

New Developments in Bronchial Challenge Testing

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Sponsored by Pharmaxis

Conflict of interest

- Speaker's bureau: Boehringer Ingelheim, Sunovion, Pharmaxis
- Trainer: Hill-Rom, Pharmaxis

Objectives

- Understand the indications and contraindications for bronchial challenge testing (BCT)
- Explain the pre-test preparation and equipment/supplies needed for various tests
- Review the testing procedures and define a positive tests
- Discuss a new challenge test using Mannitol

Definition of Bronchial Hyperresponsiveness (BHR)

- BHR –exaggerated bronchoconstriction
 - Allergens: dust mites, pollen, dander, mold, cockroach)
 - Pollutants: exhaust fumes, smog,
 - Irritants: tobacco or wood smoke, chemicals
- BHR also linked to exercise, cold air, sulphur dioxide, non-isotonic aerosols.
- These stimuli all act to cause the airways to narrow.
- BHR is the acute pathology in asthma and is linked to the inflammatory process

Asthma Is a Chronic Inflammatory Disorder

- Airway inflammation is the underlying pathology in asthma
- Inflammation leads to:
 - Airway hyperresponsiveness – rapid and exaggerated response to triggers
 - Obstruction due to bronchoconstriction – usually at least partially reversible
 - Symptoms – cough, wheeze, dyspnea, chest tightness
 - Further inflammation, airway remodeling
- Symptoms are easily appreciated, but inflammation is often overlooked

NAEPP. Guidelines update 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>

Why do Bronchial Challenge Testing?

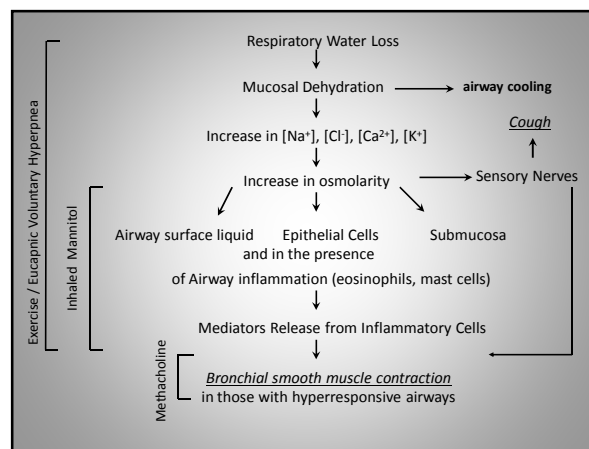
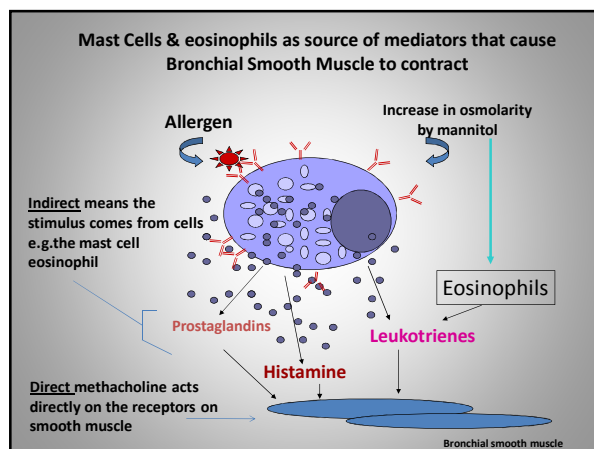
- Asthma is often misdiagnosed
- No blood test, X-ray, lab test
- Many things mimic asthma (CHF, VCD, COPD, etc)
- Subjective estimates of asthma correlate poorly to objective measures
- Treatment is often not “EBM” (NIH > NHLBI > NAEPP > EPR-3)
 - No ICS, no ICS/LABA, relying on SABA only
- BCT helps to rule in or rule out asthma (but it is still not a definitive test)

When is BCT needed?

