PRESCRIBING INFORMATION

[Pr] STERILE PROVOCHOLINE® SOLUTION, [Pr] STERILE PROVOCHOLINE® SOLUTION PLUS AND [Pr] STERILE PROVOCHOLINE® SOLUTION 16

methacholine chloride solution for inhalation
0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 mg/mL

[Pr] PROVOCHOLINE®

methacholine chloride powder USP
100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg

Cholinergic / Diagnostic Aid (Bronchial Asthma)

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N3S 7X6

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Control #119812

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Inhalation	Powder: 100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg	• N/A
	Solution: 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 mg/mL	• Sodium acetate trihydrate • Water for injection • Sodium Chloride

INDICATIONS AND CLINICAL USE

Provocholine® is indicated for:
- Diagnosis of asthma (bronchial airway hyperresponsiveness)

Provocholine® (methacholine chloride) is indicated for the diagnosis of bronchial airway hyperresponsiveness in subjects suspected of having asthma. The methacholine challenge test with Provocholine® provides a measure of the severity of asthma. The methacholine challenge test with Provocholine® may be used to confirm occupational asthma.

The product should be administered under the supervision of a qualified health professional who is experienced in the use of inhalation agents and in the management of patients experiencing severe bronchoconstriction. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Geriatrics: No data is available.
Pediatrics (<5 years of age): The safety and efficacy of methacholine challenge tests with Provocholine® have not been established in children below the age of 5 years.

CONTRAINDICATIONS

- Provocholine® (methacholine chloride) is contraindicated in patients with known hypersensitivity to this drug or to other parasympathomimetic agents.
- A repeat challenge test on the same day is contraindicated.
- β-agonists, anticholinergics and theophylline may be contraindicative (See DRUG INTERACTIONS)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
• Provocholine® is to be administered only by inhalation. **See Warnings and Precautions – General** • Provocholine® is a bronchoconstrictor agent for diagnostic purposes only, and should not be used as a therapeutic agent. **See Warnings and Precautions – General** • Sterile Provocholine® Solution 16 should only be used without prior dilution if using an approved device that regulates the dosage through its operation (consult specific manufacturer's instructions). When using Sterile Provocholine® Solution 16 with any other type of delivery system, Sterile Provocholine Solution 16 must be diluted prior to administration (see DOSAGE AND ADMINISTRATION). Administration of the MAXIMUM DOSE (16 mg/mL) without prior dilution can result in severe and sudden bronchoconstriction. • Patients with severe hyperresponsivness of airways can experience bronchoconstriction at the lowest dosages or with the diluent alone. **See Warnings and Precautions - Respiratory** • Test should not be performed on any patient with baseline FEV_1 of less than 1.5 litres or 70% of predicted value. **See Warnings and Precautions - Respiratory** • When administered orally or by injection Provocholine® is associated with nausea, vomiting, substernal pain or pressure, hypotension, fainting and transient complete heart block. **See Adverse Reactions** • When administered orally or by injection overdosage can result in a syncopal reaction, with cardiac arrest and loss of consciousness. **See Overdosage** • Baseline spirometry must be accurate. If not, the initial FEV_1 maybe underestimated, and subsequent falls after inhaling Provocholine® solutions may not be detected, resulting in too high a dose and excessive bronchoconstriction. **See Warnings and Precautions - General**

General

Provocholine® (methacholine chloride) is to be administered only by inhalation. Provocholine® (methacholine chloride) is a bronchoconstrictor agent for diagnostic purposes only, and should not be used as a therapeutic agent.

Administration of Provocholine® to patients with epilepsy, cardiovascular disease accompanied by bradycardia, vagotonia, peptic ulcer disease, thyroid disease, urinary tract obstruction or other condition that could be adversely affected by a cholinergic agent should be undertaken only if the physician feels the benefit to the individual outweighs the potential risks.

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.

Methacholine challenge test with Provocholine® 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. A physician responsible for the tests must be present in the building when tests are carried out, and available to be contacted quickly if necessary. If the physician is performing the test, another person must be available in the building to give assistance if required. The patient must never be left unattended during the test.

Emergency medication and equipment should be immediately available to treat acute respiratory distress.

Carcinogenesis, Mutagenesis and Impairment of Fertility

There have been no studies with methacholine chloride that would permit an evaluation of its carcinogenic or mutagenic potential or of its effect on fertility.

Cardiovascular

Administration of Provocholine® to patients with cardiovascular disease accompanied by bradycardia, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Endocrine and Metabolism

Administration of Provocholine® to patients with thyroid disease, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Gastrointestinal

Administration of Provocholine® to patients with peptic ulcer disease, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Genitourinary

Administration of Provocholine® to patients with urinary tract obstruction, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Neurological

Administration of Provocholine® to patients with epilepsy, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Respiratory

Severe bronchoconstriction can result from the administration of Provocholine®, if guidelines for careful administration are not followed. Patients with severe hyperresponsiveness of the airways can experience bronchoconstriction at the lowest dosages of Provocholine®, or with the diluent (or placebo, as applicable) alone. If severe bronchoconstriction occurs, it should be reversed immediately by the administration of a rapid-acting inhaled ß-agonist. Because of the potential for severe bronchoconstriction, Provocholine® challenge should not be performed in any patient with low baseline FEV_1 of less than 1.5 litres or less than 70% of the predicted value. Please consult standard nomograms for predicted values.[1]

Special Populations

Pregnancy: Teratogenic Effects - Animal reproduction studies have not been conducted with methacholine chloride. It is not known whether methacholine chloride can cause fetal harm when administered to a pregnant patient or affect reproductive capacity. Provocholine® should be given to a pregnant woman only when the benefits clearly outweigh the risks.

Nursing Mothers: It is not known if methacholine chloride when inhaled is excreted in breast milk. Methacholine challenge test with Provocholine® should be administered to nursing mothers only when the benefits clearly outweigh the risks.

Pediatric Use: The safety and efficacy of methacholine challenge tests with Provocholine® have not been established in children below the age of 5 years.

Laboratory Personnel: Provocholine® aerosol may cause bronchoconstriction in laboratory personnel and others in the same room as the patient undergoing the test. Laboratory personnel

with asthma or hay fever should take appropriate precautions when handling the material. (See SPECIAL HANDLING INSTRUCTIONS)

Information to be Provided to the Patient

To assure the safe and effective use of the methacholine challenge test with Provocholine®, the following instructions and information should be given to patients:

- Patients should be educated in the symptoms that may occur as a result of the test, and instructed to alert the test administrator of these symptoms so that the test can be stopped before pulmonary function is reduced to less than 1.5 litres.
- Women of child-bearing age should be questioned on the possibility of pregnancy (See Special Populations - Pregnancy).

ADVERSE REACTIONS

Adverse reactions associated with inhaled methacholine challenge tests are rare, and include incidences of headache, throat irritation, light-headedness and itching.

A positive reaction to methacholine challenge may produce symptoms of bronchospasm, such as chest tightness, cough or wheezing.

Incidences of severe bronchoconstriction can be avoided by limiting the challenge test to cases of potentially mild asthma, in those patients with normal or near normal FEV_1, and by cautiously increasing the dosage.

