

Drugs for Asthma

Dr. M. Shlafer

Pharm 210

© Copyright 2009, Marshal Shlafer

You may download and print one copy of this presentation for your personal educational use. You may not distribute the printed copy or the computer file to others, make additional copies in any form (printed or electronic), or make a public performance of the contents (*including for teaching or other classroom use*), whether free or for payment, without my written permission.

A “Working Definition” of Asthma

...a chronic and recurrent pulmonary condition involving airway inflammation and subsequent hyperreactivity of airway smooth muscles to a variety of bronchoconstrictor stimuli; ...in asthma, the bronchoconstriction is reversible, whether spontaneously or in response to drug therapy. (In chronic obstructive pulmonary disease — COPD... emphysema and chronic bronchitis, the bronchoconstriction is NOT reversible.)

Main Drug Classes

- **Antiinflammatories**
 - Corticosteroids
 - Leukotriene “modifiers”
 - Mast cell “stabilizers”
 - IgE antibodies
- **Bronchodilators**
 - Sympathomimetics
 - Methylxanthines
 - Antimuscarinics

Drugs Are Used For...

Long-term preventive therapy
 (“control meds”)

and/or

Acute symptom control
 (“rescue meds”)

to

↓ **Inflammation** (the key factor)

or

Bronchodilate

General Tx. Goals

- Few or no chronic symptoms day or night
- Minimal/no flare-ups
- Minimal use of short-acting β -2 agonists (i.e., little/no need for rescue)
- Minimal/no adverse drug effects
- Full daily activities w/o limitations

Corticosteroids (Glucocorticoids)

- The “cornerstone” of Tx.
- ↓ Inflammation
- Aren’t bronchodilators, may boost actions of bronchodilators
- “Restore” sympathomimetic efficacy that’s lost when it’s needed most
- “Ideal drugs... if not for side effects” — when given systemically

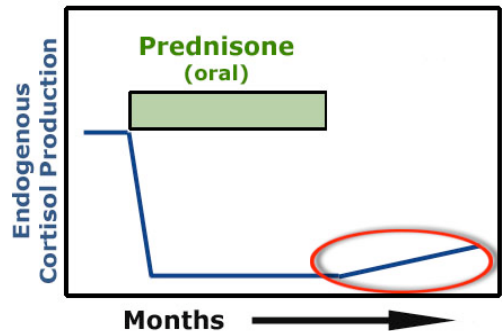
“Systemic” Corticosteroids - I.

- Parenteral
- Oral (e.g., *prednisone*)
 - Mainly one (but important) part of larger plan for severe, persistent or poorly controlled asthma
 - Cause side effects during therapy
 - Easy to start tx., harder to stop safely

Some Typical Systemic Steroid Side Effects (dose-dependent)

- Fluid/electrolyte: Renal Na, H₂O retention
- Metabolic and Endocrine
 - Altered fat, protein metabolism, hyperglycemia (a particular problem for diabetics)
 - Long-term ↓ of endogenous cortisol production, release, regulation
 - ↓ lineal growth in kids (growth-hormone-related)
- Immunosuppression
- Various CNS/mood changes

Even “brief” use of systemic steroids can cause long-term suppression of endogenous cortisol production, put patient at risk of withdrawal/adrenal insufficiency



Orally Inhaled Steroids

Example: Beclomethasone (VANCERIL)

- Minimal systemic absorption, so minimal systemic effects
- Local (airway) antiinflammatory actions
- Prophylaxis only
- Used alone or + other drugs, depending on asthma frequency, severity
- Side effects:
 - hoarseness, cough
 - thrush
- Compliance considerations

Orally Inhaled Steroids... *When Might You Use Them?*

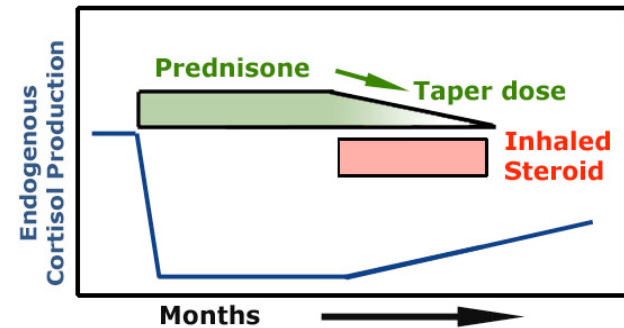
- Preferred monotherapy for mild persistent asthma (low doses)
- Low-moderate doses, ± long-acting β -agonist, for moderate persistent asthma
- High doses + long-acting β -agonist + oral steroid (if needed) for severe persistent asthma
- *Often considered the FOUNDATION of long-term control therapy*

Inhaled steroids are not associated with a “rush” of relief when used. It takes about 2 weeks of use for “noticeable” improvement to be sensed. These make for compliance issues.