- Symptoms suggest asthma but a normal PFT...
 - Questionable case (EIB, cough variant asthma)
- Asthma needs to be confirmed objectively and treated effectively at the lowest cost
 - Occupation or recreational activity where BHR could be a potential problem
 - May be useful to “step down” in treatment
 - Following exposure to an occupational irritant or allergen that has induced symptoms of asthma

2 types of BCT

- Direct tests: acts directly on the bronchial smooth muscle to cause bronchoconstriction.
 - Uses: Inhaled methacholine or histamine to cause a measurable change
 - Direct test tends to RULE OUT asthma
 - Indirect tests: cause a change in the airway and this affects mast cells
 - Release of histamine, leukotrienes, prostaglandins, etc.
 - Indirect tests tend to RULE IN asthma
 - Uses: Exercise-induced bronchospasm (EIB), Eucapnic voluntary hyperventilation (EVH)
 - Uses: Inhaled agents (mannitol, hypertonic saline, adenosine monophosphate)
- Parkerson J, Ledford D. *Annals of AAI*. 2011;106:91-96.



Bronchial Challenge Tests

- Methacholine
- Exercise
- Eucapnic voluntary hyperventilation (EVH)
- Mannitol
- Cold air
- Hypertonic saline

Check List: applies to all challenge protocols

- Spirometer calibration checked
- Medications withheld for the appropriate period of time
- No vigorous exercise in last 4 hrs & no excess caffeine
- No sign of upper or lower respiratory infection
- Spirometry done as first step. FEV₁ at baseline ≥ 70% predicted (don't test if obstruction is present)
- FEV₁ for each step is reproducible and performed to ERS/ATS criteria
- Bronchodilator and oxygen available if required
- All positive tests should check for return to baseline before discharging the patient (reverse bronchospasm with SABA)

Withholding medications

Withholding Time	Medication
8 hours	Short-Acting Bronchodilators Albuterol, terbutaline sulfate
12-24 hours	Inhaled Corticosteroids beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone
	Anticholinergic Bronchodilators ipratropium bromide
	Phosphodiesterase Inhibitors/Adenosine Receptors Theophyllines
24-48 hours	Long-Acting Bronchodilators salmeterol xinafoate, formoterol fumarate
	Inhaled Corticosteroids And Long-Acting Beta2 Agonist Combination fluticasone propionate and salmeterol xinafoate; budesonide and formoterol fumarate dehydrate

Withholding medications

Withholding Time	Medication
72 hours	Long-lasting Anticholinergics triotropium bromide
	Antihistamines: Over-the-Counter & Prescription brompheniramine maleate (Dimetapp®); diphenhydramine (Benadryl®); loratadine (Claritin®); cetirizine (Zyrtec®); fexofenadine (Allegra®); levocetirizine dihydrochloride (Xyzal®)
4 days	Leukotriene-Receptor Antagonists montelukast sodium (Singulair®)
Day of Test	Refrain from the following: * Caffeine-containing foods: coffee, tea, cola, chocolate, etc. * Vigorous exercise * Smoking at least six hours prior to testing

Methacholine Challenge Test (MCT)

- 2 methods of doing the test
 - 2 minute tidal breathing: timed interval of tidal volume breathing while inhaling aerosolized methacholine
 - 5 breath-breath dosimeter method: 5 slow, deep breaths while inhaling aerosolized methacholine
- Measure FEV₁ at 30 seconds and 90 seconds after the dose is given
 - Positive test- 20% decrease in FEV₁ from baseline (PC₂₀)
 - Negative test – entire schedule of drug is given without a 20% decrease in FEV₁
 - Each method uses increasing doses of methacholine

Methacholine dosing regimen

2 minute tidal breathing

- Baseline (3 ml NaCl)
- 0.031 mg/ml
- 0.0625 mg/ml
- 0.125 mg/ml
- 0.25 mg/ml
- 0.5 mg/ml
- 1.0 mg/ml
- 2.0 mg/ml
- 4.0 mg/ml
- 8.0 mg/ml
- 16.0 mg/ml

5-breath dosimeter

- 0.0625 mg/ml
- 0.25 mg/ml
- 1.0 mg/ml
- 4.0 mg/ml
- 16.0 mg/ml

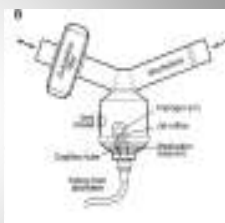
Dry methacholine is mixed with 0.9% NaCl by a pharmacist using sterile technique. Each dose must be clearly labeled. May be mixed ahead and stored under refrigeration. Must be at room temperature for test.

