

Provocholine[®]

(methacholine chloride)



Dilution Sequence Protocol

US Package Insert – Multi-Patient
(2-5 patients; requires 2 vials of Provocholine)

0.025

0.25

2.5

10

25

Provocholine 100 mg/vial (US NDC № 64281-100-06)

©Provocholine (methacholine chloride USP) powder for solution, for inhalation, is marketed in the United States, Canada and other countries. Provocholine is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma. Provocholine is a bronchoconstrictor agent for diagnostic purposes only and should not be used as a therapeutic agent. 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. For complete prescribing information, please 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 negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA(332)-1088. Provocholine is a registered trademark of Methapharm Inc. Copyright © Methapharm Inc. 2017.

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Specialty Pharmaceuticals

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Dilution Sequence Protocol

- These instructions are prepared according to the United States FDA approved Package Insert for Provocholine (NDC 64281-100-06).
- The following are step-by-step instructions to reconstitute two (2) 100 mg vials of Provocholine into the five (5) requisite concentrations for use in a Provocholine challenge for 2-5 patient testing.
- Please refer to the Provocholine package insert for full instructions and safety precautions.
- Precise sterile mixing is essential for the accuracy of the test results and to maintain patient safety.
- Only trained individuals should mix and label Provocholine solutions.



Important Notes

- Do not inhale powder during preparation of dilutions.
- Do not handle Provocholine if you have asthma or hay fever.
- Provocholine dilutions should be mixed by a pharmacist or other well-trained individual using sterile technique.
- All vials should be labeled, filling in the appropriate lot number, concentration, diluent, preparation date, initials of person preparing, and expiration dates.
- To reduce back pressure, vent vials with an extra needle as needed.
- All dilutions should be mixed in sterile USP Type I borosilicate glass vials.
- All dilutions should use one of the approved diluent options listed in your Provocholine package insert and use the same diluent throughout.



Supplies Required

Supplies required for the dilution of two (2) vials of Provocholine 100 mg for multiple patients

Quantity	Description
2	100 mg vial of Provocholine
1	100 mL diluent*
4	10 mL sterile empty USP Type I borosilicate glass vials*
2	10 mL syringes*
2	20 Gauge, 1" syringe needles*
7	Alcohol preparation pads or swabs*
1	Set of directions
1	Provocholine Dilution Sequence Check Sheet and Control Record
1	Package Insert for Provocholine

* These supplies may require alternate quantities depending on your protocol.



