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)

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 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) 100 mg powder for nebuliser solution. Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Abbreviated Prescribing Information.

Presentation: Each 20 mL vial contains 100 mg methacholine chloride, a white or off-white deliquescent crystalline powder for nebuliser solution, for inhalation, non-sterile.
Indications: This medicinal product is for diagnostic use only. Provocholine 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.
Dosage and administration: Methacholine challenge, may occasionally induce severe bronchospasm and should therefore only be conducted in specialist respiratory centres with appropriate resuscitation facilities.
Adults (aged 17 and over): Provocholine is intended for single use only. Once reconstituted, the prepared solutions should be used immediately and administered only in solution for inhalation. Before starting a Provocholine challenge test, pulmonary function must be tested and confirmed to be within the normal range. The patient's baseline FEV_1 (Forced Expiratory Volume in 1 second)/ FVC (forced vital capacity) ratio (FEV_1/FVC ratio), without exposure to nebulised diluent or Provocholine, must be greater than 70%, considered normal baseline spirometry, for the challenge test to proceed. At commencement of the test, baseline FEV_1 should be measured following exposure to nebulised diluent, without Provocholine. Baseline FEV_1 following exposure to nebulised diluent should be used to calculate any subsequent decline in FEV_1 following exposure to increasing concentrations of Provocholine. The test should be terminated if there is a 20%, or greater, decline in FEV_1 from baseline. All dilutions must be made with sterile 0.9% sodium chloride solution for injection, using empty, sterile borosilicate Type I glass vials. For preparation and administration instructions, please refer to the SmPC and the training material included on the product website www.provocholine.co.uk prior to preparation of solutions and administration.
Contraindications: Hypersensitivity to the active substance or other parasympathomimetic agents. Clinically apparent asthma, wheezing or with abnormal baseline spirometry (FEV_1/FVC ratio less than 70%). Patients treated with beta blockers. Repeated administration of Provocholine through inhalation of doses higher than the dose administered on the day of the diagnostic test. Bradycardia. Known aortic aneurysm. Heart attack or stroke in the last 3 months. Uncontrolled hypertension. Patients with myasthenia gravis undergoing treatment with cholinesterase inhibitors. Recent eye surgery. Risk from elevated intracranial pressure (e.g. cerebral aneurysm).
Warnings and Precautions: Provocholine is a bronchoconstrictor agent for diagnostic purposes only and should not be used as a therapeutic agent. Provocholine is to be administered only by inhalation. When administered orally or by injection, methacholine chloride is associated with nausea and vomiting, substernal pain or pressure, hypertension, fainting and transient complete heart block. The test should be performed in accordance to current clinical practice guidelines. Take a full clinical respiratory history, before embarking on a methacholine challenge, given the occurrence of false positive test results with methacholine in other respiratory conditions, such as after influenza, upper respiratory tract infections or immunisations, in very old patients or in patients with chronic pulmonary diseases. Challenge testing can be positive in patients with allergic rhinitis without asthma, in smokers, or in patients exposed to aerial contaminants. The challenge testing for Provocholine must only be carried out under specialist medical supervision by a doctor familiar with all aspects of the methacholine inhalation challenge testing technique, all contraindications, warnings and precautions, and the management of respiratory failure. The doctor responsible for the testing must be contactable while it is being carried out and available immediately if needed. If the doctor is carrying out the testing himself, another person must be available to assist him if needed. The patient must never be left unattended during the testing. Emergency equipment and medication must be available immediately to treat acute respiratory failure. Administration of Provocholine to patients with epilepsy, cardiovascular disease accompanied by bradycardia, vagotonia, peptic ulcer, thyroid disease, urinary tract obstruction or other conditions that could be adversely affected by a cholinergic agent should only be carried out if the doctor deems that the risk/benefit ratio to be positive for the patient. It is essential that the baseline spirometry is accurate. If the baseline spirometry is not performed or measured accurately, and the initial FEV_1 is underestimated, subsequent falls after inhaling Provocholine solutions may not be detected, resulting in too high a dose and excessive bronchoconstriction. As a result of the administration of Provocholine, severe bronchoconstriction and a reduction in respiratory function may occur. Patients with airway hyperreactivity can experience bronchoconstriction with doses as low as 0.03125 mg/ml. 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 testing is performed in patients receiving beta blockers, since it is possible that bronchoconstriction may not be reversed easily. Subjects who suffer from asthma are noticeably more sensitive to bronchoconstriction induced by methacholine than healthy subjects. To ensure the safe and effective use of challenge testing with Provocholine, patients should be informed about the symptoms that may occur as a result of the testing and how to manage them. Laboratory staff with asthma or allergies should be particularly careful and take necessary measures when handling the material or if they are performing testing on patients.
Interactions: The concomitant treatment of Provocholine and beta blockers is contraindicated. The following medications for the treatment of asthma inhibit the airways' response to Provocholine, whereby their treatment must be interrupted before the testing, due to the duration of their effect: beta agonists, anti-muscarinics and theophylline.
Fertility, pregnancy and lactation: There have been no animal reproduction studies with methacholine chloride. It is not known whether methacholine chloride can cause harm to the foetus when administered to pregnant patients or whether methacholine chloride is excreted in human milk. Provocholine should not be used during pregnancy or breastfeeding, unless the benefits clearly outweigh the risks. It is not known whether methacholine chloride affects fertility.
Effects on ability to drive and use machines: Provocholine has no influence on the ability to drive and on the use of machines.
Undesirable effects: Adverse reactions associated with inhaled methacholine challenge tests are rare, and include incidences of headache, throat irritation, light-headedness/dizziness and itching. A positive reaction to methacholine challenge may produce symptoms of bronchospasm, such as chest tightness, cough or wheezing (the frequency of which is not known) that may require reliever bronchodilators.
Overdose: Refer to SmPC.
Handling and Disposal: Do not inhale the powder. Do not handle this product if you suffer from asthma or allergies. A low resistance filter should be applied to an expiratory port of any dosing apparatus, as necessary, to prevent Provocholine aerosol from being released into the air. When using Provocholine, any unused solution should be discarded from the nebuliser after each concentration. Please consult the SmPC for further instructions.

Legal Category: POM.
NHS Price: £420.00 per carton containing 6 vials.
Marketing Authorisation Holder: ACIC EUROPE LIMITED, Leontiou, 163, CLERIMOS BUILDING, 2nd floor 3022 Limassol, Cyprus.
MA Number: PL 41697/0006
Full prescribing information available from: Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, United Kingdom.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Galen Limited on 028 3833 4974 and select the customer services option, or e-mail customer.services@galen-pharma.com. Medical information enquiries should also be directed to Galen Limited.

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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