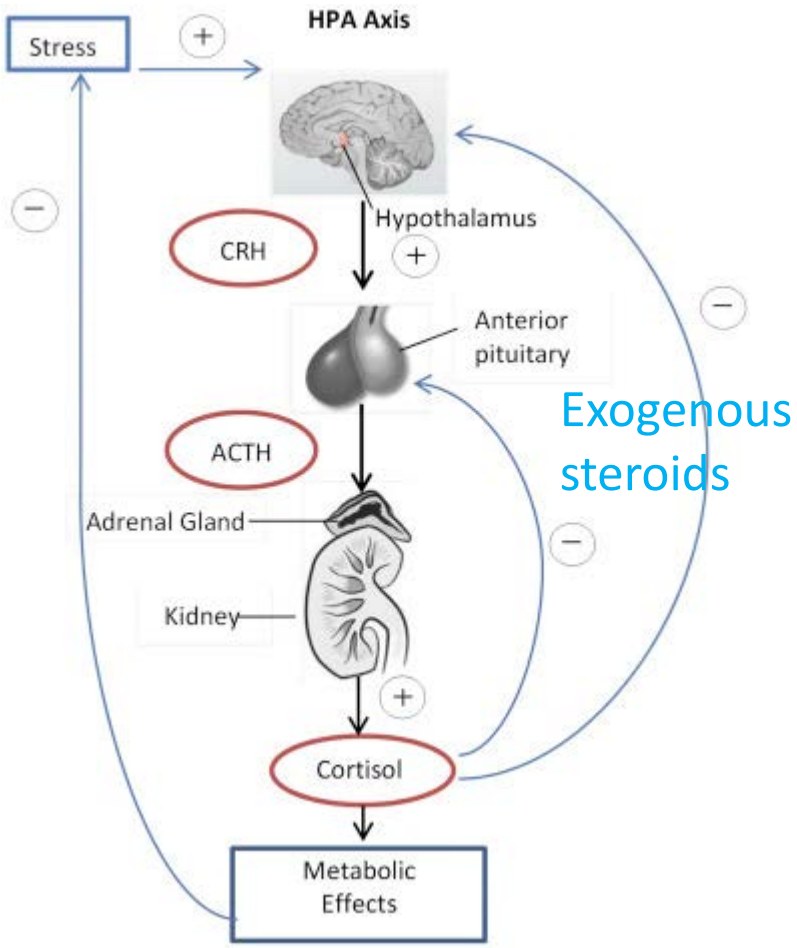
HPA – hypothalamic pituitary adrenal axis

Susceptible patients

Challenges of corticosteroid (CS) withdrawal



Hypothalamic-pituitary-adrenal axis (HPA) suppression



Suppression detectable after a few days

↓

Atrophy of the corticotrophin cells of the anterior pituitary

↓

Adrenal atrophy

Suppression may last for 6-12 months after cessation of external glucocorticoids

May never recover after very long term therapy

Kulkarni et al. Handbook of Behavioral Neuroscience, 2016

Other corticosteroid dependence

- ‘Glucocorticoid withdrawal syndrome’
  - Symptoms of apparent adrenal insufficiency despite normal HPA function and lack of disease recrudescence
  - Can occur when still receiving supraphysiological doses of corticosteroids
  - Mechanisms?
    - Tissue dependence on supraphysiological concentrations of glucocorticoids
    - Relative glucocorticoid resistance
  - Can be self limiting – median duration 10 months
- Psychological dependence
  - ‘vigorous insistence on corticosteroids out of proportion to objective signs and symptoms of inflammation’

Symptoms

Adrenal insufficiency

anorexia, fatigue, nausea, vomiting, dyspnea, fever, arthralgia, myalgia, and orthostatic hypotension, dizziness, fainting, circulatory collapse

Distinguishable only by HPA testing

'Glucocorticoid withdrawal syndrome'

anorexia, nausea, emesis, weight loss, fatigue, myalgias, arthralgias, weakness, headache, abdominal pain, lethargy, postural hypotension, fever, skin desquamation, tachycardia, emotional lability, delirium, psychotic states

Long term corticosteroid use

- Sufficient duration to have caused ‘dependence’
  - HPA axis suppression unlikely
    - <3 weeks, alternate day prednisolone <10 mg
  - HPA axis suppression likely
    - Cushingoid
    - >20mg prednisolone >3 weeks
    - Evening dose prednisolone ≥5mg more than a few weeks
  - HPA axis suppression uncertain
    - 10-20mg prednisolone/day >3 weeks
    - <10 mg prednisolone/day for more than a few weeks

McDonough et al. Curr Opin Rheumatol. 2008;20:131-7

Winifred Brady 68 years

- Started prednisolone for polymyalgia rheumatica 2014
- Dose increases for COPD exacerbations 3-4 x/year
- R Colles fracture 2017, vertebral fractures 2018, 2019
- Currently taking prednisolone 12mg/day
  - lowest dose in 2019 5mg/day
    - aches and pains, worsening breathlessness
    - faint, dizzy and fatigued
- Other medication – adcal D3 one bd, alendronic acid 70mg ow, fostair 100/6 2 puffs bd, tiotropium (handihaler) 18 micrograms od

Q1. How would you manage her long term steroid use?

