Principles of Drug Therapy

ASTHMA

Dr Channa D. Ranasinha

OUTLINE

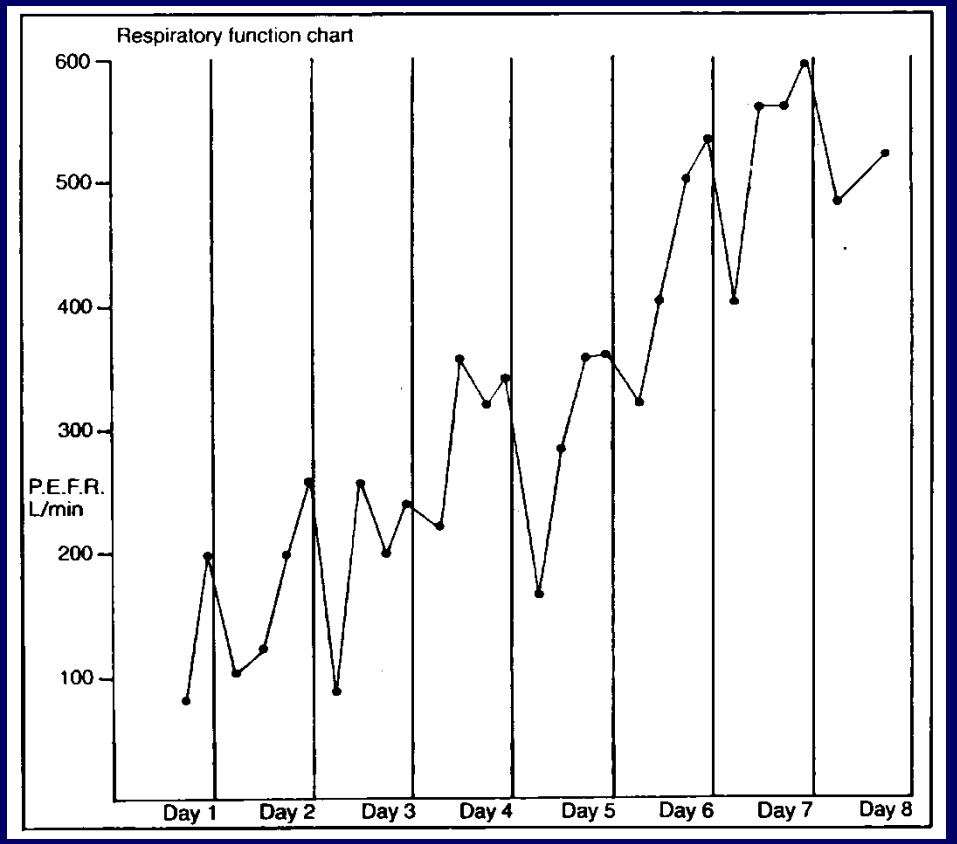
- Pathophysiology
- Drugs
  - Relievers
  - Preventers
- Therapeutics
  - devices
  - emergency treatment
  - chronic out-patient treatment

