GETTING STARTED WITH MANNITOL CHALLENGE TESTING

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Applications/Education Specialist
MGC Diagnostics
OBJECTIVES

Indications for provocation testing
Identify candidates for testing
Mannitol Provocation Test
- Mechanism of action
- Protocol
- Interpretation of results
Direct vs. Indirect Challenge testing
WHY TEST?

To assess bronchial hyper-responsiveness (BHR) or Airway hyper-responsiveness (AHR) in individuals who do not present with clinically apparent asthma
- Unexplained shortness of breath
- Chronic cough
WHO DO WE TEST?

Candidates must be able to perform quality Spirometry

Subject is 6 years of age or older

No contraindications to testing

Have withheld medications
MANNITOL

Is a naturally occurring sugar alcohol found in vegetables and fruits

Used as a pharmaceutical excipient and a food additive

Also approved as a bulk sweetener
ARIDOL/OSMOHALE

- Manufactured by Pharmaxis, LTD. AUS
- First approved for use in Australia by the TGA March 2006
- Regulatory approval in the United States October 2010
- January 2012- Medicare/Medicaid approved billing code J7665 for the Test Kit
Bronchial Challenge Testing:

95070- Inhalation bronchial challenge testing with histamine, methacholine, or similar compounds

94070- Bronchospasm provocation evaluation, multiple spirometric determinations as in 94010, with administered agents

94640- Pressurized or nonpressurized inhalation treatment for acute airway obstruction or for sputum induction for diagnostic purposes
AGENCY’S UTILIZING ARIDOL

- International Olympic Committee Medical Commission’s Independent Panel
- US Asthma Management Guidelines
- Global Initiative for Asthma Report on Global Strategy for Asthma Management and Prevention
- World Anti-Doping Agency
- Australian Asthma Management Handbook
MECHANISM OF ACTION

Mannitol as well as Exercise and EVH works indirectly to elicit bronchoconstriction. Bronchoconstriction is caused by a release of inflammatory cells in response to osmotic or allergen changes. These mediators/agonists are: Histamine, leukotrienes and prostaglandins.
MAST CELLS & EOSINOPHILS CAUSE BRONCHIAL SMOOTH MUSCLE TO CONTRACT

Allergen

Increase in osmolarity

Mast Cell

Prostaglandins

Leukotrienes

Histamine

Eosinophils

Bronchial smooth muscle
Respiratory Water Loss

Dehydration of Airway Surface Liquid

Increase in [Na⁺], [Cl⁻], [Ca²⁺], [K⁺]

Increase in Osmolarity of Airway Surface Liquid

Water Moves from Cells to Restore Airway Surface Liquid

Regulatory Volume Increase Follows Cell Shrinkage

When Inflammation is Present Mediators are Released

Prostaglandins
Leukotrienes
Histamine

Bronchial Smooth Muscle Contraction

Bronchoconstriction

Aridol™ Works Here

Direct Challenges (e.g. methacholine/histamine) Work Here
MANNITOL TESTING

FOR ORAL INHALATION ONLY
One complete diagnostic kit to measure bronchial hyperresponsiveness

Contents:
- 3 Blisters Cards: 0 mg - 1 capsule, 5 mg - 1 capsule, 10 mg - 1 capsule
- 3 Blisters Cards: 20 mg - 1 capsule, 40 mg - 15 capsules

1 Aridol device: For use with enclosed capsules only
See package insert for dosage information
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-agonist) 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).
CONTRAINDICATIONS/ADVERSE REACTIONS

Contraindications
- Known hypersensitivity to mannitol or gelatin used to make capsules
- Conditions that may be compromised by induced bronchospasm or repeated spirometry maneuvers
- Clinically apparent asthma
- FEV1 < 1.1-1.5 liters or < 70% predicted

Adverse Reactions
- Headache, pharyngolaryngeal pain, throat irritation, nausea, cough, rhinorrhea, dyspnea, chest discomfort, wheezing, retching and dizziness
RELATIVE CONTRAINDICATIONS

Pregnancy
Not any adequate studies in pregnant women, only perform if the potential benefit justifies the risk to the fetus

Nursing Mothers
Not known if mannitol is excreted in human milk
Caution should be exercised in nursing mothers

Geriatric Population
Insufficient number of subjects 50 years of age or older tested. Safety and efficacy cannot be adequately assessed
TECHNOLOGIST TRAINING/COMPETENCE