Provocholine® (methacholine chloride) is to be administered only by inhalation. When administered orally or by injection, Provocholine® is reported to be associated with nausea and vomiting, substernal pain or pressure, hypotension, fainting and transient complete heart block. (See OVERDOSAGE)

DRUG INTERACTIONS

Overview

Provocholine® (methacholine chloride) is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered in solution only, by inhalation. Methacholine chloride is the ß-methyl homolog of acetylcholine, is slowly hydrolysed by acetylcholinesterase and almost totally resistant to inactivation by non-specific cholinesterase or pseudocholinesterase.

Drug-Drug Interactions

Precaution should be taken when the inhalation challenge is performed in patients receiving any ß-adrenergic blocking agents, as it is possible that bronchoconstriction may not reverse as readily.

The following asthma and hayfever medications inhibit the response of airways to Provocholine®, and should be withheld before the test, for their duration of action: ß-agonists, anticholinergics and theophylline. Corticosteroids, cromoglycate and nedocromil, after regular use, may alter Provocholine® responsiveness but they do not do this acutely; thus, they may be continued in their regular dose before any test. The effects of other newer medications have not been investigated.

Drug-Food Interactions

Methacholine chloride can be administered without regards to timing of meals.

Drug-Herb Interactions

The interactions of methacholine chloride with herbal medications or supplements have not been established.

Drug-Laboratory Test Interactions

The interactions of methacholine chloride with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustments

For Provocholine® Powder (methacholine chloride USP), adults and children (5 years or older) are exposed to the following increasing concentrations: 0.03, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL. (See Tables 1A, 1B, 1C, 1D and 1E).

For Sterile Provocholine® Solution (methacholine chloride), adults and children (5 years or older) are exposed to the following increasing concentrations: 0.0625, 0.25, 1, 4, and 16 mg/mL.

For Sterile Provocholine® Solution Plus (methacholine chloride), adults and children (5 years or older) are exposed to the following increasing concentrations: 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL.

When using 1 vial of Sterile Provocholine® Solution 16 (methacholine chloride), adults and children (5 years or older) are exposed to the following increasing concentrations: 0.0625, 0.25, 1, 4, and 16 mg/mL. Alternatively, when using 2 vials of Sterile Provocholine® Solution 16 (methacholine chloride), adults and children (5 years or older) are exposed to the following increasing concentrations: 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL. When using in

conjunction with an approved device that delivers gradually increasing amounts of Sterile Provocholine® Solution 16 from the insertion of the maximum, supplied dosage of 16 mg/mL, manufacturer's instructions should be followed and it is not recommended to exceed a maximum total cumulative dose of 159.83 inhalation units (see Table 2).

Preparation of Dilutions:
Sterile Provocholine® Solution (methacholine chloride) and Sterile Provocholine® Solution Plus (methacholine chloride) are sterile, colourless solutions that do not require any dilution before administration. If necessary, before use, take 1 mL of the 0.0625 mg/mL solution and add 1 mL of sterile placebo solution for a resulting concentration of 0.03 mg/mL. Use immediately and discard any unused vials.

Sterile Provocholine® Solution 16 (methacholine chloride) is a sterile, colourless solution that may be used without any further dilution with approved medical devices designed to deliver gradually increasing doses of Sterile Provocholine® Solution 16 from the insertion of the maximum, supplied dosage of 16 mg/mL, or diluted to varying lower concentrations with Sterile Baseline Solution and administered by either the tidal breathing or the dosimeter technique. Use immediately and discard any unused vials.

Since the temperature of the solution affects nebulizer output, if storing Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 or Sterile Baseline Solution in the refrigerator they should be taken out and allowed to equilibrate to room temperature (approximately 30 minutes) before use.

Table 1F describes a method of producing appropriate dilutions, using a single vial of Sterile Provocholine® Solution 16.

Table 1G describes a method of producing appropriate dilutions, using 2 vials of Sterile Provocholine® Solution 16.

NOTE: The packaged dose of 16 mg/ml should not be administered as an initial dose without prior dilution unless being utilized with an approved device that regulates the dosage through its operation. It is not recommended to exceed the equivalent of 2 mg/mL of Provocholine® for the initial aerosol when using any device or testing method. Consult manufacturer's instructions and published sources.

Provocholine® Powder (methacholine chloride USP) requires dilution before use. All dilutions using Provocholine® Powder should be made with 0.9% sodium chloride solution for injection (saline) or 0.9% sodium chloride solution with 0.4% phenol (saline with 0.4% phenol) or 0.9% sodium chloride solution for injection with 0.9% benzyl alcohol (saline with 0.9% benzyl), as suggested in Table 1A for Provocholine® 100 mg/vial, Table 1B for Provocholine® 160 mg/vial, Table 1C for Provocholine® 320 mg/vial, Table 1D for Provocholine® 1280 mg/vial and Table 1E for Provocholine® 1600 mg/vial in sterile USP Type I Glass vials. After adding the 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl, shake each vial to obtain a clear solution. Check the date of preparation or expiry before using dilutions that are not freshly

prepared. **(Note: When preparing dilutions, use only the same kind of diluent to prepare all concentrations).**

Provocholine® solutions prepared from powder and using aseptic technique may be stored in a refrigerator (2° to 8°C) for up to 2 weeks. After this time, discard the vials and prepare new dilutions. Freezing does not affect the stability of the dilutions. Since the temperature of the solution affects nebulizer output, solutions should be taken out of the refrigerator and allowed to equilibrate to room temperature (approximately 30 minutes) before use.

When using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 or Provocholine® Powder, any unused solution should be discarded from the nebulizer after each concentration.

Tables 1A, 1B, 1C, 1D and 1E describe methods of producing appropriate dilutions, using a single vial of Provocholine® Powder.

NOTE: The initial dilutions of the 320 mg, 1280 mg and 1600 mg vials to obtain solutions of 32 mg/mL (320 mg and 1600 mg) or 128 mg/mL (1280 mg) are NOT to be administered to the patient during the methacholine challenge test with Provocholine®. They are only used in the preparation of the 16 mg/mL and 8 mg/mL dilutions.

When preparing dilutions using Provocholine® Powder, a sterile bacterial-retentive filter (porosity 0.22 µm) should be used when transferring a solution from each vial (at least 2 mL) to a nebulizer. This step is not required when using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus or Sterile Provocholine® Solution 16.