DEFINITION (1/3) - CLINICAL

Clinical

- partial airflow limitation

- Varies over short periods of time and with treatment

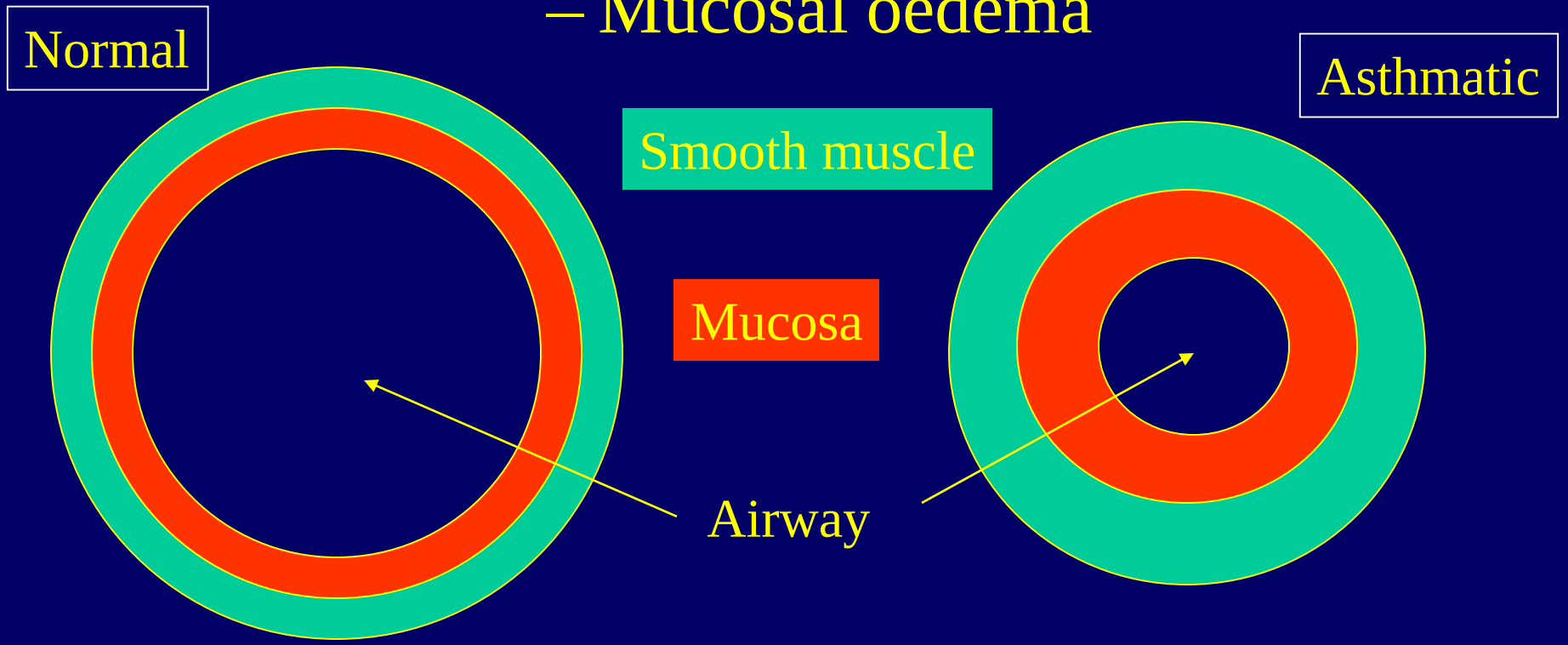


Peak flow chart with treatment

DEFINITION (2/3) - PHYSIOLOGY

– Smooth muscle constriction

– Mucosal oedema



DEFINITION (3/3) - PATHOLOGY

Site: smaller bronchi (& bronchiole)

Findings:

- smooth muscle hypertrophy
- submucous gland hypertrophy
- cellular infiltration (lympho + eosin's)

Asthma = eosinophilic bronchitis

MAST CELL DERIVED MEDIATORS

Preformed

- Histamine
- Eosinophil chemotactic factor
- Neutrophil chemotactic factor
- Neutral proteases
- Acid hydrolases
- Heparin proteoglycans

Membrane derived

- Leukotrienes
- Prostaglandins
- Thromboxanes
- Platelet activating factor

MECHANISMS FOR ASTHMA DRUG THERAPY

- Preventing mediator formation
  - Glucocorticoids, lipoxygenase inhibitors
- Preventing mediator release
  - Na cromoglycate
- Preventing mediators reaching targets
  - Leukotriene receptor antagonists
- Physiological antagonism of mediators
  - Histamine and adrenaline have the opposite effects by separate mechanisms
  - $ß_2$ agonists, theophylline

DRUGS

Relievers

- SALBUTAMOL
- terbutaline
- salmeterol
- IPATROPIUM
- THEOPHYLLINE

Preventers

- GLUCOCORTICOIDS
  - beclomethasone
  - budesonide
  - fluticasone
- Na cromoglycate

