



Mannitol Challenge Test
“The New Kid on the Block”

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Why preform a challenge test for BHR ?

- To confirm a diagnosis of asthma or EIB
- “rule out” the diagnosis asthma
- To aid in defining “best” treatment
- Research

Indirect vs Direct Bronchial Challenge

“INDIRECT”
“Indirect challenges act by causing the release of endogenous mediators that cause the airway smooth muscle to contract, with or without inducing microvascular leakage. Because the responses to these challenges are modified or even completely inhibited by inhaled steroids, the airway response to these challenges may be a closer reflection of active airway inflammation”

“DIRECT” The agonist (usually methacholine) is administered and acts directly on a specific receptor on the bronchial smooth muscle causing it to contract and the airways to narrow. Identifies airway responsiveness consistent with asthma, airway injury, recent virus infection, airflow limitation and airway remodeling.

Joos GF et al ERS Task Force Eur Respir J 2003; 21:1050-68



Bronchial Provocation Tests

Physical 'Indirect'

- Exercise
- Eucapnic voluntary hyperpnea* (hyperventilation)
- Adenosine Monophosphate
- Hyperosmolar saline or distilled water
- Dry Powder Mannitol

Pharmacological 'Direct'

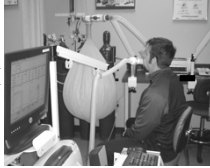
- Methacholine
- Histamine



Exercise-Induced Bronchospasm: What test modality to use?



Symptoms



EVH

Exercise

MANNITOL





MAKING THE DIAGNOSIS

- Symptoms: self-reported / observed
 - cough, wheeze, chest tightness, mucus
 - *"Only about half of those reporting symptoms have EIB"*
- Familial/clinical history
 - allergies / rhinitis
- Physical examination
 - upper respiratory tract, chest, skin
- Exclude alternate diagnoses
 - VCD for example
- Bronchial challenge
 - Presence of reversible airflow obstruction



IS SELF-REPORTED SYMPTOMS ADEQUATE TO PREDICT A POSITIVE EXERCISE TEST?

Symptom	Proportion of True Diagnosis	Sensitivity	Specificity
Cough	.66	.61	.69
Wheeze	.61	.17	.82
Chest Tightness	.63	.20	.83
Excess Mucus	.65	.22	.85

Rundell, et al. Med Sci Sports, 33,208-213 Exer 2001

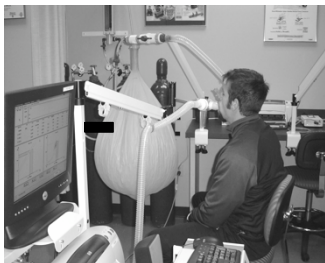


Identifying EIB

Eucapnic Voluntary Hyperpnea

Equipment

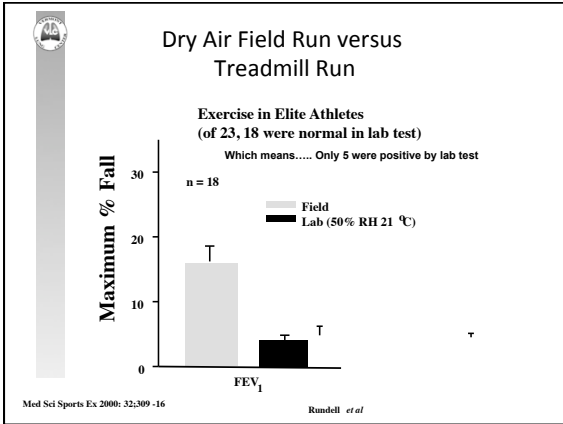
- Special Gas mixture \$\$\$
- Demand valve
- Two-way valve
- Target balloon
- Rotameter
- Tubing
- Ventilation meter
- Spirometer