Dosimeter and nebulizer

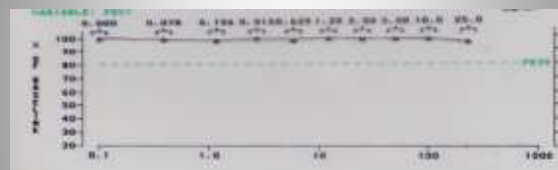
KoKo Dosimeter



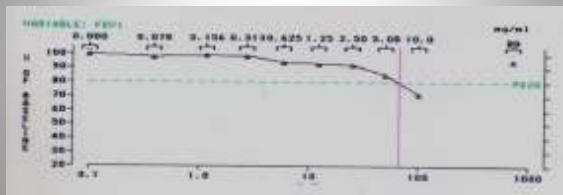
Devilbiss 646 nebulizer



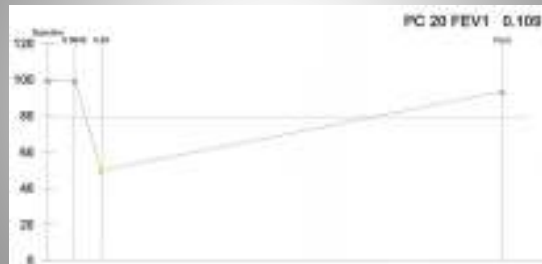
Bronchial challenge testing-negative methacholine test



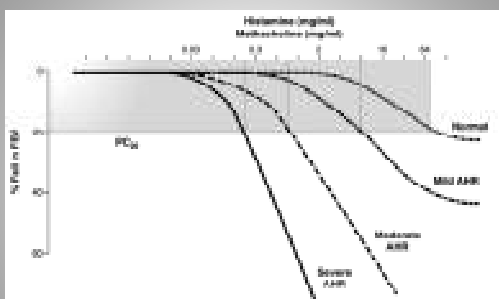
Bronchial challenge testing – positive methacholine test



Bronchial challenge testing- positive methacholine test



From the revised GINA Report, Global Strategy for Asthma Management and Prevention (2007), available on the Global Initiative for Asthma (GINA) website



*Airway responsiveness to inhaled methacholine or histamine in a normal subject, and in asthmatics with mild, moderate, and severe airway hyperresponsiveness. Asthmatics have an increased sensitivity and an increased maximal broncho-constrictor response to the agonist. The response to the agonist is usually expressed as the provocative concentration causing a 20% decline in FEV₁ (PC₂₀).

Issues with Methacholine

- Clinical Aspects:
 - Positive response is not predictive of having EIB or its severity
 - Positive response not specific for asthma
 - Negative response is helpful to rule out asthma
 - Positive response is not predictive of benefit from ICS
- Safety Aspects:
 - High concentrations of methacholine may be needed for positive response and may cause unwanted side effects

Issues with Methacholine

- Technical Aspects
 - Several nebulizers may be required and need to be cleaned & calibrated
 - Different protocols have different cut off points for AHR
 - Solutions needed to be made up by pharmacist, refrigerated & regularly discarded
 - Negative test takes 40 min using 2 minute tidal breathing protocol which is now the most highly recommended by advocates

Exercise Challenge

- Usefulness:
 - The real stimulus that produces the symptoms
 - High positive predictive value for asthma
 - Likely to be the most common trigger of an attack
 - Appropriate for assessing drug effects



Exercise Protocol

- 6 to 8 minutes at high level of exercise (% max HR)
- Monitor continuous ECG and SpO₂
 - Some labs monitor F/V loops, minute ventilation and tidal volume during exercise to assess workload
- Environmental conditions should be controlled:
 - Temp <25°C (77°F), relative humidity ≤50%
 - Nose clips needed to reduce gas conditioning by nose
- Spirometry recorded at 1 to 2 minutes post exercise then at 5, 10, 15, 20, and 30 minutes
- Positive test: 10% to 15% drop in FEV₁ from baseline

