

A statement made in the Discussion, “PEAK therefore has the potential to examine the atopic and asthmatic characteristics of a high-risk cohort with frequent intermittent wheezing episodes who are likely to have persistent asthma,” contrasts with a later statement: “PEAK cohort represents a cohort similar to the CAMP cohort but before persistent asthma has developed.” Has persistent asthma developed or not?

The information presented in this article will be of critical importance. However, we thought the inconsistencies noted distracted from the critical message of the article and left us guessing about some of the details of the study design.

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Reply

To the Editor:

We thank Dr Hopp¹ for his thoughtful response to our recent article, which allows us to explain the intent of our study better. He raises 2 main objections concerning the inclusion of modified asthma predictive index (mAPI) characteristics in the Results section and whether the children enrolled in the study have persistent asthma.

The original asthma predictive index (API) was based on data from the Tucson Children's Respiratory Study (TCRS).^{2,3} The API included frequent wheezing in the first 3 years of life and either 1 major risk factor (parental history of asthma or personal history of atopic dermatitis) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis).³ Because allergic rhinitis can be difficult to diagnose in young children without immunologic confirmation, the published API was modified for use in the Prevention of Early Asthma in Kids (PEAK) study (mAPI) to include allergic sensitization to aeroallergens as a major criterion and substitute for allergic rhinitis. Food sensitization was added as a minor criterion because its presence has been reported to be predicted for the development of asthma (references in article). The analysis in this article focused on the API and mAPI major criteria, which are the same for both indices: a parental history of asthma, a personal history of atopic dermatitis, or both. Because the children were enrolled in PEAK based on a mAPI, not the original API, we thought it was more accurate to use mAPI within the results section. This designation also allows us to report the frequency of all 3 major criteria of the mAPI within the cohort.

Regarding the second comment, persistent wheeze is defined in the TCRS as wheeze that was present in both the

first 3 years of life and at 6 years. It does not, however, imply persistent asthma symptoms as described in the National Asthma Education and Prevention Program guidelines. Thus, intermittent wheezing in the preschool years can represent many different disease phenotypes, and intermittent wheezing by itself does not predict which children will have continuation or persistence of wheezing in the older school years. If fact, 60% of children who begin wheezing at age younger than 3 years will outgrow their disease by age 6 years (transient wheezers) and an additional 20% by age 13 years (nonatopic wheezers).^{2,4} Thus, a physician diagnosis of asthma alone does not necessarily identify children who will continue to wheeze during the school years. The children in this cohort also had an average onset of wheezing at age 11.2 months (Unpublished data, Guilbert TW, November 2004). Their disease cannot be considered persistent because they still may outgrow their wheezing symptoms by age 6 years. However, using the TCRS data, the API identifies children at 4.3 to 9.8 times the risk of having continued wheezing or asthma during the school years.³ The children enrolled in the PEAK study have wheezing that is episodic and of short duration; thus, we must conclude that they do not yet have persistent disease but are at high risk to develop it.

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β -Blockers and anaphylaxis: Are the risks overstated?

To the Editor:

In the recent updated practice parameter for the diagnosis and management of anaphylaxis, the panel states that

although no epidemiological studies indicate that anaphylaxis occurs more frequently in patients with β -blockers (BBs), there is an observed risk for more serious anaphylaxis in patients receiving BBs.¹

The panel references several individual case reports of patients on BB who had severe anaphylaxis with poor response to epinephrine therapy as measured by persistent hypotension and, in some cases, profound bradycardia. Of interest, in one of the case reports, the patient was given the wrong dose of allergy extract, receiving a 1:20 dilution instead of the prescribed dose of 1:20,000.² The authors incriminate BB for these responses without any case-controlled studies to support their conclusions. By definition, all cases of fatal anaphylaxis must be epinephrine non-responsive, and most cases of fatal anaphylaxis occur in patients not receiving BB. Certainly, administering a dose of allergen extract 1000 times stronger than recommended could play the major role in the severity of the reaction in that patient. Thus, the incrimination of BB for causing more severe anaphylaxis in humans seems unsupported by the evidence at this time because it is based on individual case reports with no control group for comparison.

