Methacholine versus Mannitol Challenge in the Evaluation of Asthma

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AAAAI Annual Scientific meeting Feb 25th 2013

- Methacholine vs. Mannitol Challenge in the Evaluation of Asthma
  Monday, February 25, 2013: 4:45 PM-6:00 PM
- 1.25 CME/ 1.50 CE
- Moderator:
  - Hee-Bom Moon, MD PhD

- Primary Panelists:
  - Louis-Philippe Boulet, MD
  - Catherine Lemiere, MD
  - Sandra D. Anderson, PhD DSc

- Learning Objectives: Compare positive and negative predictive values of methacholine and mannitol inhalation tests
- Evaluate methacholine and mannitol as potential test for monitoring asthma treatment
Conflict of interest

• Dr Sandra Anderson is the Inventor on the patent that cover these applications for mannitol
• The patent is owned by her employer SSWAHS
• The rights to commercialise the intellectual property are licensed to Pharmaxis Ltd
• Dr Anderson purchased her own shares on the open market and holds no options.
• Dr Anderson is a consultant to Pharmaxis Ltd
• Dr Anderson receives a 10% share of the royalties paid to SSWAHS
Q: Why do we use methacholine and mannitol challenge in the evaluation of Asthma?

Performing the appropriate bronchial challenge test by using either a direct (methacholine) or an indirect (mannitol) stimulus to identify airway hyperresponsiveness (AHR) reduces the possibility of over and under diagnosis of asthma based on history and symptoms.
Q: When do we need to know about airway hyperresponsivness?

• Upon presentation of a person with symptoms suggestive of asthma but with normal or near to normal lung function and doubt about the diagnosis of asthma

• In a person entering an occupation or recreational activity where AHR could be a problem e.g. SCUBA diving

• In a person well-controlled on treatment for a long period in whom it may be useful to back titrate treatment e.g. the dose of steroid

• Following exposure to an occupational irritant or allergen that has induced symptoms of asthma
Q: What are the types of Bronchial Challenge Tests that are used to evaluate the airway hyperresponsiveness of asthma?

DIRECT challenge test: e.g. methacholine
The agent is administered and acts on a specific receptor on the bronchial smooth muscle causing it to contract and the airways to narrow. A positive test identifies airway hyperresponsiveness consistent with asthma or with airway injury or airway remodeling.

INDIRECT challenge test: e.g. mannitol
“Indirect challenges act by causing the release of endogenous mediators that cause the airway smooth muscle to contract, with or without effect in inducing microvascular leakage.

Q: Why do we need to know about airway hyperresponsiveness?

- In a person with normal lung function, AHR to an indirect acting stimulus such as mannitol, is consistent with the presence of airway inflammation.

- The inflammation associated with response to an indirect stimulus involves the mast cell with or without sputum eosinophilia.

- The number of these cells & concentration of mediators of bronchoconstriction are reduced with treatment with inhaled corticosteroids & AHR to exercise or mannitol is reduced or even resolved.
Q: What is the source of the mediators that cause Bronchial Smooth Muscle to contract?

**Indirect** means the bronchoconstricting stimulus comes from cells, e.g., mast cells, &/or eosinophils or nerve cells.

**Direct** means the bronchoconstricting stimulus, e.g., methacholine, acts directly on the smooth muscle.
Positive and Negative Predictive Values

• How likely is someone, with a positive test result to methacholine or mannitol, to have asthma (positive predictive value)?

• How likely is someone, with a negative test result to methacholine or mannitol, to not have asthma (negative predictive value)?
Why perform a bronchial challenge test?

Å **Is it asthma?**

to rule out asthma?
one needs a sensitive test with a high **negative** predictive value

to rule in asthma?
one needs a specific test with a high **positive** predictive value

Å **to manage asthma?**
one needs a test that correlates with the response of asthma to treatments
LEARNING OBJECTIVE

Compare positive and negative predictive values of methacholine and mannitol inhalation tests
Is Methacholine a Rule Out test?

- Methacholine challenge has been promoted for its clinical utility in excluding the diagnosis of asthma based on a negative test result and one would expect a high negative predictive value.

- Is a negative methacholine test result a rule out test with a high negative predictive value?
Is Mannitol a Rule in test?

• In contrast to methacholine, the challenges that act via release of mediators such as mannitol, are promoted as tests that confirm the diagnosis of asthma if the test result is positive but do not rule out asthma if the test result is negative. Thus one would expect a high positive predictive value but not necessarily a high negative predictive value.

• Is it valid to consider mannitol as a rule in test for asthma and if so, what is the positive predictive value?
**Tidal Breathing**
- 2 min tidal breathing
- Neb @ 0.13 L/min
- 90 μL per dose

Other aspects identical:
- Concentrations (0.03-32 mg/mL)
- Timing between doses (5 min)
- Timing of FEV₁ (30 & 90 sec)
- Calculation of PC<sub>20</sub>

**Dosimeter**
- 5 Breaths B-hold (@TLC)
- 9 μL per breath
- 45 μL per dose

<table>
<thead>
<tr>
<th>PC&lt;sub&gt;20&lt;/sub&gt;(mg/ml)</th>
<th>PD&lt;sub&gt;20&lt;/sub&gt; (µg)</th>
<th>PD&lt;sub&gt;20&lt;/sub&gt; (µmole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>800</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>0.25</td>
</tr>
<tr>
<td>0.25</td>
<td>12.5</td>
<td>0.06</td>
</tr>
</tbody>
</table>

From Cockcroft
AAAAI2010
METHODS

- Rest in lab/assess subject, Rx, etc.
- Spirometry x 3 - assure FEV$_1$ > 70%
- Diluent → doubling doses Mch q 5 min
- Single (good) FEV$_1$ @ 30 & 90’s (no FVC)
- Calculate % $\Delta$ FEV$_1$ @ each concentration
- PC$_{20}$/PD$_{20}$ from log dose vs. response curve
- Test shortening protocols optional

