



Michael Zacharisen, MD

MEDICATIONS AND ASTHMA

Case 1:



- 7 y/o (son of a respiratory therapist)
- Asthma: not controlled
- PMD: changed him from Fluticasone to Fluticasone/Salmeterol
- Within a week
 - More cough, wheezing, increased albuterol use
 - Difficulty with exercise; coughing at night
- CC: something's not right!

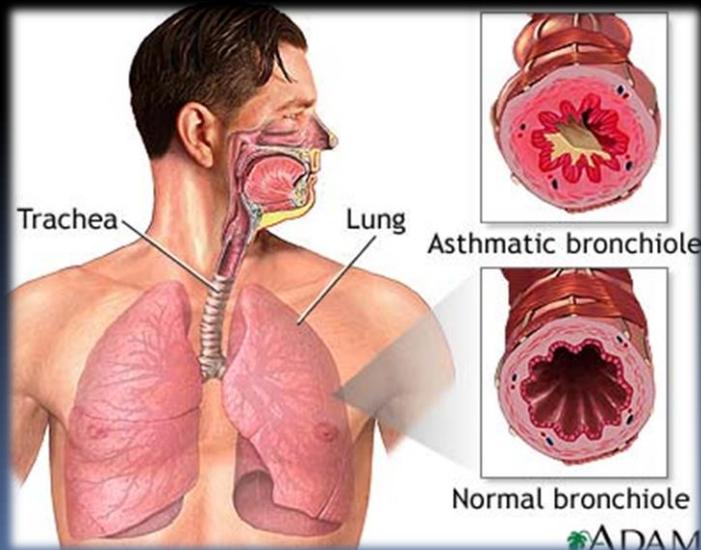
Medications Worsening Asthma

- SABA (short-acting beta agonists)
- LABA (long-acting beta agonists)
- Aspirin/NSAIDs
- Beta-blockers
- ACE inhibitors



Asthma: Pathophysiology

- Chronic Inflammation
 - Eosinophilic
 - Leukotrienes
- Bronchoconstriction
- Airway hyper-responsiveness



SABA



- Quick-relief bronchodilator
 - Albuterol (ProAir, Ventolin, Proventil)
 - Lev-albuterol (Xopenex)
 - Pirbuterol (Maxair)
- Adverse effects:
 - Transient fall in pO_2 : V/Q mismatch [increased perfusion of under-ventilated lung]; 50% of pts
 - **Paradoxical bronchospasm**: rare; can be severe
 - With: nasal congestion, flushing, itching or stridor
 - Inhalation solution (n=58), MDI (n=126) ,tablet

SABA



- Mechanism:
 - Isomer, propellant, preservatives, excipient?
 - Reports for **albuterol** and **lev-albuterol** (optical isomers-same chemical structure but mirror images)
 - Vocal cord dysfunction: solution osmolarity
- Diagnosis:
 - Bronchospasm within minutes + other symptoms
- Treatment:
 - Use suitable alternative: consider SAMA

LABA (Long-Acting Beta-Agonists)

- LABA

- Salmeterol (Serevent, in Advair)
- Formoterol (Foradil, in Symbicort & Dulera)
- Aformoterol (Brovana for COPD)

