

Respiratory Pharmacology

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Australian & New Zealand Society of Respiratory Science

CRFS Examination Study Guide

5.0 PHARMACOLOGY AND DIAGNOSTIC PROCEDURES

5.1 Pharmacology

5.1.1 Types of medications, their mode of action, duration of effect and secondary effects of drugs used to treat lung disease

5.1.1.1 Common medications with adverse pulmonary effects

5.1.2 Aerosol deposition in the lungs

5.1.3 Optimal technique for:-

5.1.3.1 Metered dose inhalers

5.1.3.2 Spacers

5.1.3.2 Breath activated inhalers

Why we need to know about respiratory pharmacology and inhalation devices?

- How long should we wait for a bronchodilator response?
- Are they going to mask a result we are looking for?

Need to know

- Mode of action
- Onset of action time
- Duration of action
- Precautions
- Adverse reactions

Session Objectives

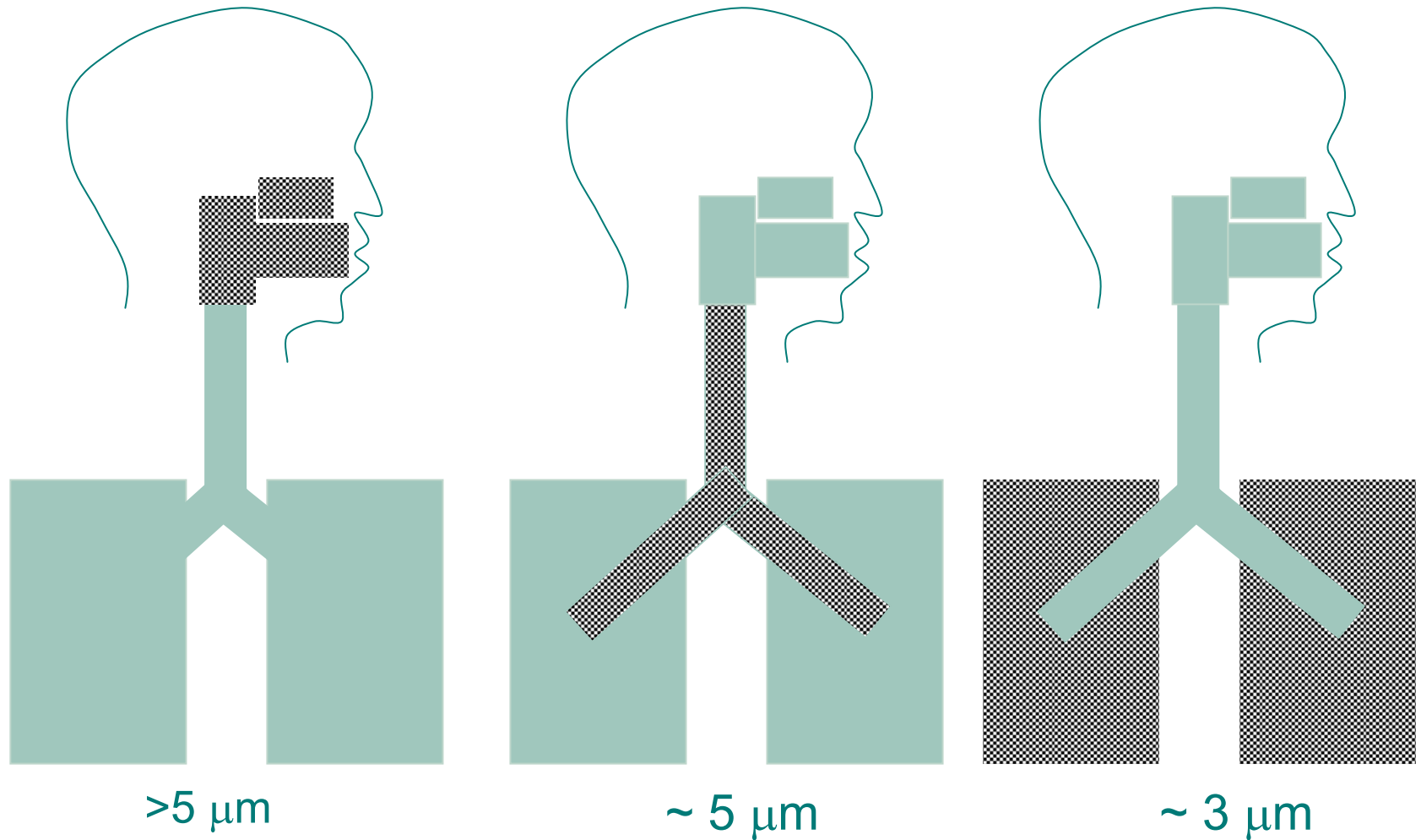
By the end of this session, participants should be able to

- List three ways aerosol is deposited in the airways
- List the different types of respiratory drugs and their mode of action

What isn't covered:

- Inhaler devices – how they work and how to use them.

