RESPIRATORY PHARMACOLOGY AND THERAPEUTIC GASES

(a) ***To describe the pharmacology of anti-asthma drugs with particular reference to beta-2 agonists, corticosteroids, anticholinergics, leukotriene antagonists and theophylline.***

Asthma → recurrent reversible airway disease a/w ↑ resistance to airflow due to:
- (i) ↑ AW mucosal inflammation and oedema
- (ii) ↑ bronchial SM tone (or bronchoconstriction)
- (iii) ↑ bronchiolar secretions
- (iv) ↑ airway hyperresponsiveness

Drugs used to treat asthma are generally administered by the "inhaled route" → b/c this:
- (1) ↑ delivery to site of action → ↑ effect
- (2) allows administration of lowest dose possible
- (3) ↓ adverse effects due to systemic absorption

Classes of drugs used to treat asthma:

(1) <u>β2 agonists</u>:

Types	(i) Short-acting agents (Eg. salbutamol) - Used to treat acute asthma (inhaled – aerosolised as MDI/spacer, or nebulised) → effect in 30 mins, lasting 4-6 hrs - Used to treat status asthmaticus (IV) (ii) Long-acting agents (Eg. salmeterol) - Used as prophylaxis to prevent asthma attack (inhaled – aerosolised as MDI/spacer) → effect lasting 12 hrs
Mechanism of action	Direct β2 adrenoceptor agonist → GPCR (Gs) → inhibits adenylyl cyclase causing ↓ IC cAMP → causes (i) relaxation of bronchial SM, (ii) ↑ ciliary clearance of mucous, and (iii) ↓ mast cell mediator release
Adverse effects	Due to systemic absorption: - β2 effects – Muscle tremor, ↓ K^+, postural hypotension - β1 effects – Tachycardia, arrhythmias, hypertension, ↑ BGL, anxiety

(2) <u>Anticholinergics</u>:

Types	Used to treat acute asthma (Eg. ipratropium → t ½ ~ 2 hrs) and as prophylaxis to prevent asthma attack (Eg. tiotropium → t ½ 6 hrs) → given via inhaled route (aerosolised as MDI)
Mechanism of action	Competitive M3 receptor antagonist → GPCR (Gq) → ↓ PLC activation causing ↓ DAG (↓ PKC) and ↓ IP3 (↓Ca^{2+}) → causes (i) relaxation of bronchial SM, (ii) ↑ ciliary clearance of mucous, and (iii) ↓ mucous secretion production
Adverse effects	- Minimal side-effects as agents are quaternary N-analogues of atropine → ionised so ↓ systemic absorption from lungs - Systemic anticholinergic effects include – dry mouth, mydriasis, tachycardia, urinary retention

(3) <u>Corticosteroids</u>:

Types	- Inhaled fluticasone, budesonide via MDI → prophylaxis against asthma attack - IV hydrocortisone → treat severe acute asthma or status asthmaticus - PO prednisolone → treat chronic or severe acute asthma
Mechanism of action	- Binds to IC glucocorticoid receptor → alters gene transcription and protein synthesis → causes: - (i) ↓ synthesis of inflammatory mediators → ↑ lipocortin production inhibits PLA2 → causing ↓ arachidonic acid generation and subsequent conversion to prostaglandins and leukotrienes - (ii) Suppression of immune response → ↓ cytokine production and ↓ immune cell activation - (iii) Upregulation of β2 receptors

	- Onset of effects are delayed (6-8 hrs) b/c of this
Adverse effects	- Inhaled steroids deposit in oropharynx → cause oral candidiasis and dysphonia - Chronic use (esp of oral or IV) → ↑ BGL, adrenal suppression, Cushingoid (Eg. central adiposity, moon facies, Etc.), thinned skin, easy bruising, myopathy

(4) Leukotriene antagonists:

Types	Montelucast and Zafirlukast → given orally
Mechanism of action	Competitive inhibition of LT receptors → ↓ effects of LTC4, D4 and E4 → relaxes bronchial SM
Adverse effects	Minimal side-effects (Eg. headaches, GI disturbances)

(5) Methylxanthines:

Types	Theophylline → given PO (as 2nd line therapy for acute asthma) or IVI (for status asthmaticus)
Mechanism of action	- Phosphodiesterase inhibitor → ↑ IC cAMP and GMP → ↓ Ca^{2+} → bronchial SM relaxation - Inhibitor of endogenous adenosine?
Adverse effects	Narrow therapeutic index: - CVS effects – Tachycardia/arrhythmias (+ve chronotropic effect), ↑ C.O. (+ve inotropic effect), hypotension (due to vasodilation) - CNS effects – ↑ alertness, tremor, nervousness, seizures and death 2° to respiratory failure - GIT effects – Anorexia, N/V - Renal effects – Weak diuretic effect (↑ GFR) - Metabolism dependent on hepatic CYP450 → ↑ drug levels with liver failure or drug inhibition of CYP450 (Eg. OCP, cimetidine, erythromycin)

(b) ***To outline the pharmacology of drugs used to treat pulmonary hypertension.***

(1) Prostanoids:
- (a) Epoprostenol
  - *Overview* – Synthetic PGI-2 given continuously by IVI (via CVC)
  - *Mechanism of action* – PGI-2 analogue that causes pulmonary arterial SM relaxation → vasodilation and ↓ PA pressures
  - *Adverse effects* – Effects of PGs (Eg. headache, flushing, N/V, ↓ BP, jaw pain, flu-like symptoms), risk of CVC insertion (Eg. thrombosis, sepsis, Etc.), and need continuous infusion due to short t ½ (pump failure can be fatal!!!)
- (b) Treprostinil
  - *Overview* – Synthetic PGI-2 given IV, S/C or inhaled route
  - *Mechanism of action* – As epoprostenol
  - *Adverse effects* – Effects of PGs (as epoprostenol) but do not need to give via CVC (can be given via continuous S/C delivery or inhaled route) and longer t ½ means pump failure is not fatal
- (c) Iloprost
  - *Overview* – Synthetic PGI-2 given inhaled route
  - *Mechanism of action* – As epoprostenol
  - *Adverse effects* – Effects of PGs (as epoprostenol) and needs to be given frequently (6-9x/day)

(2) Endothelin receptor antagonists:
- *Overview* – Bosentan → given orally
- *Mechanism of action* – Non-selective ET-1 receptor antagonist → inhibit potent vasoconstrictor effects of ET-1 → vasodilation of pulmonary artery → ↓ PA pressures
- *Adverse effects* – Hepatotoxicity, peripheral oedema, teratogenic

(3) PDE5 inhibitors:
- *Overview* – Sildenafil, Tadalafil → given orally
- *Mechanism of action* – Inhibit PDE-5 isozyme → ↑ IC cAMP/GMP → vascular SM relaxation causing pulmonary arterial vasodilation → ↓ PA pressures
- *Adverse effects* – Headaches, flushing, hypotension, epistaxis

(4) Calcium channel blocker:
- *Overview* – Long-acting forms of diltiazem or nifedipine → given orally
- *Mechanism of action* – Inhibit L-type VG-Ca^{2+} channels on vascular SM → ↓ Ca^{2+} influx → vascular SM relaxation causing pulmonary arterial vasodilation → ↓ PA pressures
- *Adverse effects* – Hypotension, bradycardia, -ve intropy (heart failure), peripheral oedema

(5) Other therapy:
- (i) Diuretics (Eg. frusemide) – Used to treat fluid retention (Ie. ↓ APO and hepatic congestion) → issues with ↓ C.O. (2° to ↓ preload), arrhythmias 2° to electrolyte disturbances (esp ↓ K^+), metabolic alkalosis
- (ii) Anticoagulation (Eg. warfarin) – Used to ↓ risk of PE → issues with bleeding
- (iii) Digoxin – Used to control HR in those with SVT and ↑ RVEF
- (iv) Supplemental O_2 therapy

(c) ***To describe the pharmacology of oxygen including its manufacture and adverse effects.***

Overview of oxygen (O_2):

- O_2 is a gaseous inorganic element that plays an essential role in oxidative phosphorylation for ATP production
- It is administered by inhalation route (up to FiO_2 of 100%) and is used clinically:
    - (1) To manage all forms of hypoxia (except histotoxic)
    - (2) As an adjunct in management of shock and treatment of CO poisoning, anaerobic infections and decompression sickness

O_2 preparation and storage:

- Preparation:
    - (1) Fractional distillation of liquid air
        - Used for commercial production
        - Based on different boiling points of O_2 and N_2
    - (2) O_2 concentrator
        - Used for home use/remote locations
        - Zeolite mesh adsorbs N_2 so remaining gas is 97% O_2
    - (3) Hydrolysis of water to O_2 and H_2
- O_2 is then stored either as (i) a compressed gas in a cylinder (at 137 bar at 15 °C), or (ii) a liquid in a vacuum insulated evaporator (at 10 bar and -180 °C) → Nb. 1 volume of liquid O_2 = 840 volume of gaseous O_2

Physicochemical properties of O_2:

Molecular formula:	O_2	Others:	Colourless, odourless, tasteless gas
MWT:	32		Supports combustion
Critical temperature:	-119 °C		An oxidant
Critical pressure:	51 atm		Non-conductor
Boiling point:	-182 °C		Paramagnetic
			Cannot be measured by IR analyser (Ie. measured by mass spect, Clarke electrode, paramagnetic analysis)

Potential adverse effects of O_2 administration:

- (1) Free radical toxicity
    - (i) Pulmonary effects (can occur at $pO_2 \approx 100$ kPa or 1 atm) – Lipid peroxidation of alveolar capillary membranes → regional lung collapse
    - (ii) CNS effects (esp at $pO_2 > 200$ kPa or 2 atm) – Anxiety, N/V, seizures
- (2) Absorption atelectasis
    - FiO_2 100% eliminates N_2 from lungs → loss of N_2 as an alveolar splint → causes atelectasis and V/Q mismatching
- (3) Respiratory depression
    - In normal patients → ↑ FiO_2 causes mild respiratory depression
    - Patients with COPD who are CO_2 retainers are dependent on hypoxia for respiration (as chronic hypercapnoea blunts CO_2-ventilatory drive) → ↑ FIO_2 impairs their hypoxic-respiratory drive → ↓ stimulation of medullary ventilatory centres → ↓ RR and MV
- (4) Retrolental fibrodysplasia in neonates
    - ↑ PaO_2 (rather than PAO_2) causes retrolental fibroplasia 2° to vasoconstriction of retinal vessels during development → thus, avoid by keeping $PaO_2 < 140$ mmHg
- (5) CNS effects
    - FiO_2 100% causes ↓ CBF 2° to cerebrovascular vasoconstriction
- (6) CVS effects

    - FiO_2 100% causes ↓ coronary perfusion (2° to coronary vasoconstriction), and mild myocardial depression (↓ HR, BP and CO)
- (7) Haematological effects
    - FiO_2 100% may interfere with RBC formation

(d) ***To describe the pharmacology of nitric oxide with particular reference to its inhaled use.***

Overview of nitric oxide (NO):

- (1) NO is an endogenous molecule (aka. Endothelium-derived relaxing factor (EDRF)) synthesised throughout the body (Eg. endothelium, neurons, macrophages/PMNL, vascular and skeletal muscle, platelets, Etc.)
- (2) Inhaled NO is used to treat pulmonary HT (following cardiopulmonary bypass or in newborns), treat severe RSHF, treat RDS in premature infants, and improve oxygenation with severe ALI/ARDS
- (3) NO is also a potential contaminant in N_2O cylinders

Production of endogenous NO:

- NO is synthesised from one of the terminal guanidine N-atoms of L-arginine in a reaction catalysed by Nitric Oxide Synthase (NOS)
- NOS belongs to a family of Ca^{2+}-activated enzymes with 2 forms:
    - (i) Constitutive – Present in endothelium (artery > vein), neurons, skeletal muscle, cardiac tissue and platelets → continuously produce NO
    - (ii) Inducible – Upregulated in endothelium (artery > vein), vascular SM, myocytes, macrophages and PMNLs in response to cytokines/endotoxins → produce large [NO] and related-free radicals → cytotoxicity and ↑ capillary leakage

Mechanism of action of NO:

- NO diffuses from the producing cells (Eg. endothelium, neuron, Etc.) into the target cells (Eg. VSMC, platelet, Etc.) → activates guanylyl cyclase (converts GTP to cGMP) → ↑ IC [cGMP] → activates various protein kinases that cause ↓ IC [Ca^{2+}] → various effects (Eg. VSMC relaxation, ↓ platelet aggregation, neurotransmission, Etc.)
- Produces localised effects only due to short t ½ (< 5 secs) → endogenous NO readily binds to Fe^{2+} of haeme-based proteins (esp Hb to form Met-Hb) where it is inactivated

