GETTING STARTED WITH MANNITOL CHALLENGE TESTING

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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

CPT CODING INFORMATION

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

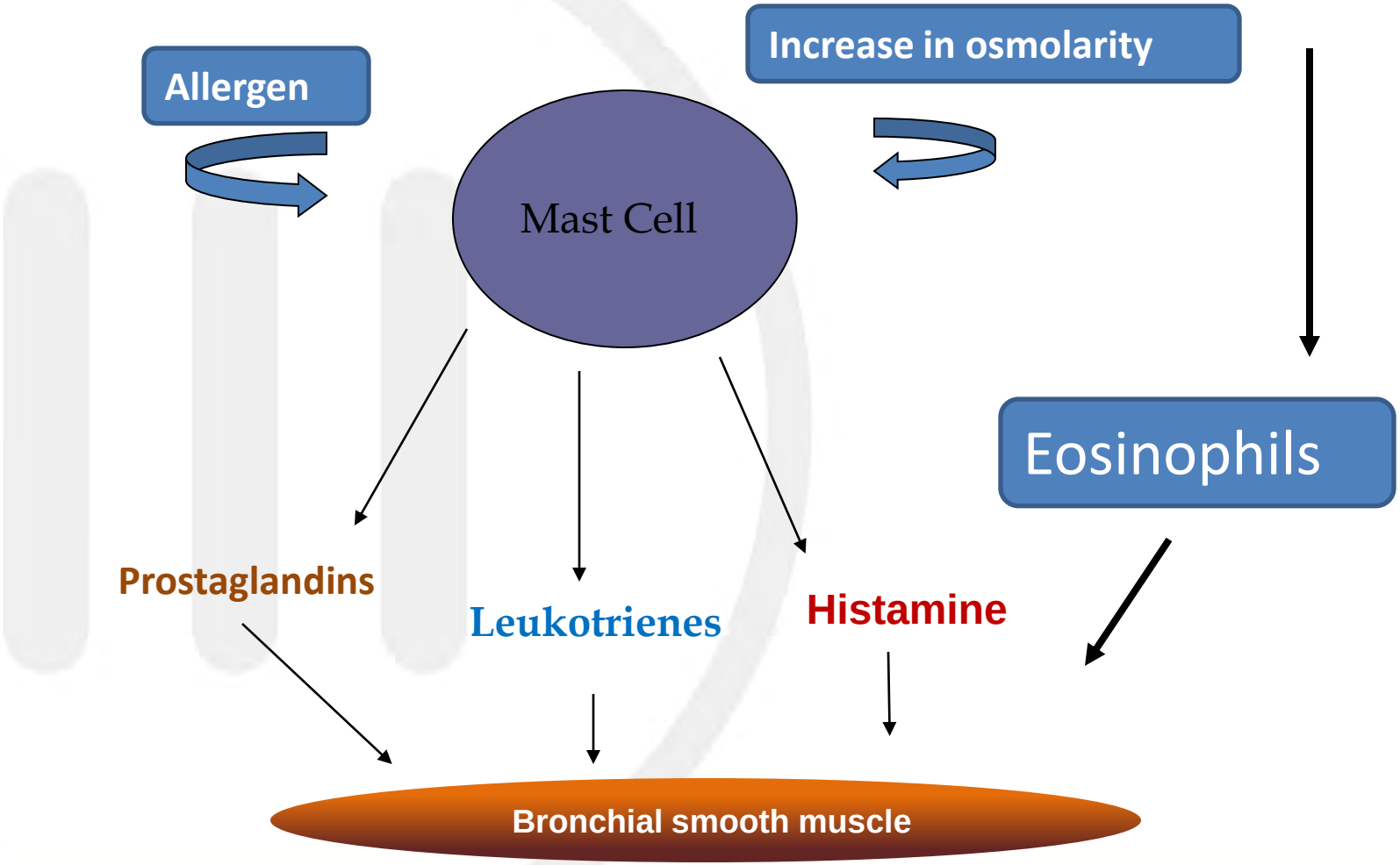
Mannitol as well as Exercise and EVH works indirectly to elicit bronchoconstriction