Aerosol Deposition



Courtesy Louise Lannefors

Mechanisms of Aerosol Deposition

- **Impaction** - Particle's momentum prevents it from changing course when there is a change in the direction of bulk air flow.
- Mainly upper airways
 - teeth, tongue, naso/oropharynx
- At or near bronchial branching points
- ↑ Impaction with ↑ air velocity, breathing frequency, particle size.

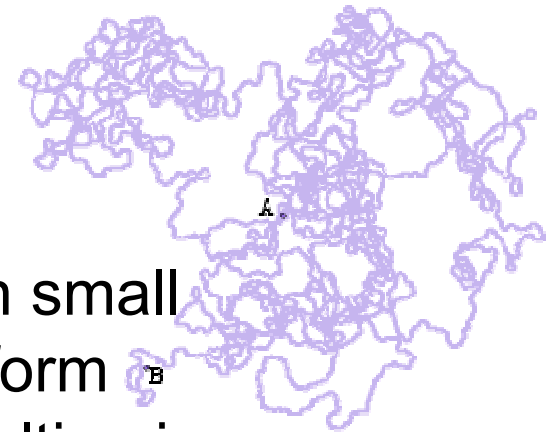
Suarez S, Hickey AJ. Resp Care 2000;45 (6):652-666

Mechanisms of Aerosol Deposition

- **Sedimentation** - when the gravitational force acting on the particle overcomes the total force of the air resistance.
- Inspired particles will fall out of the air stream at a constant rate
- Sedimentation $\propto$ residence time in the airway and particle size
- Decreases with increasing breathing rate.

Suarez S, Hickey AJ. Resp Care 2000;45 (6):652-666

Mechanisms of Aerosol Deposition

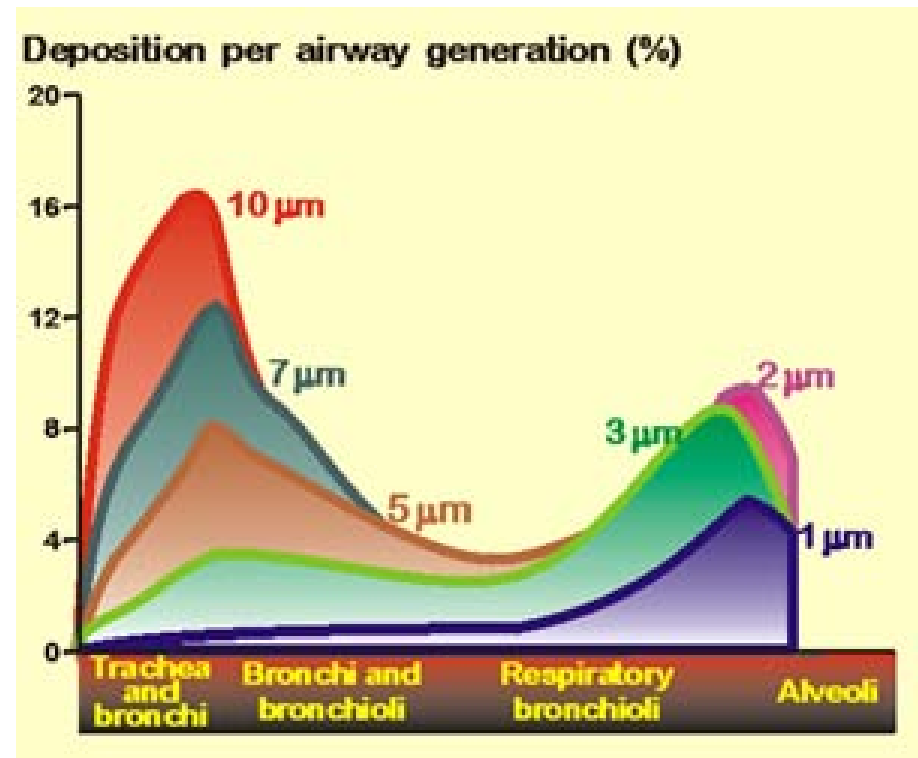


- **Diffusion** - collision of gas molecules with small aerosol particles exerts discrete non-uniform pressures at the particles surfaces – resulting in brownian motion.
- Effectiveness of brownian motion depositing particles is inversely proportional to particle diameters $<0.5\mu\text{m}$.
- Bronchioles, alveoli and airway bifurcations

