

TABLE I. Dose of budesonide and type of adverse effects

	Age (y)	Maintenance dose of budesonide	Dose of budesonide when adverse effects were reported	Adverse effect reported
1	2:4	100 µg × 1	200 µg × 4	Irritability, depression
2	5:0	200 µg × 1	200 µg × 4	Aggressiveness
3	4:0	100 µg × 2	>200 µg	Anger
4	3:0	—	200 µg × 4	Aggressiveness, excitability
5	2:3	200 µg × 1	200 µg × 2	Mood changes
6	5:0	200 µg × 1	200 µg × 4	Aggressiveness, excitability
7	4:10	200 µg × 2	200 µg × 4	Enuresis, hyperactivity
8	1:6	200 µg × 1	200 µg × 2	Hyperactivity, unrest
9	1:10	200 µg × 1	200 µg × 4	Hyperactivity, attention deficit

insufficiency.¹¹ Neuropsychologic changes are probably uncommon, but clinical experience tell us that it might not be rare in preschoolers. The relatively high number of adverse reports to the Pharmacovigilance Unit at the Medical Product Agency and our findings that 15% of the children in a prospective asthma study reported these kinds of adverse symptoms strengthens this notion. It is also obvious that if this phenomenon does exist, it is dose related. The children in this study could be treated effectively with a low dose of inhaled corticosteroids, often in combination with chromolyns, antileukotrienes, and/or β_2 -agonists without side effects.

A double-blind provocation study would be necessary to prove the possible connection between inhaled corticosteroids and neuropsychologic disturbances in preschool children, but this has up to now not been performed.

Carl-Axel Hederos, MD

Primary Care Research Unit, VC Gripen

Box 547

651 12 Karlstad

Sweden

E-mail: carl-axel.hederos@liv.se

REFERENCES

1. Satel SL. Mental status changes in children receiving glucocorticoids. Review of the literature. *Clin Pediatr* 1990;29:382-7.
2. Lewis LD, Cochrane GM. Psychosis in a child inhaling budesonid. *Lancet* 1983;2:634.
3. Meysboom RH, de Graaf-Brederveld N. Budesonide and psychic side effects. *Ann Intern Med* 1988;109:683.
4. Connet G, Lenney W. Inhaled budesonid and behavioural disturbances. *Lancet* 1991;338:634-5.
5. Melin A. Psychological disturbances as adverse effects of inhaled corticosteroids [in Swedish]. Information från Läkemedelsverket (Information from the Medical Products Agency in Sweden). 1998;4:34.
6. Stores G, Ellis AJ, Wiggs L, Crawford C, Thomson A. Sleep and psychological disturbance in nocturnal asthma. *Arch Dis Child* 1998;78:413-9.
7. Hadjikoimi I, Loader P, Bracken M, Milner AD. Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002;86:202-3.
8. Bender B, Milgrom H. Neuropsychiatric effects of medications for allergic diseases. *J Allergy Clin Immunol* 1995;95:523-8.
9. Bender BG, Iklé DN, DuHamel T, Tinkelman D. Neuropsychological and behavioural changes in asthmatic children treated with beclomethasone dipropionate versus theophyllin. *Pediatrics* 1998;101:355-60.
10. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.

11. Sim D, Griffiths A, Armstrong D, Clarke C, Rodda C, Freezer N. Adrenal suppression from high-dose inhaled fluticasone propionate in children with asthma. *Eur Respir J* 2003;21:633-6.

doi:10.1016/j.jaci.2004.03.045

Interpretation of isolated positive skin test results for mesquite tree pollen

To the Editor:

Skin testing is an essential part of the evaluation of patients with suspected IgE-mediated diseases such as allergic rhinitis. Positive skin tests are supposed to represent the presence of specific IgE antibodies to the allergens tested. IgE antibodies to specific allergens can also be detected by *in vitro* assays such as ImmunoCAP (Pharmacia Diagnostics, Uppsala, Sweden). There is a general tendency to make IgE antibodies (and have multiple positive skin tests) or not. Thus, it is unusual to see skin testing results positive for only a single allergen. We noted that we often see patients whose only positive skin test result is to mesquite pollen. This is particularly striking because mesquite trees are very rare in our location. We test for this pollen nonetheless because our military population moves frequently around the country and the world. In contrast, olive tree is thought to be our most allergenic tree pollen and is very common in our location, yet we seldom see olive tree as the sole positive skin test result. There are at least 2 possible explanations for these isolated positive skin test results to mesquite: either mesquite pollen is particularly allergenic, or the allergenic extract of mesquite pollen used for skin testing is capable of causing a non-IgE-mediated skin reaction, either direct mast cell degranulation or an irritant response. Knowing the likelihood of each of these possibilities would allow clinicians looking at an isolated positive skin test result to mesquite to determine the likelihood that it represented a true-positive result.