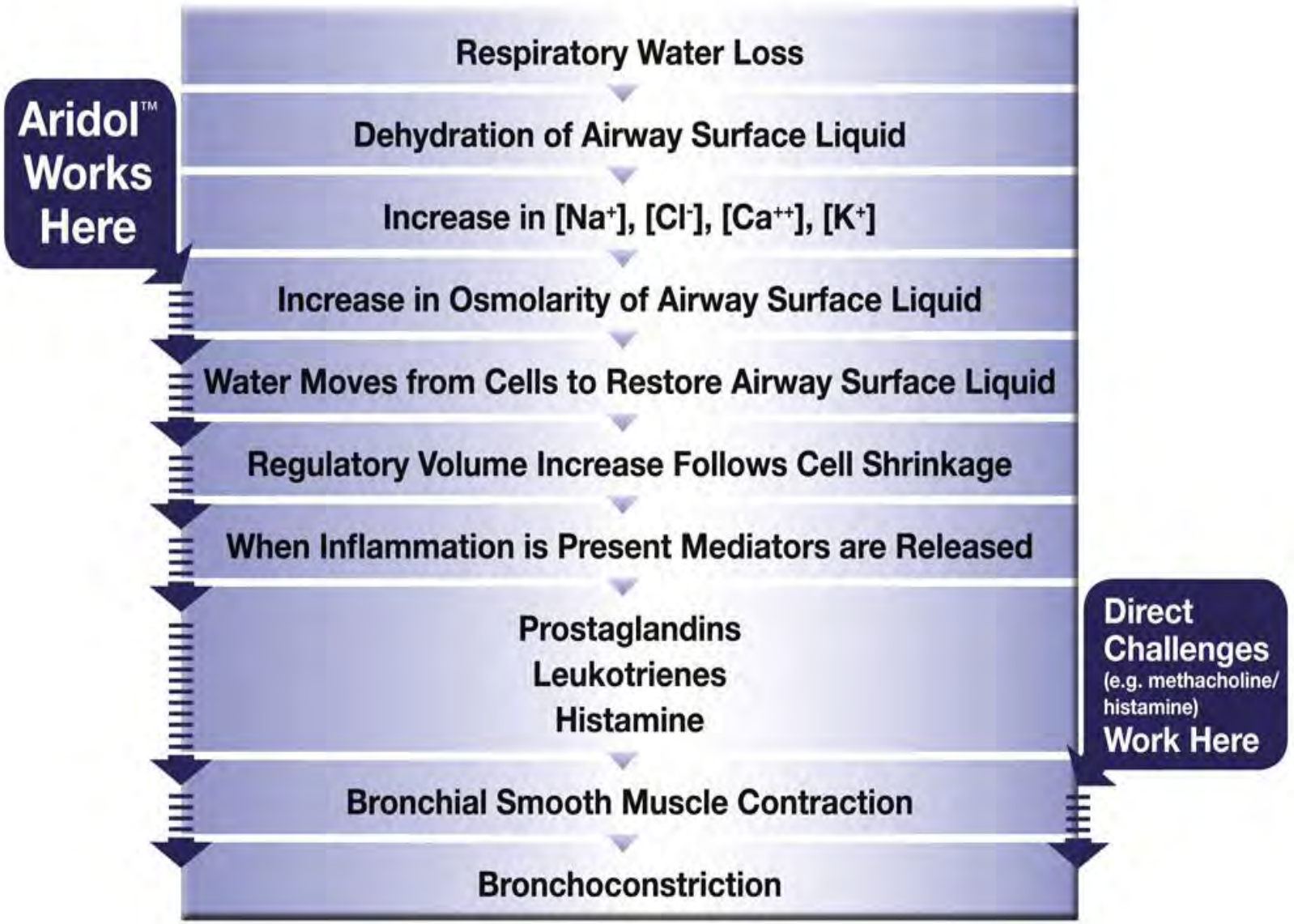
Bronchoconstriction is caused by a release of inflammatory cells in response to osmotic or allergen changes

These mediators/agonists are:

Histamine, leukotrienes and prostaglandins

MAST CELLS & EOSINOPHILS CAUSE BRONCHIAL SMOOTH MUSCLE TO CONTRACT




Respiratory Water Loss
Aridol™ Works Here
Dehydration of Airway Surface Liquid
Increase in [Na+], [Cl-], [Ca++], [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
Direct Challenges (e.g. methacholine/ histamine) Work Here
Bronchial Smooth Muscle Contraction
Bronchoconstriction

MANNITOL TESTING

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., FEV_1 <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.-1.5 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

Time to Withhold	Medication
6-8 hours	**INHALED NON-STEROIDAL ANTI-INFLAMMATORY AGENTS** e.g. sodium cromoglycate, nedocromil sodium
8 hours	**SHORT-ACTING BETA$_2$ AGONISTS** eg salbutamol, terbutaline
12 hours	**INHALED CORTICOSTEROIDS** e.g. beclomethasone dipropionate; budesonide; fluticasone propionate
12 hours	**IPRATROPIUM BROMIDE**
24 hours	**INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA$_2$ AGONISTS** eg fluticasone and salmeterol; budesonide and eformoterol
24 hours	**LONG-ACTING BETA$_2$ AGONISTS** e.g. salmeterol; eformoterol
24 hours	**THEOPHYLLINE**
72 hours	**TIOTROPIUM BROMIDE**
72 hours	**ANTIHISTAMINES** eg cetirizine, fexofenadine and loratadine
4 days	**LEUKOTRIENE-RECEPTOR ANTAGONISTS** e.g. montelukast sodium

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

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

*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.