- Montelukast
- Zafirlukast
- Zileuton

RELIEVERS

Drugs that reverse bronchoconstriction for acute attacks

$ß_2$ agonists

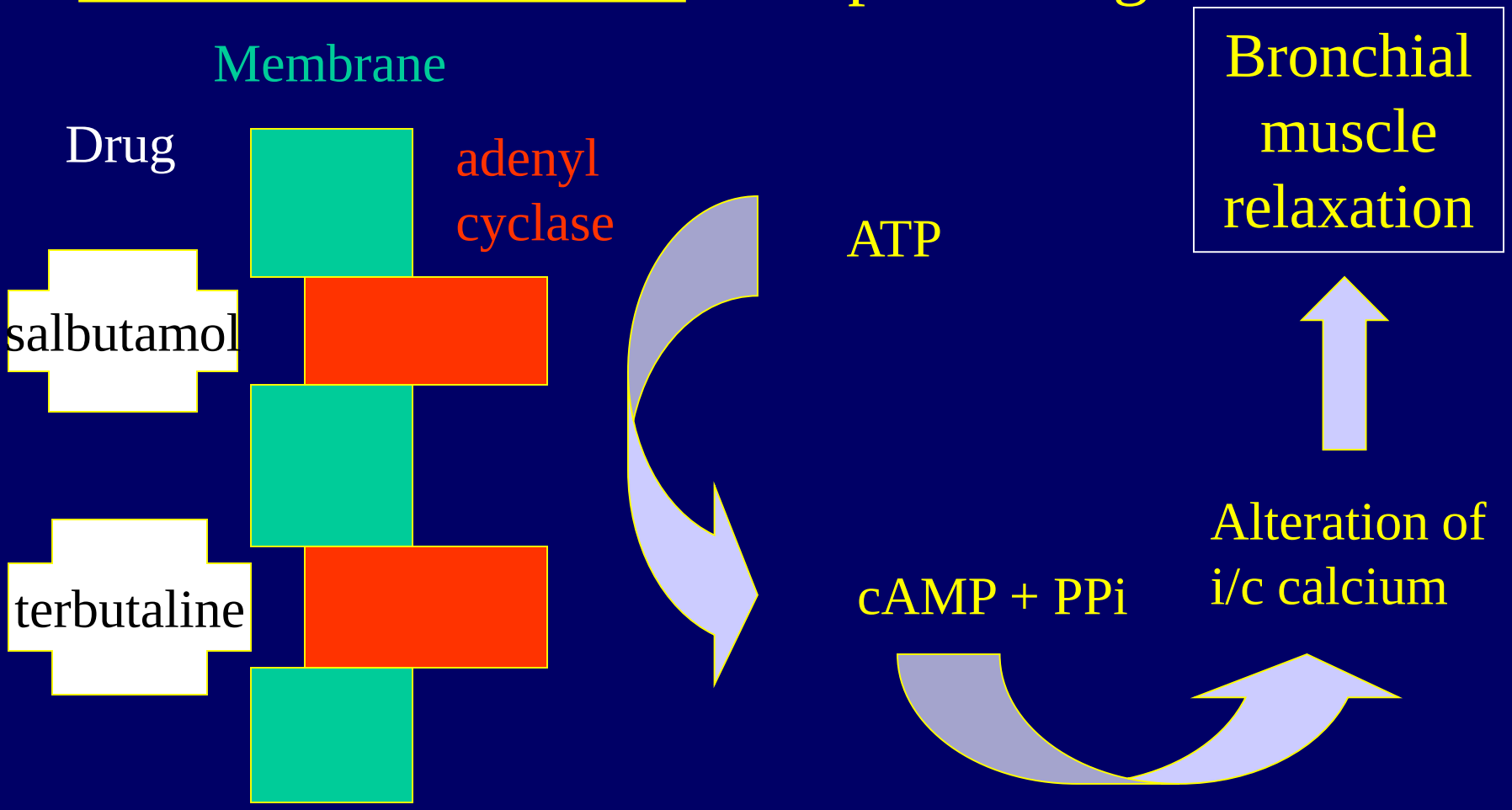
Methylxanthines

Anti-muscarinics

Anti-leukotriene agents

SHORT ACTING ß$_2$ AGONISTS

Mechanism of action: competitive agonist



SHORT ACTING ß$_2$ AGONISTS

Kinetics

- well absorbed, not metabolised by COMT, less MAO metabolism, so used orally, by inhalation and iv
- Onset 1-2 mins, duration 2-3 hrs, $t_{1/2}$ = 4hrs