Switching from Oral to Inhaled Steroids: Be Careful

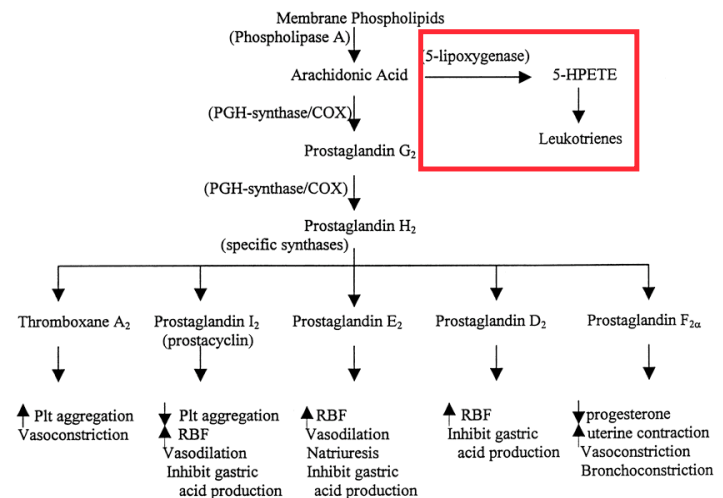
- Oral steroids....
 - suppress adrenal cortex but provide blood levels of synthetic hormone sufficient to maintain normal “stress responses”
- Inhaled steroids
 - don’t provide circulating steroid, and so...
 - don’t prevent problems occurring with discontinuing oral steroids

Switching from Oral Steroids to Inhaled Steroids: Taper Oral Agent, Overlap Both Drugs for a While



Leukotriene Metabolism and Airway Inflammation, and the Roles of “Leukotriene Modifiers” in Asthma Therapy

The Lipoxygenase Pathway



LT Receptor Antagonists

Prototype: Montelukast (SINGULAIR)

- **Block LT receptors, “interrupt” various inflammatory processes incl. bronchoconstriction, inflammatory cell migration, local edema, that occur when LTs activate their receptors**
- **Not bronchodilators *per se***
- **For control tx. only, not rescue**
- **“Modestly effective”**

LT Modifiers...

When Might You Use them*?

- **Mild-persistent symptoms, alternative to inhaled steroid (or other meds)... but using a steroid is preferred**
- **Moderate-persistent: supplement to inhaled steroid**
- **Work well for some patients, seem not to work at all for others**

Mast Cell “Stabilizers” Cromolyn and Nedocromil

- **Block Ca flux into, ↓ mediator release from, mast cells**
- **Orally inhaled**
- **Negligible toxicity, few serious side effects**
- **Me-too drug: nedocromil (TILADE)**
- **See your histamine/antihistamine notes**

Adrenergic (Sympathomimetic) Drugs for Asthma

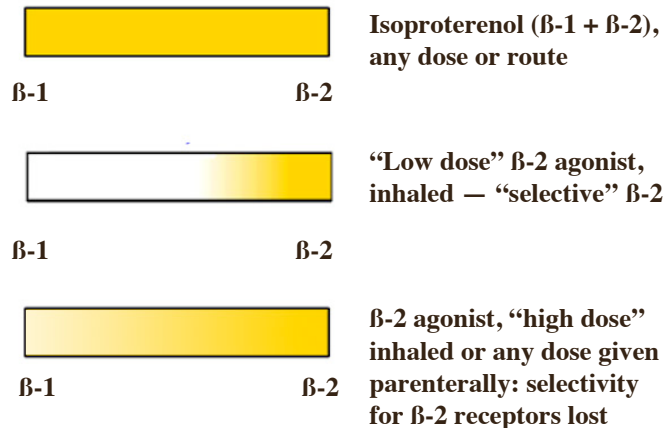
“Selective” β_2 Agonists

- **Prototype: Albuterol (PROVENTIL)**
- **Airway action:**
 - **Bronchodilation**
 - **NO antiinflammatory activity**

Sympathomimetics: Administration Routes

- **Orally inhaled**
 - » control (all) or rescue
 - » most selective for β_2 - airway effects
- **Parenteral**
 - » for acute s/sx
 - » wholly *nonselective* for β_2 /airways

The Selectivity of So-called β_2 Agonists Depends On Dose and Administration Route