From Cockcroft AAAAI2010
DEFINITIONS

\[ PC_{20} > 16 \text{ mg/ml} - \text{normal} \]
\[ PC_{20} 4-16 \text{ mg/ml} - \text{borderline} \]
\[ PC_{20} 1-4 \text{ mg/ml} - \text{mild AHR} \]
\[ PC_{20} 0.25-1 \text{ mg/ml} - \text{moderate AHR} \]
\[ PC_{20} < 0.25 \text{ mg/ml} - \text{severe AHR} \]
PROTOCOL for Dry Powder Mannitol

Progressive Protocol: 0, 5, 10, 20, 40, 80, 160, 160, 160mg
Measurements: FEV₁ Pre & 1 min post dose with highest value for FEV₁ recorded
Positive Response: Fall FEV₁ ≥ 15% or Fall FEV₁ ≥ 10% between consecutive doses
Sensitivity: PD₁₅ < 35mg = Severe PD₁₅ > 35mg < 155mg = moderate, PD₁₅ > 155 mg = mild AHR to mannitol
Reactivity: Response Dose Ratio = Final % fall FEV₁/Cumulative dose
Recovery: Bronchodilator or spontaneous

Brannan JD Anderson SD et al Respiratory Research 2005; 6:144
Anderson SD et al Respiratory Research 2009; 10:44
Sverrild A et al J Allergy Clin Immunol 2009; 24:928-932
Q: What Population Studies have been performed using mannitol and methacholine?

- Australian study A301 was the 1st Phase 3 study using mannitol as a BCT. It was carried out in well defined groups including 592 asthmatic and healthy subjects both adults and children. (Brannan JD et al. Resp Res 2005;6:144)

- USA study A305 was the 2nd Phase 3 study using both mannitol and methacholine and exercise. It was in a group of 375 subjects with symptoms of asthma who entered the study without a definite diagnosis of asthma (Anderson SD et al. Respir Res 2009: 10:4)

- Copenhagen study comprised an unselected sample of 238 young adults and mannitol and methacholine was used to identify those with respiratory physician diagnosed asthma (Sverrild A et al. J Allergy Clin Immunol 2010;124:928)

- Greek study in 88 subjects with 61 being given a diagnosis of asthma based on a reversibility test with bronchodilator (Porpodis K et al. J Thoracic Dis 2012;4(S1):AB81)

- Norwegian study: 58 young elite skiers with asthma like symptoms had provocation tests using mannitol, methacholine and dry air hyperpnea (Sue-Chu M et al. Brit J Sports Med 2010;44:827)
A 301

Study in well defined populations of asthmatic and healthy subjects

Respiratory Research

The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline

John D Brannan¹, Sandra D Anderson*¹, Clare P Perry¹, Ruth Freed-Martens¹, Anna R Lassig², Brett Charlton² and the Aridol Study Group

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* Corresponding author

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This article is available from: http://respiratory-research.com/content/6/1/144

Brannan JD Anderson SD et al Respiratory Research 2005; 6:144
http:respiratory-research.com/articles/browse.asp
A301 Phase 3 trial Per Protocol - Patients' characteristics

- 592 subjects (466 adults, 126 children) included 487 (82.3%) asthmatics and 105 non asthmatics.
- Age 6 - 83 mean 34.8 yr
- Majority had mild disease
  - Half the asthmatic cohort had infrequent symptoms
  - Only 11.3% reported symptoms interfering with normal activity.
- Majority had good lung function.
  - 50% of the asthmatics had a FEV1 > 95% of predicted.
  - The mean FEV₁ was 3.0 L in the asthmatics and 3.2 L in the non-asthmatics.
- 78.4% taking at least one medication.
  - 228 on combination therapy / 164 on monotherapy with ICS

Brannan JD et al. Respir Res 2005;6:144
### Positive and Negative Predictive values in the Phase 3 study in well defined populations A301

Brannan JD et al. Respir Res 2005; 6:144

**Including all subjects**

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic n= 487</th>
<th>Non-asthmatic n=105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol +ve</td>
<td>291</td>
<td>5</td>
</tr>
<tr>
<td>Mannitol -ve</td>
<td>196</td>
<td>100</td>
</tr>
</tbody>
</table>

**Negative Predictive value 33.7%  Positive predictive value 98.3%**

**Excluding subjects negative to mannitol taking inhaled cortico steroids**

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic = 328</th>
<th>Non-asthmatic = 105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol +ve</td>
<td>291</td>
<td>5</td>
</tr>
<tr>
<td>Mannitol -ve</td>
<td>37</td>
<td>100</td>
</tr>
</tbody>
</table>

**Negative Predictive value 72.9%  Positive predictive value 98.3%**
What did we learn from A301?

• Mannitol had a high positive predictive value and there were very few false positive tests in the healthy population.

• The low negative predictive value for mannitol to exclude clinically recognised asthma improved from 33.7% to 72.9% when the benefit of current treatment with inhaled corticosteroids was taken into account.

Including all subjects

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic n= 67</th>
<th>Non-asthmatic n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol +ve</td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>Mannitol -ve</td>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

Negative Predictive value 45.4%  Positive predictive value 97.7%

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic = 67</th>
<th>Non-asthmatic = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine + ve</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>Methacholine -ve</td>
<td>25</td>
<td>18</td>
</tr>
</tbody>
</table>

Negative Predictive value 41.9%  Positive predictive value 93.3%

47 women & 41 men 14 to 75 yrs
The clinical diagnosis of asthma was based on bronchodilator reversibility test.
COPENHAGEN STUDY was in 14-24 yr olds in a general population with asthmatics identified by a respiratory physician

Original article

Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: A random-sample population study

Asger Sverrild, MD, Celeste Porsbjerg, MD, PhD, Simon Francis Thomsen, MD, PhD, and Vibeke Backer, MD, DMSoc Copenhagen, Denmark

Background: Studies of selected patient groups have shown that airway hyperresponsiveness (AHR) to mannitol is more specific than methacholine for the diagnosis of asthma, as well as more closely associated with markers of airway inflammation in asthma.

