RESPIRATORY DRUGS

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ANTIHISTAMINES

Histamine (physiologic substance produced by body)

- Chemical mediator found in all body cells
- Released into bloodstream by mast cells in response to allergens, antigens or trauma
- Response to histamine release is generally detrimental and/or physiologically undesirable
    - **Pain - itching**
    - Increase secretion of bodily fluids - gastric, intestinal, bronchial, salivary
    - Smooth muscle contraction - significant for **bronchial constriction**
    - Cerebral blood vessel dilation
    - **Vasodilation** -> flushing, **hypotension**
    - Increased capillary permeability - > **edema** to nose, eyes and throat
    - **Anaphylaxis**: systemic response which is life threatening
        - **Hypotension**, **laryngeal edema** (respiratory arrest)
        - Generalized **hives**

Antihistamines (drugs given to counteract histamines)

MECHANISM

- Block action of histamines via **competitive inhibition** for cell **receptor sites**
    - Histamine production continues unchanged
    - Antihistamine blocks (sits on) receptor site
    - Occupied receptor site prevents histamine from entering cell
    - Histamine cannot exert its detrimental effects because it cannot enter cell

INDICATIONS

- **Allergic disorders**: seasonal, or acute allergen contact (food, plants, animal dander, etc.)
- Parkinson's disease

- **Motion sickness** and **antiemetic**
    Meclizine (Antivert), Diphendydramine (Benadryl), dimenhydrinate (Dramamine), prochlorperazine (Compazine)

    OTHER DRUG CLASSES - used for motion sickness/antiemesis
        Anticholinergics: **scopolamine (Transcop)** - probably the most common
        Phenothiazine:
            promethazine (Phenergan)
            Chlorpromazine (Thorazine), perphenazine (Trilafon)
        Cannabinoid: dronabinol (Marinol)
        Antidopaminergic: metoclopramide (Reglan)
        Trimethobenzamide (Tigan)
        Selective 5HT3: **Ondansetron (Zofran), granisetron (Kytril)**

- OTC hypnotics (Unisom, others) - this use is not widely endorsed by professionals
- Anxiolytic -only **hydroxyzine (Atarax, Vistaril)**

CLASSIFICATION

1ST Generation: **Sedating** - Cross **blood-brain barrier** - older agents
2nd Generation: **Non-sedating** or less sedating - do **not cross blood-brain barrier**

Intranasal agents: local treatment of allergic rhinitis - can cause drowsiness

RECEPTOR BLOCKADE TYPE

H1 receptors: selectively block H1 receptors - treat allergic reactions
H1 **located throughout body** - dermatitis, rhinitis, conjunctivitis, anaphylaxis, etc
Includes 1st generation and second generation agents
H2 receptors: selectively block H2 receptors - used to suppress peptic acid
H2 receptors primarily **located in GI tract** (gastric **acid)**
Includes GI agents for peptic acid e.g. ranitidine (Zantac)
H3 receptors: presynaptic receptors located on nerve terminals
H3 activation inhibits release of histamine and other neurotransmitters

COMMON ANTIHISTAMINES

H1 AGENTS

1ST Generation

diphenhydramine (Benadryl)
chlorpheniramine (Chlor-Trimeton, others)
meclizine (Antivert)
hydroxyzine (Vistaril, Atarax)
dimenhydrinate (Dramamine)

2nd Generation

fexofenadine (Allegra)
loratadine (Claritin)
cetirizine (Zyrtec)
desloratadine (Clarinex)

Discontinued agents
terfenadine (Seldane)
astemizole (Hismanal)

Intranasal agents: Azelastine (Astelin)

H2 AGENTS - GI tract agents to suppress peptic acid

cimetidine (Tigan), ranitidine (Zantac), nizatidine (Axid), famotidine (Pepcid)

SIDE EFFECTS

Problem exists with OTC self-medication of antihistamine, decongestant, antitussive and expectorants

Sedation esp with 1st generation - major problem
Patients must **not drive or operate machinery**