POLL OPEN

1 Perform a low-dose ACTH stimulation test before changing treatment

55%

2 Reduce prednisolone by 1mg/day every 2-4 weeks to 5mg/day

45%

3 Reduce prednisolone by 2.5mg/day each month to stop

0%

4 Start methotrexate and reduce prednisolone by 1mg/day per month to stop

0%

5 Switch to equivalent dose hydrocortisone for long term adrenal replacement

0%

Steroid taper – rule of thumb

Dose (prednisolone or equivalent)	Taper
>40 mg	5-10mg/day every 1-2 weeks
20-40mg	5mg/day every 1-2 weeks
10-20mg	2.5mg/day every 2-3 weeks
5-10mg	1mg/day every 2-4 weeks
≤5mg	0.5mg/day every 2-4 weeks (alternate daily doses e.g. 4mg/5mg)

What to do about withdrawal failure

- Disease reactivation
  - Check diagnosis – specialist input
  - Try steroid sparing agents
  - Wean to lowest dose that controls symptoms
    - Mild symptom flare, wait 7-10 days, pain control
    - True disease flare increase dose by 10-15%
      - If no better, double dose
    - Resume wean once symptoms reduced

Rheumatology – no real basis for diagnosis

COPD – not an indication for long term steroids – try azithromycin

What to do about withdrawal failure

- Symptoms suggestive of HPA axis suppression
  - Consider testing/endocrine input

Wean to 5mg
Endocrinology referral

HPA axis suppression

- Diagnosis
  - Test patients on ≤5mg prednisolone who can't reduce dose further due to non-disease related symptoms
  - Early morning cortisol +/- short synacthen test
    - Prednisolone cross-reacts (30%) with cortisol assays
    - Withhold for 24 hours or switch to dexamethasone before testing

HPA axis suppression

- Management
  - Mild to moderate adrenal suppression
    - Slow wean, repeat testing
  - Severe adrenal suppression
    - Long term glucocorticoid replacement with lowest dose at which they feel well e.g. 3mg prednisolone
    - Consider changing to hydrocortisone (possibly less adverse effects on bone)
- Sick day rules to prevent adrenal crisis
  - https://www.addisonsdisease.org.uk/newly-diagnosed-sick-day-rules

What to do about withdrawal failure

- If no HPA suppression
  - Non-specific withdrawal symptoms
    - Slow taper, symptom management e.g. with NSAIDs
  - Psychological dependence
    - Other support e.g. counselling, hospice
    - Consider antidepressants

Q2. Which patient is most likely to develop adrenal suppression?

POLL OPEN

1 22-yr-old woman with flexural eczema prescribed hydrocortisone cream 0.5% & Gedarel®30/1502 PO

5.56%

2 28-yr-old man with atopy and nasal polyps prescribed mometasone nasal spray 50 micrograms each nostril od and fexofenadine PO 120mg daily

11.11%

3 35-yr-old woman with asthma and ABPA prescribed Flutiform®501 2 puffs bd and itraconazole 200 mg od

55.56%

4 54-yr-old man with bilateral uveitis and sarcoidosis prescribed dexamethasone 0.1% eye drops 4 hourly

11.11%

5 66-yr-old woman with chronic otitis externa prescribed prednisolone 0.5% ear drops 2-3 every 2-4hours and tamoxifen 20mg PO od