Objective: We sought to compare AHR to mannitol and methacholine and exhaled nitric oxide (eNO) levels in a nonselected population sample.

Methods: In 238 young adults randomly drawn from the nationwide civil registration list in Copenhagen, Denmark,

Abbreviations used
AHR: Airway hyperresponsiveness
BPT: Bronchial provocation test
eNO: Exhaled nitric oxide
IQR: Interquartile range
RDR: Response-dose ratio
ROC: Receiver operating characteristic

COPENHAGEN STUDY Subject Characteristics


<table>
<thead>
<tr>
<th></th>
<th>Current asthma (n = 51)</th>
<th>No asthma (n = 187)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), (median [minimum-maximum])</td>
<td>18 (15-24)</td>
<td>19 (14-24)</td>
<td>.77</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>61% (31)</td>
<td>60% (113)</td>
<td>.87</td>
</tr>
<tr>
<td>Atopy</td>
<td>77% (39)</td>
<td>32% (60)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>29%</td>
<td>24%</td>
<td>.32</td>
</tr>
<tr>
<td>FEV₁% predicted, mean (95% CI)</td>
<td>92% (89% to 95%)</td>
<td>94% (92% to 95%)</td>
<td>.32</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, mean (95% CI)</td>
<td>0.85 (0.82-0.87)</td>
<td>0.88 (0.87-0.89)</td>
<td>.001</td>
</tr>
<tr>
<td>Use of ICS</td>
<td>16%</td>
<td>0%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

FVC, Forced vital capacity; ICS, inhaled corticosteroid.

One respiratory physician only made the diagnosis based on symptoms in last 1yr, in combination with an FeNO >30 ppb, a history of allergic rhino-conjunctivitis, dermatitis, a positive skin test response, a familial predisposition to atopic disease, non-allergic rhino-conjunctivitis or an FEV₁/FVC ratio <75%.
COPENHAGEN STUDY

**TABLE II.** Results of 238 randomly selected adolescents tested with inhaled mannitol and methacholine: 51 asthmatic subjects and 187 nonasthmatic subjects

<table>
<thead>
<tr>
<th></th>
<th>Asthma (n=51)</th>
<th>No asthma (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methacholine</td>
<td>Methacholine</td>
</tr>
<tr>
<td>Mannitol</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>12</td>
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<tr>
<td></td>
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<td>+</td>
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<tr>
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<td>4</td>
<td>2</td>
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<td>12</td>
<td>35</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>149</td>
</tr>
</tbody>
</table>

Diagnostic properties of inhaled mannitol and methacholine in 238 subjects

<table>
<thead>
<tr>
<th></th>
<th>Asthma n=51</th>
<th>Non Asthma n=187</th>
<th>Positive Predictive value</th>
<th>Negative Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>91% (78-97)</td>
<td></td>
<td>90% (88-91)</td>
<td></td>
</tr>
<tr>
<td>Methacholine</td>
<td>49% (40-56)</td>
<td></td>
<td>90% (87-93)</td>
<td></td>
</tr>
</tbody>
</table>

What did we learn from the Copenhagen study?

Mannitol PD$_{15}$ had a high positive predictive value compared with methacholine PC$_{20}$ i.e. 91% versus 49%.

That is there were many more false positive tests in non-asthmatics (n=37) using methacholine than there were using mannitol (n=3).

The negative predictive value of mannitol was the same compared with methacholine (90% vs 90%). That is the same number of people had a false negative test result.
A 305 was a population of subjects with symptoms but without a definite diagnosis of asthma at study entry.

Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma

Sandra D Anderson*1, Brett Charlton2, John M Weiler3, Sara Nichols4, Sheldon L Spector5, David S Pearlman6 and A305 Study Group6

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* Corresponding author

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Accepted: 23 January 2009

This article is available from: http://respiratory-research.com/content/10/1/4

Patient demographics (enrolled subjects)

**Age**
- Mean (SD) = 24.9 (10.6) yrs
- Range = 6 - 50 yrs

**BMI**
- Mean (SD) = 24.5 (4.7)
- Range = 14.4 – 39.9

**Gender**
- 46.4% male
- 53.6% female

**Ethnicity**
- Caucasian – 74%
- Hispanic – 9%
- Black – 9%
- Asian – 5%
- Other – 2%
**Patient characteristics at baseline (enrolled)**

<table>
<thead>
<tr>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{FEV}_1$</td>
</tr>
<tr>
<td>- Mean (SD) = 91 (8.7)% of predicted at baseline</td>
</tr>
<tr>
<td>Atopy</td>
</tr>
<tr>
<td>- 78% of subjects</td>
</tr>
<tr>
<td>$\beta_2$ reversibility</td>
</tr>
<tr>
<td>- 10.8% of all screened subjects</td>
</tr>
<tr>
<td>- 7.5% of PP subjects reversed</td>
</tr>
<tr>
<td>NAEPPPII asthma severity rating</td>
</tr>
<tr>
<td>- Mean (SD) = 1.2 (0.6)*</td>
</tr>
<tr>
<td>- * 92.2% graded at Step 1 or 2 by clinician at Visit 1, on scale 0 - 4</td>
</tr>
</tbody>
</table>

This was a group of patients with normal spirometry, mild symptoms with an unclear diagnosis.
A305 Study Design

Visit 1
Medical history
Physical exam
Skin testing
FEV₁ reversibility
Clinician eval.
- NAEPP
- likelihood of having asthma

Visit 2
Exercise challenge #1

Visit 3
Exercise challenge #2

Visit 4
Mannitol or methacholine challenge

Visit 5
Mannitol or methacholine challenge

Randomization
All visits separated from next visit by ~ 1 – 4 days
Order for mannitol and methacholine challenges was randomized within the exercise negative and exercise positives arms