SHORT ACTING ß$_2$ AGONISTS

Clinical Uses

- Acute relief of bronchospasm (& COPD)
  - prophylactically in exercise induced asthma
- Delaying premature labour

Adverse effects:

- ß$_2$ Hypokalaemia, muscle tremor
- ß$_1$ Tachycardia

LONG ACTING ß$_2$ AGONISTS

Salmeterol and formoterol

- Structural modification of salbutamol
- Lipophilic side-chains bind to sites adjacent to ß$_2$ receptor
- Increases time spent at receptor site
- Duration of action 12hrs
- Salmeterol slower onset of action, formoterol as fast as salbutamol.

CLASSIFICATION

	Fast onset	Slow onset
Short acting	salbutamol	(oral salbutamol)
Long acting	formoterol	salmeterol

ANTI-MUSCARINICS

- IPATROPIUM, oxitropium

Mechanism of action:

Competitive, non-selective anti-muscarinic, post-synaptic acetylcholine antagonism

Tone to bronchial muscle is vagal & parasympathetic

Bronchdilatation & dries up secretions

ANTI-MUSCARINICS

Kinetics

Synthetic analogues of atropine

Very little absorption across pulmonary epithelium unlike atropine

Onset slower than salbutamol

Only administered by inhaler and nebuliser

ANTI-MUSCARINICS

Clinical Uses

acute asthma and COPD

less effective than salbutamol as only Ach actions are blocked

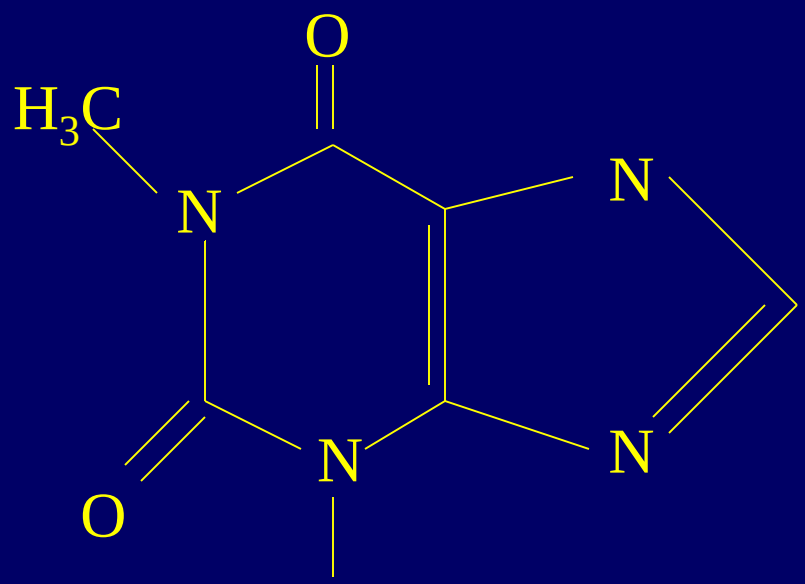
Adverse effects

Topical administration has little systemic action

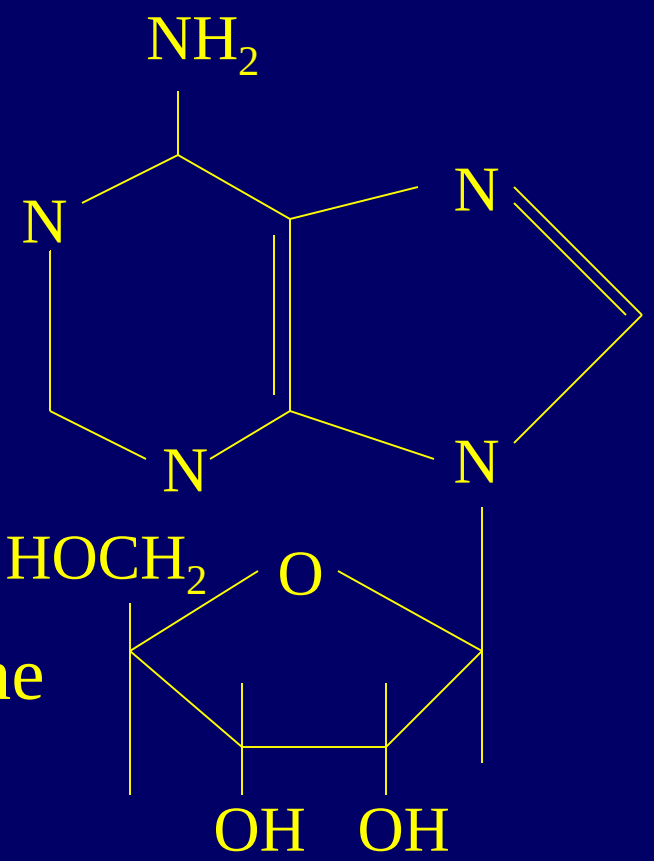
dry mouth, raised intra-ocular pressure, urinary retention, tachycardia