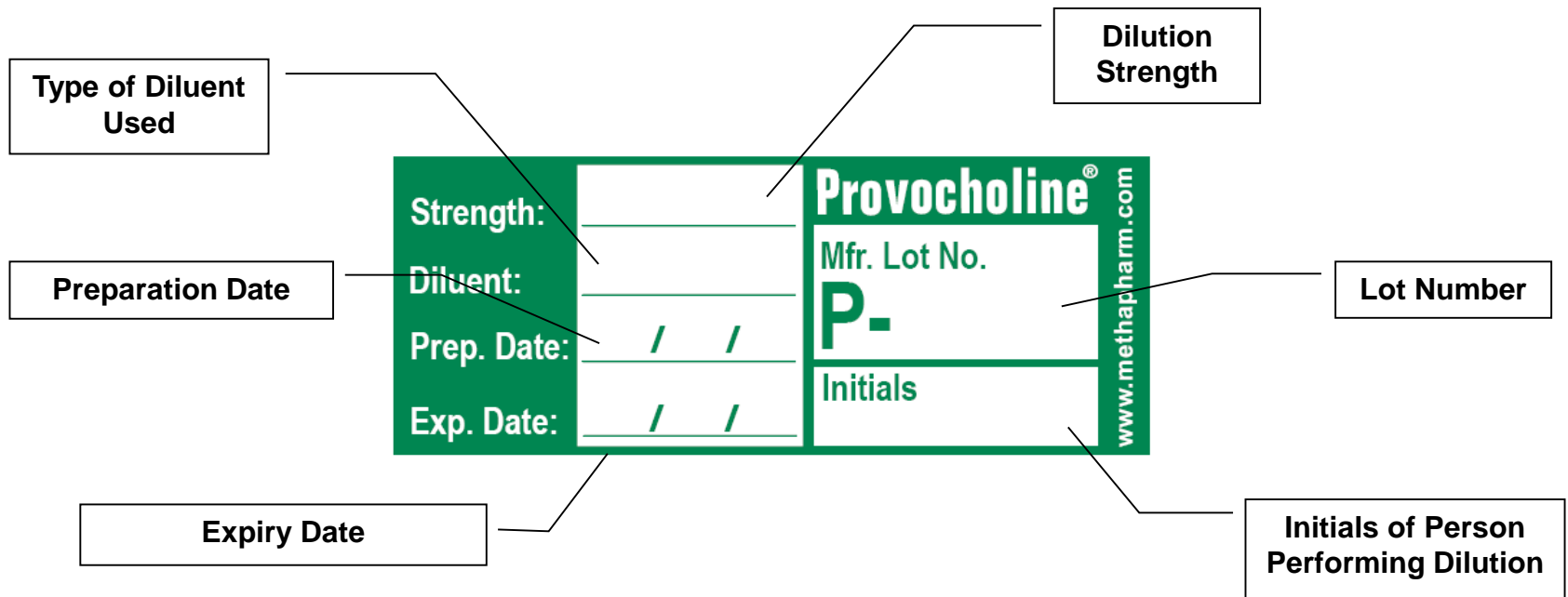
Dilution Process

TAKE Provocholine	ADD Diluent (Shake well)	OBTAIN DILUTION	VIAL NAME
Provocholine 100 mg	4 mL	25 mg/mL	Vial A₁ 25 mg/mL
Provocholine 100 mg	4 mL	25 mg/mL	Vial A₂ 25 mg/mL
3 mL from Vial A ₁	4.5 mL	10 mg/mL	Vial B 10 mg/mL
1 mL from Vial A ₂	9 mL	2.5 mg/mL	Vial C 2.5 mg/mL
1 mL from Vial C	9 mL	0.25 mg/mL	Vial D 0.25 mg/mL
1 mL from Vial D	9 mL	0.025 mg/mL	Vial E 0.025 mg/mL



Labeling

- Fill in **ALL** information on labels.
- Include **14 day expiration date** on vials A – D.
- Vial E must be prepared on the day of the challenge test.

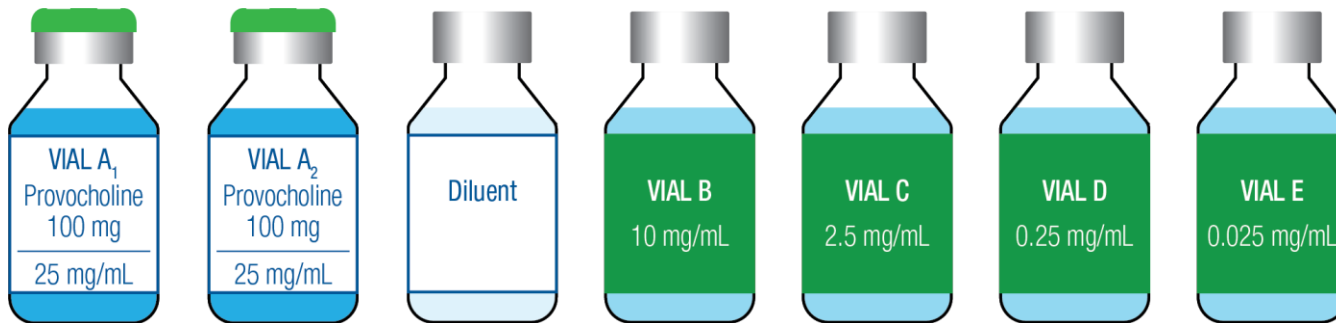


Dilution Process

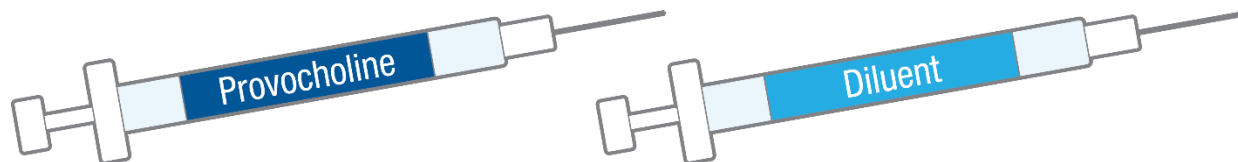


Getting Started

1. Attach labels to sterile empty vials.
2. Wipe down the stoppers of the Provocholine vials, diluent vial, and sterile empty vials with alcohol prep pads.



