

per year based on the average wholesale cost of a 150 mg vial of omalizumab of \$433.00.³

Some patients fall into the “do not dose” region on the card because of their high weight and/or IgE value. However, many of these patients could clearly be given enough omalizumab (per the formula) to suppress their IgE and yet not use more than the 750 mg omalizumab considered the dosing ceiling. The aforementioned cost-benefit analysis was based on the subset of patients who could be dosed by both the card and the formula. However, using the formula, 106 of 130 patients would be able to receive omalizumab, whereas only 69 of 130 could be dosed using the pocket card. Therefore, a great many more patients would be able to benefit from omalizumab if the dosing was regularly performed via the formula.

Although use of the formula for dosing of omalizumab could lead to large cost savings, dosing via this method will often lead to a dose that is not equal to a multiple of 150 mg (which is the size of a vial of omalizumab.) This fact could serve to make the cost savings discussed significantly smaller. However, it has occurred to us that although there is not much flexibility in the amount that can be dispensed at a given visit, there is flexibility in the dosing interval. Consider the following patient. PL becomes a candidate for therapy with omalizumab. Her serum IgE is 216 IU/mL, and her weight is 50 kg. Her dose every 28 days would be $50 \text{ kg} \times 216 \text{ IU/mL} \times 0.016 = 173 \text{ mg/28 days}$. Given that omalizumab can be given at either 2-week or 4-week intervals, we see no pharmacologic reason why any interval between these 2 points would be problematic. Therefore, using proportions, PL's dose of 173 mg/28 days could be converted to 150 mg/24 days ($173 \text{ mg/28 days} = 150 \text{ mg/24 days}$). Therefore, this patient could receive her injections every 24 days or every 3 weeks. Alternatively, if a large asthma clinic had a critical mass of patients on omalizumab, vials could be split between 2 patients. Given the 8-hour shelf life in the refrigerator after the solution has been mixed, this approach of splitting vials between patients would not be feasible for smaller clinics. Better cost savings with less waste would also occur if a second smaller vial size were made available.

We are concerned that use of this pocket card may result in increased expense for the health care system without increased efficacy for the patient. Conversely, it may deny Xolair to some patients who should clearly qualify for it. Further research is needed to clarify a more precise method of dosing this expensive medication. We wish to bring this phenomena to the attention of the readership.

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Todd Rambasek, MD^a
Mani S. Kavuru, MD^b

From ^aENT Health Services Inc, 1221 Hayes Avenue, Sandusky, OH 44870, and ^bthe Division of Pulmonary and Critical Care Medicine, Brody School of Medicine, East Carolina University, Greenville, NC.

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Safety of methacholine challenges in a multicenter pediatric asthma study

To the Editor:

Pharmacologic provocation challenges to evaluate bronchial hyperresponsiveness (BHR) are used as a clinical tool to confirm the diagnosis of asthma in special situations and as a research outcome measure to determine mechanisms and treatment efficacy. BHR is related to various measures of asthma severity¹ and has also been reported as a predictor of persistent asthma and airflow limitation in adulthood.² Most recently, its application as a tool for determining treatment modification has been found to be effective not only at improving clinical parameters of asthma control but also at alleviating airway inflammation.³ Given the relevant applications of bronchoprovocation tests, it is important to standardize and guarantee safety for use in patients. Human subject safety boards and ethics committees are requesting investigators to provide more accurate safety assessments.

The Childhood Asthma Management Program was a multicenter, randomized, clinical trial designed primarily to evaluate the long-term safety and effectiveness of 3 inhaled treatments for mild to moderate childhood asthma over 4 to 6 years, followed by an observational 4-year period (Childhood Asthma Management Program Continuation Study). Before randomization, participants had to have a history of asthma for at least 6 months in the year before screening, evidence of current asthma of mild to moderate severity during a 28-day screening period, and a methacholine FEV₁ PC₂₀ ≤ 12.5 mg/mL.⁴ A written informed consent approved by each clinical center's institutional review board was obtained from all patients and/or the parent. In this report, we evaluate the safety of methacholine provocation performed serially over an 11-year period.

