Technical Bulletin

Nebulizer Characterization for the Methacholine Challenge Test

The 2017 ERS technical standard on direct challenge testing recommends using PD_{20} to interpret methacholine challenge test results.[1] Methapharm has characterized an additional nebulizer with Provocholine® to provide this information.

Delivered Dose = **inhaled mass** (mg/min) X **respirable fraction** (% of particles <5 µm) X **inhalation time** (in minutes)

Table 1. Nebulizer Performance with Provocholine® 16 mg/mL Concentration

Adult					
Nebulizer	**Powered by** (lb/in^2)	**Flow Rate** (LPM)	**Inhaled Mass** (mg/min)	**Respirable Fraction*** (%)	**Estimated Deposition** (mg/min)
English Wright[1]	50	8	0.19	100	0.19
Hudson RCI® MicroMist® Small Volume Nebulizer	50	5	0.675	68.8	0.464

* The respirable fraction is the percentage of particles <5 µm[1]

Key Considerations When Selecting a Nebulizer:

- Nebulizers have evolved over the years and in some cases have a much higher output. The duration of tidal breathing may need to be decreased from two minutes in order to deliver the appropriate dose. In the Hudson RCI® MicroMist® Small Volume Nebulizer calculation below only one-minute of nebulization is required.

Using the nebulizer performance characteristics from Table 1, the Provocholine® dose delivered to an adult using a 16 mg/mL concentration can be calculated as follows:

English Wright (2-minute tidal breathing)
(0.19) x (1) x (2) = 0.38 mg (380 µg)

Hudson RCI® MicroMist® Small Volume Nebulizer (1-minute tidal breathing)
(0.675) x (0.688) x (1) = 0.464 mg (464 µg)

Reference: 1. Coates AL, Wanger J. Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017:49:1601526

Provocholine®
[methacholine chloride]

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The ERS technical standard recommends a starting dose between 1 and 3 µg and to not exceed a maximum dose of 800 µg.

Table 2. Dose delivered to an adult according to the ATS quadrupling concentrations protocol

Concentration	0.0625 mg/mL	0.25 mg/mL	1 mg/mL	4 mg/mL	16 mg/mL
English Wright[1] (2-minute tidal breathing)	1.48 µg	5.94 µg	23.75 µg	95 µg	380 µg
Hudson RCI® MicroMist® Small Volume Nebulizer (1-minute tidal breathing)	1.81 µg	7.26 µg	29.03 µg	116.10 µg	464.4 µg

Nebulizer Characterization Protocol

All studies were performed as per United States Pharmacopeia (USP) 1601 Products for Nebulization Characterization Tests. The Hudson RCI® MicroMist® Small Volume Nebulizer was powered by dry compressed air, regulated to 50 lb/in^2 (psi) and a flow controller set to a flow rate of 5.0 LPM. The solution used was Provocholine® (methacholine chloride) at a concentration of 16 mg/mL. The particle size distribution was measured by Next Generation Impactor (NGI). A Copley Breath Simulator was set-up using the adult profile: 500 mL for tidal volume, 15 breaths (Cycles)/min, inhalation/exhalation ratio 1:1 and a sinusoidal waveform.

PROVOCHOLINE (methacholine chloride USP) is a bronchoconstrictor agent for diagnostic purposes only and should not be used as a therapeutic agent. PROVOCHOLINE should be administered only by inhalation. Severe bronchoconstriction and reduction in respiratory function can result from the administration of PROVOCHOLINE. Patients with severe hyperreactivity of the airways can experience bronchoconstriction at a dosage as low as 0.025 mg/mL. If severe bronchoconstriction occurs, it should be reversed immediately by the administration of a rapid acting inhaled bronchodilator agent (beta-agonist). Because of the potential for severe bronchoconstriction, PROVOCHOLINE inhalation challenge should not be performed in any patient with clinically apparent asthma, wheezing, or very low baseline pulmonary function tests (e.g., FEV_1 less than 1 to 1.5 liter or less than 70% of the predicted values). Please consult standard nomograms for predicted values. If a physician is performing the test, another person must be available in the building to give assistance if required; otherwise a physician must be in the vicinity to be able to respond quickly. The patient must never be left unattended during the test. PROVOCHOLINE inhalation challenge should be performed only under the supervision of a physician trained in and thoroughly familiar with all aspects of the technique of methacholine challenge, all contraindications, warnings and precautions, and the management of respiratory distress. Emergency equipment and medication should be immediately available to treat acute respiratory distress.

Please see complete prescribing information accompanying this piece or consult the Package Insert which is available for download at www.provocholine.com or on request by calling Methapharm Medical Information at 1-800-287-7686 | 519-751-3602 ext. 7804 or faxing us at 519-751-9149. You are encouraged to report adverse reactions of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA (332)-1088. This information is provided as a professional courtesy, and is intended to provide data available to us that may assist you in deriving your own conclusions and opinions. This information is not intended to advocate any indications, dosage, or other claim that is not described in the package insert.

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