Table 1A: Preparation of Serial Dilutions Using a Single 100 mg Vial of Provocholine® Powder (methacholine chloride USP) (for both 20 mL and 50 mL vial sizes)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
100 mg Provocholine®	6.25 mL	16 mg/mL (A)
3 mL of dilution A	3 mL	8 mg/mL (B)
3 mL of dilution B	3 mL	4 mg/mL (C)
3 mL of dilution C	3 mL	2 mg/mL (D)
3 mL of dilution D	3 mL	1 mg/mL (E)
3 mL of dilution E	3 mL	0.5 mg/mL (F)
3 mL of dilution F	3 mL	0.25 mg/mL (G)
3 mL of dilution G	3 mL	0.125 mg/mL (H)
3 mL of dilution H	3 mL	0.0625 mg/mL (I)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
3 mL of dilution I	3 mL	0.03 mg/mL (J)

Table 1B: Preparation of Serial Dilutions Using a Single 160 mg Vial of Provocholine® Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
160 mg Provocholine®	10 mL	16 mg/mL (A)
3 mL of dilution A	3 mL	8 mg/mL (B)
3 mL of dilution B	3 mL	4 mg/mL (C)
3 mL of dilution C	3 mL	2 mg/mL (D)
3 mL of dilution D	3 mL	1 mg/mL (E)
3 mL of dilution E	3 mL	0.5 mg/mL (F)
3 mL of dilution F	3 mL	0.25 mg/mL (G)
3 mL of dilution G	3 mL	0.125 mg/mL (H)
3 mL of dilution H	3 mL	0.0625 mg/mL (I)
3 mL of dilution I	3 mL	0.03 mg/mL (J)

Table 1C: Preparation of Serial Dilutions Using a Single 320 mg Vial of Provocholine® Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
320 mg Provocholine®	10 mL	32 mg/mL (A)
3 mL of dilution A	3 mL	16 mg/mL (B)
3 mL of dilution B	3 mL	8 mg/mL (C)
3 mL of dilution C	3 mL	4 mg/mL (D)
3 mL of dilution D	3 mL	2 mg/mL (E)
3 mL of dilution E	3 mL	1 mg/mL (F)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
3 mL of dilution F	3 mL	0.5 mg/mL (G)
3 mL of dilution G	3 mL	0.25 mg/mL (H)
3 mL of dilution H	3 mL	0.125 mg/mL (I)
3 mL of dilution I	3 mL	0.0625 mg/mL (J)
3 mL of dilution J	3 mL	0.03 mg/mL (K)

Table 1D: Preparation of Serial Dilutions Using a Single 1280 mg Vial of Provocholine® Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
1280 mg Provocholine®	10 mL	128 mg/mL (A)
1 mL of dilution A	7 mL	16 mg/mL (B)
1 mL of dilution A	15 mL	8 mg/mL (C)
4 mL of dilution C	4 mL	4 mg/mL (D)
2 mL of dilution C	6 mL	2 mg/mL (E)
1 mL of dilution C	7 mL	1 mg/mL (F)
1 mL of dilution C	15 mL	0.5 mg/mL (G)
4 mL of dilution G	4 mL	0.25 mg/mL (H)
2 mL of dilution G	6 mL	0.125 mg/mL (I)
1 mL of dilution G	7 mL	0.0625 mg/mL (J)
1 mL of dilution G	15 mL	0.03 mg/mL (K)

Table 1E: Preparation of Serial Dilutions Using a Single 1600 mg Vial of Provocholine® Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
1600 mg Provocholine®	50 mL	32 mg/mL (A)
3 mL of dilution A	3 mL	16 mg/mL (B)
3 mL of dilution B	3 mL	8 mg/mL (C)
3 mL of dilution C	3 mL	4 mg/mL (D)
3 mL of dilution D	3 mL	2 mg/mL (E)
3 mL of dilution E	3 mL	1 mg/mL (F)
3 mL of dilution F	3 mL	0.5 mg/mL (G)
3 mL of dilution G	3 mL	0.25 mg/mL (H)
3 mL of dilution H	3 mL	0.125 mg/mL (I)
3 mL of dilution I	3 mL	0.0625 mg/mL (J)
3 mL of dilution J	3 mL	0.03 mg/mL (K)

Table 1F: Preparation of Serial Dilutions Using a Single 3-mL Vial of Sterile Provocholine® Solution 16

TAKE	ADD **Sterile Baseline Solution** (9 mg per mL sodium chloride USP and 0.66 mg per mL sodium acetate trihydrate USP in water for injection)	OBTAIN DILUTION
Sterile Provocholine® Solution 16		16 mg/mL (A)
1 mL of dilution A	3 mL	4 mg/mL (B)
1 mL of dilution B	3 mL	1 mg/mL (C)
1 mL of dilution C	3 mL	0.25 mg/mL (D)
1 mL of dilution D	3 mL	0.0625 mg/mL (E)

Note: When preparing serial dilutions using a single 3-mL vial of Sterile Provocholine® Solution 16, if needed, a 0.03 mg/mL solution can be prepared by taking 1 mL of the 0.0625 mg/mL dilution and adding 1 mL of the Sterile Baseline Solution for a resulting solution of 0.03 mg/mL.

Table 1G: Preparation of Serial Dilutions Using Two 3-mL Vials of Sterile Provocholine® Solution 16

TAKE	ADD **Sterile Baseline Solution** (9 mg per mL sodium chloride USP and 0.66 mg per mL sodium acetate trihydrate USP in water for injection)	OBTAIN DILUTION
Sterile Provocholine® Solution 16 (2 vials combined)		16 mg/mL (A)
3 mL of dilution A	3 mL	8 mg/mL (B)
3 mL of dilution B	3 mL	4 mg/mL (C)
3 mL of dilution C	3 mL	2 mg/mL (D)
3 mL of dilution D	3 mL	1 mg/mL (E)
3 mL of dilution E	3 mL	0.5 mg/mL (F)
3 mL of dilution F	3 mL	0.25 mg/mL (G)
3 mL of dilution G	3 mL	0.125 mg/mL (H)
3 mL of dilution H	3 mL	0.0625 mg/mL (I)
3 mL of dilution I	3 mL	0.03 mg/mL (J)

Administration

General Procedures:
The challenge test must be conducted in a pulmonary function laboratory or clinic, by adequately trained personnel, for safety and accuracy.

The FEV_1 value should be established before and after diluent or placebo inhalation. After determination of the post-diluent or post-placebo baseline pulmonary function, the predicted value of a positive response is then calculated from the mean before diluent or placebo inhalation.

The methacholine challenge is performed by giving a subject increasing serial concentrations of Provocholine®, after determining baseline FEV_1. When using Provocholine® Powder, baseline FEV_1 is determined with inhaled normal saline control or normal saline control containing 0.4% phenol or normal saline control containing 0.9% benzyl **(Note: Use the same diluent that the Provocholine® powder has been reconstituted with)**. When using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, baseline FEV_1 is determined with the Sterile Placebo Solution. When using Sterile Provocholine® Solution 16, baseline FEV_1 is determined with the Sterile Baseline Solution. A subject to be challenged must have an FEV_1 of at least

70% of the predicted value. A common error giving inaccurate results is caused by not taking a full inspiratory breath prior to baseline FEV_1 determination. **Consult a physician if the FEV_1 falls below 1.5 litres. Do not leave the patient unattended at any time**.

An inhaled ß-agonist must be administered after a methacholine challenge test with Provocholine® to expedite the return of the FEV_1 to baseline and to relieve any discomfort of the subject. Most patients revert to normal pulmonary function within 10 to 20 minutes following administration of a ß-agonist.

In order to produce interpretable results, it is important to calibrate nebulizers to produce a standard output, and validate the reproducibility of the delivery system. Suitable nebulizers and standard settings are discussed in published sources.

Two methods of administration of the methacholine challenge test with Provocholine® have been widely used in current clinical practice; the tidal breathing method and the dosimeter method. The tidal breathing technique requires the patient to breathe normally, over a two-minute period, a constantly generated aerosol of Provocholine®. By contrast, the dosimeter method requires the patient to take five full breaths of Provocholine® aerosol generated by an appropriate dosimeter to produce a specific dose per breath. Additional, delivery devices and methods have been described in the literature. Approved manufacturer's instructions should be followed when using these devices. With all techniques, the test is stopped if the FEV_1 falls by 20% or more from the mean baseline FEV_1. The dose concentration and the percent fall in FEV_1 are then used to calculate either the provocative concentration to cause a fall in FEV_1 of 20% (PC_{20}), or the provocative dose (PD_{20}).