METHYLXANTHINES

Include theophylline, aminophylline and choline theophyllinate



Theophylline



adenosine

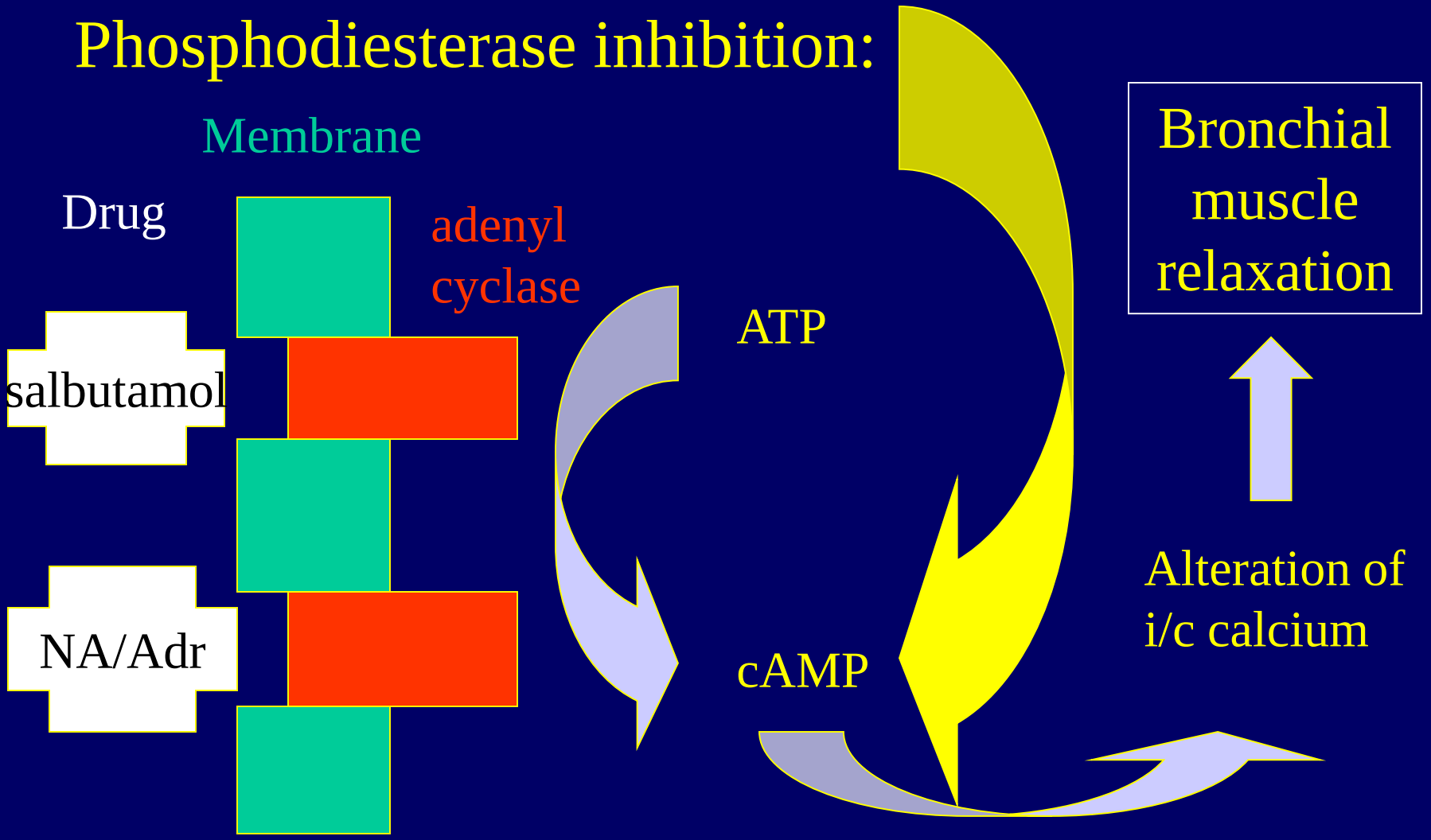
METHYLXANTHINES

Mechanisms of action

- adenosine receptor antagonism
- direct effects on calcium concentration
- phosphodiesterase inhibition
  - inhibits the breakdown of cAMP

METHYLXANTHINES

Phosphodiesterase inhibition:



METHYLXANTHINES

Kinetics

- fully and rapidly absorbed