Exercise Challenge

Limitations:

- Exercise choice is limited
- Unable to exercise for the test?
- Elite athletes may be difficult
- Exercise may need to be sports specific
- 'Dry' air for best results
- Safety issues
 - May have severe bronchospasm post exercise (greater risk for large falls in FEV₁)
 - If using a treadmill – required speeds are high
- Cost and resources

Eucapnic Voluntary Hyperventilation (EVH)

• Usefulness

- High sensitivity to identify EIB
- Protocol and inspired air conditions can be easily adjusted to simulate conditions of a specific sport (e.g. rowing, cross country skiing, cycling)
- Negative test = low risk of EIB
- Mediators the same as for EIB
- Equipment less expensive compared with exercise

Protocol for EVH

- Cold air (relative humidity near 0%) breathed at high level of ventilation
 - Target ventilation is between 30 to 70% of the MVV
- CO₂ levels kept stable by using special gas mixture
 - ~5% CO₂ 21% O₂ balance N₂
- Hyperventilation maintained for 4 to 6 minutes
- Spirometry measured at 1, 5, 10, 15, 20 minutes post exercise
- 15% decrease in FEV₁ from baseline is positive

EVH testing during Olympics in Athens 2004



EVH Limitations

- Special gas mixture needed (~5% CO₂ 21% O₂ balance N₂)
- Less sensitive if <6 minutes or V_E < 30 x FEV₁
- 6-min protocol 30 x FEV₁ can provoke severe fall in FEV₁

Mannitol Bronchial Challenge Test



Indications for mannitol BCT

- The assessment of bronchial hyperresponsiveness (BHR) in patients 6 years of age and older who do not have clinically apparent asthma.

Limitations of Use: mannitol is not a stand alone test or a screening test for asthma. Mannitol should be used only as part of a physician's overall assessment of asthma.

All bronchial challenge tests, including mannitol, have Boxed Warnings

- **WARNING: RISK OF SEVERE BRONCHOSPASM**
- See Full Prescribing Information
- 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. Bronchial challenge testing with ARIDOL should only be conducted by trained professionals under the supervision of a physician familiar with all aspects of the bronchial challenge test and the management of acute bronchospasm. Medications (such as short acting inhaled beta-agonists) and equipment to treat severe bronchospasm must be present in the testing area. If severe bronchospasm occurs it should be treated immediately by administration of a short acting inhaled beta-agonist. 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 <1-1.5 liters or <70% of the predicted values).

Clinical application

- Use in patients with an FEV₁ ≥ 70% of predicted.
- Should be used:
 - As part of a physician's overall assessment of asthma
 - To detect exercise-induced bronchoconstriction [EIB]
 - To evaluate unspecified chronic cough
 - To test patients who have issues performing other challenge tests