Suarez S, Hickey AJ. Resp Care 2000;45 (6):652-666

Maximising Aerosol Deposition

- Aerosol diameter < 5 μ m (ideally 2-3 μ m)
- Slow, steady inhalation
- Breath hold at end inspiration



Suarez S, Hickey AJ. Respi Care 2000;45 (6):652-666

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Picture from: http://www.spirxpert.com/brrespuk/particle_deposition.htm

Inhalation Devices

NOT being covered in this session, but will need to know

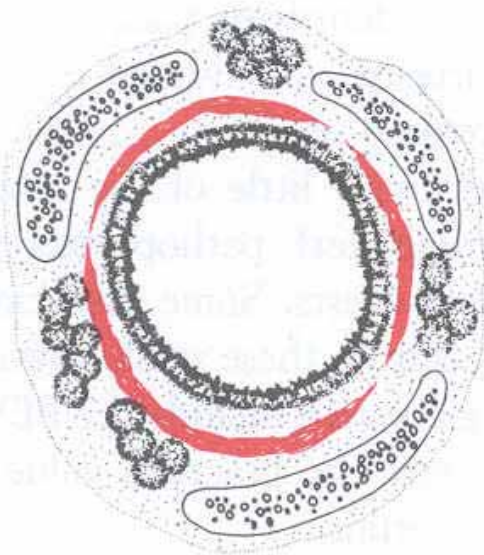
- Optimal technique for
 - Metered dose inhalers
 - Spacer devices
 - Breath activated inhalers
- Basic operation/function of nebuliser

Respiratory Pharmacology



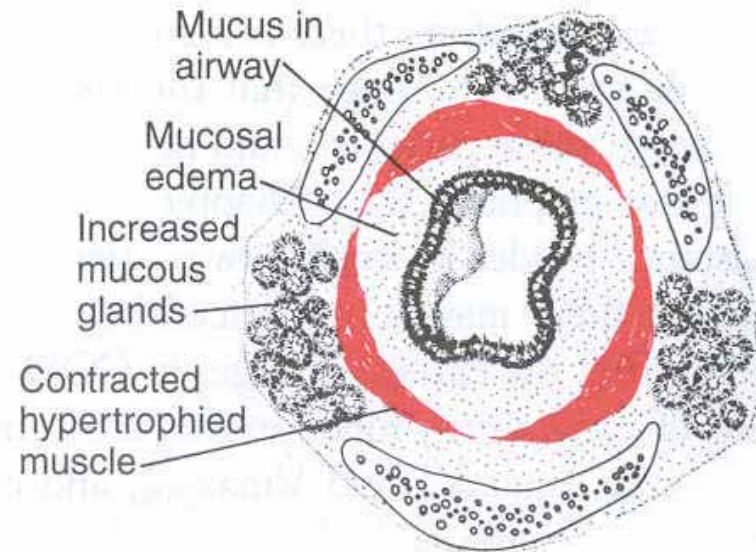
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Airway structure changes in asthma