Anticholinergic effects:
Dry mouth, drying of secretions (nasal, oral, etc.)
Urinary retention (contraindicated BPH, other bladder neck obstruction)
Increased intraocular pressure (contraindicated with glaucoma)

Hematologic (rare): hemolytic anemia, pancytopenia

Contraindicated with BPH, urinary retention, glaucoma
- Many **OTC** preparations contain antihistamines
- **Ill-advised for the elderly**
- OTC products advertise "senior cough syrup" (free of antihistamines/decongestants)

DECONGESTANTS

- Most preps can be purchased OTC resulting in potential for interactions and adverse effects
  - Many clients do not "count" OTC meds when asked re medications
  - Many falsely assume that OTC meds are benign and without potential for problems
  - Health care provider must **establish RX and OTC meds when taking history**
  - **Combinations** with antihistamine and/or decongestants, antipyretics are common
  - **Avoid in the elderly** esp those with **hypertension**

- Some decongestant preps are available as RX - usually in combo with other agents

Mechanism: **sympathomimetics** - "mimic" the sympathetic NS ("flight or flight") response
Accounts for many of the side effects: hypertension, tachycardia, etc.
Accounts for the therapeutic effects
Constriction of arterioles in nasal passage -> reduce edema
Dilate bronchioles - help to clear secretions which are causing coughing

Indications
- **Nasal congestion** (rhinitis, sinusitis, URI,)
- **Ocular congestion** (vernal conjunctivitis, "red eyes")

Cautious/Contraindications:
Cautious use: **hypertension, hyperthyroidism**
- Sympathomimetic effect will raise further raise BP and increase HR
- Limited use in well controlled hypertension may be appropriate

Contraindicated: narrow-angle glaucoma, MAO-inhibitor or tricyclic therapy

Side effects
CNS: headache, **nervousness**, tremors, blurred vision
CV: **tachycardia, palpitations**, hypertension, arrhythmias
ENT: nasal irritation and/or dryness, sneezing, **rebound nasal congestion**

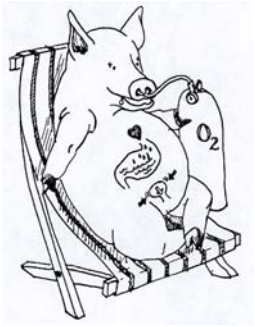
Rebound nasal congestion with prolonged use (> 3 days) - **rhinitis medicamentosa**

- Rebound (greater than original) congestion of nasal vessels
- Users can become "addicted" to decongestants -> require constant use to relieve congestion

REVIEW OF AUTONOMIC NERVOUS SYSTEM

SYMPATHETIC NS - Fight or Flight

- **Increase BP and HR**
- Mobilize energy stores
- Increase blood flow to skeletal muscle
- Divert blood flow away from skin and internal organs
- **Dilation of pupils and bronchiole**



PARASYMPATHETIC NS - Rest and Digest

- "Vegetative" functions
- Digestion, elimination, urination, defecation
- Acts to balance/oppose sympathetic NS
- Essential to maintain life

COMMON DECONGESTANTS

pseudoephedrine Hcl (Sudafed)
oxymetazoline Hcl (Afrin)
phenylephrine Hcl (Neo-Synephrine)
tetrahydrozoline (Visine, Murine) *
phenylpropanolamine (Entex) - withdrawn

note: many OTC combination products contain decongestants
e.g. **Dimetane, Robitussin CF**, **Contact**, **NyQuil,** etcl

* **ocular decongestant** (vernal conjunctivitis, "red eyes")

ANTITUSSIVES

- Indicated to **suppress cough reflex**
- Particularly appropriate in **when cough is excessive or nonproductive** or where results in **excessive fatigue** or **interrupts sleep**
- Both **narcotic** and **non-narcotic** preparations are available
- Avoid with productive cough which clears secretions

- Mechanism: varies with agent
    - Centrally acting: inhibit cough reflex in medulla (opiates, DM)
    - Locally acting: inhibit cough receptors in throat, trachea: (benzoates)

- Available as both OTC and RX products
    - OTC most commonly in **combination with other agents** (decongestants, expectorants)
    - RX: preparations contain either opiates or DM, often in combo with other agents