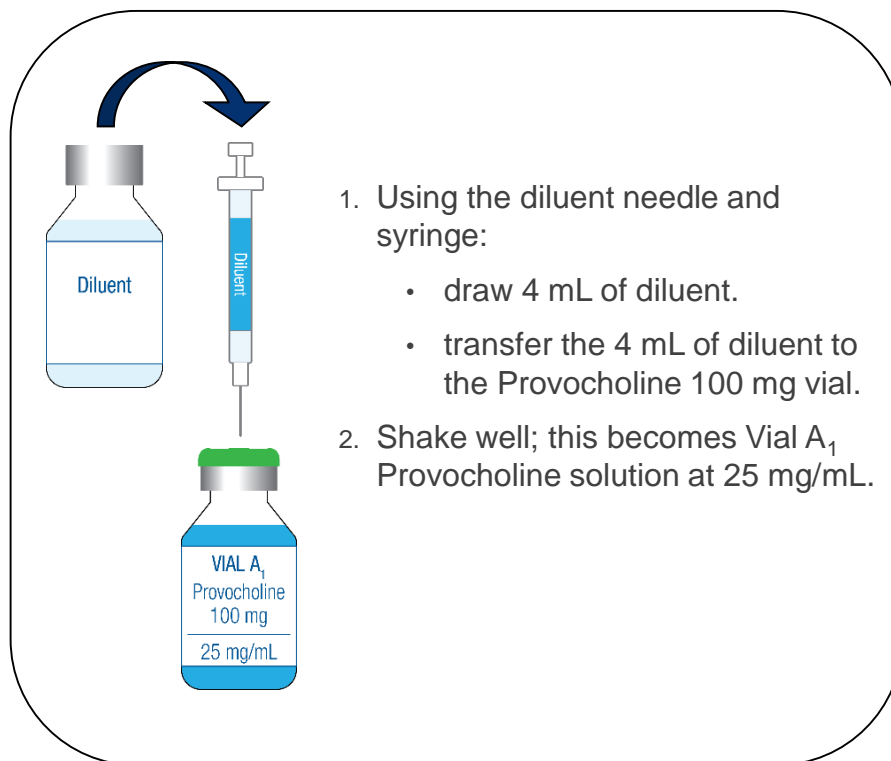
3. Label two (2) appropriately sized syringes (one for Provocholine, one for diluent), and attach needles to each.



