Bronchoprovocation committee report

Since the 1970s, the Bronchoprovocation Committee of the American Academy of Allergy and Immunology has been concerned with the standardization of inhalation provocation-challenge procedures. The 1975 publication by the Committee in THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY[1] has remained a valuable resource for clinicians. The multicenter evaluation of methacholine (Provocholine; Roche Laboratories, Nutley, N.J.), which involved many of the Committee members, led to FDA approval of the product in December 1986. Until that time, only methacholine obtained without FDA sanction was available for challenge.

The current protocol for Provocholine involves the inhalation of saline followed by five concentrations of Provocholine: 0.025, 0.25, 2.5, 10, and 25 mg/ml. With the dosimeter method, five inhalations of each of these concentrations is delivered, followed by spirometry. A decrease in FEV_1 of $\geq 20\%$ from the baseline FEV_1 after saline denotes significant sensitivity, the degree of which is conveyed by the PD_{20}.

Although tidal volume method has not been used during studies to evaluate Provocholine, it has been used as an alternative to the dosimeter method, since studies have demonstrated similar results for both methods.[2] The tidal volume method involves the direct delivery of methacholine from a Wright nebulizer or an alternative type that is known to have similar characteristics. The patient breathes from a face mask or mouthpiece, receiving saline diluent and then progressive concentrations of methacholine, each for 2 minutes, with spirometry performed after this procedure.

It is now commonly accepted that methacholine sensitivity is an indiginous feature of asthma, although it exists with other conditions also.[3] Methacholine challenge is a valuable clinical tool in supporting a clinical diagnosis of asthma. It is a valuable research tool in the study of pharmacologic mechanisms and the duration of action of drugs for asthma and for evaluating the natural history of bronchial hyperresponsiveness.

From the Bronchoprovocation Committee, American Academy of Allergy and Immunology.

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Abbreviations used

FDA: Food and Drug Administration

PD_{20}: Provocative dose of methacholine causing a 20% fall in FEV_1

To evaluate the impact of the availability of methacholine challenge as a clinical tool, the Bronchoprovocation Committee designed a questionnaire that was mailed to the membership. Four thousand questionnaires were distributed and 1150 were returned. The Committee was favorably impressed by the magnitude of the response and by the interest in the challenge technique conveyed by the many comments that were received. It is likely that this response rate underreports the number of physicians who are interested in and use bronchoprovocation, since we are aware that in many group practices, only one questionnaire was returned as representative of the opinions of an entire group of physicians.

The key issues of the questionnaire are summarized in Table I, and the number of responses to each question are indicated. Many of the responders offered comments. A group of individuals echoed the theme that they prefer to rely on a therapeutic trial to define airway responsiveness, although the reasons varied greatly (Table II). Among the comments assigning positive value to the clinical challenge are testimonials to the benefits for sorting diagnostic dilemmas and making decisions about long-term use of anti-inflammatory therapy (Table III). Negative comments about the procedure were concerned with overuse of procedures, the possibility of falsely equating positive reactivity with clinical asthma, and occasional adverse reactions by patients and staff (Table IV). Responders were asked for their suggestions, and these were numerous. The suggestions included requests for less expensive Provocholine, premixed concentrations, fewer concentrations, a simpler protocol, and metered-dose inhalers for delivery (Table V).

These comments require some historical perspective on Provocholine. Before Hoffmann-LaRoche came forward to fund research with methacholine, aimed at achieving FDA approval, the drug was only

TABLE I. Bronchoprovocation questionnaire (total number of questionnaires received, 1150)

1. Do you or have you used methacholine for bronchoprovocation challenge	
No	472
Yes	665
Provocholine	359
Methacholine	356
Not familiar with methacholine	31
Do not see patients with lower respiratory tract symptoms	8
Methacholine challenge not useful	66
No expertise to perform challenge	165
Concerned with patient illness as a result of challenge	146
Other	159
2. Using methacholine prior to availability of Provocholine	
Yes	499
No	424
3. Where challenges are performed	
Office	429
Hospital	400
Other	74
4. Patient groups challenge is used	
Children 3-5 (yr)	62
Children 6-12 (yr)	375
Teenagers	537
Adults	700
5. Who perform challenge	
Myself	190
Technician	379
Nurse	251
Other	90
6. Physician on premises	
Yes	730
No	14
7. Average usage	
Daily	32
Weekly	148
Monthly	273
Other (see comments)	305
8. Administration	
Continuous nebulization with face mask	186
Intermittent nebulization with dosimeter	421
Other (see comments)	104
9. Doses used	
Package insert protocol	393
Other protocol	222
10. Difficulty with use	
Dilution preparation	
Yes	10
No	536
Moderate to severe symptoms	
Yes	78
No	429