- **Dextromethorphan (DM)** - now target of teenage **drug abuse**
    - **Non-opioid** cough suppressant
    - Chemically related to opioids but does not cross blood-brain barrier in normal dosing
    - Can cause CNS effects in high dosing - newer source of drug abuse
    - Common agents: **Robitussin DM, Benylin DM, Delsym, Vicks Formula 44**

Narcotic cough suppressants commonly prescribed
- Very effective; nonaddictive for short-term use; relatively low abuse potential
- Cause **significant sedation and drowsiness** - no driving or machine operation
- Potentiate sedation with other sedating agents - synergistic effect
    - Alcohol, barbiturates, hypnotics, sedatives, TCA, phenothiazine
    - Concomitant use can result in excessive sedation
- **Constipation** can be side-effect

COMMON NARCOTIC COUGH SUPPRESSANTS

Codeine: (as codeine phosphate) direct depressant on cough center of medulla
- Onset 15-30 min; duration 3-4 hrs
- **Robitussin A-C, Dimetane DC, Phenergan with Codeine, others**
- Metabolized liver; excreted urine
- S/E: lightheadedness, dizziness sedation, sweating, nausea and constipation

Hydrocodone
- Usually in combo with other ingredients
- **Tussionex, Entuss-D, Hycomine, Hycodan, Vicodin Tuss**
- Weak analgesic and strong antitussive

COMMON NON-NARCOTIC COUGH SUPPRESSANTS

Dextromethorphan HBr
- Most frequently used cough suppressant
- **Robitussin DM, Rondec DM, Humibid DM**; many others
- d-isomer of codeine analogue of levorphanol
- Minimal CNS depression; no analgesic
- No constipation or habituation
- Frequent combo with other products
- 30 mg dose equals 15 mg codeine
- Mechanism: unclear, probably depresses cough center medulla

Benzonatate (Tessalon Perles)
- Structurally related to tetracaine
- Exerts local anesthetic action on stretch receptors thus dampens cough
    - Respiratory passages
    - Lungs pleural
- Does not alter respiratory center at recommended dosages

SIDE EFFECTS
- Sedation, dizziness, nasal congestion, constipation, nausea, GI upset
- Pruritus, skin eruptions, burning in eyes,"chilly" sensation, numbness in hands
- Large doses: CNS stimulation

Carbetapentane tannate (**Rynatuss** and other products by Wallace Pharm)
- Used to control coughing from colds, allergies
- Infrequently used in cough preps in contrast to DM
- Anticholinergic effects

EXPECTORANTS:

- Clinical effects (reportedly)
    - Removes viscous mucus from respiratory tree
    - Stimulates secretions of lubricating fluid

- Efficacy of most non-prescriptive products subject to debate

- Probably no more effective than high fluid intake (6-10 glasses H20) and humidification
- Little evidence to support relief of dry irritative cough via increasing soothing fluid
    - Same effect as cough drop or lozenge
    - Inclusion in preps add little value
- Adverse reactions are rare; few side effects

COMMON EXPECTORANTS

Guaifenesin (Humibid, Robitussin, many others)
- Syrup or long acting tables; no evidence 1 more effective than other
- Questionably effective; low s/e profile

Iodinated glycerol (Tussi Organidin) - removed from market

Potassium iodide (SSKI)
- Enhance secretion of respiratory fluid and decrease viscosity and tenacity of mucus.
- Efficacy not conclusively established
- Iodinated glycerol off market at request of FDA

Ammonium chloride
- Used primarily as systemic and urinary acidifier for metabolic alkalosis
  - Correct chloride depletion
  - Assist urinary excretion of certain basic drugs
- Expectorant in OTC preps; efficacy doubtful
- Use is discouraged

Terpin hydrate:
- Liquid form to stimulate respiratory secretions
- Gastric upset and drowsiness; give with H20