Consecutive full aeroallergen skin test panels (consisting of 6 grasses, 15 trees, 11 weeds, 8 molds, cat, dog, cockroach, and 2 dust mites) in our clinic were reviewed to determine how often mesquite was the only positive skin test result of any kind, how often mesquite was the only positive pollen skin test result but with some other nonpollen aeroallergen positive, and how often mesquite

TABLE I. Comparison of skin test and ImmunoCAP results

Skin test results	n	%	Mesquite	Olive	ImmunoCAP results		
					Drawn	Positive	%
Mesquite only positive	22	2.3	+	—	10	0	0
Mesquite only positive pollen	18	1.9	+	—	11	0	0
Mesquite only positive tree	39	4.1	+	—	16	1	6
Olive only positive	4	0.4	—	+	2	2	100
Olive only positive pollen	3	0.3	—	+	1	0	0
Olive only positive tree	32	3.4	—	+	10	5	50
Mesquite positive, olive positive, other tree positive or negative	162	17.2	+	+			
Positive for mesquite					12	4	33
Positive for olive					12	9	75
Mesquite positive, olive negative, other tree positive	85	9.0	+	—			
Mesquite negative, olive positive, other tree positive	78	8.3	—	+			
Mesquite negative, olive negative, other tree positive	110	11.7	—	—			
All tree negative, other pollen positive	144	15.3	—	—			
All pollen negative, other aeroallergen positive	103	10.9	—	—			
All aeroallergen negative	141	15.0	—	—			
Total skin test panels	941		326 35%	279 30%			

was the only positive tree pollen skin test result but with some other nontree pollen positive. As control groups, we similarly determined how often olive tree was the only positive skin test result, only positive pollen, or only positive tree pollen, and how often both mesquite and olive tree pollens were positive with or without other positive skin test results. Subjects whose skin tests met these criteria were asked to consent to having blood drawn for a confirmatory ImmunoCAP test. The skin test results and *in vitro* test results were compared. The skin test panels reviewed covered a period when extracts from 2 different manufacturers (Hollister-Steir, Spokane, Wash, and Greer, Lenoir, NC) were used. *Prosopis juliflora* var *glandulosa* was the source for the mesquite pollen from both skin test extract manufacturers as well as the ImmunoCAP. Similarly, *Olea europaea* was the source for the olive tree pollen extracts for both *in vivo* and *in vitro* studies.

Nine hundred forty-one consecutive skin test panels were reviewed (Table I). Overall, 326 (35%) were positive for mesquite, and 279 (30%) were positive for olive tree. Twenty-two (2.3%) had mesquite as the only positive skin test result. Eighteen (1.9%) had mesquite as the only positive pollen but had some other, nonpollen aeroallergen positive. The corresponding numbers for olive tree pollen were 4 (0.4%) and 3 (0.3%), $P < .001$ for both compared with mesquite. When the positive mesquite skin test result was isolated—that is, was the only positive skin test result, only positive pollen, or only positive tree pollen—this result was virtually never supported by a positive ImmunoCAP result. Although the finding of a similarly isolated positive skin test result to olive tree pollen was much less frequent, when it did occur,

this result was much more often supported by a positive ImmunoCAP result. When a positive skin test result was found to both mesquite and olive tree, the mesquite was more likely to be supported by a positive ImmunoCAP result, but still only half as often as olive tree.

The possibility that the isolated positive skin tests to mesquite pollen were a result of a defective lot of extract was considered; however, the rate of isolated positive skin test results to mesquite extract was similar during periods when extracts from either manufacturer were used (data not shown). The possibility that the ImmunoCAP might simply not be able to detect specific IgE antibody to this particular allergen was considered. However, the manufacturer states that they assay each lot of each allergen with positive control sera to ensure allergen uptake. Further, the fact that a small number of positive mesquite skin test results in the present study were confirmed by positive ImmunoCAP results suggests that the test has the capacity to detect specific IgE antibodies to mesquite. *In vitro* assays for specific IgE antibody have generally been considered somewhat less sensitive than skin tests. This may be a result of the waning of serum IgE levels while mast cells still have IgE bound to their surface receptors. However, there is no reason to think that this phenomenon would apply more to mesquite pollen than to other extracts. The possibility that there could be cross-reactivity with acacia, a pollen related to mesquite but not used in our skin test panel, was evaluated. None of the sera evaluated from subjects with positive skin test results to mesquite were positive on ImmunoCAP testing to acacia. However, an as yet unidentified cross-reactivity remains a possible explanation.

