2008a(4)/2006a(1): Outline the pharmacological management of bronchoconstriction in acute severe asthma. Include mechanisms of action and potential adverse effects

**General:** Asthma is a **chronic disease** characterised by **airways** hyperresponsiveness

- ↑Bronchial smooth muscle tone → bronchoconstriction
- ↑Mucous production
- Acute attack → gas trapping / ↑physiological dead space

**Acute management bronchoconstriction**

**Supplemental O₂**

- ↑FiO₂ → ↑alveolar O₂ in areas undergoing gas exchange
- Adverse effects:
  - Removal of **hypoxic pulmonary vasoconstriction** to non-ventilated units → ↑shunt → ↓O₂ content of blood

**Adrenaline:** Non-specific α/β adrenoceptor agonist

- **Route:** Nebulised (direct airways, ↓systemic effects); IM; IV
- **Dose:** 1mg neb; 1mg IMI
- **MOA:**
  - β₂ agonist effect: GₛPCR → ↑adenyl cyclase → ↑cAMP → ↓Ca
  - ↓bronchial smooth muscle tone → ↓airways resistance
  - ↓mucous production → ↓airways resistance
- **Adverse Effects:** 2° α/β agonist effects systemically
  - α₁: peripheral vasoconstriction → ↑BP; cutaneous constriction (pallour); difficulty with obtaining venous access
  - β₁: ↑HR, precipitate arrhythmias
    - ↑MRO₂ → ischaemia
  - Nausea, abdominal pain
  - ↓insulin → ↑BSL

**Salbutamol:** Selective β agonist (β₂ > β₁)

- **Route:** Nebulised
- **Dose:** 5mg neb
- **MOA:**
  - Non-selective β agonist, nebulised further ↓systemic effects
  - GPCR → ↑adenyl cyclase → ↑cAMP → ↓Ca
    - ↓bronchial smooth muscle tone
    - ↓secretions
- **Adverse Effects:** related to systemic β agonist effects
  - β₁: ↑HR; palpitations
  - β₂: stimulation of skeletal muscle → tremour
    - sweating
    - postural hypotension (vasodilator)
  - Removal of hypoxic pulmonary vasoconstriction → needs supplemental O₂
  - ↓K⁺ by ↑intracellular shift
  - N&V
  - ↑BSL
Ipratropium Bromide: Anticholinergic (Atrovent)
- Route: Nebulised
- Dose: 500μg
- MOA: Competitive inhibition of mAChR (M3) on bronchial smooth muscle
  → GPCR → blockade → ↓phospholipase C → ↓DAG, IP₃ ↓Ca
  o ↓bronchoconstriction effect of vagal stimulation
  o Inhibit ACh enhancement of mediator release from mast cells
  o Nil change in secretions
- Adverse Effects:
  o Minimal systemic effects via neb
  o Unpleasant taste

Corticosteroids: Minimal effect in acute setting as onset ~6-8hrs after admin
- Route:
  o PO: Prednisolone 1mg/kg
  o IV: Hydrocortisone 100 – 300mg tds
- MOA: Bind to intracellular receptors to augment gene transcription / translation
  o ↓inflammatory mediators: ↓phosphlipase A₂ production → ↓arachidonic acid → ↓PG / leukotrienes / IL production
    ▪ ↓leakiness of capillaries → ↓oedema
- Adverse Effects:
  o ↑BSL (↑gluconeogenesis)
  o Adrenal suppression → inhibition of hypothalamic-pituitary-adrenal axis → Addisons → must wean if high dose > 5 days
  o Loss of subcutaneous connective tissue
  o ↓platelet aggregation (↓arachidonic acid → ↓TXA₂) → ↑bleeding

Methylxanthines: Theophylline / aminophylline
- Route: IV / PO / PR
- Dose:
  o PO: 900mg divided doses
  o IV 5mg/kg bolus; infusion 0.5mh/kg/hr
- MOA: Phosphodiesterase III inhibitor
  o ↓breakdown of cAMP → ↑cAMP → ↓Ca → bronchial relaxation
  o ↓influx Ca into smooth muscle → stabilises membrane
  o Antagonises adenosine effect on mast cells → stabiliser
- Adverse Effects:
  o CVS: positive inotrope/chronotrope → ↑CO; ↓SVR → ↓BP
    ▪ Arrhythmogenic at high doses → VF
  o Inhibition of hypoxic pulmonary vasoconstriction → supplement O₂
  o CNS stimulant → ↑risk seizure; ↓CBF
  o ↑gastric acid production
  o ↓gastric motility
  o Diuretic → ↓Na reabsorption; ↑K excretion (hypokalaemia)
  o Narrow therapeutic index

Volatile Anaesthetic Agents
- Route: inhaled

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- MOA: ↓smooth muscle tone NANC (non-adrenergic, non-cholinergic)
- Adverse effects:
  - Minimal if in the course of anaesthetic
  - ↑fraction → ↓BP

*Helium (Heliox)*
- MOA: Lower density (and specific gravity) than air / O₂
  - During turbulent flow → ↑velocity cf O₂
  - ↓work of breathing
  - Improves oxygenation
- Adverse Effects:
  - Minimal
  - Needs to be on machine
  - ↓inspired O₂ cf O₂ alone

*Magnesium*
- Route IV
- Dose: 20mmol
- MOA: Smooth muscle relaxation → Ca channel blockade → ↓Ca
  - ↓neutrophilic burst rate → ↓inflammatory mediator release
- Adverse Effects:
  - Sedation
  - Hypocalcaemia