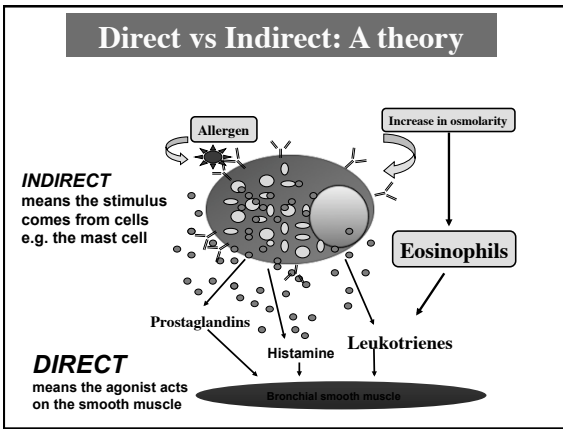


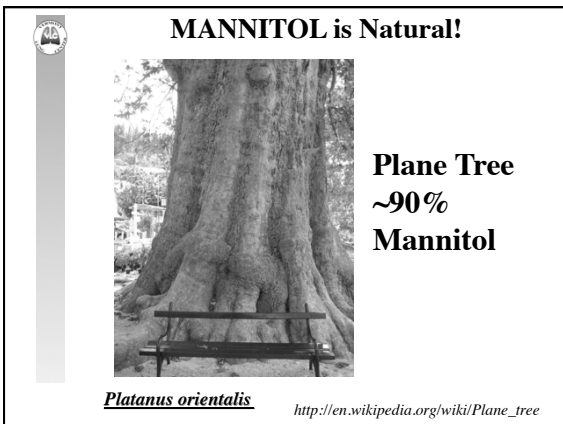


EIB: Basics

- **Measurement:** FEV₁
- **Exercise:** treadmill run
- **Index of Intensity:** >90% estimated HRmax
- **Duration:** 8 minutes
- **Inspired air conditions:** room T, H₂O < 5 mg/L (bottled "dry" medical air)
- **Times of Measurement:** Pre & 5, 10, 15 & 20 min post challenge
- **Positive Response:** Fall FEV₁ >10%







Mannitol – a natural substance

- Mannitol is the active ingredient in Aridol
- Sugar alcohol found in most vegetables
- White crystalline free-flowing granules
- Approved as bulk sweetener
- An osmotic agent diuretic

PM_{2.5}
Combustion particles, organic compounds, metals, etc.
< 2.5 μm (measured in diameter)

PM₁₀
Dust, pollen, mold, etc.
< 10 μm (measured in diameter)

HUMAN HAIR
50-70 μm (measured in diameter)

FINE BEACH SAND
90 μm (measured in diameter)

Mannitol

Spray Dried Mannitol

C(C(C(C(C(C(CO)O)O)O)O)O)O

Image courtesy of the U.S. EPA

Mannitol: Asthmatics vs Normal

Asthmatic subjects experienced a 15% or greater fall in FEV₁
n = 25

Non-asthmatic subjects did not experience a 15% fall in FEV₁
n = 14

Anderson SD et al AJRCCM 1997 156:758

Mannitol–PD₁₅ correlates to the severity of bronchial hyperresponsiveness

Dry Powder Mannitol

Level of BHR

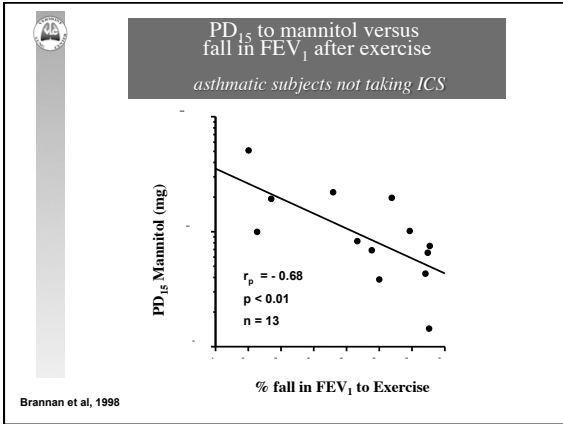
- Severe ≤ 35 mg
- Moderate ≤ 155 mg
- Mild > 155 mg
- Normal

% Fall FEV₁

Cumulative dose of mannitol (mg)