Mannitol protocol

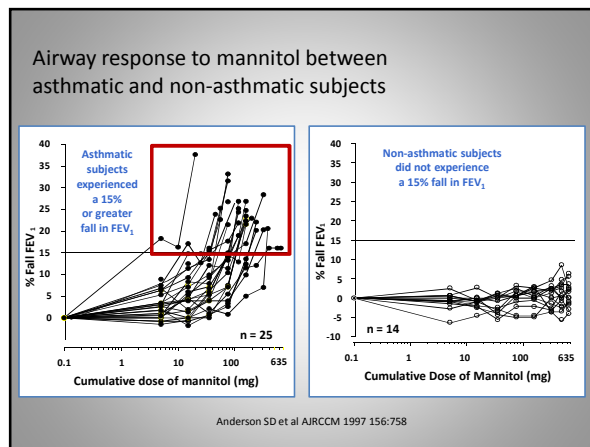
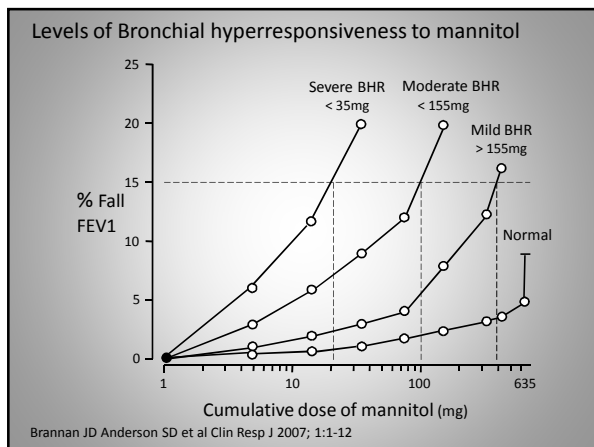
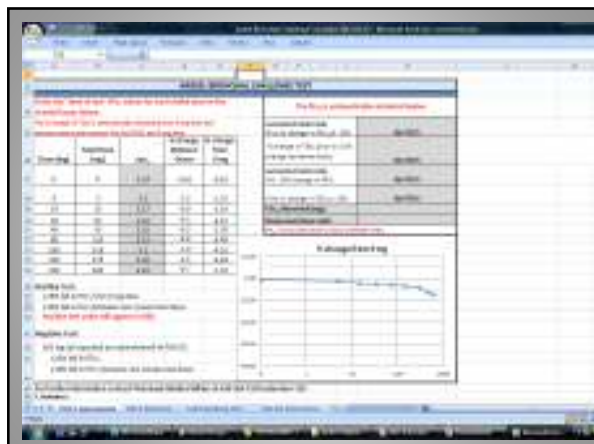
- **PROGRESSIVE PROTOCOL**
 - Inhaled doses: 0, 5, 10, 20, 40, 80*, 160*, 160*, 160* mg
 - **MEASUREMENTS**
 - Two FEV₁: 1 minute post dose. Pick the best
 - After each FEV₁ maneuver, the next dose is immediately administered followed again by two FEV₁ maneuvers one minute later.
 - Each dose is to follow on as soon as possible after the last to maintain the osmotic gradient. A negative test result may not be valid if time exceeds 35 min.
- * 2 to 4 capsules used for inhalation (40 mg dose)

• POSITIVE TEST

- A positive response is achieved when the patient experiences either:
 - 15% fall in FEV₁ from baseline (0 mg dose)
 - 10% incremental fall in FEV₁ between doses

• NEGATIVE TEST

- A cumulative dose of 635 mg of mannitol has been administered and a positive response has not been met



Dry powder inhaler – single patient use, disposable
All doses of mannitol are in this kit and ready to use

Performing the Mannitol Challenge Test

A quick summary

- Load and pierce the capsule
- Tilt head and hold inhaler at a 45° angle
- Inhale – controlled and deep
- Start 60 sec. timer & have pt. hold breath 5 sec.
- Exhale away from the inhaler at end of the 5 sec. breath hold
- Check that capsule is empty after each inhalation
- Record (2) FEV₁ maneuvers. Stop or go on as indicated

Mannitol “A-305”

- Study aims
 - To determine *the safety and efficacy* of inhaled mannitol compared with methacholine .
 - To predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma
- Signs & symptoms – suggesting mild asthma
 - H & P, PFT, skin testing. 375 subjects (aged 6-50 years) completed whole study
 - Exercise test (2 times)
 - Assess by MD to diagnose or rule out asthma
- Blinded test
 - BCT by mannitol
 - BCT by methacholine
- All results compared

The aims and methods of A-305

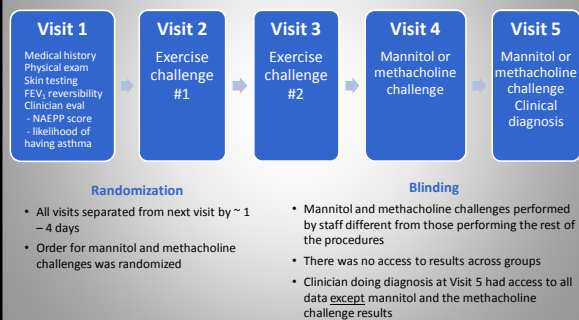
•Methods

- 509 subjects enrolled. The intent-to-treat population was 391 subjects.
- 375 subjects (aged 6-50 years) completed all 4 study tests.
- Subjects had signs and symptoms suggestive of asthma according to the NAEPPII questionnaire, but without a firm diagnosis or exclusion of asthma as a diagnosis.