> Aside – SNP and organic nitrates (Eg. GTN) exert their pharmacological effects via spontaneous release of NO or metabolism to NO in SM cells

Physiological effects of NO:

System	Physiological effects	Pathophysiology
CVS	- Regulates basal vasodilator tone (and vascular resistance) of systemic and pulmonary arterioles → flow-induced shear stress and pulsatile arterial flow causes continuous local NO production → vasorelaxant effect - Main autoregulatory factor of regional blood flow (esp cerebral and pulmonary BF) → ↑ local NO production by endothelium 2° to ↓ PaO_2 → ↑ CBF and PBF - Direct –ve ino- and chronotropy	- NO deficiency → Essential HTN and cerebral vasospasms after SAH (as NO inactivated by Hb in bleed) - NO excess → Septic shock and cirrhosis (hypotension, hyperdynamic state and ↑ capillary leakage)
Respiratory	- Regulates basal vasodilator tone (and vascular resistance) of pulmonary arterioles → opposes hypoxic-induced pulmonary vasoconstriction - May cause bronchodilation	- NO deficiency → Pulmonary HT
CNS and PNS	- CNS – NO is a NT in neurons within brain/spinal cord → released in response to glutamate excitation of NMDA receptors → role in arousal, pain and memory	- Suppression of NO → ↑ anaesthesia 2° to ↓ CNS excitation (MAC-sparing effect)

	- PNS – NO is a NT in non-Adr/non-cholinergic neurons → controls GI motility (via ENS) and blood flow within corpus cavernosum (penile erection)	- NO excess → Epilepsy, morphine-induced constipation
Haematological and immunological	- Endothelium-derived NO inhibits platelet aggregation/activation - Cytokines/endotoxins stimulate NO synthesis in macrophages/PMNL → degrade phagocytosed pathogens - High avidity for Hb (1500x ↑ cf. CO!)	- NO deficiency → ↑ infection risk, ↑ atherosclerosis 2° to platelet aggregation/vasoconstriction - NO excess → ↑ bleed risk, ↑ inflammation

Clinical use of inhaled NO:

- Indications:
  - (i) Treat pulmonary HT (following cardiopulmonary bypass or in newborns)
  - (ii) Improve oxygenation with severe ALI and ARDS
  - (iii) Treat severe RSHF
  - (iv) Treat RDS in premature infants
- Mechanism:
  - (i) Selectively relaxes and dilates pulmonary vessels
    - Inhaled NO diffuses from alveoli to pulmonary vasculature → causes pulmonary arteriolar vasodilation in proportion to degree of pulmonary vascular resistance via aforementioned MOA of NO → ONLY has significant effect on ↓ PVR if there is underlying pulmonary vasoconstriction (Ie. a/w hypoxia)
    - Lacks systemic effects (Ie. hypotension, bleeding) due to rapid metabolism
  - (ii) Also induces bronchodilation
- Clinical effects:
  - (i) Bronchodilation
  - (ii) Improved V/Q matching and PaO_2 (↑ PBF through well-ventilated lung regions)
  - (iii) ↓ RV pressures, PAP and PVR
  - (iv) ↑ RVEF and C.O.
- Pharmacokinetics:
  - Highly lipid soluble → diffuses across membranes readily
  - Rapidly metabolised (t ½ < 5 secs) → inhaled NO is converted nitrates/nitrites in O_2, and in blood it avidly binds to Hb to form met-Hb
- Delivery:
  - Dose of 10-40 ppm delivered into inspiratory circuit of ventilatory via a synchronised inspiratory injection system → maintains constant inspired [NO] despite changes in minute ventilation
  - Requires accurate monitoring via chemiluminescence or electrochemical analysis (accurate to 1 ppm!)
- Side-effects and issues:
  - (i) Met-Hb → rarely significant unless risk factors present (Ie. children, MetHb reductase deficiency, concurrent oxidising drugs)
  - (ii) Severe rebound hypoxaemia and PHT with abrupt cessation (thus, wean slowly!)
  - (iii) Pulmonary toxicity → NO is oxidised to NO_2 (esp with high FIO_2), which is cytotoxic → thus, close monitoring of NO delivery is essential
  - (iv) Scavenging may be required if unit poorly-ventilated → limit environmental NO levels < 25 ppm for 8 hrs (time-weighted average)

Contraindications – MetHb, ICH, bleeding diathesis, severe LVF