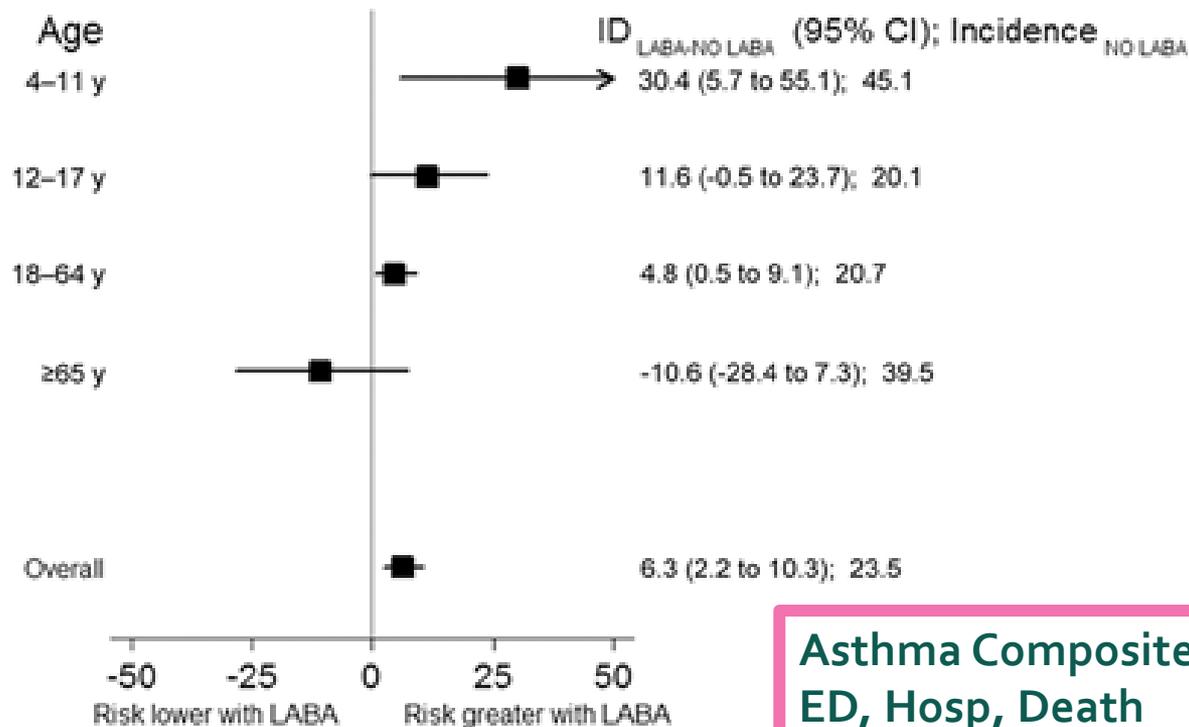
- “Black Box Warning” and 2/18/2010 “Safety Announcement”

- “Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma.”



Risks of LABA according to age

Incidence difference for asthma composite index according to age for LABA versus no-LABA therapy.



Asthma Composite Index:
ED, Hosp, Death

Asthma composite incidence difference per 1000 patient-years

McMahon A W et al. *Pediatrics* 2011;128:e1147-e1154

60,954 total pts in 110 trials, 2 deaths (4-17 y/o) in 9807 kids

©2011 by American Academy of Pediatrics

PEDIATRICS®

LABA: FDA Recommendations

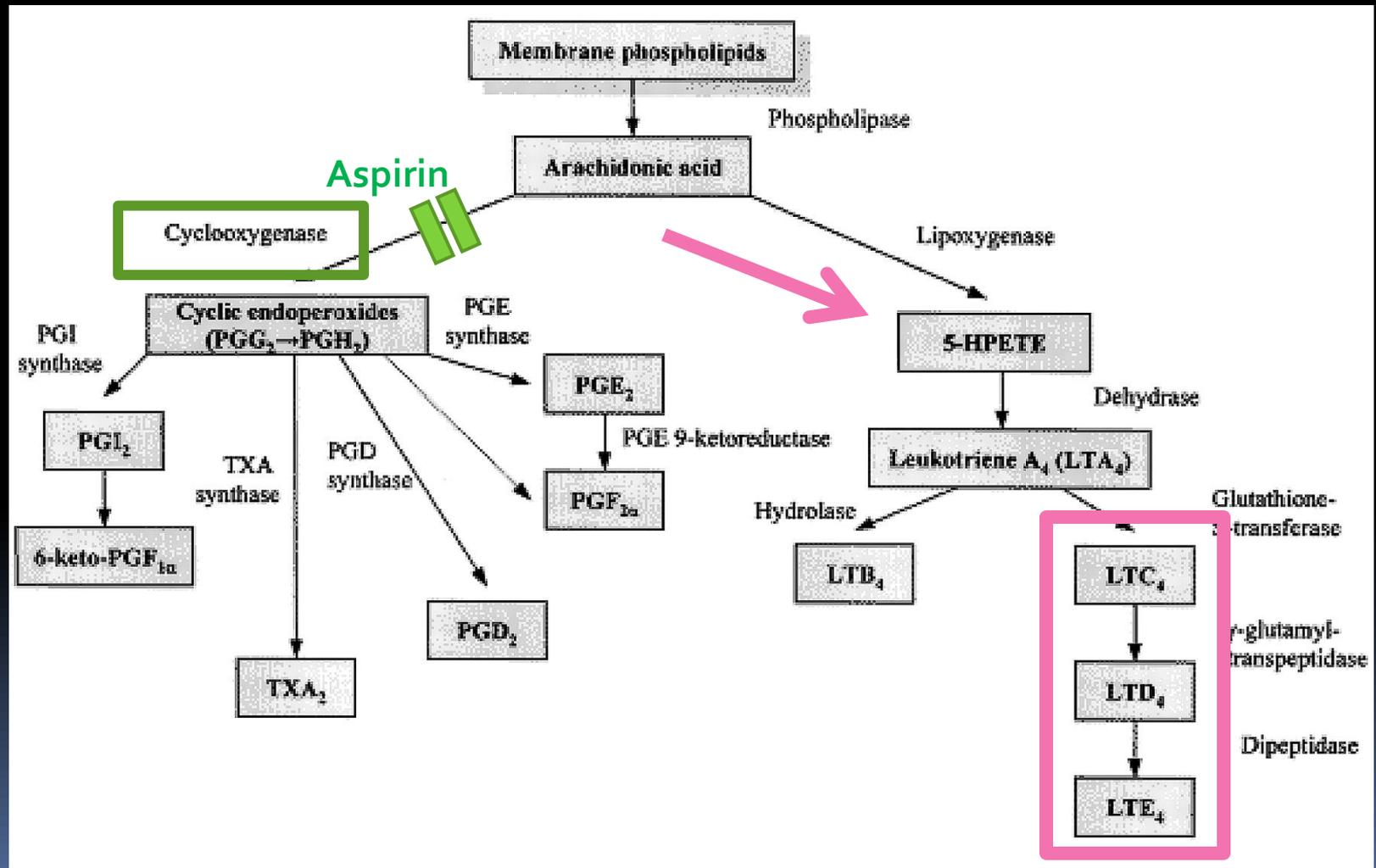
- Use of LABAs is contraindicated without the use of an asthma controller medication such as ICS. Single-ingredient LABAs should **NOT** be used alone.
- LABAs should only be used long-term in pts whose asthma cannot be adequately controlled on ICS.
- LABAs should be used for the **shortest duration of time** required to achieve control of asthma and discontinued, if possible, once asthma is controlled.
- Pediatric/adolescent pts who require addition of a LABA to ICS should use a **combination product** to ensure compliance with both medications.