Dilution Process



Step 1: Preparing Vials A₁ Provocholine 25 mg/mL Solution



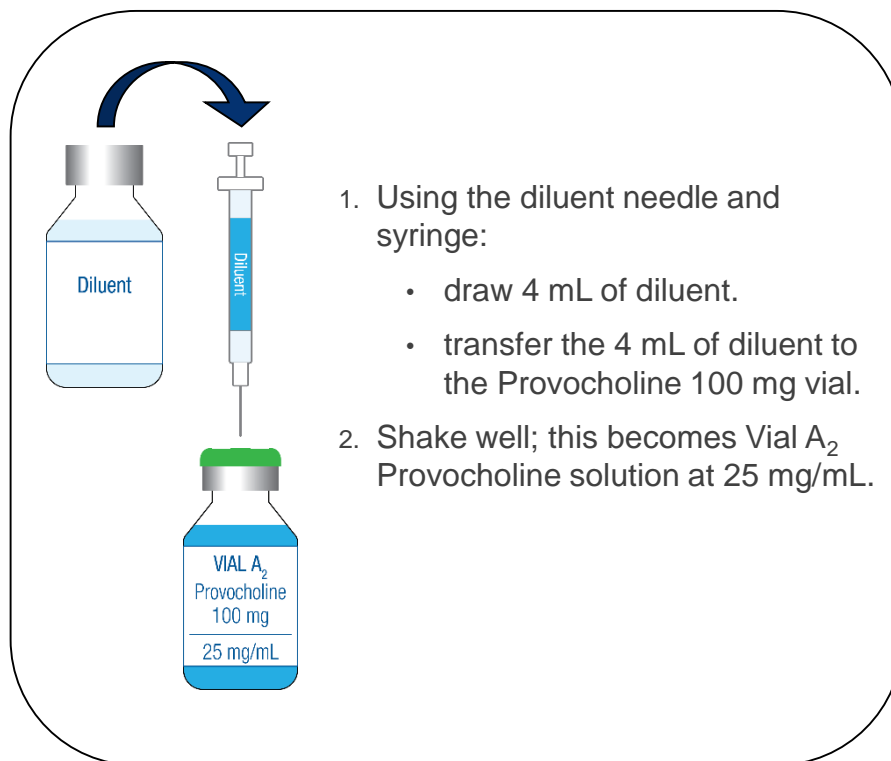
After completing Step 1

Vial A₁ contains 4 mL of Provocholine solution at 25 mg/mL.

Dilution Process



Step 2: Preparing Vials A₂ Provocholine 25 mg/mL Solution



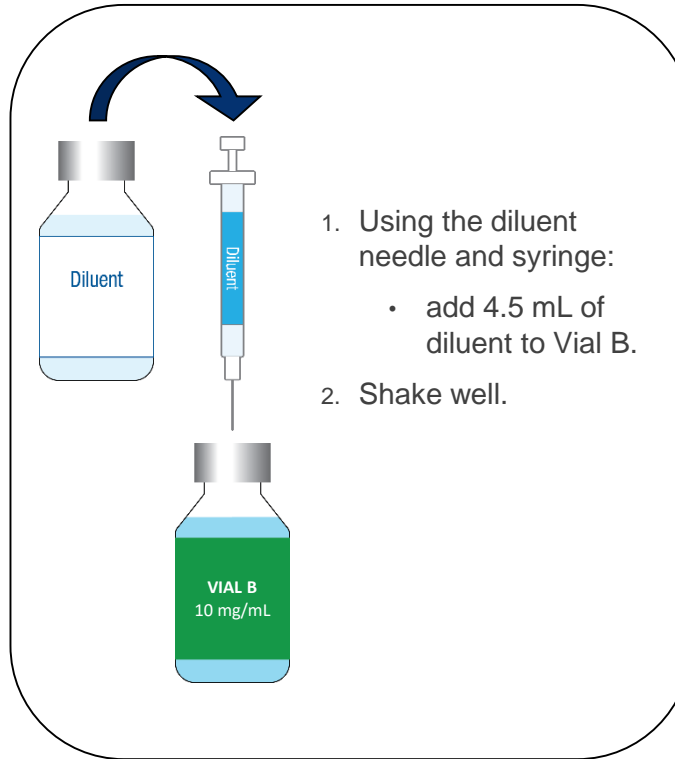
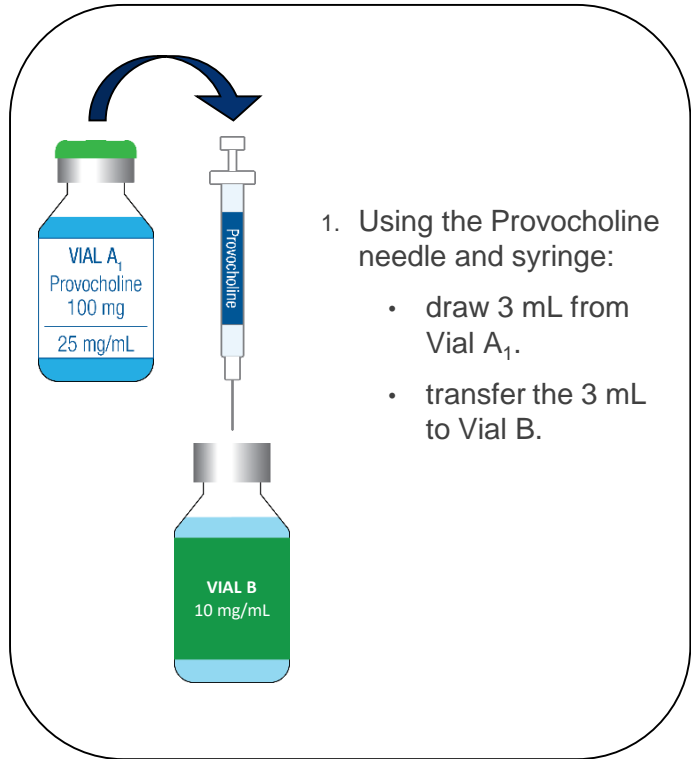
After completing Step 2