Acetylcysteine (n-acetyl cysteine): Mucomyst, Mucosil
- Decreases viscosity of pulmonary mucus
- Face mask or mouth piece; tent or croupette if large quantities
- Nebulizer may not allow sufficient penetration into obstructed bronchiolar passages
- Not for routine use in bronchial asthma because irritating and possible reflex bronchospasm.
- Prompt removal of liquified secretions necessary; mechanical suction prn.
- Can also be given for OD of acetaminophen - blocks formation of toxic metabolites

BRONCHODILATORS

- Several classes of drugs which reverse airway constriction - primarily used to treat **asthma**
  - **Sympathomimetic bronchodilators** e.g. epinephrine
  - **Anticholinergic agents** e.g. ipratropium bromide (Atrovent)
  - **Adrenergic agents** (B2-agonist) - example albuterol (Proventil)
  - **Methylxanthines** - example: theophylline (Theodor)

REVIEW OF THE PATHOPHYSIOLOGY OF ASTHMA

Clinical Features

- Airway hyperresponsiveness
- Airway inflammation
- Reversible airway obstruction
- Respiratory muscle spasm
- Thickening of respiratory mucosa related to edema
- Excessive secretion of viscous mucus

Mechanism

1. Symptoms result secondary to exposure to provoking factors
   - Trigger substances: dust, pollen, etc.
   - Release of endogenous allergen mediators via antigen-antibody reaction *
     - Histamine - Leukotrienes
     - Eosinophil chemotactic factor * Release is from mast cells
   - Substances interact w bronchiole smooth muscle to cause contraction
   - Atopic asthma: appears without exposure to provoking agent
     - Associated with other allergic disorders
     - Young persons; progressively severe

2. Activation of parasympathetic reflex pathways
   - Hypersensitive in asthma
   - Reflex parasympathetic response triggers release of acetylcholine (ACh)
   - ACh constricts bronchiole smooth muscles
   - Triggering factors: **mast cell allergens, cold, stress, infection, exercise**

Airway inflammation - key role in asthma treatment

- **Inflammatory** changes trigger **hyperresponsiveness-bronchoconstriction**
  - Occur in airway walls: mast cell degranulation, lymphocyte infiltration
  - Typified by migration of inflammatory cells and edema

- **Locally-acting antiinflammatory agents reduce airway hyper-responsiveness**
  - Inhaled steroids: **triamcinolone (Azmacort), fluticasone (Flovent)**, others
  - Mast cell stabilizers: **Nedocromil (Tilade) - Cromolyn (Intal)**
  - Leukotriene inhibitors: **montelukast (Singulair)**, others

- Acute attack:
  - Adrenergic bronchodilators**: Alupent (Proventil), salmeterol (Serevent)**, others
  - **Epinephrine** (SQ or IV) if severe or life-threatening

SYMPATHOMIMETIC BRONCHODILATORS used in treatment of bronchial asthma and other COPDs

- **Epinephrine** (parenteral) relieves respiratory distress during an acute asthmatic attack
    - Used parenterally (IV or SQ) in severe life-threatening attack
    - Also available as OTC prep: **Primatene Mist**
- Ephedrine: less potent bronchodilator with pronounced central excitatory effects

ANTICHOLINERGIC AGENTS

- Commonly used in COPD - **Ipratropium bromide (Atrovent**) - main clinical agent used
- Effective bronchodilators - most commonly used for COPD
- Naturally occurring belladonna alkaloids (atropine) used for many years to treat asthma
- S/E with systemic use limits there usefulness
- Inhalation therapy with **ipratropium (Atrovent)** used as bronchodilator
    - Quaternary amine
    - Poorly absorbed from bronchial tree thus local effect
    - Useful in asthma from irritants, smoking, emotional stress
- Combination product is available **Combivent (ipratropium bromide and albuterol)**
- Useful in treating bronchitis and emphysema
- Mechanism: anticholinergic action on bronchioles
    - Prevent increase in cyclic guanosine monophosphate (GMP) from parasympathetic nerve activation
    - Blocks activity from increased vagal (parasympathetic) activity
    - Blocks contraction of bronchiolar smooth muscle:
    - Blocks increase in mucus secretion
    - May inhibit acetylcholine-induced release of allergenic mediators from mast-cells

SIDE EFFECTS:

- Exacerbation of symptoms
- Cough, dryness of oropharynx, gastric upset, nervousness, anticholinergic effects
- Also common: dizziness, H/A, palpitations, skin rash, blurred vision

CONTRAINDICATIONS

- Allergy to atropine or its derivatives
- Allergy to soya lecithin, peanut or related foods (inhaler)

PRECAUTIONS

- Not for primary treatment of acute attack
- Avoid eyes
- Narrow-angle glaucoma, BPH and bladder neck obstruction
- Pregnancy category B; nursing mothers

XANTHINES: use is increasingly less frequently due to side effect profile

Side effects are significant esp with rapid IV administration - need **slow IV administration**

SIDE EFFECTS

Tachycardia, palpitations, cardiac arrhythmias, dizziness, angina-like pain, hyperventilation, hypotension, **CNS excitation,** headache, nausea, vomiting, **tremors**, seizure (rare)

XANTHINE BRONCHODILATORS

aminophyllin (Phyllocontin, Truphylline)
dyphylline (Dilor, Dyflex, Lufyllin, Neothylline)
oxtriphylline (Choledyl)
theophylline (Theo-Dur, Slo-Phyllin)

- Weaker bronchodilator vs B2 agonists
  - Less effective vs B2 agonist
  - More toxic thus less frequently used
- Available in time-released oral form
- Can measure **blood levels**:
- **Narrow therapeutic window** - potential for **toxicity**
- Should **wean off** gradually to avoid withdrawal symptoms
  - Withdrawal is similar to caffeine (related compound)
  - **Headaches** including migraine

ADRENERGIC AGENTS (B2-AGONIST)

B-adrenergic agonists (aka **beta-agonists** or **B2-agonists**)

Most commonly used of the various types of bronchodilators

Stimulate **beta 2 receptors** found most in the lung ("flight or flight" response) resulting in **bronchodilation**

ADRENERGIC ANTAGONISTS

Beta-adrenergic blockers
- B1 - cardioselective
- B2 - nonselective

Alpha 1 adrenergic blockers
- Alpha1 antagonist (eg prazosin)
- Nonselective (phenoxybenzamine)

Previously was mainstay of asthma treatment; - **no longer first line therapy** * **Inhaled steroids** are considered first line agents.

SIDE EFFECTS

- Side effects due to non-selectivity
  - Affects not only lungs but other organs as well
  - Nonselective effects increase at higher doses

Tachycardia, jitteriness, cardiac stimulation, palpitations, tremor, nervousness, headache, excitement

SELECTIVE B2 ADRENERGIC BRONCHODILATORS

- **Albuterol** (Proventil, Ventolin, Volmax)
- **Metaproterenol** (Alupent, Metaprel)
- **Pirbuterol** (Maxair)
- **Salmeterol** (Serevent)
- **Terbutaline** (Brethaire, Brethine, Bricanyl) *
- **Bitolterol** (Tornalate)
- **Isoetharine** (Arm-a-Med Isoetharine, Beta-2, Bronkosol)
- **Isoproterenol** (Isuprel) **

* used for **preterm labor** since it nonselectively affects smooth muscle
** potent but less used due to high side effect profile

* Mounting evidence that chronic use of inhaled **adrenergic bronchodilator** may be associated with **increased mortality and morbidity**. Inhaled steroids to prevent inflammatory process is encouraged as first-line approach

** Nebulized inhalation treatments with a face mask often used routinely for children too young to use inhalers. Inhalation therapy used in adults in emergency (ER, office visit) setting for acute exacerbation and also inpatient settings where more intense therapy is indicated

- Most agents available as **metered-dose inhalers**
- Albuterol: numerous formats including solution for nebulized inhalation treatments **
  Ventolin: syrup, Rotacaps, nebules, solution, metered dose inhaler
  Proventil: syrup, Repetabs, HFA inhaler, solution, metered dose inhaler

COMMON BETA-2 AGONISTS

LONG ACTING B2 AGONISTS

salmeterol (Serevent)
- Not for acute exacerbations
- Not a substitute for inhaled corticosteroids
- Can use for exercise-induced asthma (45 minutes before); school day/gym