TABLE I. Cont'd

11. Adverse reactions among staff	
Coughing	
Yes	92
No	486
Wheezing	
Yes	63
No	511
Other lower respiratory symptoms	
Yes	15
No	488
Other symptoms	
Yes	11
No	505
12. Challenge contribution to care	
Improved diagnosis of asthma	
Yes	650
No	41
Knowledge leads to therapeutic decisions	
Yes	242
No	266

TABLE II. Comments on use of methacholine challenge

Prefer therapeutic trial
Believe it should be performed in a hospital setting
Afraid of litigation
Too busy
Too expensive for patients
Have not needed it enough to justify
Have considered, but not made the effort
Local hospital or pulmonologist does it—more cheaply made by hospital or pharmacy
Not enough volume to justify cost in office
Not reimbursable by insurance

TABLE III. Comments on positive value of methacholine challenge

Avoids inappropriate use of asthma medications
Helpful for workup of cough and cough-variant asthma
Helpful for occupational asthma questions
Helps with decision about anti-inflammatory drugs

TABLE IV. Comments on negative values of methacholine challenge

Overuse for money
Staff reaction if not vented well
One late reaction
Diagnosis of asthma without clinical correlates
Given to known subjects with asthma

TABLE V. Suggestions

Make it less expensive
Make it easier to make dilutions
Premixed bottles
Metered-dose inhalers with various doses
Better availability of dosimeter
Simplify protocol
Need clearer explanation of equipment and protocol

available as a laboratory reagent, not for human use. Although the likelihood of profitability was small, Hoffmann-LaRoche funded multicenter trials with a truncated version of the protocol published by the Bronchoprovocation Committee in 1975. Several years and much discussion by the Bronchoprovocation Committee resulted in a protocol that was briefer than previous protocols while it remained both safe and discriminating. The five dosage levels (0.025, 0.25, 2.5, 10, and 25 mg/ml) appeared to satisfy those goals. There has been some sentiment that a 5 mg/ml concentration would be a helpful addition when a patient's level of response was assessed. It is unfortunate that the current packaging of Provocholine does not allow for this addition. Nevertheless, to our knowledge, there have been no serious adverse events as a result of the jump from 2.5 to 10 mg/ml. Con-

sidering the cost/benefit ratio, it is unlikely that the pharmaceutical industry or the FDA will perceive a need to pursue changes in the current protocol or in delivery methods.

As a general guideline for clinical practice, patients who have a 20% or more drop in FEV_1 at 0.025 mg/ml are considered to have severe bronchial hyperresponsiveness, whereas 0.25 and 2.5 mg/ml levels indicate moderate and 10 and 25 mg/ml concentrations indicate mild hyperresponsiveness. For the actual determination of a PD_{20}, a dose-response curve graph must be constructed, plotting change in FEV_1 against the log of methacholine concentration. In general, a $PD_{20} \geq 0.2$ mg/ml is considered severe; >0.2 to 2 mg/ml, moderate; and >2 to 25 mg/ml, mild. There are only minimal data concerning drops in peak expiratory flow rate and forced expiratory flow rate between 25% and 75% that correlate with this 20% change in FEV_1. Although severely and moderately hyperresponsive patients are likely to have a degree of asthma that might best be managed by long-term therapy, mild responders are less likely to need aggressive therapy. These very general comments should serve only as guidelines. The physician who orders a provocative challenge must interpret the results in the context of the patient's particular history. Numerous reviews on the clinical and research use of methacholine challenge are available. Although certain pharmacologic interventions have the ability to alter methacholine sensitivity, bronchial hyperresponsiveness will often remain the same, even when good control of asthma symptoms and pulmonary function stability have occurred. Thus, serial measurements of methacholine sensitivity in clinical practice, as a method to judge asthma control, cannot be recommended.

Some responders expressed desire to learn more about methacholine challenge and, specifically, to have more input concerning the equipment involved and the procedure. At upcoming meetings of the American Academy of Allergy and Immunology, hands-on workshops will address these needs. These new workshops will allow physicians to "walk through the procedure." Presentations and demonstrations will also take place at Allied Health Programs. The Bronchoprovocation Committee is gratified that its interest in inhalation challenge has permeated both research and clinical arenas.

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REFERENCES

1. Chai H, Farr RS, Froehlich LA, et al. Standardization of bronchial inhalation challenge procedures. J ALLERGY CLIN IMMUNOL 1975;56:323.
2. Ryan G, Dolovich MB, Roberts RS, et al. Standardizations of inhalation bronchoprovocation tests: two techniques of aerosol generation and inhalation compared. Am Rev Respir Dis 1981;123:195-9.
3. Townley RG, Hopp RJ. Inhalation methods for the study of airway responsiveness. J ALLERGY CLIN IMMUNOL 1987;80:111-27.

Correction

In the article by Michoud et al. entitled, "Effect of salbutamol on gastroesophageal reflux in healthy volunteers and patients with asthma," J ALLERGY CLIN IMMUNOL 1991:87:762-7, the legend of Fig. 1, page 764, should read *LES gradient* instead of *LES resting pressure*. This error does not affect the results or their interpretation.