- widely distributed: emergency loading dose
  - theophylline very lipophilic only orally
  - aminophylline more soluble po or iv
- metabolised in liver
  - prolonged in heart failure and cirrhosis
  - metabolised by CYT P450 enzymes

METHYLXANTHINES

Clinical uses: not a first line drug

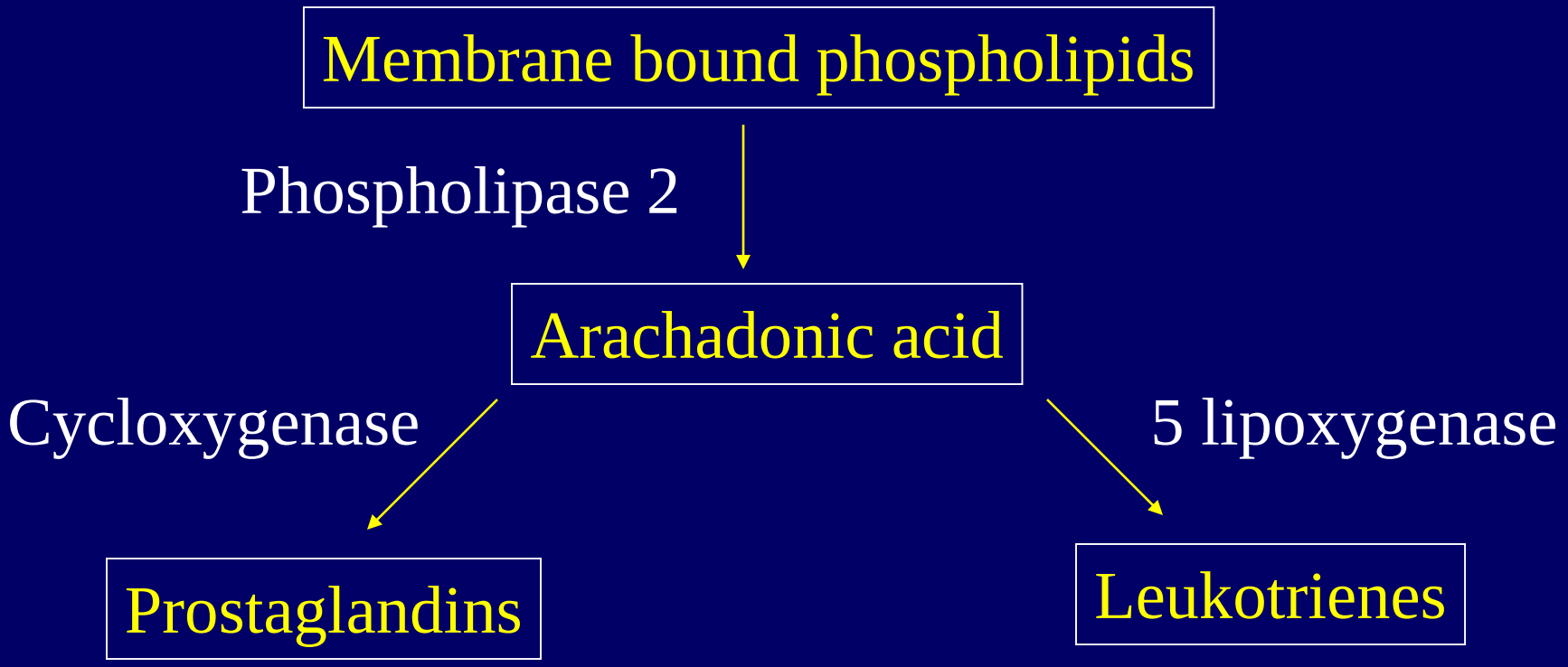
- Bronchodilator
- Cardiac stimulant
- Vasodilator
- Central stimulant
- Diuretic