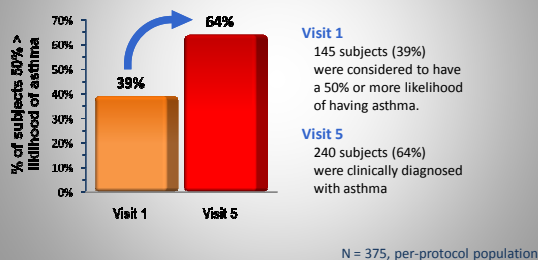
Mild asthmatics comprised the study population of A-305

- **No definitive diagnosis**
 - NAEPPII scores (mean 1.2 on scale 1 to 4) helped support that these subjects had an unconfirmed diagnosis.
- **A very mild group of patients**
 - All had normal FEV₁
 - Only 7.5% (28) subjects were reversible to β_2 agonists.
 - *In patients with a NAEPPII score of 1-2, physicians cannot rely on reversibility to diagnose asthma.*
- **22% of patients non-atopic**
 - This was the first large study of mannitol to include a significant number of non-atopic patients.

The study design of A-305

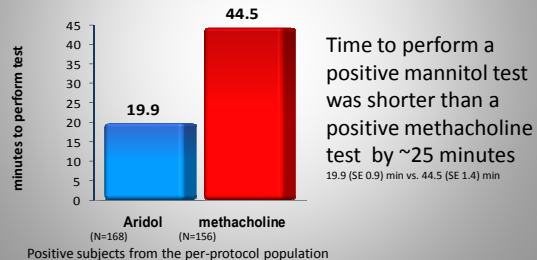


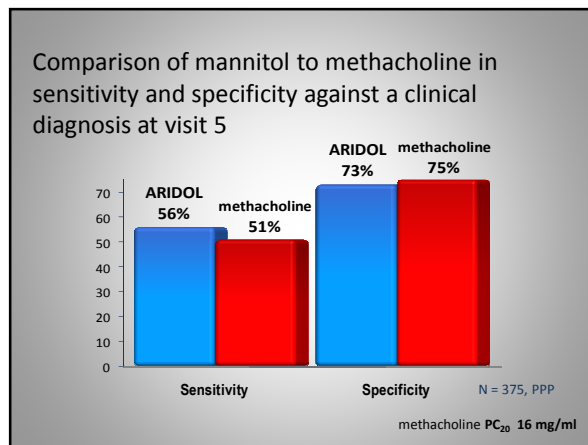
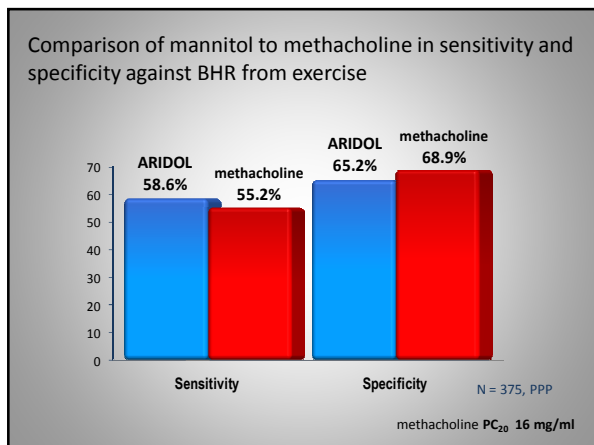
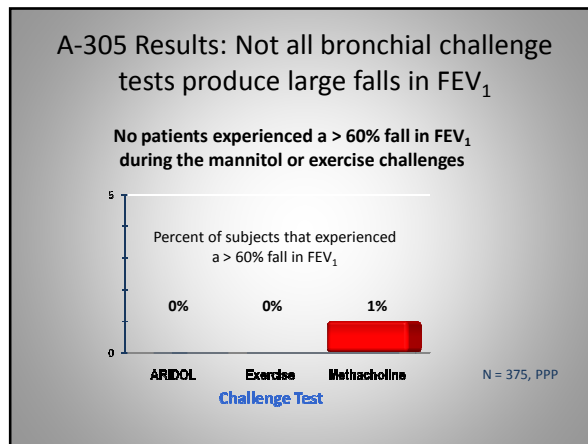
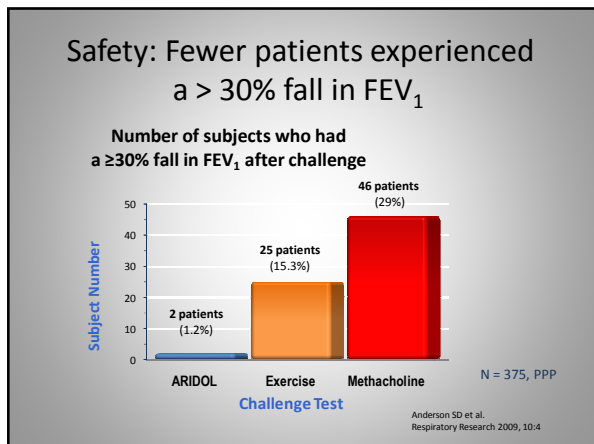
A-305 Results: A significant difference in asthma diagnosis from visit 1 to 5