A previous study of the prevalence of sensitization to aeroallergens in California found mesquite to be the second most commonly positive tree pollen skin prick test result, in 36.4% of those tested (olive tree pollen was most common, at 42.4%).¹ Another study specifically in Southern California found mesquite to be the most common positive pollen skin prick test result, at 42% (in the same study, olive tree was 28%).² The authors of this second study found positive RASTs, but only if the mesquite pollen extract was concentrated, and positive nasal challenges in those with positive skin tests. They acknowledged that the nearest mesquite trees were 50 miles away from the study site, but found pollen resembling mesquite in local air samples. Published reports of air sampling in San Diego, Calif, show olive tree pollen but no mesquite pollen.³ Another possible route of sensitization is inhalation of mesquite wood smoke or the ingestion of food cooked over burning mesquite wood.⁴ However, regardless of the route or method of sensitization, if a positive skin test result to mesquite represents the presence of IgE antibody, this antibody should be demonstrable *in vitro*. The frequency of isolated positive skin test results to mesquite pollen, and their lack of confirmation by ImmunoCAP, in the present study suggest that these positive skin test results represent non-IgE-mediated reactions. A previous animal study demonstrated "...the histamine-releasing activity of extracts of ... pollens in the skin of guinea pigs which are not sensitized with the pollens. ..."⁵ The pollen extract most capable of causing this direct mast cell degranulation was mesquite. Mesquite pollen also contains unique peptidases (peptidase IIms),⁶ which could possibly alter mast cell biology.

In summary, despite the fact that there is olive tree pollen but no mesquite pollen in the air in San Diego, as many people have positive skin test results to mesquite pollen as to olive tree pollen, and mesquite comes up as an isolated positive skin test result much more often than olive tree. Most such isolated positive skin tests to mesquite pollen are not substantiated by a positive *in vitro* specific IgE (ImmunoCAP) to mesquite pollen. We conclude that when mesquite tree pollen results in an isolated positive skin test result, it likely represents a false-positive result. In some patients, this allergen extract apparently has the ability to cause direct mast cell degranulation. Whether by an IgE-mediated mechanism or by direct mast cell degranulation, in areas of the country or world where mesquite pollen is actually present in the air, contact could presumably result in mast cell-mediated symptoms.

John M. Kelso, MD
Allergy Division
Naval Medical Center
San Diego, CA 92134-5000

The Chief, Navy Bureau of Medicine and Surgery, Washington, DC, Clinical Investigation Program sponsored this study (S-03-084) as required by NSHSBETH 6000.41B. The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government.

REFERENCES

- Galant S, Berger W, Gillman S, Goldsobel A, Incaudo G, Kanter L, et al. Prevalence of sensitization to aeroallergens in California patients with respiratory allergy. Allergy Skin Test Project Team. *Ann Allergy Asthma Immunol* 1998;81:203-10.
- Novey HS, Roth M, Wells ID. Mesquite pollen—an aeroallergen in asthma and allergic rhinitis. *J Allergy Clin Immunol* 1977;59:359-63.
- Street DH, Hamburger RN. Atmospheric pollen and spore sampling in San Diego, California, I: meteorological correlations and potential clinical relevance. *Ann Allergy* 1976;37:32-40.
- More D, Whisman L, Whisman B, Jordan-Wagner D. Identification of specific IgE to mesquite wood smoke in individuals with mesquite pollen allergy. *J Allergy Clin Immunol* 2002;110:814-6.
- Imamura T, Di Virgilio S, Bagarozzi DA Jr, Matheson N, Travis J. Induction of histamine release from non-immunized guinea pigs: a possible involvement of lectin-like factor(s) in pollinosis. *Int Arch Allergy Immunol* 1996;111:161-5.
- Matheson NR, Travis J. Purification and characterization of a novel peptidase (IIms) from mesquite (*Prosopis velutina*) pollen. *J Biol Chem* 1998;273:16771-7.

doi:10.1016/j.jaci.2004.05.011

Latex allergens are not detectable in reconstituted smallpox vaccine or vaccine vial stoppers

To the Editor:

In December 2002, plans to immunize military personnel, first responders, health care workers, and public health workers against smallpox were released. The Centers for Disease Control and Prevention (CDC) developed smallpox vaccination guidelines stating that smallpox vaccine should not be administered to individuals with a history of latex allergy because of possible release of latex allergens from rubber vial stoppers into smallpox vaccine (<http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/smallpox-vax-clinic-guide.pdf>; accessed May 2004). Concerns have been expressed about the potential for latex allergen exposure from natural rubber stoppers in vaccine vials, including smallpox vaccine, and the possibilities of latex sensitivity after vaccine administration. Because no information is available regarding the actual composition of smallpox vaccine vial stoppers (natural rubber vs synthetic rubber) and because we were unable to find any data relating to latex allergy and smallpox vaccine, we investigated whether such latex allergens could be identified in reconstituted smallpox vaccine.

Smallpox vaccine (Dryvax; Wyeth Laboratories, Marietta, Pa) is provided as a lyophilized multidose vaccine (100 dose vials) that must be reconstituted. The vaccine diluent is a 50% glycerol and 0.25% phenol solution that contains trace amounts of neomycin, streptomycin, polymyxin B, and chlortetracycline. The vaccine is ideally stored at 2°C to 8°C and, once reconstituted, should be used within 15 days. Reconstitution is performed by drawing up the vaccine diluent provided with the vaccine and injecting the diluent into the vaccine vial after cleaning the vial stopper with an alcohol wipe and allowing it to dry.

After obtaining permission from the CDC to use only one recently outdated and reconstituted vial of smallpox