Familiar with ATS document and specific test Procedure, Minimum of 20 supervised tests
Proficient at spirometry testing
Have knowledge of contraindications to test
Know when to terminate testing
Able to deliver inhaled bronchodilator
Familiar with emergency procedures
Competent in equipment set up/functionality
TECHNICIAN SAFETY

Methacholine Challenge Testing
Mandatory: Two complete air exchanges/hr
Optional: Dosimeter, Drug prepared under a fume hood, exhaust ventilation, HEPA cleaner exhalation filters

Mannitol Challenge Testing
Dry powder, no need for ventilation, filters
No operator exposure has been linked to asthma development
INFLUENCING FACTORS
## DRUG WITHHOLDING TIMES

<table>
<thead>
<tr>
<th>Time to Withhold</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 hours</td>
<td><strong>INHALED NON-STERoidal ANTI-INFLAMMATORY AGENTS</strong> e.g. sodium cromoglycate, nedocromil sodium</td>
</tr>
<tr>
<td>8 hours</td>
<td><strong>SHORT-ActING BETA₂ AGONISTS</strong> e.g. salbutamol, terbutaline</td>
</tr>
<tr>
<td>12 hours</td>
<td><strong>INHALED CORTICOSTEROIDS</strong> e.g. beclomethasone dipropionate; budesonide; fluticasone propionate</td>
</tr>
<tr>
<td>12 hours</td>
<td><strong>IPRATROPIUM BROMIDE</strong></td>
</tr>
<tr>
<td>24 hours</td>
<td><strong>INHALED CORTICOSTEROIDS PLUS LONG-ActING BETA₂ AGONISTS</strong> e.g. fluticasone and salmeterol; budesonide and eformoterol</td>
</tr>
<tr>
<td>24 hours</td>
<td><strong>LONG-ActING BETA₂ AGONISTS</strong> e.g. salmeterol; eformoterol</td>
</tr>
<tr>
<td>24 hours</td>
<td><strong>THEOPHYLLINE</strong></td>
</tr>
<tr>
<td>72 hours</td>
<td><strong>TIOTROPIUM BROMIDE</strong></td>
</tr>
<tr>
<td>72 hours</td>
<td><strong>ANTIhISTAMINES</strong> e.g. cetirizine, fexofenadine and loratadine</td>
</tr>
<tr>
<td>4 days</td>
<td><strong>LEUKOTRIENE-RECEPTOR ANTAGONISTS</strong> e.g. montelukast sodium</td>
</tr>
</tbody>
</table>

**Foods:** Ingestion of significant quantities of coffee, tea, cola drinks, chocolate or other food containing caffeine may decrease bronchial responsiveness. These substances should be withheld on the day of the test.

**Exercise:** Vigorous exercise should not be performed prior to testing on the day of the test.

**Smoking:** Patients should refrain from smoking for at least 6 hours prior to testing.
### TABLE 3

**FACTORS THAT INCREASE BRONCHIAL RESPONSIVENESS**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Duration of Effect</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to environmental antigens</td>
<td>1-3 wk</td>
<td>25</td>
</tr>
<tr>
<td>Occupational sensitizers</td>
<td>Months</td>
<td>55, 56</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>3-6 wk</td>
<td>57, 58</td>
</tr>
<tr>
<td>Air pollutants</td>
<td>1 wk</td>
<td>59</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Uncertain*</td>
<td>60</td>
</tr>
<tr>
<td>Chemical irritants</td>
<td>Days to months</td>
<td>61</td>
</tr>
</tbody>
</table>

*Studies of the acute effects of smoking on airway hyperreactivity and methacholine challenge testing are not consistent (60). There is some evidence of a brief acute effect that can be avoided by asking subjects to refrain from smoking for a few hours before testing.*
ARIDOL TEST PROCEDURE
EQUIPMENT NEEDED

ARIDOL Bronchial Challenge Kit

Spirometer, mouthpiece and noseclips

Timer

Calculator

Bronchodilator
ARIDOL CHALLENGE TEST KIT

3 blister packs containing 19 capsules
ARIDOL TEST PROCEDURE
Inhaler is single patient use

During exhalation, have the patient exhale away from inhaler to minimize humidity in the inhaler

Pierce the capsules only once, multiple punctures may split/fragment the capsule

Do not use gloves when handling capsules, may cause static, inhibiting capsule movement
IMPORTANT TEST INFORMATION

If static is suspected (capsule not “rattling” during inspiration), firmly tap the base of the inhaler with one hand while holding the inhaler at a 45 degree angle, mouthpiece facing downward to ensure capsule is not dislodged.
IMPORTANT TEST INFORMATION

Mannitol is a dry powder and may cause a dry throat or cough. This is not unusual and is expected. It is permissible to allow the subject to sip water throughout procedure.