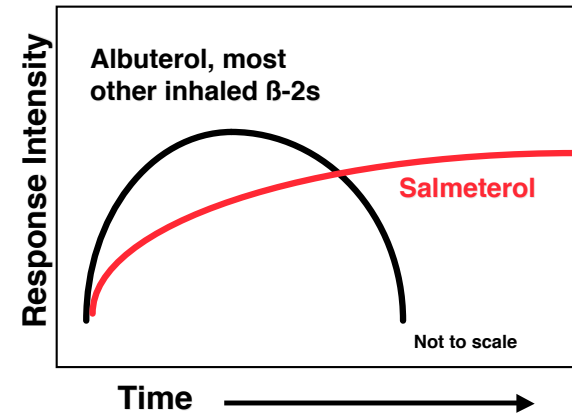
Rapidly-Acting Inhaled Sympathos

The *only* meds Pts can self-medicate with to stop an attack quickly (rescue)

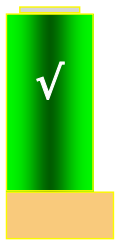
Salmeterol (SEREVENT)

- β -2 agonist with *slow onset, long duration*, vs. albuterol and most others, and so a control med only
- NOT suitable for rescue
- NOT a substitute or replacement for corticosteroids when corticosteroids are indicated
- Recent FDA warnings re: fatalities

Salmeterol (SEREVENT)



Inhaled Drugs for Rescue Therapy?



Short-Acting
Sympathomimetic,
e.g., albuterol:
Yes



Salmeterol,
steroid,
cromolyn:
No!

Sympathomimetics: Problems, Limitations

- Tolerance
 - Long-term (overuse)
 - Acute: adrenergic bronchodilators lose much of their bronchodilator efficacy in the face of severe hypoxia, acidosis
- Side Effects (β_1 & β_2)
 - Cardiac/CV
 - Skeletal muscle tremor
 - Metabolic

What Is “Overuse” of Short-Acting Sympatho Inhaler for “Rescue?”

- Per some docs: > once a day
- Per NIH: > twice a week
- Refill more than 2x/yr.

In the “final stages” of asthma, when blood pH falls dramatically (respiratory acidosis), and blood pO_2 does too (hypoxia), airway smooth muscle cells lose their ability to respond well to bronchodilators.

We “restore” the responsiveness by:

- giving the patient O_2
- correcting blood pH, and
- giving them a parenteral corticosteroid

Other Sympathomimetic Bronchodilators

- Isoproterenol
- Ephedrine
- Epinephrine

Methylxanthines

Prototype: Theophylline

Largely outmoded and potentially dangerous bronchodilators

Methylxanthines: Limitations, Problems

- *Very low margin of safety*
- **Must normalize dose to body wt., adjust dose further in other ways**
- **Common drugs (P450 inhibitors or inducers) interact to alter metabolism, half-life, blood levels**
- **Side effects**
 - **CNS stimulation most common**
 - CV stimulation
 - GI irritation/ulcerogenesis
- **Many formulations that aren't equipotent**

Important

Due to low margin of safety, DDIs, SEs, relatively low efficacy, toxicity, other “problems,” and availability of better drugs, methylxanthine use is seldom justified as “primary” therapy; regardless, they should be prescribed only by physicians very familiar with the drug and its potential adverse effects — i.e., pulmonologists

Theophylline Toxicity

- **Progressive CNS stimulation**
- **Primary cause of death:**
 - » **seizures → apnea during seizures**

Antimuscarinics

- ↓ ACh-mediated bronchoconstriction
- **Atropine:** inhaled, for status asthmaticus
- **Ipratropium (ATROVENT)**
 - Inhaled, quaternary, limited absorption
 - FDA-approved for COPD
- **Concerns w/ “routine” use of systemic antimuscarinics in ambulatory patients (next slide)**

Airways Before, After Systemic Antimuscarinic



Before: Airways constricted, LOTS of thin, watery mucus formed.



After: Airways dilated, mucus volume reduced a bit, *but* mucus becomes very viscous and lodges in, and blocks, airways (unless we can do something to avoid/treat it)

What other drugs or drug classes cause atropine-like side effects?

If systemic antimuscarinics pose problems for patients with even mild-moderate asthma, why in the world would we use atropine for severe/life-threatening asthma (status asthmaticus)?

Drugs to Avoid ...or Use Very Cautiously*

- β -Blockers
- Muscarinic agonists
- ACh Esterase inhibitors
- Antimuscarinics (systemic)
- NSAIDs (\downarrow formation of bronchodilator PGs)
- Diuretics (can cause dehydration, which thickens mucus)

* You should be able to figure out why.