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)

Provocholine®
(methacholine chloride)

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

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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.

WARNING: SEVERE BRONCHOCONSTRICTION

Severe bronchoconstriction can result from Provocholine administration (including the lowest dose). The use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV_1 < 60% predicted or adults with FEV_1 < 1.5 L. Because of the potential for severe bronchoconstriction, the use of Provocholine in patients with clinically apparent asthma or wheezing is not recommended *[see Warnings and Precautions - Part 5 of Prescribing Information]*.

Emergency equipment and medication should be immediately available to treat acute respiratory distress. If severe bronchoconstriction occurs, reverse immediately with a rapidacting inhaled bronchodilator agent (β-agonist) *[see Warnings and Precautions - Part 5 of Prescribing Information].*

If baseline spirometry is not performed or is measured inaccurately, the initial FEV_1 may be underestimated. In this situation, decreases in FEV_1 may not be detected after administration of escalating Provocholine doses, which may result in administration of unnecessary higher doses and an increased risk for excessive bronchoconstriction *[see Warnings and Precautions - Part 5 of Prescribing Information].*

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 1-866-701-4636. 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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