Normal

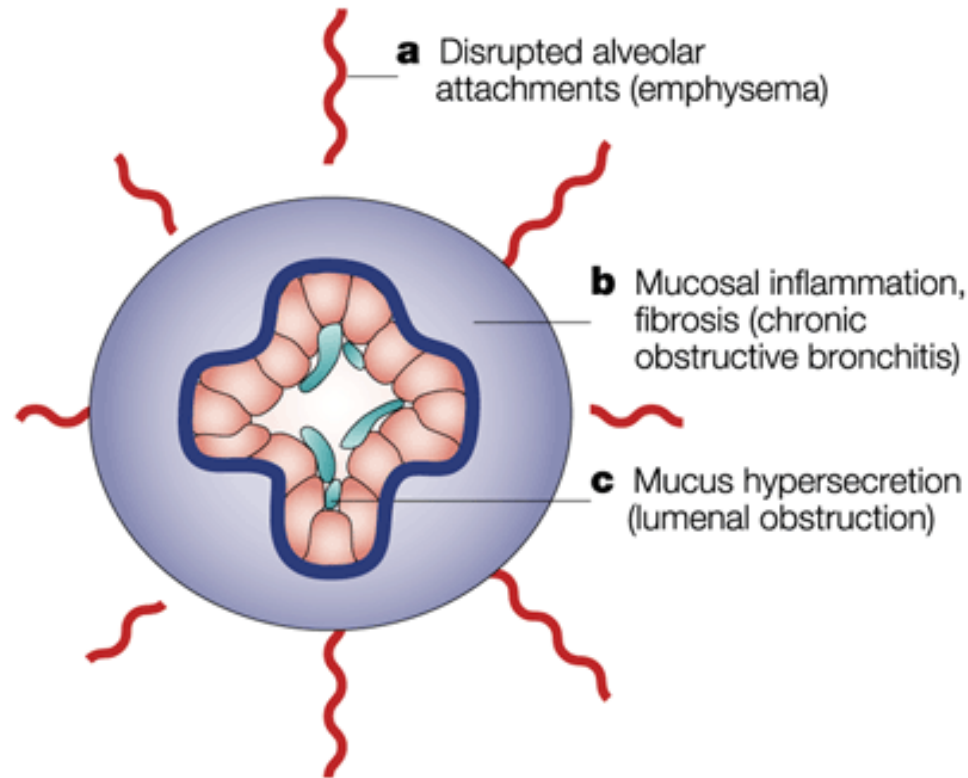
A



Asthma

B

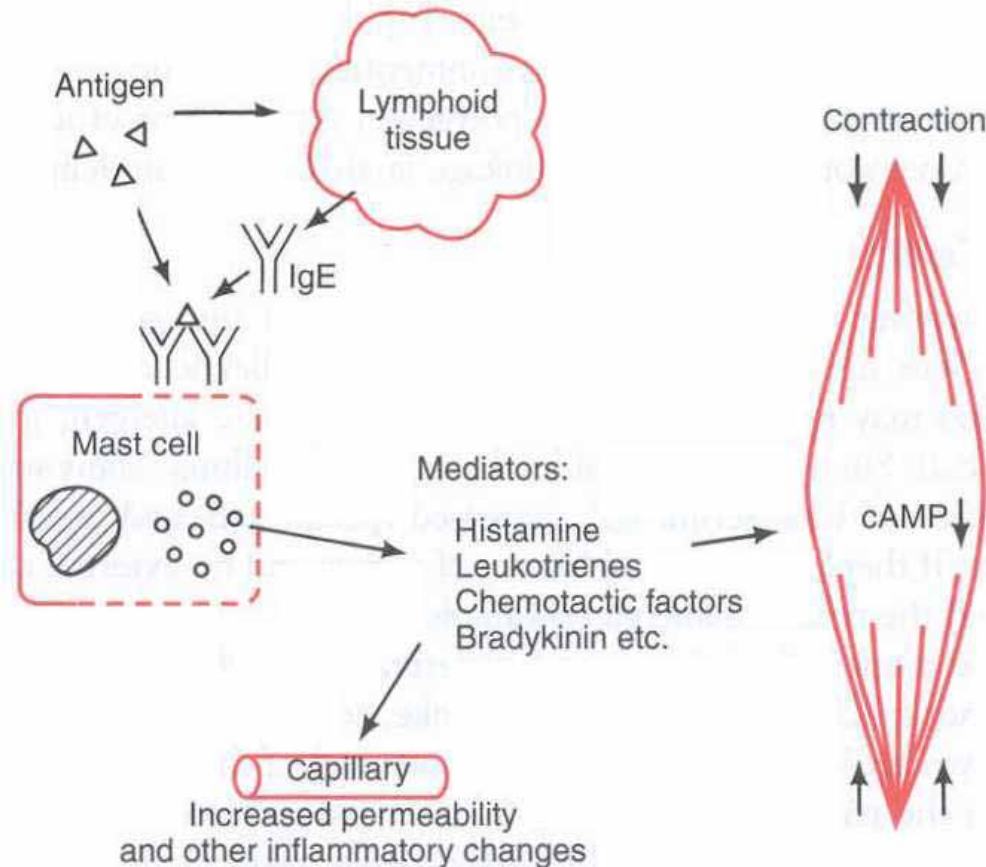
Airway structure changes in COPD



Nature Reviews Drug Discovery **1**; 437-446 (2002)

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Example of Pathogenic changes in Allergic asthma



Sympathomimetic Drugs

- Mimic the stimulation of the sympathetic nervous system.
- Two groups:
 - Specific adrenoreceptor agonists
 - » Beta 2 receptor agonists, including salbutamol and related compounds
 - Less specific agonists which have more general action on adrenoreceptors.