In a 1980 study, Smith et al report the physiologic manifestations of anaphylaxis in 2 venom-sensitive subjects who developed severe anaphylaxis with profound hypotension after laboratory-induced hymenoptera stings in the intensive care setting.³ The authors concluded that even high concentrations of epinephrine (7 mg intravenously in one patient and 3.5 mg intravenously in the other) did not initially reverse the hypotension. They speculate on reasons the subjects were not responsive to epinephrine. They conclude that "it was difficult to evaluate the effectiveness of our own intervention in the patients with shock. Indeed we do not know whether the medical treatment affected either the recovery time or ultimate outcome. The length of time between our therapeutic interventions and a significant clinical response suggests to us the disturbing possibility that there might be no ideal therapy for severe anaphylaxis even under optimal conditions."

Because refractory anaphylaxis by definition is epinephrine non-responsive, then epinephrine non-responsiveness of anaphylactic patients on BB should not be attributed to the BB unless one is able to demonstrate, through controlled studies, an increase in frequency and/or severity of anaphylactic reactions compared with controls not on BB.

Four controlled studies address the risk of BB in anaphylaxis, and all show no increased frequency or severity of anaphylaxis in patients on BB. The panel failed to cite the study by Hepner et al, which I believe is the longest and largest prospective study comparing the frequency of anaphylactic reactions in patients on immunotherapy with and without concurrent BB. In this study, the frequency of systemic reactions to immunotherapy among 68 patients on BB therapy was compared with that of 3110 patients not on BB who received allergen immunotherapy for a year. Their study concluded that BB did not increase the frequency of systemic reactions in patients receiving immunotherapy. In fact, the frequency of systemic reactions was actually less than expected compared

with the control group. There was only 1 reaction during the year among the 68 patients on BB, and this reaction was easily reversed. They concluded that BB agents as normally used in clinical practice do not increase the frequency of systemic reactions in patients receiving immunotherapy, but they could not draw a conclusion regarding the severity of the reactions because only 1 reaction occurred in the BB group.⁴

A prospective study by Greenberger et al⁵ did not show an increase in anaphylaxis in patients who received radiographic contrast media for cardiac angiography while on BB.

A recent retrospective analysis by Muller et al⁶ comparing the risk of venom immunotherapy (VIT) in patients with cardiovascular disease with and without BB did not find an increased, but instead a slightly lower, although not significant (12% BB vs 16.7% control), incidence of systemic allergic reactions during VIT injections. In addition, the reactions that did occur were not more severe than in the control group, and patients receiving BB were able to continue VIT.

Is anaphylaxis more severe in patients on BB? A study by Alam et al⁷ at the Cleveland Clinic (which may not have been available to the consensus panel at the time of its publication) reported the outcomes of treatment of anaphylaxis in patients on and off BB at the time of anaphylaxis. Surprisingly, they found the time required to resuscitate the patients on BB was actually significantly shorter than that required for the patients not on BB. They found no significant difference between the 2 groups for surviving resuscitation, 1-month survival, and length of hospital stay. The fatality rate of patients receiving BB was 3%, whereas the fatality rate of those without BB was 8.5%. However, because of sample size, the difference in fatality rates was not statistically significant.

Thus, the best medical evidence available indicates that there is not an increase in the frequency or severity of anaphylaxis in patients receiving BB when given inhalant and venom allergy injections and radiographic contrast media.