Proventil Repetabs (extended release albuterol sulfate)

SHORT ACTING B2 AGONISTS

albuterol sulfate (Proventil)
bitolterol mesylate (Tornalate)
pirbuterol acetate (Maxair, Maxair Autohaler)
terbutaline (Brethaire, Brethine, Bricanyl)

- Provide quick relief; pretreat exercise-induced asthma.
- Patient who needs only 1-2 times per week, needs antiinflammatory as well

INHALED CORTICOSTEROIDS

- Synthetic steroids with glucocorticoid activity
- Improve pulmonary function
- **Reduce need for adrenergic bronchodilators** or other antiasthmatics
- Decrease bronchial reactivity to substances (allergens which cause bronchial constriction)
- **First line therapy for mild asthma** *
    - Inhaled bronchodilators used for acute bronchospastic episodes.
    - Chronic use of B2-agonist can worsen asthmatic symptoms and increase M/M
    - Decrease local inflammatory process
- Inhaled steroids have reduced incidence of adverse effects vs systemic steroids
- Synergistic effects on bronchial smooth muscle when used with other antispasminogenics
- **Effect seen within 2-4 weeks**

- Caution when transferring from systemic to inhaled due to **suppression of H-P-A axis**
    - Inhaled steroids have little if any systemic absorption - no axis suppression
    - Exogenous PO steroids suppress normal levels for months
    - **PO steroids may be needed** during times of sudden demand on adrenal function during transition period (trauma, stress, surgery, etc.)
- Available in **metered-dose inhalation units** (inhalers)
- Used in **combination with B-2 agonist agents** (also available as inhalers)
- Combination inhalers available **salmeterol and fluticasone (Advair)**

* Inflammation of respiratory tree has well established role in increased susceptibility of bronchiospasm in response to spasmogens

SIDE EFFECTS

- Throat irritation, coughing, dry mouth
- Hoarseness
- Oral and pharyngeal fungal infections
    - Reduced w gargling and mouth rinsing
    - Reduced with use of **spacer devices**

LONG-TERM USE INHALED AGENTS

- Associated with bone demineralization although less so than with systemic steroids *

- Steroid use in children is traditionally avoided due to growth suppression *

- Other side effects of systemic steroids would NOT appear to be a problem with inhaled agents
    - Immunosuppression
    - Fluid retention
    - Suppression of H-P-A axis

COMMON STEROIDS

INHALED CORTICOSTEROIDS (long-term control)

beclomethasone dipropionate
- Beclovent
- Vanceril
- QVAR

budesonide (Pulmicort)
flunisolide (AeroBid)
fluticasone propionate (Flovent), **triamcinolone acetate** (Azmacort)

SYSTEMIC STEROIDS

methylprednisolone
prednisolone, prednisone

* Newer agents (**fluticasone**) are complete destroyed on first-pass through liver thus may be safer - approved for use in children as young as 2 yrs

NASAL STEROIDS

- Used to control allergic rhinitis: seasonal or perennial
- No systemic absorption - no systemic side effects
- Can be used in combination with inhaled and/or systemic steroids
    - Asthma has high correlation with allergies
- Research suggests agents are effective with onset of use versus delayed benefit