16.67%

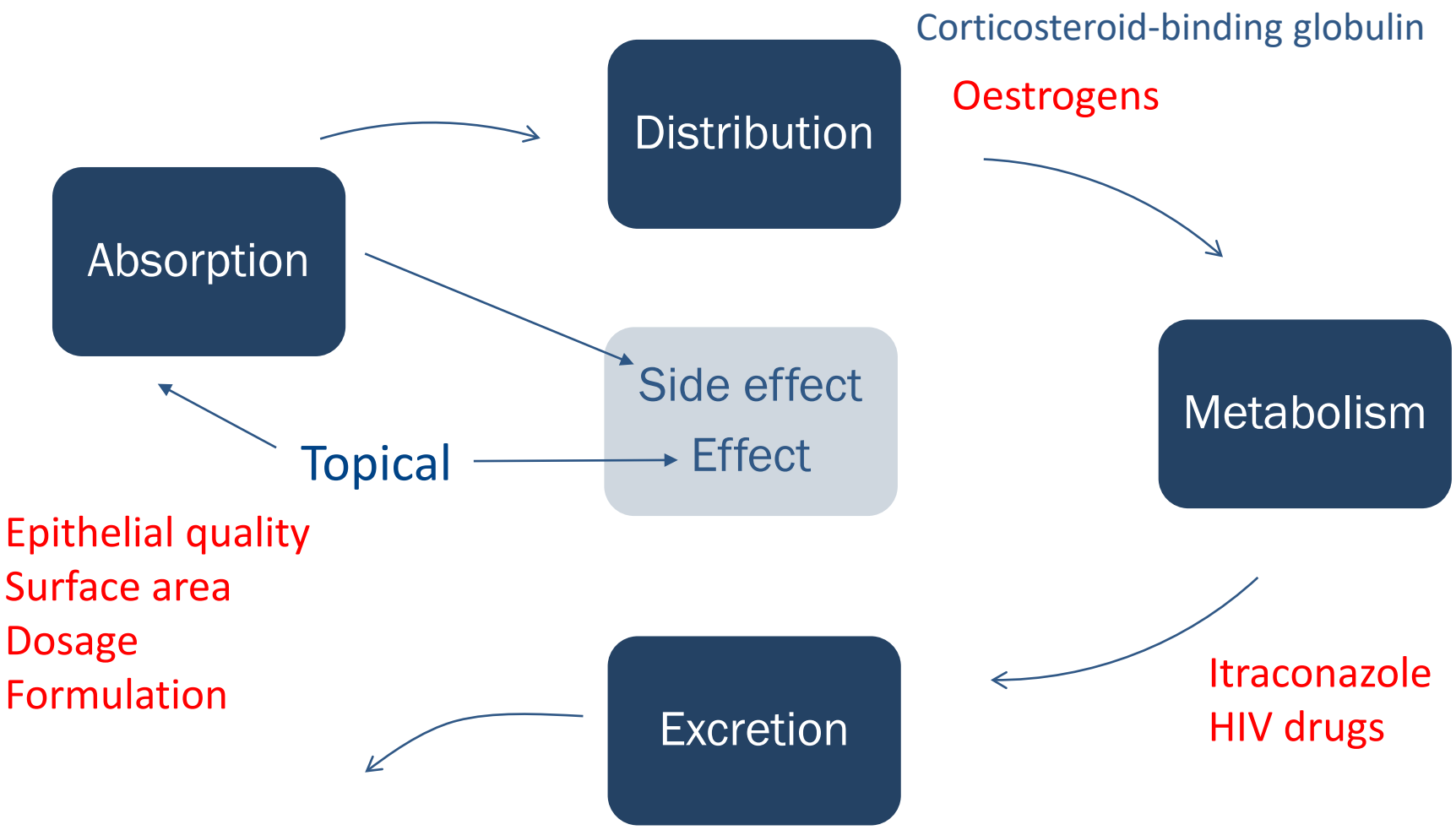
1. Fluticasone 50, formoterol 5
2. Ethinylestradiol 30 micrograms, Desogestrel 150 micrograms

Pharmacodynamics

Corticosteroid	Relative glucocorticoid receptor binding affinity
Fluticasone furoate	2989
Mometasone furoate	2100
Fluticasone propionate	1775
Beclomethasone dipropionate (BMP)*	1345
Ciclesonide (des-CIC)*	1200
Budesonide	935
Triamcinolone acetonide	233
Flunisolide	190
Dexamethasone	100
Prednisolone	12
Hydrocortisone	~2.5

Daley-Yates. Br J Clin Pharmacol. 2015;80:372-80

Pharmacokinetics



Q2. Which patient is most likely to develop adrenal suppression?

A. 22-yr-old woman with flexural eczema prescribed hydrocortisone cream 0.5% & Gedarel®30/150[2] PO

B. 28-yr-old man with atopy and nasal polyps prescribed mometasone nasal spray 50 micrograms each nostril od and fexofenadine PO 120mg daily

C. 35-yr-old woman with asthma and ABPA prescribed Flutiform®50[1] 2 puffs bd and itraconazole 200 mg od

D. 54-yr-old man with bilateral uveitis and sarcoidosis prescribed dexamethasone 0.1% eye drops 4 hourly

E. 66-yr-old woman with chronic otitis externa prescribed prednisolone 0.5% ear drops 2-3 every 2-4hours and tamoxifen 20mg PO od

1. Fluticasone 50, formoterol 5
2. Ethinylestradiol 30 micrograms, Desogestrel 150 micrograms

Summary

- Aim: maximum disease control, minimum cumulative dosage
- Start to withdraw steroids as soon as disease is controlled (or not after adequate trial)
- Long term therapy for >3 weeks can cause dependence
  - HPA axis suppression, glucocorticoid withdrawal syndrome, psychological dependence
- Taper long term treatment to minimise risk of disease recurrence and withdrawal effects
- Consider endocrinology input for withdrawal failure of prednisolone ≤5mg to distinguish HPA suppression from other reactions