Sympathomimetic Drugs

- Beta-2 receptor agonists have an action both on bronchial smooth muscle cells and mast cells ($\uparrow$ cAMP), resulting in bronchodilation and decreased cellular release of inflammatory mediators.
- Also may improve ciliary beat frequency, and reduce airway oedema



http://www.medscape.com/viewarticle/413163_3

Sympathomimetic Drugs

	B2 agonist	Brand names	Type	Onset of action (inhalation)	Peak Activity	Duration of Action
Short Acting	Salbutamol	Ventolin Asmol Epaq Airomir	Reliever	1-5 mins	50 min	4-6 hrs
	Terbutaline	Bricanyl	Reliever	rapid	60 min	4-5 hrs
Long Acting	Eformeterol	Oxis Foradile	Symptom Controller	1-3 mins	1-2 hrs	~ 12 hrs
	Salmeterol	Serevent	Symptom Controller	10-20 mins	3-4 hrs	~ 12hrs

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Sympathomimetic Drugs

- Adverse effects (main listed only)
 - tachycardia (SVT, AF), tremor, anxiety/nervousness,
 - ↑ dose - hypokalaemia, hyperglycemia
- Drug interactions
 - sympathomimetics, beta blockers, digoxin, xanthine derivatives, steroids, diuretics.

Anticholinergic Drugs

- Act on muscarinic receptors – part of the parasympathetic nervous system.
- Inhibit vagally mediated reflexes by competitively inhibiting acetylcholine (neurotransmitter) at the muscarinic receptor on bronchial smooth muscle – leads to bronchodilation
- Tiotropium - selectively inhibits M3 receptors on airways smooth muscle
- Used more in the treatment of COPD than asthma



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Anticholinergic Drugs

	Anti-cholinergic	Brand names	Type	Onset of action (inhalation)	Peak Activity	Duration of Action
Short Acting	Ipratropium bromide	Atrovent	Reliever	3 - 5 min	1.5 - 2 hrs	Up to 6 hrs
Long Acting	Tiotropium bromide	Spiriva	Symptom controller	30 min	-	~ 24hrs

Anticholinergic Drugs

- Adverse reactions (main)
 - Dry mouth, constipation, urinary retention, other anticholinergic effects, glaucoma, cough, tachycardia, bronchospasm.
- Drug interactions
 - ipratropium - B2 agonists, xanthines (additive)
 - tiotropium - other anticholinergics

Methylxanthines

- Mechanism of action not well understood
- Xanthines may relax smooth muscle and increase diaphragm contractility
- Offer no better bronchodilation than beta agonists in routine use.
- Therapeutic dose close to toxic dose

Drug	Brand Name	Route	Peak Activity	Duration
Theophylline	Neulin	oral	1.5-2hrs	Take 6 hrly
	Nuelin SR	oral	4-6hrs	Take 12 hrly
Aminophylline	Aminophylline	IV	-	-

Methylxanthines

- Adverse reactions (main)
 - Tachycardia, ventricular arrhythmia, palpitations, CNS disturbances, coagulation times shortened, GI upset, haematemesis
- Drug interactions (main)
 - Other xanthines, alcohol, beta blockers, cimetadine, propranolol
 - Many others.....



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Leukotriene Receptor Antagonists

- Oral administration
- Selectively antagonise leukotriene receptor (CysLT1) for LTC₄, LTD₄ and LTE₄ (mainly released from mast cells and eosinophils)
- Binding of the leukotriene receptor inhibits physiological action of mediators resulting in relaxation of smooth muscle and some reduction of inflammation mediated by leukotrienes
 - Monteleukast thought to inhibit pathway by binding to receptor site without any agonist activity.
 - Zafirleukast thought to antagonise contractile activity of mediators.