A-305 Results: A positive challenge test in half the time

Time to perform a positive challenge





A-305 Results: Mannitol provided equivalent test in half the time

Clinical Benefits

- Demonstrate that mannitol and methacholine were equal to identify BHR and identify a clinical diagnosis of asthma
- There were no serious adverse events associated with the tests; both were generally well tolerated and safe
- Sensitivity and specificity of methacholine and mannitol for a clinical diagnosis of asthma was equivalent, but low because of the mild asthma status in these patients
- Mannitol test takes half the time of methacholine challenge and requires minimal preparation and clean-up

Comparison of Bronchial Provocation Tests

Test	Equip	Cost	Convenience	Safety	Test time	Sensitivity	Specificity
Cold Air	-	-	-	+/-	-	+/-	+/-
EVH	-	-	-	+/-	+/-	+/-	+/-
Exercise	-	-	-	-	-	+/-	+/-
Methacholine	+/-	+/-	+/-	-	+/-	-	+/-
Mannitol	+	+	+/-	+	+	+/-	+/-

Symbols: + superior, +/- intermediate, - inferior

Parkerson J, Ledford D. *Annals of AAI*. 2011;106:91-96.

Conclusion

“The mannitol challenge test has the following advantages over other indirect bronchoprovocation tests:

- a standardized test kit,
- minimal required equipment,
- relative low cost,
- ease of administration,
- a consistent dose response,
- enhanced safety,
- and ease of performance.”

Parkerson J, Ledford D. *Annals of AAI*. 2011;106:91-96

Drug and CPT Coding

- Product Reimbursement : HCPCS Code
 - J7665 Mannitol approved effective Jan 1, 2012
- Bronchial Challenge Testing: CPT Codes
 - 95070 Inhaled bronchial challenge testing(not including necessary PFTs) with histamine, methacholine, or similar compounds
 - 94070 Bronchospasm provocation evaluation, multiple spirometric determinations with administered agents (eg with antigens, cold air, methacholine)
 - 94640 Pressurized or nonpressurized inhalation treatment for acute airway obstruction or sputum induction for diagnostic purposes (eg with nebulizer, MDI, or IPPB)

Drug and CPT Coding

- Evaluation and Management: CPT Codes

99201-99205	Eval and Mgt... new patient visit
99211-99215	Eval and Mgt ...Established patient visit
99241-99245	Eval and Mgt... Outpatient consultation

Thanks for listening!

- www.thoracic.org/statements
 - **Pulmonary Function and Exercise Testing**
 - Guidelines for Methacholine and Exercise Challenge Testing-1999 (2000)

Questions?

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