Tidal Breathing Method:
The following method is based on the use of the Wright nebulizer. If using other nebulizer models, consult published sources on methacholine challenge tests for the appropriate operation of alternate nebulizers.

1. Using a 3 mL syringe and needle, draw up 2-3 mL of Sterile Placebo Solution, if using Sterile Provocholine® Solution, or Sterile Provocholine® Solution Plus, or Sterile Baseline Solution if using Sterile Provocholine® Solution 16, or use the diluent for Provocholine® Powder (0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl) when using Provocholine® Powder and place it in the nebulizer vial. Attach the nebulizer and necessary tubing to an appropriate compressed gas source.

2. At this time, the subject should be told that subsequent aerosols may produce mild cough, chest tightness or shortness of breath. Tell the subject that if these symptoms become uncomfortable, to remove the face mask or mouthpiece and to stop inhaling the aerosol immediately. Try to avoid suggesting that these symptoms will definitely develop, as suggestion alone can lower the FEV_1. Remember that perception of airway narrowing can vary considerably between subjects, making it advisable to watch and listen for other signs such as wheeze and an altered pattern of breathing. Instructions to cease inhaling the aerosol if symptoms become troublesome should be repeated before every dose.

3. Instruct the patient to relax and breathe the aerosol quietly (tidal breathing) for 2 minutes.

4. Keeping the nebulizer well away from the patient, adjust the flow meter so that the nebulizer is operating at the calibrated output (0.13 mL/min for the Wright nebulizer).

5. Apply a nose clip and place the face mask loosely over the nose and mouth (or the mouthpiece in the mouth). Start the stopwatch immediately. The nebulizer should be kept vertical. The patient should hold the nebulizer so as to avoid warming the solution, and subsequently altering the output.

6. After exactly two minutes, remove the nebulizer from the patient's mouth, turn off the flow meter, and discard the solution.

7. Measure the FEV_1 30 and 90 seconds after the end of the inhalation. These values may be left at ATPS. If the FEV_1 at 90 seconds is the same or lower than that at 30 seconds, the measurement must be repeated at 3 minutes and, if needed, at 2 minute intervals until the FEV_1 starts to rise. To avoid tiring the patient, the FEV_1 should only be measured once on each occasion. If it is not technically satisfactory, it should be repeated after 10 seconds.

8. If the FEV_1 falls by 20% or more from the mean baseline FEV_1 (ATPS) or to less than 1.0 litre, no further inhalations are given. (A physician should be consulted if the FEV_1 falls below 1.5 litres.) If the FEV_1 has fallen by 16% or more from baseline, it is unwise to give further doses. The PC_{20} may be extrapolated from the last two points of the dose response curve.

9. For Provocholine® Powder, the concentration of the first aerosol of Provocholine® is 0.03 mg/mL. Subsequent doses are given at approximately 5-minute intervals in doubling concentrations. (0.0625, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/mL).

   For Sterile Provocholine® Solution or Sterile Provocholine® Solution 16 (using 1 vial) the concentration of the first aerosol of Provocholine® is 0.0625 mg/mL. Subsequent doses are given at approximately 5-minute intervals in quadrupling concentrations. (0.25, 1.0, 4.0 and 16.0 mg/mL).

   For the Sterile Provocholine® Solution Plus or Sterile Provocholine® Solution 16 (using 2 vials), the concentration of the first aerosol of Provocholine® is 0.0625 mg/mL. Subsequent doses are given at approximately 5-minute intervals in doubling concentrations. (0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/mL).

   In all circumstances above, it is optional to adjust the first aerosol of Provocholine® to 0.03 mg/mL (see TABLES 1F and 1G and PREPARATION OF DILUTIONS section).

10. Repeat steps 1 through 8 with each increasing concentration of Provocholine® until the FEV_1 has fallen by 20% or more from baseline, or the FEV_1 is 1.5 litres or less, or the highest concentration has been given. Do not give any further aerosols of Provocholine®.

11. After the test is completed, give the patient 2 puffs of a ß-agonist. Wait 10 minutes and measure the FEV_1 and VC. Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.

12. After the test, reusable nebulizers should be sterilized according to manufacturer's recommendations. Disposable nebulizers should be discarded appropriately.

Dosimeter Method:
The following method is based on the use of a DeVilbiss jet nebulizer attached to a Rosenthal-French dosimeter operating at 20 psi and a period of 0.6 seconds per actuation. If using other nebulizers or dosimeters, consult manufacturer's instructions and published sources on methacholine inhalation challenge for the appropriate operation of alternate nebulizers and dosimeters. The dosimeter should be calibrated to ensure accurate dose delivery and re-calibrated whenever the length of the tubing is changed.

All solutions are delivered from functional residual capacity (FRC) to total lung capacity (TLC). Factors that influence the response to inhalation challenge, and which should be consistent, are nebulizer output and inspiratory time.

The FEV_1 value should be established before and after diluent or placebo inhalation. After determination of the post-diluent or post-placebo baseline pulmonary function, the predicted value of a positive response is then calculated from the mean before diluent or placebo inhalation.

1. Solution is put in the nebulizer, and the necessary tubing attached to the dosimeter. The aerosol is generated by the compressed air delivered at 20 psi through the nebulizer. The output is controlled by a solenoid valve that is triggered by the inspiration and is kept open for 0.6 seconds. A nose clip is used. The subjects are instructed to inhale slowly from the functional residual capacity (FRC) to total lung capacity (TLC). During the inhalation, the vent of the nebulizer should be kept open.

2. Baseline pulmonary function is established with five inhalations of Sterile Placebo Solution if using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, or Sterile Baseline Solutions is using Sterile Provocholine® Solution 16 or use the diluent for Provocholine® Powder (0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl), and the baseline FEV_1 noted. A subject to be challenged must have an FEV_1 of at least 70% of the predicted value, when tested with the diluent. Spirometry is measured within 5 minutes of the fifth inspiration of placebo solution.

3. At this time, the subject should be told that subsequent aerosols may produce mild cough, chest tightness or shortness of breath. Tell the subject that if these symptoms become uncomfortable, to remove the mouthpiece immediately. Try to avoid suggesting that these symptoms will definitely develop, as suggestion alone can lower the FEV_1. Remember that perception of airway narrowing can vary considerably between subjects, making it advisable to watch and listen for other signs such as wheeze and an altered

pattern of breathing. Instructions to cease inhaling the aerosol if symptoms become troublesome should be repeated before every step up in concentration.

4. As with the tidal breathing technique, serial concentrations of Provocholine® are administered. Five inhalations of each concentration are taken, followed by measurement of FEV_1 within 5 minutes of the last inhalation at each dosage. One inhalation unit is defined as one inhalation of a solution of Provocholine® containing 1 mg/mL. Because doses are taken in rapid succession, the units are expressed as cumulative units, as shown is Table 2 below.