Methacholine testing was performed by trained and certified technicians. Physicians were available on site to evaluate the child and initiate treatment as necessary. The procedure was performed at least 4 hours after the use of a short-acting bronchodilator and 24 hours after the last use of a long-acting bronchodilator or theophylline. The tests were not performed within 4 weeks of an upper respiratory tract infection, other serious illness, or use of oral steroids;

if the FEV₁ at baseline was < 70% of predicted; or if the patient was pregnant.

The procedure was modified from the methods of Cockcroft et al.⁵⁻⁷ After a control diluent, doubling doses (from 0.098 to 25 mg/mL in 3 mL solution) were administered for 2 minutes via a face mask or mouthpiece connected to the Wright nebulizer calibrated to a specific flow meter (9 L/min; Western Enterprises, Westlake, Ohio). Spirometry was performed at baseline and 90 seconds after each concentration. The concentration that provoked a 20% fall from postdiluent FEV₁ was obtained by linear interpolation of the logarithmic dose-response curve expressed as PC₂₀. Participants who completed the challenge without a 20% drop in FEV₁ were assigned a value of 37.5 mg/mL.

If the challenge was terminated because the participant's FEV₁ fell at least 20% from the postdiluent value, albuterol (2 inhalations with an AeroChamber [Monaghan Medical Corporation, Plattsburgh, NY]) was administered, and spirometry was repeated after 15 minutes. An additional treatment of 2 inhalations of albuterol was given if the FEV₁ did not increase to ≥90% of the prediluent value. If FEV₁ value was still <90% of the prediluent value, the supervising physician could take the appropriate medical action because the child could not be discharged from the clinic until the FEV₁ had returned to at least 90% of prediluent level. If the challenge was terminated after inhalation of 25 mg/mL dose and the child's FEV₁ was ≥ 90% of the prediluent value, a bronchodilator was not given. Data regarding occurrence and severity (per participant's assessment on a scale of none, mild, moderate, or severe) of symptoms were collected.

Before May 1994, stock solutions were prepared at individual clinics from generic methacholine crystals using phenol-buffered saline or saline with benzyl alcohol. From May 1994 to June 2001, the serial dilutions of methacholine were prepared quarterly by the University of Iowa College of Pharmacy and distributed by the Drug Distribution Center. Since June 2001, Provocholine (Methapharm Inc, Brantford, Ontario, Canada) has been used and dilutions prepared by individual sites. The solutions were stored in a refrigerator at about 4°C.

A total of 8118 methacholine provocations were performed in 1041 children (60% boys; 68% white) over an 11-year period. Detailed characteristics of the study participants are described elsewhere.⁸ Ages at the time of challenges were 5 to 9 years in 20.7% of challenges, 10 to 14 years in 49.9%, 15 to 19 years in 26.2%, and 20 to 24 years in 3.2%. Baseline mean (95% CI) FEV₁% predicted was 96.3 (95.9-96.4). Of the 8118 challenges, 24 were not completed (16 because of severe symptoms and/or refusal to continue, 5 because of calculation errors and software problems, 1 because of a fire alarm, and 2 with no specific reason provided). Eighty-three percent of the completed challenges had an FEV₁ PC₂₀ ≤ 12.5 mg/mL. Significant BHR was found for this group, with FEV₁ PC₂₀ geometric mean (95% CI) 1.40 (1.36-1.44) mg/mL.