Blinding
Mannitol and methacholine challenges performed by staff different from those performing the rest of the procedures
There was no access to results across groups
Clinician doing diagnosis at Visit 5 had access to all data except mannitol and the methacholine challenge results
Methacholine and mannitol were equally sensitive for identifying bronchial hyperresponsiveness in the population

- **Methacholine** (5 breath dosimeter method)
  \[ PC_{20} \leq 16 \text{ mg/ml (fall in FEV}_1\text{ of 20\% from baseline)} \]
  \[ n=156 \text{ were positive} \]

- **Mannitol**
  \[ PD_{15} \leq 635 \text{ mg (fall in FEV}_1\text{ of 15\% from baseline)} \] (or subject experienced a 10\% between dose fall in FEV\(_1\))
  \[ 168 \text{ were positive} \]

- **Exercise** (8 minute treadmill challenge)
  \[ \text{FEV}_1\text{ fall } \geq 10\% \text{ from baseline on at least 1 of 2 exercise tests} \]
  \[ n=163 \text{ were positive} \]
METHACHOLINE

The positive predictive value was 78.2%
The negative predictive value was 46.1%
Thus a negative test was not useful to rule out asthma

<table>
<thead>
<tr>
<th></th>
<th>Clin Dx +ve n=240</th>
<th>Clin Dx –ve n= 135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine +ve</td>
<td>122 GM 2.14 mg/ml</td>
<td>34 2.04 mg/ml</td>
</tr>
<tr>
<td>Methacholine -ve</td>
<td>118 &gt; 16 mg/ml</td>
<td>101 &gt; 16 mg/ml</td>
</tr>
</tbody>
</table>

Diagnosis by a Respiratory Physician on basis of comprehensive information only such as History, Examination, FEV₁ Reversibility two exercise tests, Skin tests and Questionnaires

Anderson SD et al Respir Res 2009: 10:4
The positive predictive value was 78.8%
The negative predictive value was 48.2%
A positive test **was useful to rule in asthma**

<table>
<thead>
<tr>
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<th>Clin Dx +ve n=240</th>
<th>Clin Dx –ve n=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol +ve</td>
<td>134</td>
<td>36</td>
</tr>
<tr>
<td>Mannitol -ve</td>
<td>106</td>
<td>99</td>
</tr>
</tbody>
</table>

Diagnosis by a Respiratory Physician on basis of History, Examination, FEV₁ Reversibility 2 exercise tests, Skin tests Questionnaires

Anderson SD et al Respir Res 2009:10:4
What did we learn about methacholine from A 305?

- That Methacholine was no more sensitive for identifying AHR than mannitol or exercise and no more sensitive than mannitol for identifying a clinical diagnosis of asthma.

- There was a high rate of methacholine negative test results (49%) in those given a clinical diagnosis of asthma by a respiratory physician at the end of the study.

- Based on comprehensive information that included History, FEV$_1$ reversibility, two exercise tests, skin tests, questionnaire (the results of the methacholine or mannitol test results were withheld) suggests that:
  
  - a negative methacholine test result should not be relied upon to rule out a diagnosis of asthma in subjects with symptoms of asthma but without a definite diagnosis.
  
  - The importance of these observations is that it is subjects with these characteristics who are most likely to be referred for testing.
What did we learn about Mannitol as a rule in test?

- Mannitol was as sensitive as methacholine for identifying BHR.

- Mannitol was never less sensitive than methacholine to identify a clinical Diagnosis of asthma when cut points of 8, 12 or 16 mg/ml were used.

- The clinical utility of a mannitol positive test result was upheld by the low number of false positive tests in A301 and Copenhagen studies & the high concordance (78.5%) between a clinical Dx at Visit 5 & a positive mannitol in A305.
Mannitol positive subjects compared with mannitol negative subjects

• In mannitol +ve subjects a PC$_{20}$ Methacholine was more frequent (66% vs 25%) and the PC$_{20}$ significantly lower 1.64 vs 3.54 mg/ml $p<0.001$ (Anderson SD et al Respir Res 2009)

• In mannitol +ve subjects EIB was more common (57% vs 33%) and more severe 21±10% vs 16±7% $p<0.001$) (Anderson SD et al Respir Res 2009;10:4)

• In mannitol +ve subjects FeNO was significantly higher 47 vs 19 ppb (Sverrild S et al JACI 2010)

• In those with eosinophilic asthma 82% are +ve to mannitol (Porsbjerg et al J Asthma 2009:46)
Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers

Malcolm Sue-Chu,1,2 John D Brannan,3 Sandra D Anderson,3 Nora Chew,4 Leif Bjermer5

Methods Exhaled nitric oxide concentration ($F_{ENO}$), spirometry and bronchial challenge in random order with methacholine, AMP and mannitol were consecutively performed on three study days in the autumn. Specific IgE to eight aeroallergens and a self-completed questionnaire about respiratory symptoms, allergy and asthmatic medication were also performed on day 1. Eucapnic voluntary hyperventilation (EVH) and field exercise tests were randomly performed in 33 of the skiers on two study days in the following winter.
High Prevalence of airway hyperresponsiveness to methacholine, and low prevalence of response to AMP and Mannitol in Young skiers with and without symptoms of asthma.

Sue Chu et al Brit J Sports Med 2010
Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers

Malcolm Sue-Chu,¹,² John D Brannan,³ Sandra D Anderson,³ Nora Chew,⁴ Leif Bjermer⁵

Conclusions  Methacholine hyperresponsiveness is more common in asymptomatic skiers and is a poor predictor of hyperresponsiveness to mannitol and hyperpnoea. The low prevalence of hyperresponsiveness to indirect stimuli may suggest differences in the pathogenesis of methacholine hyperresponsiveness in elite skiers and non-athletes.
What about methacholine as a Rule in test?

• Many clinicians use a positive methacholine test result as diagnostic of asthma at a $PC_{20}<16 \text{ mg/ml}$.

• Many factors however can contribute to AHR to methacholine.