Table 2: Cumulative Inhalation Units

Serial Concentration	Number of Breaths	Cumulative Units per Concentration	Total Cumulative Units
0.03 mg/mL*	5	0.15	0.15
0.0625 mg/mL	5	0.3	0.45
0.125 mg/mL	5	0.625	1.08
0.25 mg/mL	5	1.25	2.33
0.5 mg/mL	5	2.5	4.83
1 mg/mL	5	5	9.83
2 mg/mL	5	10	19.83
4 mg/mL	5	20	39.83
8 mg/mL	5	40	79.83
16 mg/mL	5	80	159.83

* If using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus or Sterile Provocholine® Solution 16, this concentration can be prepared (See PREPARATION OF DILUTIONS section)

5. If the FEV_1 falls by 20% or more from the mean baseline FEV_1 (ATPS) or to less than 1.0 litre, no further inhalations are given. (A physician should be consulted if the FEV_1 falls below 1.5 litres.) Partial doses (fewer than 5 inhalations) may be given if the FEV_1 is between 15% and 20% less than baseline control, in order to protect against an excessive fall in pulmonary function.

6. After the test is completed, give the patient 2 puffs of a ß-agonist. Wait 10 minutes and measure the FEV_1. Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.

7. After the test, reusable nebulizers should be sterilized according to manufacturer's recommendations. Disposable nebulizers should be discarded appropriately.

Shortening the Test Procedure:
Technicians should be well versed on the longer procedure before attempting a shorter version. Shortening the test does run the risk of inadvertently giving the patient too high a dose; always err on the side of safety and give a lower dose when in doubt. If clinical history suggests that the patient may not have asthma or that their asthma is very mild, then the lowest concentration may be omitted, as described below:

1. Starting Concentrations in Adults

As a guide, the first concentration of Provocholine® can be based on the following criteria:

a) If FEV_1/VC >80% AND FEV_1 >70% predicted AND FEV_1 falls <10% after the diluent or placebo inhalation AND the patient's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.125 mg/mL*
Daily bronchodilators	0.25 mg/mL
Occasional bronchodilators (< once/day)	1.0 mg/mL
No medications	2.0 mg/mL**

* Use 0.0625 mg/mL when 0.125 mg/mL concentration is not available (i.e. Sterile Provocholine® Solution and when using 1 vial of Sterile Provocholine® Solution 16).

** Use 1.0 mg/mL when 2.0 mg/mL concentration is not available (i.e. Sterile Provocholine® Solution and when using 1 vial of Sterile Provocholine® Solution 16).

b) If FEV_1/VC <80% OR FEV_1 <70% predicted AND FEV_1 falls <10% after the diluent or placebo inhalation AND the patient's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.03 mg/mL*
Other or no medications	0.125 mg/mL**

c) If a patient's FEV_1 falls by 10% or more after the diluent or placebo inhalation, or if asthma symptoms do not appear to be well controlled, **DO NOT** omit any concentrations, and start patient at 0.03 mg/mL*.

* If using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus or Sterile Provocholine® Solution 16, this concentration can be prepared (See PREPARATION OF DILUTIONS section).

** Use 0.0625 mg/mL when 0.125 mg/mL concentration is not available (i.e. Sterile Provocholine® Solution and when using 1 vial of Sterile Provocholine® Solution 16).

2. Starting Concentrations in Children

a) If FEV_1/VC >80% AND the child's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.03 mg/mL*
Daily or occasional bronchodilators	0.0625 mg/mL
No medications	0.25 mg/mL

* If using Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus or Sterile Provocholine® Solution 16, this concentration can be prepared (see PREPARATION OF DILUTIONS section).

b) If FEV_1/VC <80% OR if asthma symptoms do not appear to be well controlled, **DO NOT** omit any concentrations, and start patient at 0.03 mg/mL.

3. Omission of Concentrations

If, after the first concentration of Provocholine®, there has been no evidence of any significant fall in the FEV_1 (less than 5% from mean baseline) and there is **NO** clinical evidence of any bronchoconstriction (chest tightness, cough or wheezing), the next dose may be omitted. As soon as there is any evidence of symptoms or a fall greater than 5% from mean baseline FEV_1, **DO NOT** omit any further concentrations. If a concentration is omitted, it is important to stress before every subsequent inhalation that the subject should remove the face mask/mouthpiece as soon as they experience any breathing or chest discomfort. The above also applies when using Sterile Provocholine® Solution Plus and when using serial dilution preparations using 2 vials of Sterile Provocholine® Solution 16 diluted as per Table 1F for use with the tidal breathing or dosimeter method.

For Sterile Provocholine® Solution product, do not omit any concentrations as this product already follows a quadrupling of concentrations.

When using only 1 vial Sterile Provocholine® Solution 16 diluted for use with the tidal breathing or dosimeter method, do not omit any concentrations as this product already follows a quadrupling of concentrations. For Sterile Provocholine® Solution 16, when used in conjunction with medical devices designed to administer gradually increasing concentrations from a single dose of Provocholine®; manufacturer's instructions should be followed. It is not recommended to exceed the equivalent of a quadrupling of doses with any delivery system.

Calculation and Interpretation of Results:
Either the provocative concentration or the provocative dose causing a 20% fall in FEV_1 (PC_{20} or PD_{20}) may be calculated as described below:

1. Calculation of PC_{20}

With either the tidal breathing method or the dosimeter method, airway responsiveness may be expressed as that concentration of Provocholine® provoking a fall in FEV_1 of 20% (PC_{20}). The percent fall in FEV_1 can be calculated using the mean baseline FEV_1, as shown below:

$$\% \text{ fall in } FEV_1 = \frac{\text{mean baseline } FEV_1 - \text{lowest } FEV_1 \text{ post-Provocholine}^{®}}{\text{mean baseline } FEV_1} \times 100$$

The percent fall in is then plotted against the rising concentration of Provocholine® (log scale). The PC_{20} is obtained by linear interpolation between the last two points, as shown in Figure 1.

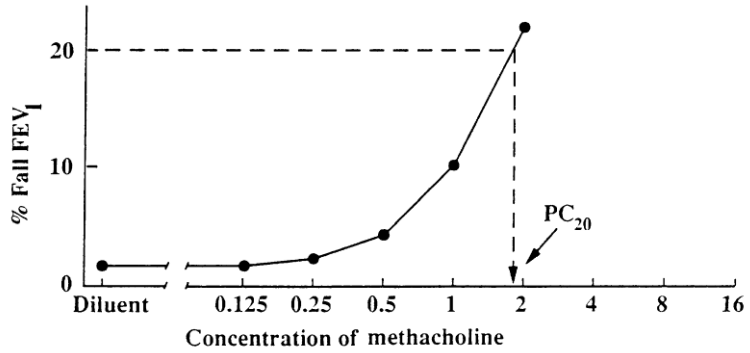


Figure 1: Calculation of PC_{20}

Alternatively, the PC_{20} may be calculated as follows:

$$PC_{20} = \text{antilog}\left[\log C_1 + \frac{(\log C_2 - \log C_1)(20 - R_1)}{(R_2 - R_1)}\right]$$

Where:
C_1 = second last concentration (<20% FEV_1 fall)
C_2 = last concentration (>20% FEV_1 fall)
R_1 = % fall FEV_1 after C1
R_2 = % fall FEV_1 after C2

2. Calculation of PD_{20}

The FEV_1 from the best spirogram at each dose is plotted on semilog paper (see example Figure 2, below) and a dose response curve constructed. The dose is expressed as cumulative units, either moles or breath units, where 1 mg/mL is equal to 0.5 moles or 10 breath units. The curve starts at 100%, and the last data point should be at 80% of saline control or lower. From this curve, the PD_{20}, the provocation dose of agonist necessary for a 20% drop in FEV_1, can be interpolated. The PD_{20} is the measure of the sensitivity to Provocholine®. Patients who do not respond to five inhalations of Provocholine® at the 16 mg/mL concentration can be said to have a negative challenge.