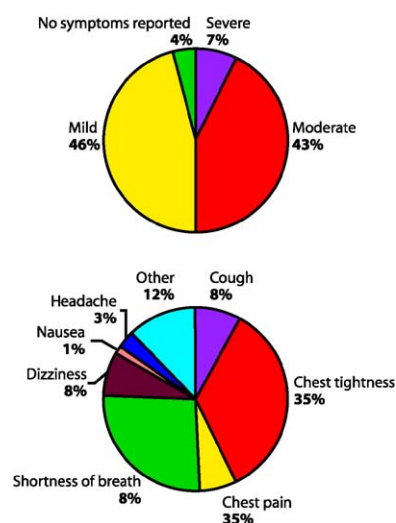


FIG 1. A, Distribution of positive (FEV₁ PC₂₀ ≤ 12.5 mg/mL) and incomplete methacholine challenges (N = 6745) by highest symptom severity reported. Severe: reported at least 1 severe symptom; Moderate: reported no severe and at least 1 moderate symptom; Mild: reported no severe nor moderate and at least 1 mild symptom. **B,** Types of symptoms reported as severe (N = 805) during positive and incomplete methacholine challenges (N = 6745). "Other" complications included wheeze, distal cyanosis, throat pain, tightness, itchiness, or dryness, fatigue or lethargy, increased phlegm or mucus or nasal congestion/pruritus, shakiness, itchy chin or eyes, lightheadedness, jaw sensation, muscle ache, stomach cramps, and visual problems.

No serious adverse events, such as death or transfer to an emergency facility, occurred. Albuterol and nebulized ipratropium bromide use (ie, for severe symptom relief or in addition to that mandated by the protocol when FEV₁ was <90% of prediluent value) was reported for 420 (5.2%) and 3 (0.0%) challenges, respectively. In 32 (0.4% of 7498 challenges with postreversal values) instances in which bronchodilator treatment did not reverse the FEV₁ to ≥90% of prediluent value, the mean ± SD FEV₁% recovery from the lowest value of the test to the value at discharge was 39.7% ± 20.2%. In only 5 challenges did the patients have an increase from the lowest to discharge of <20% (6, 10, 18, 18, 19). All were thought to be clinically well enough to be discharged.

In 7% of the positive (FEV₁ PC₂₀ ≤ 12.5 mg/mL) and incomplete challenges, participants reported having at least 1 severe symptom (Fig 1, A). Chest tightness, shortness of breath, and cough made up the majority of symptoms reported as severe (Fig 1, B). Other events reported as severe were wheeze, distal cyanosis, throat pain, tightness, itchiness, or dryness, fatigue or lethargy, increased phlegm or mucus or nasal congestion/pruritus, shakiness, itchy chin or eyes, lightheadedness, jaw sensation, muscle ache, stomach cramps, and visual problems. The participant with "distal cyanosis" noted by staff received 3.12 mg/mL dose; baseline and test FEV₁% predicted were 105 and 82 with an improvement to 100 after albuterol. He had 4 subsequent uneventful challenges later in the study.

There was no significant difference in mean (95% CI) prebronchodilator FEV₁% predicted (96.7 [95.8-96.4] vs 96.1 [95.8-96.4], respectively; $P = .2$) between challenges in which patients reported any severe symptom ($n = 552$) and those in which patients did not ($n = 7566$). The difference in percent FEV₁ drop at the time of a positive test between the 2 groups was statistically significant (29.4 [28.7-30.1] vs 27.1 [26.9-27.3], respectively; $P < .0001$), but small.

Evaluation of BHR can be well tolerated based on the safety profile from this multicenter study of more than 8000 methacholine challenges performed over a period of 11 years in children with mild to moderate asthma, using a standardized protocol. No serious outcomes occurred, and in only 0.4% of challenges did the patients not reverse to $\geq 90\%$ of baseline FEV₁% predicted values after a bronchodilator treatment. Severe symptoms were reported in only 7% of the positive and incomplete challenges. These symptoms were not unexpected in bronchoprovocation challenges and are easily reversible.

Ronina A. Covar, MD^a
Ryan Colvin, MPH^b
Gail Shapiro, MD^c
Robert Strunk, MD^d

From ^athe National Jewish Medical and Research Center, 1400 Jackson Street Denver, CO 80206; ^bthe Johns Hopkins Center for Clinical Trials, Baltimore, Md; ^cNorthwest Allergy and Asthma Center, Seattle, Wash; and ^dSt Louis Children's Hospital, St Louis, Mo.

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