Vial A₂ contains 4 mL of Provocholine solution at 25 mg/mL.

Dilution Process



Step 3: Preparing Vial B Provocholine 10 mg/mL Solution



After completing Step 3

Vial A₁ contains 1 mL of Provocholine solution at 25 mg/mL.

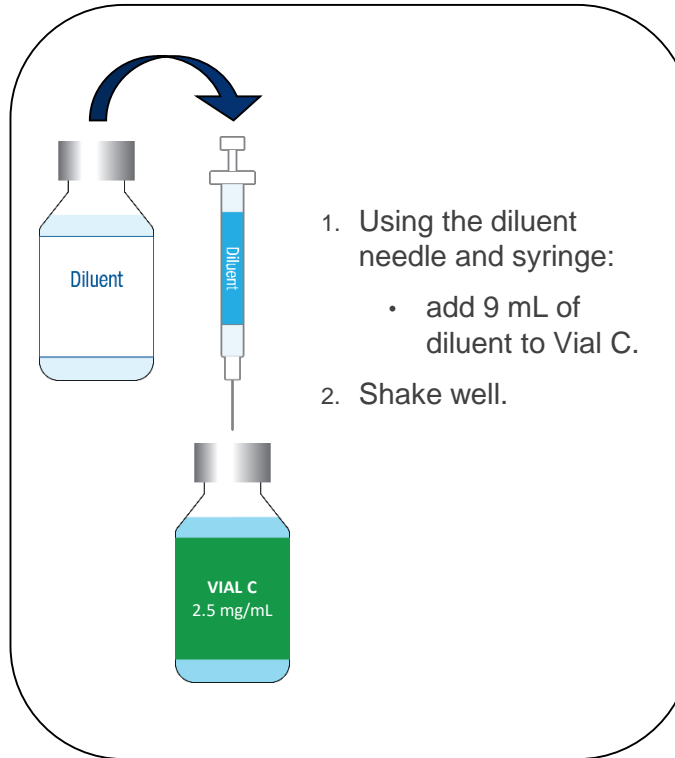
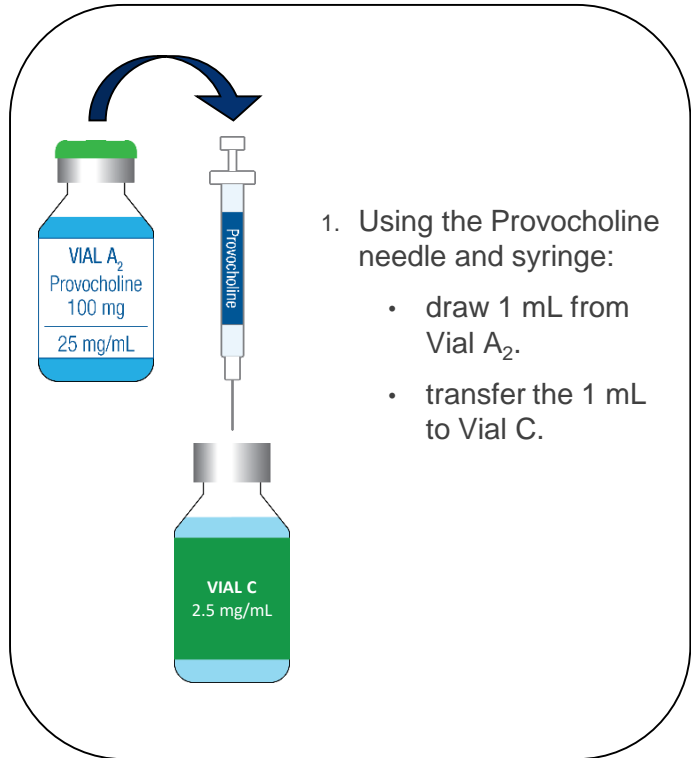
- AND -

Vial B contains 7.5 mL of Provocholine solution at 10 mg/mL.