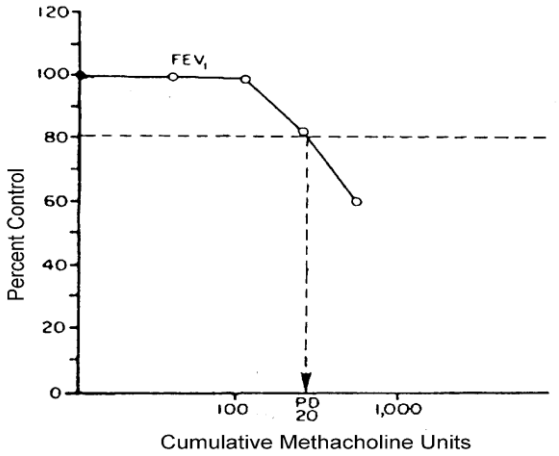


Figure 2: Airway responsiveness to Provocholine® (PD_{20}), expressed as cumulative units (either moles or breath units)

3. Interpretation of Results

In clinical trials, most asthmatics had a positive response at the 10 mg/mL concentration or less. Results can be interpreted with respect to the presence or absence of asthma only if the initial FEV_1/VC is >70%. The cut-off point between normal and increased responsiveness is a PC_{20} of 8 mg/mL, or a PD_{20} of 4 cumulative μmoles or 80 cumulative breath units. (Figure 3). Increased responsiveness is arbitrarily graded as borderline if between 4 and 8 mg/mL (2 and 4 μmoles or 40 and 80 breath units), as mild between 2 and <4 mg/mL (1 and <2 μmoles or 20 and 40 breath units), as moderate if between 0.25 and <2 mg/mL (0.125 and <1 μmoles or 5 and <20 breath units), and as severe if <0.25 mg/mL (<0.125 μmoles or <2.5 breath units). Patients with a PC_{20} >16 mg/mL (or a PD_{20} >8 μmoles or >160 cumulative breath units) are unlikely to have current symptoms due to asthma. When the PC_{20} is between 2 and 16 mg/mL, or the PD_{20} is between 1 and 8 μmoles or 20 and 160 cumulative breath units, current symptoms due to asthma are likely to be mild, infrequent or absent. Current symptoms of asthma are usual when the PC_{20} is <2 mg/mL, or the PD_{20} is <1 μmoles or <20 cumulative breath units.

NOTE: When using a single dose automatic provocation device system to administer Provocholine®, the equivalent of the above values will need to be calculated, as appropriate.

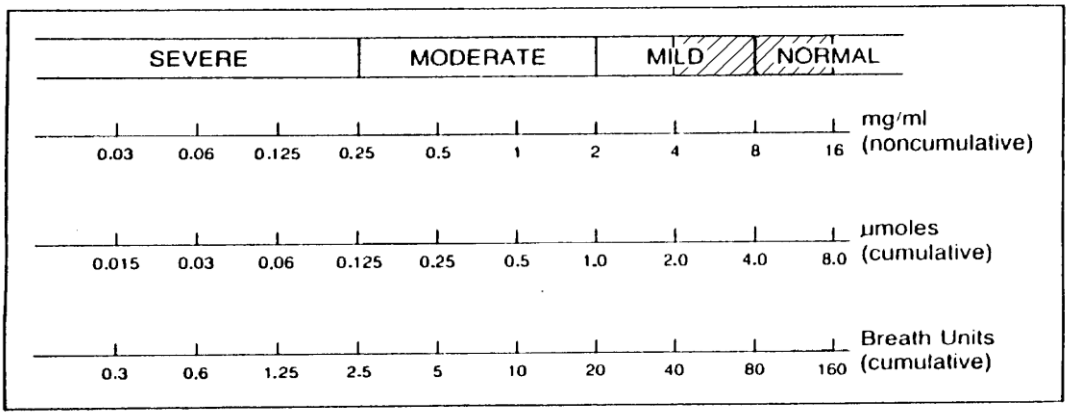


Figure 3: Comparison of Provocholine® airway responsiveness expressed as PC_{20} (mg/mL), using the tidal breathing method, and expressed as PD_{20} (cumulative µmoles and cumulative breath units) using the dosimeter method.

OVERDOSAGE

Provocholine® (methacholine chloride) is to be administered only by inhalation. When administered orally or by injection, overdosage with Provocholine® can result in a syncopal reaction, with cardiac arrest and loss of consciousness. Serious toxic reactions should be treated with 0.5 mg to 1 mg of atropine sulfate, administered IM or IV.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Provocholine® (methacholine chloride) is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered in solution only, by inhalation, for diagnostic purposes.

Methacholine chloride is the ß-methyl homolog of acetylcholine and differs from the latter primarily in its greater duration and selectivity of action. Bronchial smooth muscle contains significant parasympathetic (cholinergic) innervation. Bronchoconstriction occurs when the vagus nerve is stimulated and acetylcholine is released from the nerve endings. Muscle constriction is essentially confined to the local site of release because acetylcholine is rapidly inactivated by acetylcholinesterase.

Compared with acetylcholine, methacholine chloride is more slowly hydrolysed by acetylcholinesterase and is almost totally resistant to inactivation by non-specific cholinesterase or pseudocholinesterase.

When a solution containing Provocholine® is inhaled, subjects with current asthma are more sensitive to methacholine and bronchoconstrict at lower doses than healthy subjects. This difference in response is the pharmacologic basis for the Provocholine® inhalation diagnostic challenge. The test is most useful diagnostically when there are current symptoms consistent with asthma and when the forced expiratory volume at one second (FEV_1) is normal at >70% predicted. A normal result excludes current asthma (variable airflow limitation), but does not exclude past asthma.

Pharmacodynamics

When there is chronic airflow limitation with an FEV_1/VC of <70%, the test can be abnormal due to other pathophysiological causes such as smoker's bronchitis, emphysema or cystic fibrosis. The challenge may also be positive in patients with allergic rhinitis without symptoms of asthma, or in patients who have had or will in the future develop asthma symptoms.

Certain drugs can affect the pharmacodynamic response to Provocholine® (See Drug-Drug Interactions)

STORAGE AND STABILITY

Temperature:

- Store unopened vials of Provocholine® Powder at room temperature (15° to 30°C).
- Store Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 and Sterile Baseline Solution between 5° to 25°C.

Other:

- Do not use Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 and Sterile Baseline Solution if the solution is discoloured.

Reconstituted Solutions:

- Freezing does not affect the stability of dilutions made with Provocholine® and 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl.
- Provocholine® Powder reconstituted with 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl, using aseptic technique, may be stored under refrigeration (2° to 8°C) for up to 2 weeks.
- Store any dilutions of Sterile Provocholine® Solution 16 prepared using Sterile Baseline Solution for the shortest expiry period indicated on the original product vials at 5°to 25°C (except for any 0.03 mg/mL dilutions which should be prepared only before use and discarded immediately after use).