• AHR at $PC_{20}<16 \text{ mg/ml}$ can reflect airway injury from breathing large volumes of unconditioned air (e.g. cross country skiers or skaters) cigarette smoking or inhalation of pollutants (e.g. swimmers) or remodelling of the airways in response to childhood asthma.

• The findings of positive methacholine responses in elite athletes both with and without symptoms of asthma suggest that we should question if a positive methacholine test result is always consistent with a diagnosis of asthma.
LEARNING OBJECTIVE

• Evaluate methacholine and mannitol as potential test for monitoring asthma treatment
Monitoring Response to ICS treatment measuring AHR with DIRECT STIMULI

- Airway hyperresponsiveness (AHR) to direct stimuli e.g. methacholine and histamine may reflect a fixed component such as a change in airway calibre from airway remodelling or a variable component due to inflammation or both.

- Thus AHR to methacholine can be documented either in the presence of currently active airway inflammation or in its absence as may be the case in those with airway remodelling from past asthma or from environmental injury as occurs in elite skaters, skiers and swimmers.

- While daily treatment with adequate doses of inhaled corticosteroids (ICS) reduces AHR to methacholine the $PC_{20}$ remains well below 8 mg/ml even after many weeks or months of treatment presumably because a component of AHR is due to airway remodelling and injury.
Change in direct AHR to inhaled corticosteroids

PD$_{20}$
$\mu$g

PC$_{20}$
mg/ml

Dose (mcg)  Duration (wks)  
Reddel 1600  64  
du Toit 1000  12  
Jenkins 500  6  
Foresi 1000  6  
Lim 1600  4  
Sont 800  104  

Modified from Brannan et. al. Clin Respir J 2007; 1
Monitoring Response to ICS treatment measuring AHR with INDIRECT STIMULI

- Most attacks of asthma that occur in daily life are due to stimuli that act indirectly, by release of mediators from inflammatory cells, and these mediators cause smooth muscle contraction and airway narrowing.

- Airway hyperresponsiveness (AHR) to indirect stimuli e.g. exercise and mannitol indicates currently active airway inflammation i.e. the inflammatory cells are present in sufficient numbers and the mediators in a sufficiently high concentration for a responsive bronchial smooth muscle to contract.

- Treatment daily with adequate doses of inhaled corticosteroids (ICS) would be expected to resolve or significantly reduce AHR due to inflammation such that an exercise or mannitol test would become negative within the time a patient would be expected to comply with ICS treatment e.g. 8-12 weeks.

- For example, the majority of children & adults with exercise-induced bronchoconstriction (EIB), or AHR to mannitol treated daily with ICS for 3 to 8 weeks are likely to have a significant reduction or even complete resolution of their EIB or AHR to mannitol.
Treatment goal with steroids is clear for an indirect test, i.e. until response is within the normal range (usually takes 8–12 weeks)

% Fall in FEV$_1$

$\begin{align*}
\text{Pre} & \quad \text{Post} \\
100 \, \mu g/\text{day for 12 weeks} & \\
10/14 \ (71\%) & \\
\end{align*}$

$\begin{align*}
\text{Pre} & \quad \text{Post} \\
200 \, \mu g/\text{day for 12 weeks} & \\
9/14 \ (64\%) & \\
\end{align*}$

FEV$_1$ 100 ± 12% predicted

FEV$_1$ 101 ± 10% predicted

Budesonide
Jonasson G. *Pediatr Allergy Immunol* 2000;11:120–5; personal communication
Exercise response after 3 weeks of Rx

Group 1

FEV$_1$
91% ± 3.5
92% ± 3

Baseline 3 weeks CIC

FEV$_1$
93% ± 2.8
91.6% ± 2.8

Group 2

FEV$_1$
87.6% ± 4.1
89.6% ± 4.6

Baseline 3 weeks CIC

FEV$_1$
88.4% ± 4.0
90.5% ± 4.2

Exercise response following ciclesonide low (40, 80 µg/day) & high doses (160, 320 µg/day) in those with >5% and <5% eosinophils

Changes from baseline were compared within a group (*) and between groups (†) for each dose level at p<0.05 ANOVA. The >5% sputum eosinophil group showed a significantly greater change from baseline for high-dose versus low-dose (‡) ciclesonide.

Duong M, et al. Chest 2008;133:404-11,
ORIGINAL ARTICLE

Budesonide reduces sensitivity and reactivity to inhaled mannitol in asthmatic subjects

JOHN D. BRANNAN,¹ HEIKKI KOSKELA,² SANDRA D. ANDERSON¹ AND H. KIM CHAN³

¹Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia, ²Kuopio University Hospital, Kuopio, Finland and ³Faculty of Pharmacy, University of Sydney, NSW, Australia
AHR to mannitol resolved or reduced after 6-9 wk of ICS

**SENSITIVITY**

- Before Rx: 78 (51, 117) mg
- After Rx: 289 (202, 414) mg
- No PD$_{15}$
- p < 0.001

**REACTIVITY**

- 95% CI in healthy subjects 0.004 % fall/mg

**Response Dose Ratio to Mannitol**

RDR = Response (%) / Dose (mg)

Brannan et al. Respirology 2002; 7: 37-44
Sensitivity and Validity of Three Bronchial Provocation Tests To Demonstrate the Effect of Inhaled Corticosteroids in Asthma*

Heikki O. Koskela, MD; Liisa Hyvärinen, MD; John D. Brannan, PhD; Hak-Kim Chan, PhD; and Sandra D. Anderson, PhD, DSc

CHEST 2003; 124:1341–1349,
AHR to mannitol resolved or reduced after 12-24 weeks of treatment with 1000 mcg of budesonide

7/17 (41%) unresponsive after 3 m Rx & 82% were unresponsive at one visit

Koskela H et al. CHEST 2003;124:1341-9
The frequency of symptoms, daily doses of relief medication, and sum symptom score before and at 3 m and 6 m of Rx with budesonide.
Predictive Markers of Asthma Exacerbation during Stepwise Dose Reduction of Inhaled Corticosteroids