Therefore, it appears that the practice parameter statement (p S515) that patients receiving BB are at increased risk for more serious anaphylaxis, thus making BB therapy a relative contraindication for allergen immunotherapy, is based on theory and not evidence-based medicine. There is a historic parallel regarding BB use in congestive heart failure. In the 1970s, BBs were contraindicated in congestive heart failure on theoretical considerations only. Their use at that time would have been considered medical malpractice. Today, based on medical evidence, BBs are found to reduce the mortality of patients with congestive heart failure and thus have become the standard of care for such patients.⁸ It is thought that the BBs reduce mortality in congestive heart failure by decreasing fatal cardiac arrhythmias. Is it possible that BBs could also be protective in anaphylaxis? Is it possible that ventricular fibrillation is the defining fatal event in anaphylaxis and BBs may help prevent that? With the current evidence available, this remains a consideration.

Why is it so important to the clinician that this practice parameter includes the controlled studies mentioned instead of relying on theory or single case reports? BBs now have so many medical benefits (vascular headaches, congestive heart failure, atherosclerotic heart disease, hypertension, benign essential tremor, and so forth) that they are used in a significant percentage of the population. Similarly, allergy immunotherapy is useful in a significant portion of the population with allergy.

To deny the concurrent use of BB and allergen immunotherapy on the basis of theoretical considerations or individual case reports when the evidence from the best clinical studies shows no increased risk to the population seems unnecessarily overly cautious. In addition, it poses a medical-legal risk to physicians that does not appear to be justified. We believe the panel should reconsider its position regarding BB and allergen immunotherapy to at least state that at this time, there is no evidence to show increased risk and severity of anaphylactic reactions in patients on BB. In fact, the best evidence at this time seems to indicate no increase in severity and frequency of anaphylaxis in patients receiving BB. We should not allow theory to trump evidence from controlled studies.

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Reply

To the Editor:

We thank Drs Michael and Martin Miller¹ for their thoughtful comments. To begin a response, it would probably be best to look first at the references they cited to support their contention that β -blockers do not represent a relative contraindication to the administration of immunotherapy.

The most recent of these was the article by Muller and Haeberli² which looked at the risk of venom immunotherapy in patients with cardiovascular disease taking β -blockers. We believe that the analysis of this article by Drs Miller and Miller¹ is incorrect. In fact, if one reads the discussion of the article, the authors of the study come to the same conclusion as did our guidelines. In fact, the intention of the article, as opposed to the interpretation by Drs Miller and Miller,¹ was not to assess the risk per se of β -blockers in patients receiving venom immunotherapy, but to see whether patients who could not be taken off β -blockers and who were in need of immunotherapy could be administered the therapy safely.

It should be noted that the authors state quite clearly they were looking at a subgroup of patients who absolutely required the administration of both treatments. In fact, it was the authors' first choice to discontinue a β -blocker where possible. In their study, 44 patients were on β -blockers at the time of their visit to the clinic for evaluation and treatment of a systemic reaction to an insect sting. In 31 of these patients, the β -blocker was replaced by another drug. In 26 of these, it was their recommendation to replace the β -blocker, and in the other 5, the decision was made by the family practitioner. In 9 others, the β -blocker was stopped during dose increase and then reintroduced when the maintenance dose was reached. In 4 patients, 3 with coronary heart disease and 1 with a severe ventricular arrhythmia, it was considered too risky to stop the β -blocker. They then began venom immunotherapy according to an ultrarush protocol over a period of 4.5 hours "under close monitoring of electrocardiogram, blood pressure, and respiration in the Intensive Care Unit for 24 hours."

The other patients taking β -blockers during their study had been newly started on β -blocker treatment during maintenance therapy with venom. The authors further state, "theoretical and clinical evidence for a risk of severe and difficult to treat allergic reactions, favored by the use of beta-blockade during immunotherapy, is certainly strong," and they cite several references to substantiate this statement. Furthermore, in conclusion, they state, "we think that the contraindication for beta-blocker use during venom immunotherapy should not be considered as absolute, but as a relative (contraindication), as was already proposed in a recent World Health Organization document on specific allergy vaccination." Thus, the authors' own conclusions were identical to those of the updated guidelines—specifically, that use of β -blockers is a relative contraindication to immunotherapy.

Another study cited by Drs Miller and Miller¹ was a prospective study by Greenberger et al³ that did not