Time is critical to maintain the osmotic gradient, prolonged intervals between doses may affect validity of test results and must be avoided.
## DOSE STEPS FOR ARIDOL

Mannitol dose steps for bronchial challenge testing with ARIDOL

<table>
<thead>
<tr>
<th>Dose #</th>
<th>Dose mg</th>
<th>Cumulative Dose mg</th>
<th>Capsules per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>155</td>
<td>2 x 40 mg</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>315</td>
<td>4 x 40 mg</td>
</tr>
<tr>
<td>8</td>
<td>160</td>
<td>475</td>
<td>4 x 40 mg</td>
</tr>
<tr>
<td>9</td>
<td>160</td>
<td>635</td>
<td>4 x 40 mg</td>
</tr>
</tbody>
</table>
PREPARING THE INHALER

Remove Cap

Open, load capsule then close keeping upright

Pierce capsule by fully depressing piercing buttons Keeping inhaler upright
DOSING THE PATIENT

Tilt inhaler downward at a 45 degree angle. Noseclips may be used.

Subject should tilt head back slightly, inhaler at 45 degree angle. Lips tight.
Controlled deep inhalation.
Hold breath for 5 seconds. Capsule should rattle during inhalation.

Remove inhaler from mouth and exhale, resuming normal breathing.

Check capsule after each inhalation. If capsule is not emptied a second immediate inhalation may be required.

Vents allows user to inspect proper capsule placement.
TESTING PROCEDURE

Perform baseline spirometry according to ATS/ERS recommendations

Establish FEV1. FEV1 should be $\geq 70\%$ of predicted

Administer 0 mg ARIDOL using inhaler

Measure FEV1 after 60 seconds. Two efforts should be performed. Record the highest FEV1 as the Baseline

Acceptability criteria must be met
TESTING PROCEDURE

If the highest FEV1 has a ≥ 10% drop from the Pre- challenge maneuver stop the test

Calculate target FEV1 (Baseline x 0.85) Record this value

Continue with dosing scheme until highest dosage completed (635 mg) or a positive test obtained
TESTING PROCEDURE

Percent decrease in FEV1 is compared to 0 mg dose

Following the administration of each dose, the patient must perform two acceptable maneuvers after sixty seconds

Avoid delays between doses to ensure osmotic gradient is maintained

Test should be completed in ≤ 35 minutes
DATA INTERPRETATION

Positive test:
PD_{15} - 15% fall in FEV1 from baseline (0 mg dose)
10% fall in FEV1 between two consecutive dosages

Negative Test:
Cumulative dose of 635 mg without meeting above criteria
DATA INTERPRETATION

What if the subject has a positive test between the pre-challenge and 0 mg dose?

Test is considered positive

? Clinical meaning

? FVC maneuver induced bronchospasm
TESTING TIME

Aridol
Positive test: 20 minutes

Methacholine
Positive Test: 45 minutes

Recovery time to 95% of baseline FEV1:
Aridol- 21.6 min (SD 9.0)
Methacholine-21.06 min (SD 6.96)

Comparison of Mannitol and methacholine to predict exercised-induced bronchoconstriction and a clinical diagnosis of asthma
Anderson, Charlton, Weiler et al; Respir Res 2009
ARIDOL CHALLENGE TESTING ADVANTAGES

- Standardized test kit
- Minimal required equipment
- Relative low cost
- Ease of administration
- Consistent dose response
- Enhanced safety
- Ease of performance

Parkerson J, Ledford D.
Annals of AAI. 2011; 106:91-96
PD-15 CALCULATOR FOR ARIDOL

Calculator available on the ARIDOL website
www.us.aridol.info/calculator
In this example, the patient had both a 10% change from previous dose as well as a > 15% drop in FEV1
ARIDOL TRAINING VIDEO

Aridol® Training Presentation

It is important that any healthcare professional conducting an Aridol® challenge test is highly proficient in spirometry and has received specific product training prior to performing the test.

This website is not designed to assist in providing training in spirometry, but does include an Aridol training presentation designed to assist healthcare professionals who will perform the test.

This presentation is a tool to assist in the training of healthcare professionals performing Aridol challenge tests. It is not designed to replace comprehensive interactive training. For more information on product training please contact Pharmacia by selecting Contact Us.