GUIDELINES FOR METHACHOLINE CHALLENGE AND EXERCISE CHALLENGE TESTING-1999

ARIDOL TEST PROCEDURE

EQUIPMENT NEEDED

ARIDOL Bronchial Challenge Kit

Spirometer, mouthpiece and noseclips

Timer

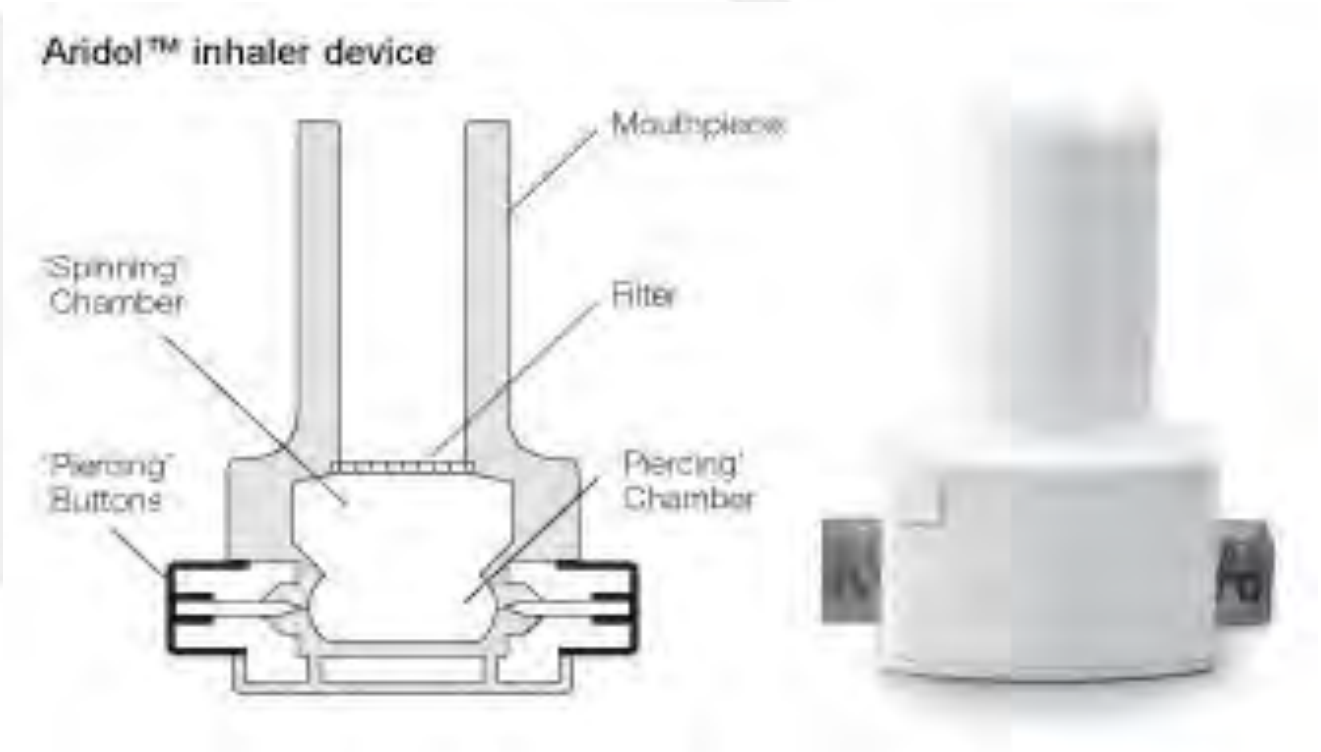
Calculator

Bronchodilator

ARIDOL CHALLENGE TEST KIT

3 blister packs

ARIDOL TEST PROCEDURE



IMPORTANT TEST INFORMATION

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

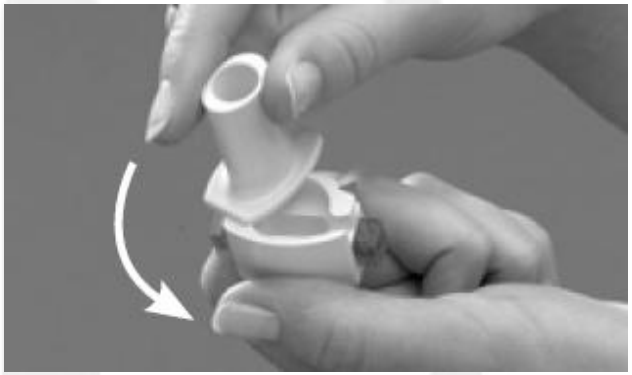
DOSE STEPS FOR ARIDOL

Mannitol dose steps for bronchial challenge testing with ARIDOL

Dose #	Dose mg	Cumulative Dose mg	Capsules per dose
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2 x 40 mg
7	160	315	4 x 40 mg
8	160	475	4 x 40 mg
9	160	635	4 x 40 mg

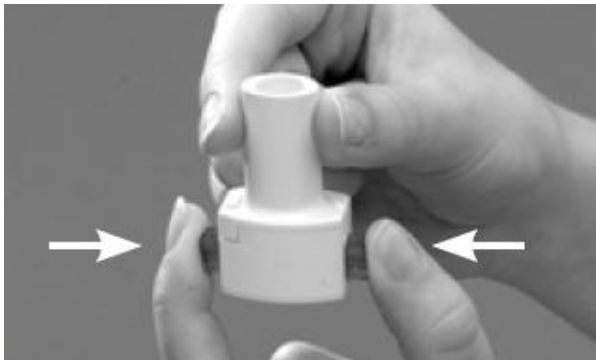
PREPARING THE INHALER

Remove Cap



Open, load capsule then close keeping upright

Pierce capsule by fully depressing piercing buttons
Keeping inhaler upright



DOSING THE PATIENT

Vents allows user to inspect proper capsule placement

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

TESTING PROCEDURE

Perform baseline spirometry according to ATS/ERS recommendations

Establish FEV1. FEV1 should be ≥ 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