INTRANASAL STEROIDS

Beclomethasone dipropionate	Aqueous nasal spray	**Beconase AQ**	1-2 sprays each nostril qd	Allergic and vasomotor rhinitis; prophylaxis of nasal polyp recurrence
Beclomethasone dipropionate	Nasal spray/inhaler	**Beconase**	1 spray each nostril bid-qid	Refractory allergic rhinitis; prophylaxis of nasal polyp recurrence
Beclomethasone dipropionate	Aqueous nasal spray	**Vancenase AQ Double Strength**	1-2 sprays in each nostril qd	Allergic and vasomotor rhinitis; Prophylaxis of nasal polyp recurrence
Beclomethasone dipropionate	Nasal inhaler	**Vancenase Pockethaler**	1 spray each nostril bid-qid	Allergic and vasomotor rhinitis; prophylaxis of nasal polyp recurrence
Budesonide micronized suspension	Aqueous nasal spray	**Rhinocort Aqua**	1-2 sprays each nostril qd	Seasonal or perennial allergic rhinitis symptoms in patients 6 years or older
Budesonide micronized suspension	Nasal spray	**Rhinocort**	2 sprays each nostril qd	Seasonal or perennial allergic rhinitis in adults and children; non allergic rhinitis in adults
Flunisolide solution	Nasal spray	**Nasalide**	2 sprays each nostril bid	Refractory allergic rhinitis
Flunisolide	Aqueous nasal spray	**Nasarel**	2 sprays each nostril bid; may increase to 2 tid	Seasonal or perennial rhinitis
Fluticasone propionate	Aqueous nasal spray	**Flonase**	2 sprays in each nostril qd or 1 spray in each nostril bid	Seasonal and perennial allergic and nonallergic rhinitis
Mometasone furoate	Aqueous nasal spray	**Nasonex**	2 sprays in each nostril qd. Begin 2-4 weeks before pollen season	Seasonal or perennial rhinitis
Triamcinolone acetate	Aqueous nasal spray	**Nasacort AQ**	2 sprays in each nostril qd	Seasonal and perennial allergic rhinitis

Triamcinolone acetate	Aqueous nasal spray	**Nasacort**	2 sprays in each nostril qd	Seasonal and perennial allergic rhinitis
Triamcinolone acetate	Nasal spray	**Tri-Nasal**	2 sprays in each nostril qd; For faster onset 4 sprays in each nostril qd or 2 sprays in each nostril bid; reduce dose as condition improves	Treatment of seasonal and perennial allergic rhinitis symptoms

MAST CELL STABILIZERS

MAST CELL STABILIZERS

cromolyn sodium (Intal)
intranasal cromolyn (Nasalcrom)
nedocromil (Tilade)

CROMOLYN SODIUM (INTAL)

- Adjuvant **antiinflammatory agents** for management of **bronchial asthma**

- **Not as potent** as inhaled steroids and require more doses per day (compliance issues)
- **No intrinsic bronchodilator** activity
- **Not for acute attacks**

- Available as **inhalation agent (metered dosing)** and as solution for nebulization
- Commonly as used for children to counteract inflammation so as to avoid use of steroids *

* Nebulizer treatments for children, even very young children, frequently involve albuterol solution and cromolyn sodium solution placed into nebulizer and administered via face mask

MECHANISM

- **Stabilizes mast cell** membrane
- Inhibits release endogenous allergens from mast cells (inflammatory response)
  - **Histamines**
  - **Leukotrienes**
- May increase cyclic AMP in bronchioles

DOSING

- Adults and children > 5 yrs: 2 puffs QID or 2 puffs 10-60 min before precipitant
- Children 2-5 yrs: 1 amp in nebulizer QID or 60 min before precipitant

PRECAUTIONS

- Pregnancy class B; approved for use in children 2 yrs and older
- Lactation
- Avoid abrupt cessation of therapy
- Coronary artery disease or arrhythmias (inhaler)
- Discontinue if eosinophilic pneumonia occurs

AVAILABLE MODALITIES

- Solution (2 ml amps) for use with nebulizer
- **Metered dose inhaler**: 8.1 g (112 inhalations); 14.2 gm (200 inhalations)
- **Intranasal spray** - see below

INTRANASAL CROMOLYN (NASALCROM)

- Indicated for **allergic rhinitis**
- 1 spray each nostril 3-6 times per day
- Side effects are rare; drug is well tolerated
- Effects apparent within several weeks
- Use antihistamines or decongestants initially

ADVERSE REACTIONS

Bronchospasm, throat irritation, bad taste, cough, wheezing, nasal congestion, aphylaxis

NEDOCROMIL (TILADE)

- **Inhaled anti-inflammatory** similar to cromolyn
- Maintenance therapy of mild to moderate bronchial asthma
- **No intrinsic bronchodilator** effects; **not for acute attacks**
- **Bad taste** can be a problem with compliance
- QID dosing - compliance issues