SPECIAL HANDLING INSTRUCTIONS

Provocholine® is a potent bronchoconstrictor. Do not inhale the powder. Do not handle this material if you have asthma or hay fever. 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 of the room.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Provocholine® Powder:

- 100 mg – in 20 mL and 50 mL amber glass vials in boxes of 6 and 12 vial
- 160 mg – in 20 mL amber glass vials in boxes of 6 and 12 vials
- 320 mg – in 20 mL amber glass vials in boxes of 6 and 12 vials
- 1280 mg – in 20 mL amber glass vials in boxes of 6 and 12 vials
- 1600 mg – in 50 mL amber glass vials in boxes of 1 vial
- 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl must be used to reconstitute the powder
- Administered via inhalation using a nebulizer

Sterile Provocholine® Solution:

- Each carton contains one 3-mL vial each of five concentrations (0.0625 mg/mL, 0.25 mg/mL, 1 mg/mL, 4mg/mL and 16 mg/mL) and one 3 mL vial of sterile placebo solution (for baseline FEV_1 testing).
- Each 3-mL vial of Sterile Provocholine® Solution contains: 0.0625 mg, 0.25 mg, 1 mg, 4 mg or 16 mg per mL methacholine chloride USP, 0.66 mg per mL sodium acetate trihydrate and 9 mg per mL sodium chloride in water for injection, sodium hydroxide and/or acetic acid glacial for pH adjustment.
- Each vial of Sterile Provocholine® Solution has a rubber stopper and a flip off seal. The flip off seals are colour coded to represent each of the five various strengths. Please refer to the table below:

Strength	Colour
0.0625 mg/mL	White
0.25 mg/mL	Avocado
1 mg/mL	Brown
4 mg/mL	Yellow
16 mg/mL	Red

The colour of the flip off seal for sterile solution placebo is clear.

Sterile Provocholine® Solution Plus:

- Each carton contains one 3-mL vial each of nine concentrations (0.0625 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL and 16 mg/mL) and one 3 mL vial of sterile placebo solution (for baseline FEV_1 testing).

- Each vial of Sterile Provocholine® Solution Plus contains: 0.0625 mg, 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg or 16 mg per mL methacholine chloride USP, 0.66 mg per mL sodium acetate trihydrate and 9 mg per mL sodium chloride in water for injection, sodium hydroxide and/or acetic acid glacial for pH adjustment.
- Each vial of Sterile Provocholine® Solution Plus has a rubber stopper and a flip off seal. The flip off seals are colour coded to represent each of the nine various strengths. Please refer to the table below:

Strength	Colour
0.0625 mg/mL	White
0.125 mg/mL	Cool Green
0.25 mg/mL	Avocado
0.5 mg/mL	Blue
1 mg/mL	Brown
2 mg/mL	Black
4 mg/mL	Yellow
8 mg/mL	Orange
16 mg/mL	Red

The colour of the flip off seal for sterile solution placebo is clear.

Sterile Provocholine® Solution 16:

- Each 3mL vial of Sterile Provocholine® Solution 16 contains: 16 mg per mL methacholine chloride USP, 0.66 mg per mL sodium acetate trihydrate and 9 mg per mL sodium chloride in water for injection, sodium hydroxide and/or acetic acid glacial for pH adjustment. Each vial has a rubber stopper and a red flip off seal, and packaged in individual cartons.

- Each 3 mL vial of Sterile Baseline Solution to be used with Sterile Provocholine® Solution 16 contains: 0.66 mg per mL sodium acetate trihydrate and 9 mg per mL sodium chloride in water for injection. Each vial has a rubber stopper and a clear flip off seal, and packaged in individual cartons.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

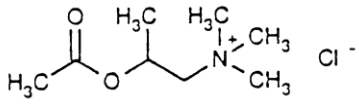
Common name: Methacholine Chloride USP

Chemical Name: 1-Propanaminium, 2-(acetyloxy)-N,N,N-trimethyl-, chloride

Molecular Formula: $C_8H_{18}ClNO_2$

Molecular Mass: 195.69

Structural Formula:



Physicochemical Properties: Methacholine Chloride USP is a white to practically white deliquescent compound that is soluble in water, alcohol and chloroform and insoluble in ether. Aqueous solutions are neutral to litmus.

CLINICAL TRIALS

Study demographics and trial design

In 1,500 patients with asthma and 500 non-asthmatics (either atopic or nonatopic), over 90% of asthmatics had high- or medium-positive responsiveness to methacholine chloride. Less than 5% of individuals with hay fever or nonatopic normal subjects showed a high-positive response. Twenty-seven percent of hayfever patients had a negative response compared to 49% of normals. Hayfever patients and normals had about the same incidence of low-positive responses. Thirty percent of hay fever patients had a medium-positive response compared to 18% of normals from families with a history of asthma and 8% of normals from control families. Asthmatics were different from all other groups. Hay fever patients were different from normals of normal families only.[36]

Among current asthmatics, the severity of asthma determined the bronchial sensitivity of subjects to methacholine challenge. This sensitivity varied from 100 to several thousand times that of normal subjects. However, in former asthmatics, the degree of bronchoconstriction was also related to the severity of past asthma symptoms. The mean sensitivity of former asthmatics was approximately one-tenth that of current asthmatics.[36]

Study results

In population-based studies, the prevalence of methacholine chloride hyperresponsiveness is 8 to 15%. While the degree of responsiveness of asthmatics does not distinguish them from non-asthmatics, asthmatics respond to a lower mean dose.[32] Asthmatics that are less responsive and generally have milder and more stable disease. Interpretation is easiest when the result is either substantially positive (a PC_{20} <1 mg/mL or a PD_{20} <10 cumulative breath units), or decidedly negative (minimal change in the FEV_1 with the highest dose delivered).[32] The cut-off point between normal and increased responsiveness is considered to be a PC_{20} of 8 mg/mL or a PD_{20} of 4 μmoles (cumulative).[19,36]

A dosimeter technique was used to test 766 children aged 9 years, who showed symptoms of asthma but had normal resting pulmonary function. Within two months, the dosimeter method was used to retest 79 of these patients. A further 30, 22 of whom showed reactivity, were challenged with the tidal breathing method. Twenty-five percent of the children had evidence of airway reactivity, revealed either by resting airflow obstruction relieved by salbutamol or by responsiveness to inhalation of methacholine chloride. The dosimeter method was suitably repeatable, and the tidal breathing method was equally sensitive in detecting reactivity to methacholine chloride. In only four children was the difference in PC_{20} between the two techniques greater than a twofold concentration step. A paired t test showed no bias from one method to the other.[31]

The usefulness of the methacholine challenge test with Provocholine® in confirming suspected asthma was determined in 1,105 subjects of 5 to 80 years of age; 189 were current asthmatics and 916 were non-asthmatics. Non-asthmatics were further categorized as: 143 atopics from asthma families; 66 atopics from normal families; 326 nonatopics from asthma families; and 381

nonatopics from normal families. Subjects were challenged with methacholine chloride, using the dosimeter method. Methacholine chloride challenge was shown to be a helpful tool in affirming the pretest probability of asthma.[25]