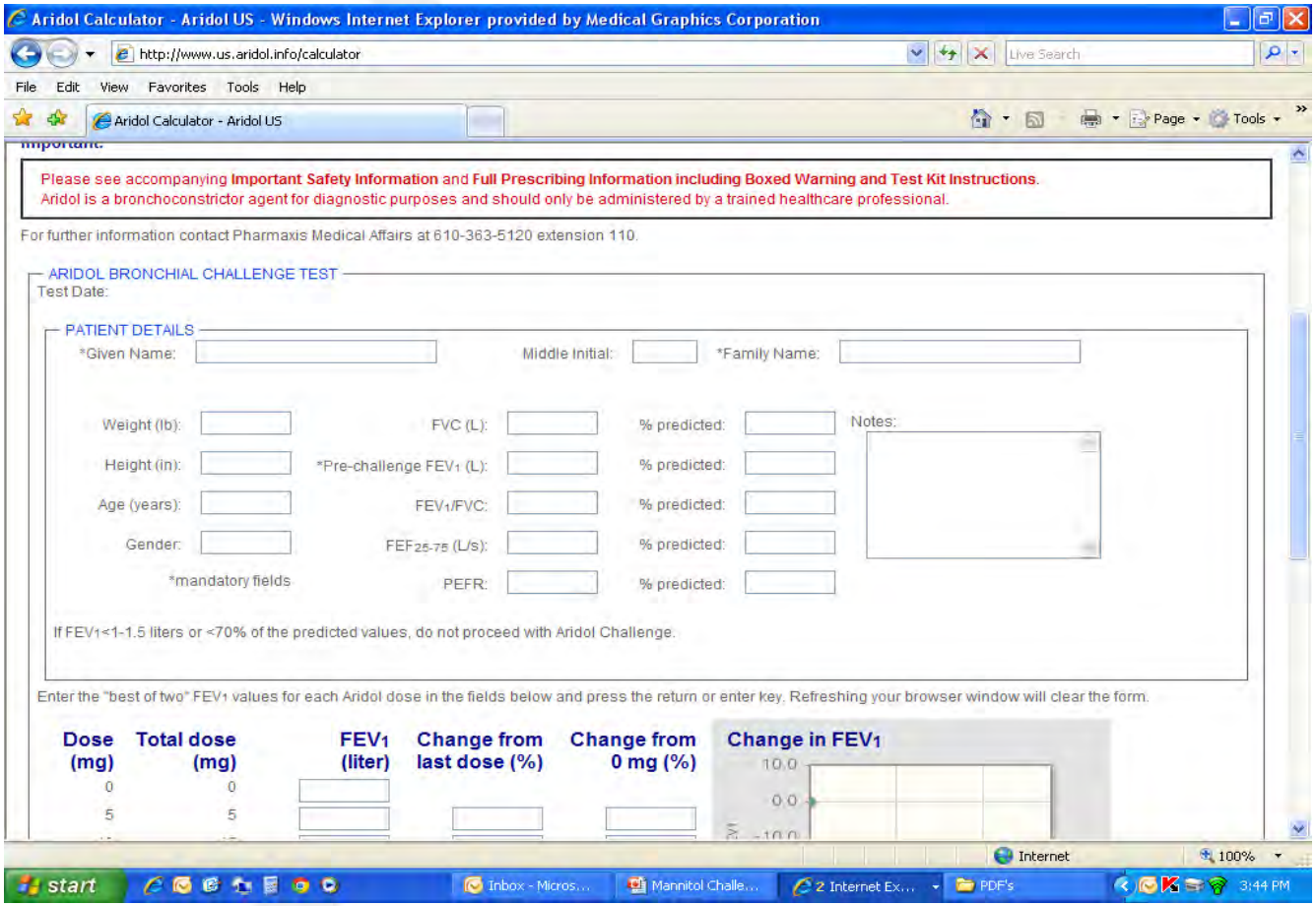
ARIDOL CHALLENGE TESTING ADVANTAGES

- 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



PD-15 CALCULATOR FORM

PD15 Calculator Page 1 of 1

PD15 Calculator for ARIDOL® (mannitol inhalation powder) Bronchial Challenge Test Kit

Important:

Please see accompanying **Important Safety Information** and **Full Prescribing Information including Boxed Warning and Test Kit Instructions.**
Aridol is a bronchoconstrictor agent for diagnostic purposes and should only be administered by a trained healthcare professional.

For further information contact Pharmaxis Medical Affairs at extension 110.