JÖRG D. LEUPPI, CHERYL M. SALOME, CHRISTINE R. JENKINS, SANDRA D. ANDERSON, WEI XUAN, GUY B. MARKS, HEIKKI KOSKELA, JOHN D. BRANNAN, RUTH FREED, MORGAN ANDERSSON, HAK-KIM CHAN, and ANN J. WOOLCOCK

Institute of Respiratory Medicine, University of Sydney, New South Wales, Australia; and Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

To identify predictors for failure of ICS dose reduction with loss of control, we measured AHR to histamine and mannitol and noninvasive markers of airway inflammation as measured by sputum eosinophils and eNO in patients with stable asthma.
Back titration of steroid dose

- The airway response to both an indirect (mannitol) and a direct (histamine) stimulus was measured at baseline in people well controlled on ICS.
- 24 subjects had AHR (PD_{15}) to mannitol and 15 a (PC_{20}) to histamine at baseline.
- The ICS dose was halved every 2 m & response to mannitol measured
- On the initial visit 23 had no AHR or response to mannitol and at the final visit 9 were still unresponsive with 7 still off ICS 2 m later.
- A PD_{15} mannitol at baseline did not predict failure of dose reduction
- A PD_{15} mannitol <635 mg during the dose reduction had 90% sensitivity and a specificity 42% to predict failure of dose reduction.
- Neither FEV_{1} nor PEF % predicted nor FeNO ppb were markers for failed reduction although sputum eosinophils >6% had a 90% sensitivity and 58% specificity to predict failure and an exacerbation.
Comparison of values before the last successful ICS reduction and the values before the failed ICS reduction in the same 26 subjects
Mean values (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Successful reduction</th>
<th>Exacerbation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDR mannitol</strong></td>
<td>0.05 (0.03-0.08)</td>
<td>0.09 (0.06-0.15)</td>
<td>0.003</td>
</tr>
<tr>
<td>Exhaled NO (ppb)</td>
<td>18.4 (14.9-22.8)</td>
<td>18.5 (12.9-26.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>FEV$_1$ predicted (%)</td>
<td>87.4 (81.1-93.8)</td>
<td>86.9 (79.7-92.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>FVC predicted (%)</td>
<td>88.7 (82.7-92.7)</td>
<td>87.5 (81.2-94.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>PEF predicted (%)</td>
<td>84.3 (80.5-92.1)</td>
<td>82.6 (79.4-83.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>PEF (lowest % best)</td>
<td>85.5 (81.9-87.8)</td>
<td>82.9 (78.3-86.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>Sputum neutrophils (%)</td>
<td>26 (13.5-38.5)</td>
<td>18.6 (8.5-28.7)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Sputum eosinophils (%)</strong></td>
<td>7.9 (3.9-11.8)</td>
<td>22.5 (11.4-33.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sputum macrophages (%)</td>
<td>56.8 (45.5-68)</td>
<td>58.6 (47.5-69.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Sputum lymphocytes (%)</td>
<td>3.2 (0.4-6.1)</td>
<td>0.53 (0.1-0.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sputum mast cells (%)</td>
<td>0.09 (-0.03-0.2)</td>
<td>0.4 (-0.4-1.2)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

RDR: %fall FEV$_1$ at the last dose/cumulative dose mg; FEV$_1$: forced expiratory volume in one second; FVC: forced expiratory volume; PEF: peak expiratory flow rate

Leuppi et al., *AJRCCM* 2001; 163: 406-12
PD$_{15}$ <635mg 90% sensitivity
Levels of responsiveness to mannitol and of sputum eosinophilia are both predictors of the likelihood of success or failure of ICS dose reduction at any given time. Our subjects were clinically well controlled and symptom free before the failed ICS reduction, suggesting that mannitol responsiveness and sputum eosinophils provide information additional to that provided by symptoms.
Return of the PD$_{15}$ to mannitol in previously well controlled subjects after stepwise dose reduction of ICS and is not reflected in a change in FEV$_1$

Redrawn from Leuppi JD et al, AJRCCM 2001;163:406-412
Earlier studies by Sont J et al AJRCCM 1999 used methacholine and guidelines and Green R et al Lancet 2002 used or eosinophils and guidelines
Current asthma management guidelines advocate adjusting the dose of inhaled corticosteroid (ICS) against symptoms, lung function, and reliever use to achieve optimal control.\textsuperscript{1,2} However, present guidelines do not recommend any method for noninvasive assessment of asthmatic inflammation. It is known that despite good control, persistent airway inflammation and associated airway hyperresponsiveness (AHR) lead to airway remodeling, even in asymptomatic subjects.\textsuperscript{3}

The present study considered the use of a primary care management tool to reduce AHR as measured by indirect challenge using the osmotic stimulus of mannitol challenge. Mannitol is becoming of increasing interest, as it acts by indirect release of inflammatory mediators, which closely mimics physiologic stimuli.\textsuperscript{7,8}
STAMINA Trial using a treatment strategy aimed at reducing AHR to mannitol versus treatment using BTS guidelines.