Dilution Process



Step 4: Preparing Vial C Provocholine 2.5 mg/mL Solution



After completing Step 4

Vial A₂ contains 3 mL of Provocholine solution at 25 mg/mL.

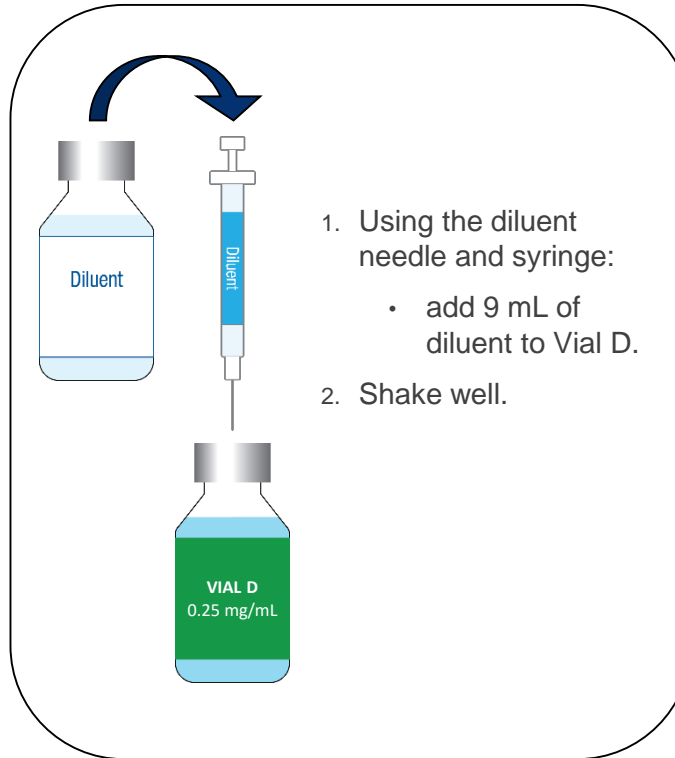
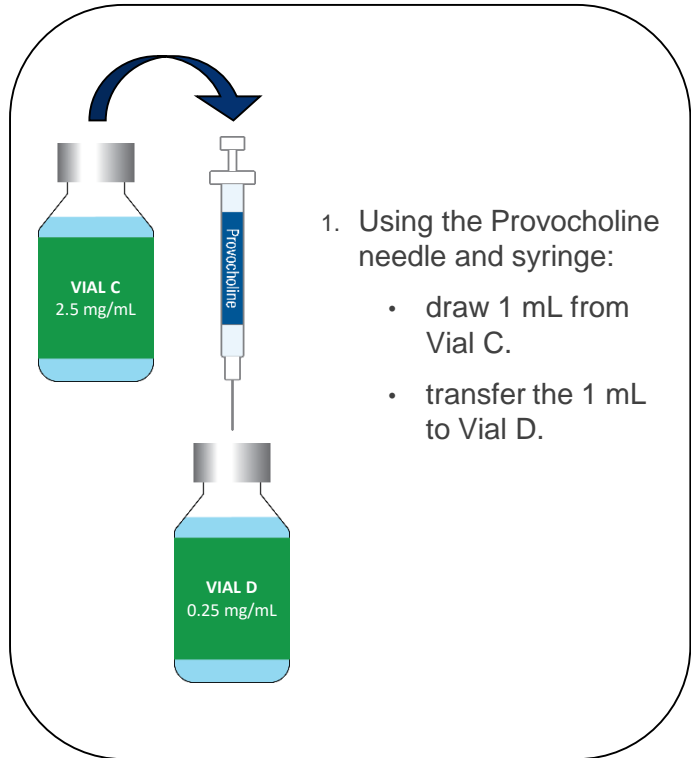
- AND -

Vial C contains 10 mL of Provocholine solution at 2.5 mg/mL.