ARIDOL BRONCHIAL CHALLENGE TEST

Test Date: **12 / 13 / 2012** (m/d/y)

PATIENT DETAILS

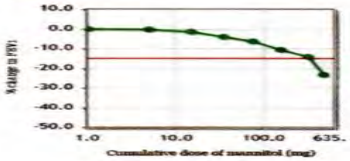
*Given Name:	Subject		Middle Initial:		*Family Name:	Test	
Weight (lb):	170	FVC (L):	4.47	% predicted:	91	Notes:	
Height (in):	69	*Pre-challenge FEV_1 (L):	3.52	% predicted:	95		
Age (years):	50	FEV_1/FVC:	79	% predicted:			
Gender:	m	FEF_{25-75} (L/s):		% predicted:			
*mandatory fields		PEFR:		% predicted:			

If FEV_1<1-1.5 liters or <70% of the predicted values, do not proceed with Aridol Challenge.

Enter the "best of two" FEV_1 values for each Aridol dose in the fields below and press the return or enter key. Refreshing your browser window will clear the form.

Dose (mg)	Total dose (mg)	FEV_1 (liter)	Change from last dose (%)	Change from 0 mg (%)
0	0	3.47		
5	5	3.46	-0.288	-0.288
10	15	3.42	-1.156	-1.441
20	35	3.33	-2.632	-4.035
40	75	3.25	-2.402	-6.340
80	155	3.10	-4.615	-10.663
160	315	2.98	-3.871	-14.121
160	475	2.66	-10.738	-23.343
160	635			

Change in FEV_1



CALCULATED RESULTS

POSITIVE TEST RESULT

A ≥ 15% fall in FEV_1 has occurred since the 0 mg dose. Do NOT continue with the Challenge Test.

A positive result is defined as a ≥ 15% fall in FEV_1 from the FEV_1 at 0 mg dose or ≥ 10% fall in FEV_1 between consecutive doses.

The PD_{15} — provocative dose to cause a 15% fall in FEV_1 — will be calculated and displayed if a ≥ 15% fall in FEV_1 occurs.

The RDR — Response / Dose ratio — will be calculated if a positive result occurs.

Dose prior to ≥ 15% fall in FEV_1 (mg):	315	Fall in FEV_1 prior to ≥ 15% fall (%):	14.121
Total dose at positive result (mg):	475	Actual fall at positive result (%):	23.343
PD_{15} dose (mg):	328	Response / Dose ratio:	0.049

PD15 Calculator by Intraversed™

12/13/2012

In this example, the patient had both a 10% change from previous dose as well as a > 15% drop in FEV1

ARIDOL TRAINING VIDEO

DIRECT VS. INDIRECT CHALLENGE TESTING

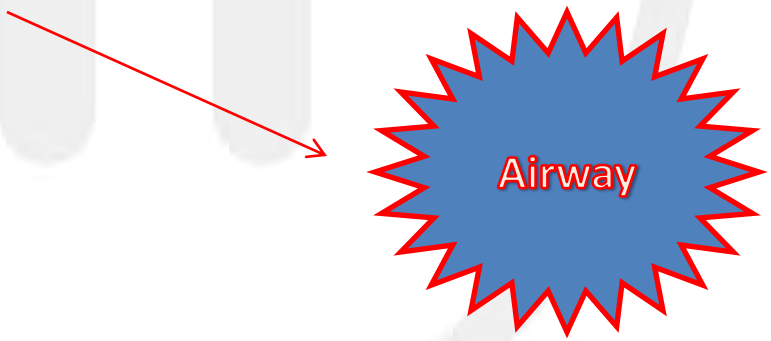
VS

AIRWAY HYPER-RESPONSIVENESS

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

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

$$\text{specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}$$

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

Measure	Direct (Methacholine)	Indirect (Mannitol)
Muscle function	++++	++
Airway caliber	++++	±
Inflammation	++	++++
Dose needed	Low	High
Dose limitation	No	Yes
Sensitivity	High	Low
Specificity	Fair	High
Diagnostic	Rule out	Rule in, assess for EIB

\+ = 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

WILL MANNITOL REPLACE METHACHOLINE?

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

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?

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
- Respiratory Care, January 2012
- Multidisciplinary Respiratory Medicine, April 2011 76-78 Claudio M. Sanguinetti
- Comparison of Mannitol and methacholine to predict exercised-induced bronchoconstriction and a clinical diagnosis of asthma Anderson, Charlton, Weiler et al; Respir Res 2009
- Parkerson J, Ledford D. Annals of AAI. 2011; 106:91-96