MECHANISM: **inhibits** bronchoconstrictor response to **mast cell allergens**

MODALITIES:
- **Tilade Metered Dose Inhaler** (16.2 gm - 104 sprays)
- **Tilade Nebulizer Solution** 0.5% (2 ml amps

DOSING
- Inhaler: 2 sprays QID - adults and children > 6 yrs
- Nebulizer solution:
  - Under 2 years not recommended
  - 2 yrs and older; adult 1 amp by nebulizer QID
  - 2-5 yrs w mild asthma 1 amp by nebulizer TID

PRECAUTIONS
- Monitor when reducing systemic or inhaled steroids
- Cough, bronchospasm
- Pregnancy category B; nursing mothers

ADVERSE REACTIONS
- **Unpleasant taste**
- Dysgeusia
- Upper respiratory symptoms
- GI upset

LEUKOTRIENE ANTAGONISTS

AGENTS : **Zafirlukast (Accolate), zileuton (Zyflo), montelukast (Singular)**

- **Not for use with acute attacks**
- Antiinflammatory effect is **less potent than inhaled corticosteroids**
- May be more convenient for mild persistent vs inhaler
- May reduce quantity of inhaled/PO steroids for severe patients
- Good for ASA-induced asthma
  Protects against environmental substances to which ASA-sensitive patients have cross-reactions

MECHANISM

- Competitive leukotriene D4 and E4: components slow-reacting substance anaphylaxis
- Cysteinyl leukotriene production and receptor occupation correlated with asthma pathophysiology
  - Airway edema
  - Smooth muscle
  - Altered cellular activity associated w inflammatory process

LEUKOTRIENE ANTAGONISTS

Zileuton (Zyflo):
Zafirlukast (Accolade)
Montelukast (Singular) -

COMPARISON OF AGENTS

Zileuton (Zyflo): unfavorable side effect profile - QID dosing is 600 mg QID

Hepatotoxic - requires qid dosing
- Evaluate liver function before and during therapy
- Caution with ETOH consumption
- Discontinue with signs of liver disease

Interactions
- Must reduce dosing of theophylline 50%
- Can increase PT with anticoagulation therapy
- Potentiates warfarin, theophylline
- Monitor with drugs metabolized by CYP3A4

- Adverse reactions: **dyspepsia, pain, nausea, asthenia, H/A, myalgia, others**
- Not indicated for use with children, pregnancy category C; not for lactation

Zafirlukast (Accolade) - 20 mg BID (empty stomach)

- Children's dosing: 7-11 yrs 10 mg bid; 12+ years: dose as adult
- Can increases PT with anticoagulation therapy
- Bid dosing - take on empty stomach (1 h before; 2 h after meals)
- Few cases of Churg-Strauss syndrome
- Decreased levels with erythromycin and theophylline; increased levels w ASA
- Potentiates warfarin, may increase theophylline levels
- Caution with drugs which are metabolized by elements of cytochrome system
    - CYP2C9: tolbutamide, phenytoin, carbamazepine
    - CYP34A: dihydropyridine Ca agonists, cyclosporine, cisapride
- Adverse reactions
    - H/A, infections (respiratory tract), GI upset, pain, fever
    - Elevated liver enzymes (rare: follow up if occurs)
- Indicated for children 7 yrs and older; pregnancy category B
- Not recommended for use with nursing mothers
- Caution when withdrawing from oral steroids

Montelukast (Singular) - 10 mg QD HS - most commonly used agent

- Once daily (qd) dosing
- Children's dosing: chew tabs
    - 2-5 yrs: one 4 mg chew tab in pm
    - 6-14 yrs: one 5 mg chew tab in pm
    - 15 years or older: dose as adult
- Relatively clean side effect profile
    Adults: H/A, asthenia/fatigue, fever, GI disturbances
    Children: flu/cold symptoms, ear/leg pain, thirst, urticaria
- Monitor with drugs that induce CYP450 (phenobarbital, rifampin)
- Indicated for children 2 years and older, pregnancy category B
- Caution when withdrawing from oral steroids
- Caution with nursing mothers