METHYLXANTHINES

Adverse Effects

- Narrow therapeutic index: Harmful dose / Effective dose
- Nausea, vomiting, cardiac arrhythmias, epileptic seizures
- Monitor plasma levels
  - therapeutic range 10-20mg/l

LEUKOTRIENE MODIFIERS



LEUKOTRIENE MODIFIERS

Mechanism of Action

Leukotrienes are among the most important mediators

- 5 lipoxygenase inhibitor: zileuton
- LTD_4 competitive receptor antagonists:
  - montelukast and zafirlukast
- bronchodilator & anti-inflammatory action
- exact place in treatment unclear

PREVENTERS

Do not cause bronchodilatation (acutely)

no use for acute treatment

‘Anti-inflammatory action’

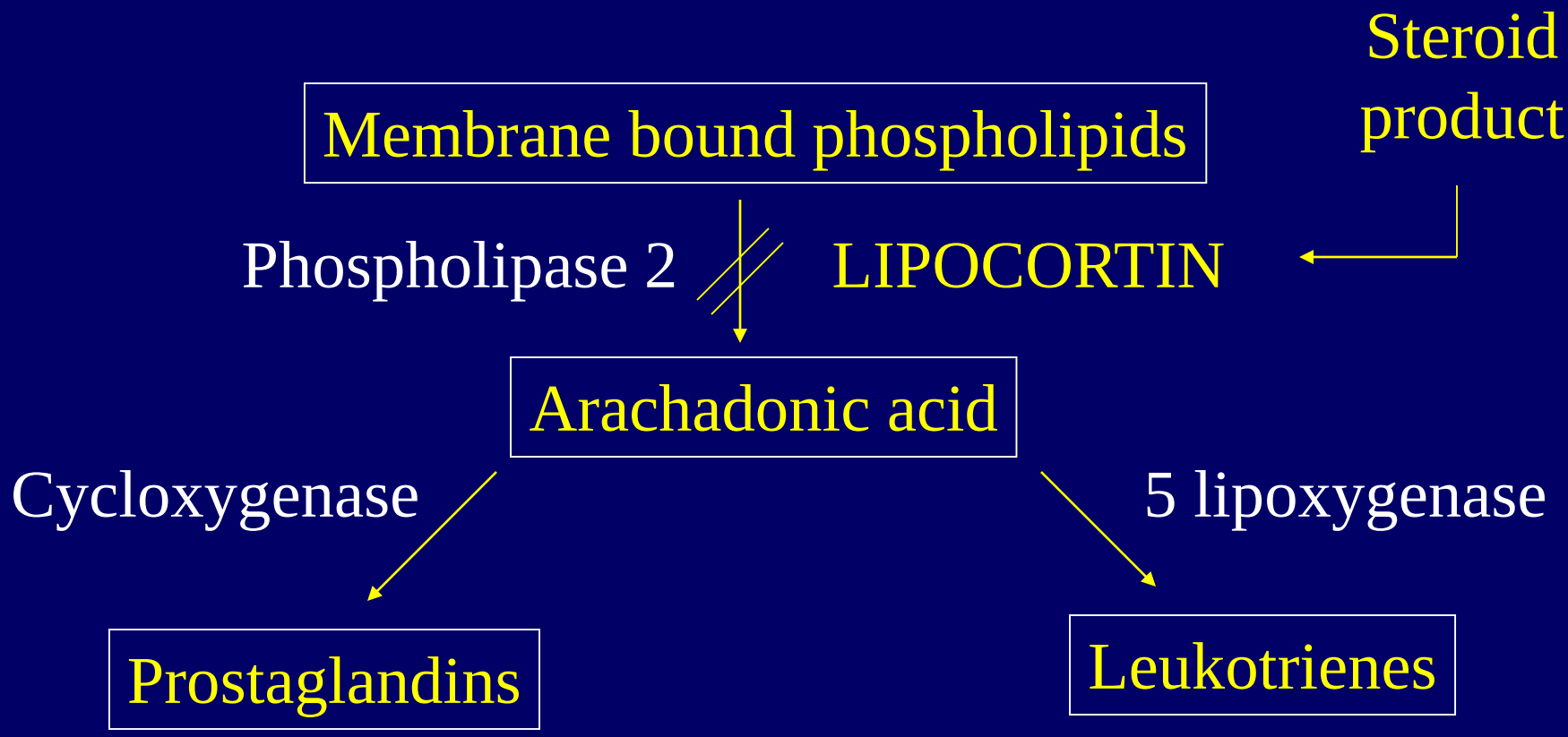
- reduce bronchial hyper-reactivity
  - reduce entry of inflammatory cells
  - inhibit release of mediators from cells
  - reduce formation of mucosal oedema by mediators

GLUCOCORTICOIDS

Systemic: PREDNISOLONE
Hydrocortisone

Topical: BECLOMETHASONE
Budesonide
Fluticasone

GLUCOCORTICOIDS



GLUCOCORTICOIDS

Kinetics

- metabolised in the liver
- $t_{1/2}$ 1-3 hrs
  - shortened by P450 enzyme induction
  - increase dose

Clinical Uses

- anti-inflammatory effect

GLUCOCORTICOIDS

Adverse Effects

many and serious, usually after long term use