- The AHR strategy involved adjusting ICS dose every 2 months until mannitol PD$_{10}$<635 mg and measuring outcome by a number of inflammatory indices including FeNO, eosinophilic cationic protein (ECP) AHR to methacholine, symptom and reliever use. LABAs or LT antagonists not permitted.
- When the dose of ICS was adjusted in accordance with AHR to mannitol there was a significant reduction in FeNO (p<0.05) and ECP (p<0.05) AHR to mannitol (p<0.0001) methacholine (p<0.05) symptoms (p<0.005) & reliever use (p<0.001)
- When the treatment strategy involved adjusting ICS dose based on changes in PEF, FEV$_1$, reliever use or symptom scores there were no significant changes in indices of inflammation
- There was no change in FEV$_1$ or PEF or AQLQ in response to ICS

(Lipworth BJ et al Chest 2012:141;607-15)
Methods

Ciclesonide dosing regimen in both groups:

• step #1  80 ug/day
• step #2 160 ug/day
• step #3 320 ug/day
• step #4 480 ug/day
• step #5 640 ug/day
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 58)</th>
<th>AHR group (n = 61)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53.7 (1.7)</td>
<td>53.2 (1.6)</td>
<td>ns</td>
</tr>
<tr>
<td>FEV$_1$ %</td>
<td>85.1 (1.9)</td>
<td>84.0 (2)</td>
<td>ns</td>
</tr>
<tr>
<td>PEF %</td>
<td>87.0 (2.6)</td>
<td>91.2 (2.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Mannitol PD$_{10}$ (mg)</td>
<td>114.7 (81.9–161)</td>
<td>108.9 (76.7–155)</td>
<td>ns</td>
</tr>
<tr>
<td>Methacholine PC$_{20}$ (mg/ml)</td>
<td>0.85 (0.55–1.32)</td>
<td>0.84 (0.54–1.28)</td>
<td>ns</td>
</tr>
<tr>
<td>FeNO (pbb)</td>
<td>24.9 (19.6–31.6)</td>
<td>25.7 (21.6–30.7)</td>
<td>ns</td>
</tr>
<tr>
<td>ICS (ug/day)</td>
<td>156.4 (9.98)</td>
<td>153.9 (14.8)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data shown as mean (SEM) or geo mean (95%CI)  
Lipworth BJ et al Chest 2012;141:607-612
**Improvements in Symptoms and reliever use & morning peak flow in group whose dose guided by airway response to mannitol**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End Study</th>
<th>Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHR Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=58</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PEF am</td>
<td>372.7</td>
<td>412.6</td>
<td>39.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Night Symptoms</td>
<td>0.29</td>
<td>0.07</td>
<td>-0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Day Symptoms</td>
<td>0.53</td>
<td>0.26</td>
<td>-0.27</td>
<td>0.0002</td>
</tr>
<tr>
<td>Reliever use</td>
<td>0.97</td>
<td>0.36</td>
<td>-0.61</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Control Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=61</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PEF am</td>
<td>392.5</td>
<td>411.1</td>
<td>19.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Night Symptoms</td>
<td>0.18</td>
<td>0.17</td>
<td>-0.01</td>
<td>0.87</td>
</tr>
<tr>
<td>Day Symptoms</td>
<td>0.46</td>
<td>0.37</td>
<td>-0.09</td>
<td>0.35</td>
</tr>
<tr>
<td>Reliever use</td>
<td>0.75</td>
<td>0.67</td>
<td>-0.08</td>
<td>0.70</td>
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</tbody>
</table>

Lipworth BJ et al Chest 2012;141:607-612

*
No significant change in spirometry peak flow or quality of life in either Control or AHR group

<table>
<thead>
<tr>
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<th>AHR Group n=58</th>
<th>Control Group n=61</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End Study</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;%</td>
<td>83.6 (1.9)</td>
<td>86.3% (1.9)</td>
</tr>
<tr>
<td>PEF%</td>
<td>89.2 (2.0)</td>
<td>88.5 (2.6)</td>
</tr>
<tr>
<td>FVC%</td>
<td>91.5 (1.9)</td>
<td>93.0 (2.4)</td>
</tr>
<tr>
<td>AQLQ</td>
<td>5.9 (0.10)</td>
<td>6.5 (0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>2.0 (-3.6-7.6)</td>
<td>1.7 (-4.7-8.1)</td>
</tr>
<tr>
<td>p value</td>
<td>0.48</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;%</td>
<td>85.6% (2.0)</td>
<td>88.0 (2.8)</td>
</tr>
<tr>
<td>PEF%</td>
<td>92.3 (2.7)</td>
<td>94.3 (3.3)</td>
</tr>
<tr>
<td>FVC%</td>
<td>92.7 (1.9)</td>
<td>94.0 (2.6)</td>
</tr>
<tr>
<td>AQLQ</td>
<td>6.0 (0.11)</td>
<td>6.2 (0.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
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<td>1.7 (-4.7-8.1)</td>
</tr>
<tr>
<td>p value</td>
<td>0.48</td>
<td>0.59</td>
</tr>
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</table>

Lipworth BJ et al Chest 2012;141:607-612
**Significant improvement in Methacholine responsiveness, FeNO and ECP in the group whose dose of steroids was guided by AHR to mannitol**

<table>
<thead>
<tr>
<th>AHR Group</th>
<th>Baseline</th>
<th>End of Study</th>
<th>Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methacholine</strong></td>
<td><strong>PC\textsubscript{20} (mg/ml)</strong>\textsuperscript{*}</td>
<td>0.84(0.54-1.28)</td>
<td>2.43(1.19-4.95)</td>
<td>1.54(0.43-2.6)</td>
</tr>
<tr>
<td><strong>Mannitol</strong></td>
<td><strong>PD\textsubscript{10} (mg)</strong>\textsuperscript{*}</td>
<td>108.9(76.7-155)</td>
<td>482(319.9-726)</td>
<td>2.1(1.37-2.84)</td>
</tr>
<tr>
<td><strong>FeNO (pbb)\textsuperscript{†}</strong></td>
<td>25.7(21.6-30.7)</td>
<td>18.8(15.9-22.3)</td>
<td>1.37(1.06-1.78)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ECP (ug/L)\textsuperscript{†}</strong></td>
<td>16.8(12.8-22)</td>
<td>11.1(8-15.5)</td>
<td>1.51(0.99-2.29)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>OUCortisol/C (mmol/10h)\textsuperscript{†}</strong></td>
<td>4.00(3.14-5.09)</td>
<td>4.21(3.38-5.25)</td>
<td>0.95(-0.67-1.33)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Lipworth BJ et al Chest 2012;141:607-612
**NO Significant improvement in Methacholine responsiveness, FeNO and ECP in the control group whose dose of steroids was guided by BTS Clinical Guidelines**

