Technical Bulletin

Nebuliser Characterisation 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] An additional nebuliser has been characterised 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. Nebuliser Performance with Provocholine® 16 mg/mL Concentration

Adult					
Nebuliser	**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 Nebuliser	50	4.5	0.505	75.1	0.379

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

Key Considerations When Selecting a Nebuliser:

- Nebulisers 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 Nebuliser calculation below only one-minute of nebulisation is required.

Using the nebuliser 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 Nebuliser (1-minute tidal breathing)
(0.505) x (0.751) x (1) = 0.379 mg (379 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 Doubling Concentrations Protocol

Concentration (mg/mL)	0.03125	0.0625	0.125	0.25	0.5	1	2	4	8	16
English Wright[1] **Delivered Dose in µg** (2-minute tidal breathing)	0.74	1.48	2.97	5.94	11.88	23.75	47.5	95	190	380
Hudson RCI® MicroMist® Small Volume Nebuliser Delivered Dose in µg (1-minute tidal breathing)	0.74	1.48	2.96	5.92	11.84	23.69	47.38	94.75	189.5	379

Nebuliser Characterisation Protocol

All studies were performed as per United States Pharmacopeia (USP) 1601 Products for Nebulisation Characterisation Tests. The Hudson RCI® MicroMist® Small Volume Nebuliser was powered by dry compressed air, regulated to 50 lb/in^2 (psi) and a flow controller set to a flow rate of 4.5 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) is indicated in adults (aged 17 and over) to detect bronchial airway hyperreactivity, to assist in the diagnosis of asthma when the clinical history is suggestive of the condition but there is normal spirometry and the diagnosis remains uncertain after additional evaluation. Provocholine® is a bronchoconstrictor agent for diagnostic purposes only and is to be administered by inhalation. The testing should be conducted under specialist medical supervision by a doctor familiar with all aspects of the methacholine challenge test, all contraindications, warnings and precautions. The patient must never be left unattended during the test. Emergency equipment and medication must be available immediately to treat acute respiratory failure. Laboratory staff with asthma or allergies should be particularly careful and take necessary measures when performing the test on patients. As a result of the administration of Provocholine®, severe bronchoconstriction and a reduction in respiratory function may occur. If severe bronchoconstriction occurs, this must be immediately reversed by administration of a rapid-acting inhaled bronchodilator agent (beta-agonist), precautions for which must be taken when the inhalation challenge test is performed in patients receiving beta-blockers since it is possible that bronchoconstriction may not be reversed easily. Contraindications include hypersensitivity to the active substance or other parasympathomimetic agents or abnormal baseline spirometry (FEV_1/ FVC ratio less than 70%). Adverse reactions associated with inhaled methacholine challenge tests are rare, and include incidences of headache, throat irritation, light-headedness and itching.

Please see the complete SmPC at www.provocholine.co.uk or call MWK Healthcare Medical Information at +44 (0)1691 664243. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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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