BUT these are life saving drugs

- Metabolic: diabetes, osteoporosis, growth retardation, spread of infection
- Psychiatric: depression & euphoria
- Cardiovascular: hypertension
- Adrenal suppression

GLUCOCORTICOIDS

PREDNISOLONE, hydrocortisone

Systemic agents

Prednisolone po onset 12-24 hrs

HC iv onset 6-8 hrs

Used for acute deteriorations as systemic actions are beneficial

GLUCORTICOIDS

BECLOMETHASONE, budesonide, fluticasone

- Topical agents, direct to target site (still 20% only reaches) pulmonary epithelium

- Can use very small doses, so small but definite systemic absorption (pulmonary and GI)
- Budesonide & fluticasone extensive 1st pass metabolism: destroyed

Na CROMOGLYCATE

Mechanism of action unclear: stabilises the mast cell membrane when in allergen contact = preventer

Poor GI and good pulmonary absorption, so given by inhalation

Useful for extrinsic (allergic) asthma esp kids

Remarkably non toxic

SUMMARY

- Pathophysiology
  - bronchoconstrictor & inflammatory disease
- Drugs
  - Relievers: acute attack ⟶ bronchodilatation

    ß2 agonists, anti-muscarinics, methylxanthenes, leukotriene modifiers
  - Preventers: prophylactic ⟶ reduce inflammation

    glucocorticoids (topical & systemic)