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Baseline</th>
<th>End of Study</th>
<th>Change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTS</td>
<td>Methacholine PC(_{20}) (mg/ml)*</td>
<td>0.85(0.55-1.32)</td>
<td>1.59(0.95-2.67)</td>
<td>0.9(-0.07-1.87)</td>
</tr>
<tr>
<td></td>
<td>Mannitol PD(_{10}) (mg)*</td>
<td>114.7(81.9-161)</td>
<td>168.5(103-275)</td>
<td>0.7(-0.2-1.5)</td>
</tr>
<tr>
<td></td>
<td>FeNO (pbb)†</td>
<td>24.9(19.6-31.6)</td>
<td>23.7(18.0-31.2)</td>
<td>1.05(0.7- 1.5)</td>
</tr>
<tr>
<td></td>
<td>ECP (ug/L)†</td>
<td>11.8(8.5-16.4)</td>
<td>9.8(7.1-13.5)</td>
<td>1.2(0.76-1.9)</td>
</tr>
<tr>
<td></td>
<td>OUCortisol/C (mmol/10h)†</td>
<td>3.62(2.78-4.74)</td>
<td>3.62(2.93-4.46)</td>
<td>1.00(-0.70-1.4)</td>
</tr>
</tbody>
</table>

Lipworth BJ et al Chest 2012;141:607-612
Dose of inhaled steroid (Ciclesonide)

306ug (95%CI 241-370) difference between AHR vs Control (P<0.0001)

Lipworth BJ et al Chest 2012;141:607-612
What are the clinical implications?

• In a primary care setting repeated mannitol challenge (as PD_{10}) is safe to use in mild to moderate asthmatics to assess AHR

• Further long-term studies are required in more severe patients to fully define its clinical role as an asthma inflammometer
A 301 Phase 3 study for Registration
December 9th 2005 6:144

Research

The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline

John D Brannan¹, Sandra D Anderson*¹, Clare P Perry¹, Ruth Freed-Martens¹, Anna R Lassig², Brett Charlton² and the Aridol Study Group

Address: ¹Department of Respiratory Medicine, 11 West, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia and ²Pharmaxis Ltd., Unit 2, 10 Rodborough Rd, Frenchs Forest NSW 2086, Australia

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* Corresponding author

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Study in well defined populations of asthmatic and healthy subjects
A 301 Phase 3 study showed mannitol has a high specificity i.e. a positive response in a healthy subject is unlikely

<table>
<thead>
<tr>
<th>“Gold Standard” Clinicians Diagnosis</th>
<th>Clin Dx</th>
<th>Clin Dx Adjusted For ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol n = 492</td>
<td>59.8</td>
<td>94.5</td>
</tr>
<tr>
<td>Mannitol Sensitivity Specificity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol n = 333</td>
<td>89.0</td>
<td>95.0</td>
</tr>
<tr>
<td>Mannitol Sensitivity Specificity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity increased from 60 to 89% when data adjusted for the confounding effect of benefit from treatment with inhaled corticosteroids (ICS) and mannitol negative subjects taking ICS are removed. Age 6 - 83 yrs (Mean 34.8 yr)

Brannan JD Anderson SD et al 2005 Respiratory Research 6: 144
<table>
<thead>
<tr>
<th>Caucasian Adults</th>
<th>Asthmatic taking ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A301 Study</strong></td>
<td>Positive (PD$_{15}$)</td>
</tr>
<tr>
<td>N (% Females)</td>
<td>129 (69%)</td>
</tr>
<tr>
<td>% taking ICS with LABA</td>
<td>60.4%</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.4±15.5</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>166.7±9.0</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2±5.8</td>
</tr>
<tr>
<td>FEV$_1$ % Predicted screening</td>
<td>91.3±12.2</td>
</tr>
<tr>
<td>Mannitol PD$_{15}$ (Geomean)</td>
<td>134.8 (110,165)</td>
</tr>
<tr>
<td>Geomean RDR (%fall FEV$_1$/mg)</td>
<td>0.1064</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.0873,0.13</td>
</tr>
<tr>
<td>Percent with &gt; 10% fall FEV$_1$</td>
<td>100%</td>
</tr>
<tr>
<td>Atopic</td>
<td>94.5%</td>
</tr>
<tr>
<td>Coughed in last week</td>
<td>53%</td>
</tr>
</tbody>
</table>

Brannan JD et al J Allergy Clin Immunol 2012 Letter
# Advice relating to mannitol test outcome

<table>
<thead>
<tr>
<th>Mannitol Positive*</th>
<th>Mannitol Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not on ICS</strong></td>
<td><strong>Using ICS</strong></td>
</tr>
<tr>
<td>Asthmatic with</td>
<td>Check technique &amp;</td>
</tr>
<tr>
<td>active airway</td>
<td>Adherence &amp;</td>
</tr>
<tr>
<td>inflammation that</td>
<td>Maintain or</td>
</tr>
<tr>
<td>will respond to</td>
<td>increase ICS</td>
</tr>
<tr>
<td>ICS</td>
<td>dosage</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not on ICS</strong></td>
<td><strong>Using ICS</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
</tr>
<tr>
<td>of asthma</td>
<td></td>
</tr>
</tbody>
</table>

*PD15 = 15% fall in FEV1 to a dose ≤ 635 mg*
Why challenge with Mannitol?

**Advantages:**
- High positive predictive value for Clinical Dx of asthma
- Dose-response curve obtained
- Median time taken for +ve test 17 min, -ve test 26 min
- More than one mediator involved LT's, Hist, PGD$_2$
- Positive test predicts potential for EIB
- Negative test in asthmatic = good control of asthma
- Response dose ratio can guide back titration of steroid
- Positive test = currently active airway inflammation
- Identifies those who would benefit from Rx with ICS

**Disadvantage:**
- Some cough during challenge
- 55% of those taking ICS will have a negative test