Dilution Process



Step 5: Preparing Vial D Provocholine 0.25 mg/mL Solution



After completing Step 5

Vial C contains 9 mL of Provocholine solution at 2.5 mg/mL.

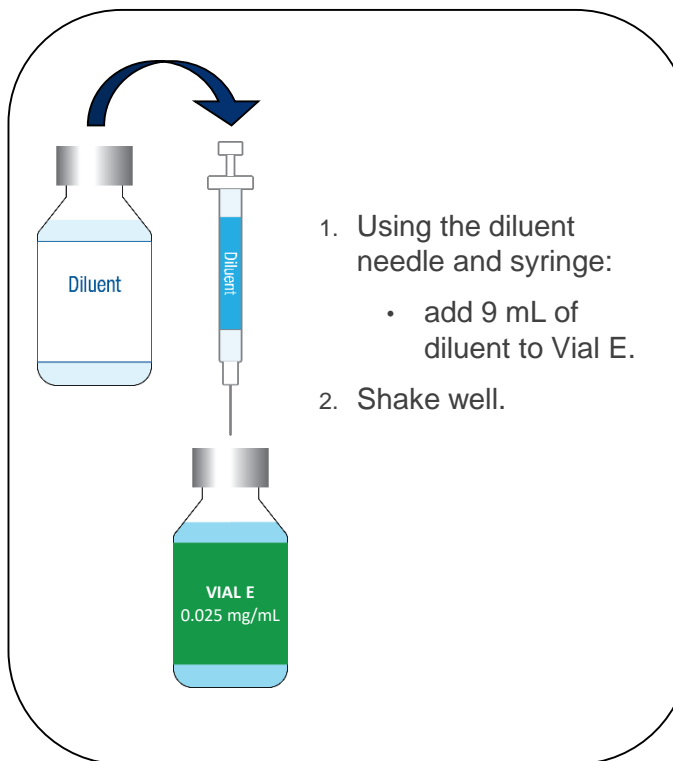
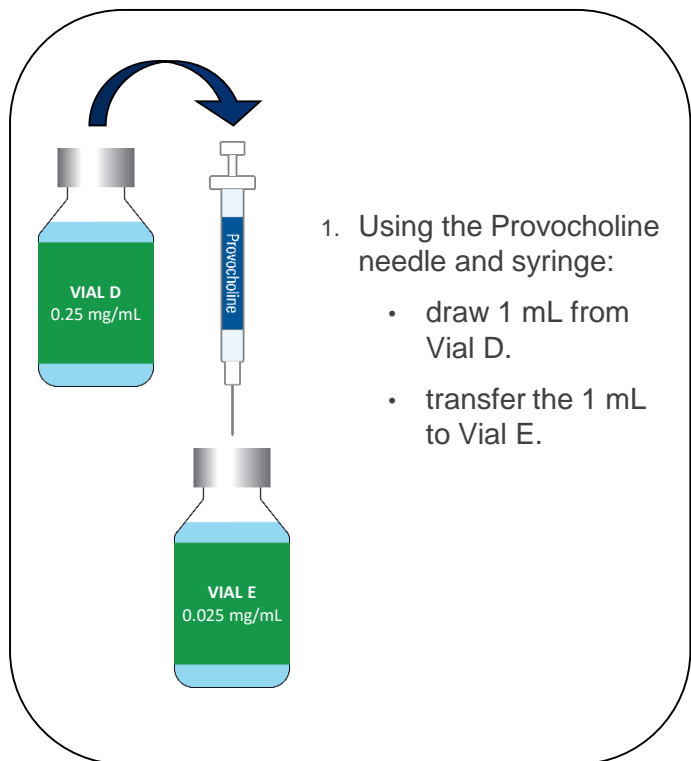
- AND -

Vial D contains 10 mL of Provocholine solution at 0.25 mg/mL.

Dilution Process



Step 6: Preparing Vial E Provocholine 0.025 mg/mL Solution



After completing Step 6

Vial D contains 9 mL of Provocholine solution at 0.25 mg/mL.