Leukotriene Receptor Antagonists

- Should not be used in acute asthma
- May be useful in exercise induced asthma and aspirin sensitive asthma
- Must be taken regularly for benefit of prophylaxis

Leukotriene Receptor Antagonists	Brand names	Type	Peak Activity	Duration of Action
Monteleukast Sodium	Singulair	Prophylactic	3-4 hrs	~ 24hrs
• Zafirlukast	Accolate	Prophylactic	3-4 hrs	~10 hrs

Leukotriene Receptor Antagonists

- Adverse Reactions (main)
 - Zafirlukast - hepatotoxicity, bleeding, rash, respiratory infection, alopecia, systemic eosinophilia, eosinophilic pneumonia.
 - Montelukast - Headache; abdominal, joint pain; GI upset; hypersensitivity reactions; agitation, aggressive behaviour; palpitations
- Drug interactions
 - Zafirlukast - Warfarin; theophylline; erythromycin; terfenadine; aspirin
 - Montelukast - aspirin

Nedocromil Sodium and Cromoglycate Sodium

- Chloride Channel Blockers
- Mast cell stabilisers
- Mechanism not fully understood
- Thought to block allergen-induced bronchospasm
- Not direct bronchodilators - block airway inflammation pathways by inhibiting release of inflammatory chemolactic and smooth muscle contracting mediators
- Useful in exercise-induced asthma



Nedocromil Sodium and Cromoglycate Sodium

Chloride Channel Blockers	Brand names	Type	Onset of action	Duration of Action
Nedocromil sodium	Tilade	Preventative	Few minutes	Several hours
Cromoglycate sodium	Intal Cromese	Preventative		

Non-steroidal anti-inflammatory medication

Can be used prior to exercise (prophylactically)

Nedocromil Sodium and Cromoglycate Sodium

- Adverse reactions
 - Nedocromil Sodium - Headache; GI upset; cough, pharyngitis, bronchospasm; taste disturbance
 - Cromoglycate Sodium - Transient bronchospasm, throat and tracheal irritation.
- Drug interactions
 - Nil observed.

Inhaled Corticosteroids



- Potent anti-inflammatory agents used in the management of asthma.
- The benefits of inhaled corticosteroids include a reduction in airway inflammation, a decrease in mucus secretion and airway oedema, and a reduction in airway hyper-responsiveness
- Action: thought to reduce the synthesis and secretion of a variety of inflammatory mediators (prostaglandins and leukotrienes) and cytokines

Inhaled Corticosteroids

Corticosteroid	Brand Name	Type
Beclomethasone diopropionate	Qvar	Preventative
Fluticasone propionate	Flixotide	Preventative
Budesonide	Pulmicort	Preventative
Ciclesonide	Alvesco	Preventative

Regular use over weeks to reduce inflammation

Inhaled Corticosteroids

- Adverse reactions (main)
 - Oropharangeal candidiasis, hoarseness, throat irritation, paradoxical bronchospasm, hypersensitivity reactions
 - minimal systemic effects from inhalation meds
- Drug interactions
 - Fluticasone, Budesonide, Ciclesonide- Potent CYP3A4 inhibitors (eg ketoconazole)

Combination medications

- Symptom controller and preventative medication

Symptom controller	Preventative	Brand name
Salmeterol	Flixotide	Seretide
Eformeterol	Budesonide	Symbicort



Practice Exam Question 9

Small airway resistance increases with which of the following?

1 - asthma

2 - emphysema

3 - beta-adrenergic blockade

4 - cholinergic blockade

A 1, 2 and 3

B 1 and 3

C 2 and 4

D 4 only

Practice Exam Question 11

Particles greater than 10 microns in diameter are deposited mainly in the:

- A pharynx
- B trachea
- C alveoli
- D bronchioles

Practice Exam Question 39

Mast cells in human lungs:

- A are situated mainly in the mucosal layers of the airways
- B release mediators if stimulated with histamine inhalation
- C may have their mediator release reduced by pre-treatment with cromoglycate
- D are mostly situated in central rather than peripheral airways

Practice Exam Question 71

A baffle is used on a nebuliser to:

- A break the aerosol into smaller particles
- B entrain room air
- C alter oxygen concentration
- D heat the gas above room temperature

Practice Exam Question 96

Inhaled ipratropium bromide:

- A is synergistic with salbutamol in the treatment of asthma
- B is tasteless
- C stimulates the bronchial cholinergic receptors
- D reaches peak effect slower than salbutamol

Practice Exam Question 97

Which of the following is a common side effect of steroid metered dose aerosol inhalers:

- A cataracts
- B adrenal suppression
- C osteoporosis
- D candidiasis

Have we achieved our objectives?

By the end of this session, participants should be able to

- List three ways aerosol is deposited in the airways ✓
- List the different types of respiratory drugs and their mode of action ✓

On your own – revise aerosol delivery devices – how they work and how to use them.

References - Respiratory Pharmacology

- Mims Online.
Found at URL: <http://www.mims.hcn.net.au>
- The Therapeutic Guidelines- Respiratory.
Found at URL: <http://www.etg.hcn.net.au/>