Aspirin



- **AERD**: Aspirin-Exacerbated Respiratory Disease
- Within **3 hrs** of taking aspirin or NSAID
 - Asthma flares
 - Nasal congestion and discharge.
 - Reactions can be violent/lead to severe difficulty breathing.

Mechanism of Action: Aspirin



How common is aspirin allergy?

- Depends on population being tested. Usually occurs in adults.
- General population, prevalence is **0.6% to 2.5%**.
- Up to **21%** of pts with asthma will have asthma triggered by aspirin.
- **30-40%** with nasal polyps and chronic sinusitis



Aspirin Allergy: Diagnosis & Treatment

- Diagnosis:
 - History
 - No available skin test or blood test
- Treatment:
 - Avoid aspirin & NSAIDs
 - Leukotriene modifiers/LO inhibitors
 - Aspirin desensitization





These Common Medicines Contain Aspirin

Alka Seltzer	Equagesic Tablets	Panasal
Anacin	Equazine	Percodan Tablets
Arthritis Pain Formula	Excedrin Extra-Strength Analgesic	Persistan
Arthritis Foundation Pain Reliever	Excedrin Migraine	Pravigard
ASA Enseals	Fiogesic	Rhinocaps
Arthritis Strength Bufferin	Fiorgen PF	Robaxisal Tablets
Analgesic Caplets	Fiorinal (most formulations)	Sine-Off: Sinus Medicine Tabs- Aspirin Formula
ASA Suppositories	Fiortal	Roxiprim
Ascriptin, Ascriptin A/D	Gelpirin	Saletto
Aspergum	Genprin	Salocol
Asprimox	Gensan	Sodol
Axotal	Heartline	Soma Compound Tablets
Azdone	Headrin	Soma Compound with Codeine
Bayer (most formulations)	Isollyl	St. Joseph Adult Chewable Aspirin
BC Powder and Cold Formulations	Lanoprinal	Suprin
Bufferin	Lortab ASA Tablets	Synalgos-DC Capsules
Buffets II	Magnaprin	Tenol-Plus
Buffex	Max Strength Arthritis Pain Formula by makers of Anacin	Trigesic
Cama Arthritis Pain Reliever	Marnal	Tri-pain
COPE	Micrainin	Talwin Compound
Dasin	Midol	UN-aspirin
Darvon Compound 65	Momentum	Ursinus
Dolprin #3	Norgesic Forte	Vanquish Analgesic Caplets
Easprin	Norwich Regular Strength aspirin	Wesprin Buffered
Ecotrin (most formulations)	PAC analgesic tabs	Zee-Seltzer
Empirin Aspirin	Pain Reliever Tabs	ZORprin
Epomate	Orphengesic	
	Painaid	

These are Nonsteroidal Anti-Inflammatory Drugs (NSAID)