- AND -

Vial E contains 10 mL of Provocholine solution at 0.025 mg/mL.

NOTE:

Vial E must be prepared on the day of the challenge test.

Transfer all dilutions (in vials A through E) to nebulizer through the 0.22 μ m sterile bacterial retentive filter (Millex GV®).*

*Do not attach filter until AFTER solution has been drawn into syringe.

Conclusion



Storage Instructions

- Provocholine powder should be stored at 59° to 86°F (15° to 30°C).
- Dilutions A through D (25 mg/mL through 0.25 mg/mL) should be stored at 36° to 46°F (2° to 8°C) in a refrigerator for no more than 2 weeks.
- Freezing does not affect the stability of dilutions A through D (25 mg/mL through 0.25 mg/mL).
- Vial E (0.025 mg/mL) must be prepared on the day of the challenge test.

Conclusion



Summary of Procedure

1. Attach two (2) needles to two (2) 10 mL syringes and label one (1) for Provocholine and one (1) for diluent.
2. Remove plastic covers from Provocholine and diluent vials; line up all sterile empty vials.
3. Fill in information and attach labels to the Provocholine and sterile empty vials.
4. Wipe down the stoppers of the Provocholine vials, diluent vial, and sterile empty vials with alcohol prep pads.
5. Using the diluent syringe, add 4 mL of diluent into the Provocholine 100 mg vial. Shake well. This becomes **VIAL A₁ – 25 mg/mL**.
6. Using the diluent syringe, add 4 mL of diluent into the Provocholine 100 mg vial. Shake well. This becomes **VIAL A₂ – 25 mg/mL**.
7. Using the Provocholine syringe, draw 3 mL from Vial A₁ and transfer to Vial B. Using the diluent syringe, draw 4.5 mL of diluent and transfer to Vial B. Shake well. This becomes **VIAL B – 10 mg/mL**.

Conclusion



Summary of Procedure

8. Using the Provocholine syringe, draw 1 mL from Vial A₂ and transfer to Vial C. Using the diluent syringe, draw 9 mL of diluent and transfer to Vial C. Shake well. This becomes **VIAL C – 2.5 mg/mL.**
9. Using the Provocholine syringe, draw 1 mL from Vial C and transfer to Vial D. Using the diluent syringe, draw 9 mL of diluent and transfer to Vial D. Shake well. This becomes **VIAL D – 0.25 mg/mL.**
10. Using the Provocholine syringe, draw 1 mL from Vial D and transfer to Vial E. Using the diluent syringe, draw 9 mL of diluent and transfer to Vial E. Shake well. This becomes **VIAL E – 0.025 mg/mL.**

Conclusion



Summary of Procedure

NOTE

- To reduce back pressure, vent vials with an extra needle as needed.
- Vial E must be prepared on the day of the challenge test.
- Transfer all dilutions (in vials A through E) to nebulizer through the 0.22 μm sterile bacterial retentive filter (Millex GV®).*

*Do not attach filter until AFTER solution has been drawn into syringe.

Conclusion



Dilution Check Sheet and Control Record

PROVOCHOLINE DILUTIONS FOR CHALLENGE TESTING

Date: _____ Prepared by: _____ Checked by: _____

Provocholine (see label on vial) Lot Number: _____ Expiration Date: _____

Diluent _____ Lot Number: _____ Expiration Date: _____

TAKE Provocholine	ADD Diluent (Shake well)	OBTAIN DILUTION	VIAL NAME	INITIAL
Provocholine 100 mg	4 mL	25 mg/mL	Vial A ₁ - 25 mg/mL	
Provocholine 100 mg	4 mL	25 mg/mL	Vial A ₂ - 25 mg/mL	
3 mL from Vial A ₁	4.5 mL	10 mg/mL	Vial B - 10 mg/mL	
1 mL from Vial A ₂	9 mL	2.5 mg/mL	Vial C - 2.5 mg/mL	
1 mL from Vial C	9 mL	0.25 mg/mL	Vial D - 0.25 mg/mL	
1 mL from Vial D	9 mL	0.025 mg/mL	Vial E - 0.025 mg/mL	