The methacholine challenge test with Provocholine® is used to help investigate whether asthma is of occupational or non-occupational origin. The incidence of cough, wheezing, and shortness of breath in the workplace ranges from 2 to 15 percent in various series.[6] Increases in airway responsiveness associated with periods at work provide useful supportive evidence to pulmonary function records.[9]

DETAILED PHARMACOLOGY

In vitro studies with tracheal, bronchial or lung tissue from several species indicate that methacholine chloride consistently produced a dose-related contraction. Lung tissue appeared to be less sensitive than other portions of the respiratory tract.[8,10]

Pharmacologic studies of the pulmonary effects of methacholine aerosol in the guinea pig, dog, pig and monkey showed dose-related increases in pulmonary resistance and decreased dynamic compliance.[5,14,16,22]

TOXICOLOGY

The acute (24-hour) oral LD_{50} of methacholine chloride and related compounds is 1100 mg/kg in the mouse and 750 mg/kg in the rat.[23]

Cynomolgus monkeys were exposed to a 2% (20 mg/mL) aerosol of methacholine chloride in acute (10-minute) and subchronic (7-day) inhalation toxicity studies. In the former study, animals exposed to the aerosol for up to 10 minutes demonstrated an increase in respiratory rate and decrease in tidal volume after 30 seconds. These changes peaked at 2 minutes and were followed by a rise in pulmonary resistance and a decrease in compliance. Pulmonary function returned to normal 20 to 25 minutes after exposure ended. In the 7-day study, monkeys were given daily inhalations equivalent to the maximum and roughly five times the maximum standard human dose. Although the typical pulmonary response/recovery sequence was observed, distinct changes in airway resistance were noted at the end of the study. These changes were not rapidly reversed in the maximum equivalent standard-dose group, which was observed for 9 weeks.[5]

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PART III: CONSUMER INFORMATION

Pr Sterile Provocholine® Solution,
Pr Sterile Provocholine® Solution Plus and
Pr Sterile Provocholine® Solution 16
methacholine chloride solution for inhalation

Pr Provocholine®
methacholine chloride powder USP

This leaflet is part III of a three-part "Product Monograph" published when Pr Provocholine® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Pr Provocholine®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provocholine® is used as part of a breathing test called a methacholine challenge test. This test is used to help your doctor decide if you have asthma. It can also be used to measure how severe your asthma is or to confirm whether or not you have occupational asthma.

What it does:
Provocholine® can cause muscles in the airways to tighten. When a Provocholine® mist is inhaled, people with asthma are much more likely to react to it than people without asthma.

During this test, a healthcare professional will measure your lung function before and after each dose of Provocholine®. The test will be stopped if:

- Your lung function drops to the target level.
- You have reached the highest dose of Provocholine and your lung function has not dropped to the target level.
- Your healthcare professional determines you are unable to continue with the test due to symptoms.

At the end of the test, you may be given a reversal agent. Your healthcare professional will measure your lung function to make sure your breathing is back to normal before you are sent home.

When it should not be used:
- Provocholine® should not be used by patients who have had an abnormal reaction to this or similar drugs.
- You should not have more than one test with this drug on the same day.
- Provocholine® should not be used in children under 5 years of age.
- Lung function tests should be performed by a healthcare professional prior to starting a test with Provocholine®. If the results are too low, the healthcare professional may decide not to proceed with the test and to contact the physician who ordered the test.

What the medicinal ingredient is:
The medicinal ingredient in Provocholine® is called methacholine chloride USP.

What the important nonmedicinal ingredients are:
There are no nonmedicinal ingredients in Pr Provocholine® Powder.

The nonmedicinal ingredients in Pr Sterile Provocholine® Solution, Pr Sterile Provocholine® Solution Plus, Pr Sterile Provocholine® Solution 16 and Sterile Baseline Solution are sodium acetate trihydrate, sodium chloride and water for injection.

What dosage forms it comes in:
Provocholine® comes in the following dosage forms –
Powder – 100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg
Solution – 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16 mg/mL and placebo

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Provocholine® is to be administered only by inhalation by a qualified healthcare professional.
- Provocholine® is a diagnostic drug only, and should not be used to treat disease.
- Test should not be performed on any patient experiencing difficulty breathing on the day of the test.
- Patients with lung disease may experience symptoms at very low doses and should warn the healthcare practitioner immediately if symptoms are present.

BEFORE you take a breathing test with Provocholine® talk to your doctor or respiratory therapist if:
- You have epilepsy.
- You have an ulcer.
- You have thyroid disease.
- You have an obstructed urinary tract.
- You have any type of heart disease.
- You have an irritable vagus nerve.
- You are pregnant.
- You are nursing.

INTERACTIONS WITH THIS MEDICATION

Some drugs may affect the safety of a breathing test with Provocholine®. Speak with your doctor if you are taking any other medications.

There are also many drugs that can affect the results of a breathing test with Provocholine®. These drugs may need to be stopped prior to the test. If you are taking any other medications, ask your doctor if you should stop taking them prior to the test and for how long.

PROPER USE OF THIS MEDICATION

Usual dose:
For Provocholine® Powder, adults and children (5 years or older):

- 0.03, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL.

For Sterile Provocholine® Solution and Sterile Provocholine® Solution 16 (using 1 vial), adults and children (5 years or older):

- 0.0625, 0.25, 1, 4, and 16 mg/mL.

For Sterile Provocholine® Solution Plus and Sterile Provocholine® Solution 16 (using 2 vials), adults and children (5 years or older):

- 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL.

Overdose:
Provocholine® should never be administered by any route other than inhalation. When administered by mouth or by injection overdosage can result in fainting, with loss of consciousness and heart attack.

Missed Dose:
N/A

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Adverse reactions to Provocholine® are uncommon. There have been some reports of headache, throat irritation, light-headedness and itching.

A positive reaction to a breathing test with Provocholine® may cause symptoms such as chest tightness, cough or wheezing.

Provocholine® is to be administered only by inhalation. When administered orally or by injection there have been reports of nausea and vomiting, chest pain or pressure, low blood pressure, fainting and heart attack.

This is not a complete list of side effects. For any unexpected effects while taking Provocholine®, notify the healthcare professional immediately so that the test may be stopped. If unexpected effects are noticed following the completion of the test, contact your physician.

HOW TO STORE IT

NOTE: Provocholine® is a diagnostic drug. It should never be removed from the clinic and/or pulmonary function lab.

Temperature:
Store unopened vials of Provocholine® Powder at room temperature (15° to 30°C).
Store Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 and Sterile Baseline Solution between 5°to 25°C.

Other:
Do not use Sterile Provocholine® Solution, Sterile Provocholine® Solution Plus, Sterile Provocholine® Solution 16 and Sterile Baseline Solution if the solution is discoloured.

Freezing does not affect the stability of dilutions made with Provocholine® Powder and 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl alcohol.

Reconstituted Solutions:
Provocholine® Powder reconstituted with 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl alcohol, using aseptic technique, may be stored under refrigeration (2° to 8°C) for up to 2 weeks.
Store any dilutions of Sterile Provocholine® Solution 16 prepared using Sterile Baseline Solution for the shortest expiry period indicated on the original product vials at 5°to 25°C (except for any 0.03 mg/mL dilutions which should be prepared only before use and discarded immediately after use).

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found obtained by contacting the sponsor, Methapharm Inc., at: 1-800-287-7686

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