Actron Caplets	Daypro	Ketorolac	Nuprin
Advil	Diclofenac	Lodine	Orudis KT
Advil migraine	Etodolac	Meclofenamate	Oxaprozin
Aleve	Feldene	Mefenamic acid	PediaCare Fever
Altran	Fenoprofen	Meloxicam	Piroxicam
Anaprox DS	Flurbiprofen	Menadol	Ponstel
Ansaid	Genpril	Midol IB	Relafen
Arthrotec	Ibuprofen	Mobic	Saletto 200
Bayer Select Pain Relief Formula caplets	Ibuprofen	Motrin IB	Sulindac
Children's Motrin	Indomethacin	Nabumetone	Toradol
Clinoril	Indocin	Nalfon	Voltaren
	Ketoprofen	Naprosyn	

Beta-Adrenergic Receptor Blocker: (Beta Blocker)

- Beta-blocker use
 - Hypertension
 - After a Myocardial infarction
 - Angina and arrhythmias
 - Other: Glaucoma, migraine
- Recognized by: "olol"
 - Non-selective:
 - Propranolol (Inderal), timolol, nadolol, sotalol, levatol
 - Cardio-selective:
 - Atenolol, acebutolol, bisoprolol, esmolol, metoprolol



Beta-Blocker: what we have all been taught.

- Asthma treatment: beta-agonist (albuterol)
- Beta-positive  Beta-blocker
- From small trials from 1970-1980's
 - In pts with reversible airway disease, beta-blockers may increase airway reactivity and bronchospasm, decrease response to inhaled or oral beta-agonists. Even nonselective beta-blocker eye drops for glaucoma can cause worsening of lung function.
- **Controversy: Is this still true now?**

Beta-blockers: new millennium

- **Cardio-selective beta-blockers** (affinity for beta-1 rc) theoretically result in fewer adverse effects on the lungs
- Block response to beta stimulation and selectively block beta-1 rc with little or no effect on beta-2 rc, except at high doses.
- Beta receptors:
 - Located on: airway epithelium, mucus cells, other airway cells.

Beta-blocker in Asthma



- Cardio-selective beta-blocker to mild-moderate asthma pt.
 - Limited decrease in FEV₁ (5%) after **single dose**
 - No change in FEV₁ after **continued** administration
 - Preserved & sufficient response to beta2-agonists (albuterol)
 - A Cochrane review in 2002 of 19 studies found that beta-blockers did not adversely affect respiratory function in the short term

Beta-blocker in Asthma



- Can Beta-blocker be used to “treat” asthma?
 - **Mice studies:** long term treatment decreased BHR, BAL cell counts (eos) and cytokines (IL-5, IL-10, IL-13). Anti-inflammatory properties?
 - **Human studies:**
 - N=10, using Nadolol improved BHR after 9 wks (2008)
 - AJRCCM: randomized placebo-controlled study in 2013 revealed no positive effect of treatment with a nonselective β -blocker on airway responsiveness to methacholine, PFTs, and symptoms in pts with mild to moderate asthma (mean FEV₁ 93% predicted) treated with medium dose ICS.

Beta-blockers in Asthma

Summary:

- Caution in severe asthma
- Caution in active bronchospasm
- Potentially useful in pts with chronic heart failure and angina at high risk
- Use cardio-selective agent at usual doses
- **Not** ready to begin “treating” asthma with beta-blockers

ACE inhibitor

- **A**ngiotensin **C**onverting **E**nzyme inhibitor
- Treat heart disease and high blood pressure
- Ex: "pril": captopril, enalapril, benazepril, fosinopril, lisinopril, moexipril, ramipril, etc
- Not really asthma, but cough can be confused with asthma
- 10% of patients develop cough
 - 2% of chronic cough
 - 16-25% of pts treated---cough)



ACEi-Induced Cough

- **Hours to days** within starting (may not notice or report cough for months); rarely it begins months later.
- **Tickle sensation** in throat
- May reduce threshold for cough due to other etiologies
- Treatment: discontinue & avoid ACEi
- Resolution: avg. **26 days** after stopping ACEi

Case 1

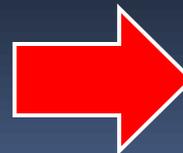
- Pt diagnosed with adverse response to LABA
- He was placed on ICS only
- Within days, his symptoms improved (back to baseline) and made other changes to medication regimen



Medications Worsening Asthma

Summary:

- Be aware of possibility
- Be attentive to response to medications
- Avoid that drug/class of drug if reaction
- Use suitable alternatives
- Wear medical ID bracelet
- Desensitization (for some)
 - Aspirin



Thanks...