For information about ARIDOL®, please call one of our Regional Customer Care Specialists at:
1-888-416-1828
DIRECT VS. INDIRECT CHALLENGE TESTING

VS

PROVOCHOLINE®
Tankable Form of Choline
100 mg

aridol™
(mannitol inhalation powder)
Bronchial Challenge Test Kit

FOR ORAL INHALATION ONLY.
One complete diagnostic kit to measure bronchial hyperresponsiveness.

Contents:
5 Blister Cards
3 mg - 1 capsule
20 mg - 1 capsule
40 mg - 1 capsule
80 mg - 1 capsule
160 mg - 1 capsule

ANTICIPATE AND SOLVE UNMET NEEDS

PROVIDE UNMATCHED SERVICE AND SUPPORT

RELENTLESSLY MAKE IMPROVEMENTS
There are two components of AHR:

- **Variable**
  - (Inflammation)

- **Persistent**
  - (Structural)
DIRECT VS INDIRECT CHALLENGE TESTING

Direct stimulation has a high sensitivity for diagnosing Asthma due to the high negative predicted value but it has low specificity to distinguish between asthmatic and Normal subjects affected with chronic airflow limitation.

Indirect stimulation has a low sensitivity for diagnosing Asthma due to high negative predicted value, it has high specificity in distinguishing between asthmatic and Normal subjects.

Multidisciplinary Respiratory Medicine, April 2011 76-78
Claudio M. Sanguinetti
DIRECT VS INDIRECT CHALLENGE TESTING

\[
sensitivity = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}
\]

\[
specificity = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}
\]
DIRECT VS INDIRECT CHALLENGE TESTING

Direct challenges are the choice for excluding Asthma.

Indirect challenges are indicated to confirm the Presence of Asthma, especially exercise induced asthma.

Multidisciplinary Respiratory Medicine, April 2011 76-78
Claudio M. Sanguinetti
WILL MANNITOL REPLACE METHACHOLINE?

Methacholine elicits contraction to airway smooth muscle
Mannitol elicits airway inflammation

Methacholine has higher sensitivity and lower specificity
Negative test rules out asthma, positive test can occur in other conditions as well

Mannitol has lower sensitivity and higher specificity
Positive test largely reflects existing inflammation

What is the Best Pulmonary Diagnostic Approach for Wheezing Patients with Normal Spirometry? William W Busse, MD
Respiratory Care, January 1, 2012. 39-49
COMPARISON OF DIRECT AND INDIRECT CHALLENGES

<table>
<thead>
<tr>
<th>Measure</th>
<th>Direct (Methacholine)</th>
<th>Indirect (Mannitol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle function</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Airway caliber</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>Inflammation</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Dose needed</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Dose limitation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Specificity</td>
<td>Fair</td>
<td>High</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Rule out</td>
<td>Rule in, assess for EIB</td>
</tr>
</tbody>
</table>

+ = strength of the relationship (greater number of + indicates greater strength)
± = uncertain but probably no relation
EIB = exercise-induced bronchospasm.

What is the Best Pulmonary Diagnostic Approach for Wheezing Patients with Normal Spirometry? William W Busse, MD Respiratory Care, January 1, 2012. 39-49
WILL MANNITOL REPLACE METHACHOLINE?

These two agents detect different components of Airway hyper-responsiveness.

Provides the clinician with effective tools to detect Airway hyper-responsiveness.

Availability of 2 different stimuli gives the clinician another approach if one test is negative but a high level of suspicion for asthma still remains.

What is the Best Pulmonary Diagnostic Approach for Wheezing Patients with Normal Spirometry? William W Busse, MD

Respiratory Care, January 1, 2012. 39-49
Having available both approaches will allow for a greater overall ability to detect and establish the existence of AHR and, hence, the likely existence of asthma.
WILL MANNITOL REPLACE METHACHOLINE?

Comparing methacholine to mannitol, responses from asthmatic subjects overlap, but with significant variability. This variability indicates that the provocative agents may be acting on the different factors (structural vs. variable) causing AHR. These findings suggest that perhaps both direct and indirect challenges may be needed to confirm the diagnosis, if one challenge is negative but the pre-test probability of asthma is high.

Gregg L Ruppel and Paul L Enright
Pulmonary Function Testing
Respiratory Care, January 2012 57:1 165-175
REFERENCES

- ATS Guidelines for Methacholine and Exercise Challenge Testing, 1999
- [www.us.aridol.info/home](http://www.us.aridol.info/home)
- Respiratory Care, January 2012
- Multidisciplinary Respiratory Medicine, April 2011 76-78
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- Comparison of Mannitol and methacholine to predict exercised-induced bronchoconstriction and a clinical diagnosis of asthma
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