Note: Level of BHR does not imply level of asthma severity

Anderson & Brannan Clin Rev All Immunol 2003; 24: 27-54




ARIDOL[®]
(mannitol inhalation powder)
Bronchial Challenge Test Kit

- Mannitol**— its Clinical Application
- Mannitol can be used in patients with an FEV₁ >70% of predicted:
 - As part of a physician’s overall assessment of asthma
 - Detect exercise induced bronchoconstriction [EIB]
 - Unspecified chronic cough
 - Test patients who have practical issues with other challenges

ARIDOL® – the challenge test

- Dry powder capsules
- Standardized inhaled particle size
- Delivered in escalating doses
- Inhaler included
- Spirometer required



ARIDOL® – a standardized kit that does not require reconstitution

Benefits

- Complete ready-to-use standardized test kit for the assessment of BHR
- No dilutions to prepare
- No special equipment required to administer
- Demonstrated safety and efficacy
- Minimized risk for asthmatic technicians
- Time efficient
 - Positive test: <20 min
 - Negative test: <30 min

Mannitol– the challenge specifics

- Type of Test: Indirect bronchial provocation test for bronchial hyperresponsiveness
- Inhaled agent: Dry powder mannitol
- Progressive Protocol: 0, 5, 10, 20, 40, 80, 160, 160, 160 mg
- Measurements : FEV₁ 1 min post dose
- Positive Response: Fall in FEV₁ >15% from baseline or >10% between doses
- Expression of result: PD₁₅ or response/dose ratio
- Time taken: <20 minutes to a positive test <30 minutes to a negative test
- Recovery: Spontaneous recovery to baseline FEV₁ in 30 minutes (or rapid recovery with BD)

Anderson SD et al AJRCCM 1997;156:758-765, Brannan JD et al, AJRCCM 1998; 158:1120-6



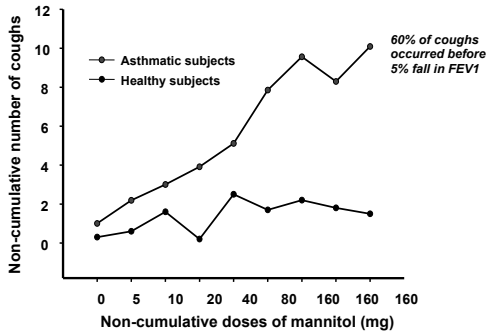
All bronchial challenge tests have boxed warnings

Warning: Risk of Severe Bronchospasm.

Mannitol, the active ingredient in ARIDOL acts as a bronchoconstrictor and may cause severe bronchospasm. Bronchial challenge testing with ARIDOL is for diagnostic purposes only. Only trained professionals under the supervision of a physician who are familiar with the management of acute bronchospasm should perform bronchial challenge testing with ARIDOL. Medications (such as short acting inhaled beta-agonist) and equipment to treat severe bronchospasm must be present in the testing area. Because of the potential for severe bronchoconstriction, bronchial challenge testing with ARIDOL should not be performed in any patient with clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV₁ < 1.5 liters or < 70% of the predicted values).



Cough during mannitol challenge in asthmatic & non-asthmatics



Koskela H et al, CHEST 2004 125:1985-92



ARIDOL® — reported problems during use

• Cough

- Insure inhalation technique
 - Inhalation rate (optimum 60L/min)
 - Head tilt (to avoid impaction)
 - Sip water (during & after challenge)



• Static

- Dry powder - Tap base of inhaler
- Latex gloves - No gloves/tweezers
- Inhalation rate - Use optimum inhalation rate



Mannitol- Pros

- Complete test kit provided
- Does not require extra equipment to administer;
 - i.e dosimeter
 - only stop watch, calculator, spirometer
- No dilutions, preparation, clean-up or sterilization
- Efficient to perform
 - Negative test: less than 30 min
 - Positive test: less than 20 min
- Generally well tolerated
- Minimized risk for asthmatic technicians



Mannitol- Cons and ?

- Limited experience outside of Australia and white populations
- Reproducibility is unclear or low
- Sensitivity may be low
- Sensitivity and specificity not well characterized
- Unclear what is a clinically meaningful response.
- Emerging technology



Thank You for
Your Attention

**Any
Questions?**
