

Local reactions during allergen immunotherapy do not require dose adjustment

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Background: The recent World Health Organization position paper on allergen immunotherapy states that local reactions to immunotherapy are not predictive of subsequent systemic reactions. Nevertheless, in clinical practice dose adjustment after local reactions continues to be recommended, presumably in an effort to prevent future systemic reactions.

Objective: We sought to determine whether dose adjustment versus no adjustment for local reactions during allergen immunotherapy influences the occurrence of subsequent systemic reactions.

Methods: In a single-site allergy clinic before October 1, 1997, local reactions after allergen vaccine injection resulted in adjustment of the subsequent dose. After October 1, 1997, no dose adjustments were made for immediate and late local reactions. For the same 9-month period before and after the change in local reaction dose-adjustment policy, systemic reaction rates were compared retrospectively. For individuals experiencing a systemic reaction, local reaction rates and local reactions immediately preceding a systemic reaction were also compared before and after the policy change.

Results: Comparing the 9-month period (October 1996-June 1997) preceding the policy change and the 9 months (October 1997-June 1998) after the change in policy, the systemic reaction rates (0.80% and 1.01%, respectively) were not statistically different ($P = .24$). Among those experiencing a systemic reaction, the rate of local reactions was unchanged (7.3% and 4.7%, respectively; $P = .07$), and the rate of local reactions immediately preceding a systemic reaction did not increase (18.8% and 10.5%, respectively; $P = .37$). The sensitivity of a local reaction predicting a systemic reaction at the next immunotherapy dose was 15%.

Conclusions: A local reaction is a very insensitive predictor for a subsequent systemic reaction at the next allergen vaccine dose. Dose adjustment for most local reactions is unnecessary and may delay therapy, increase costs, and put the patient at increased risk of dose administration errors. (*J Allergy Clin Immunol* 2000;106:840-3.)

Key words: Allergen vaccine, immunotherapy, anaphylaxis

Local reactions associated with allergen immunotherapy are a common occurrence and are defined as reactions occurring in the immediate vicinity of the injection site.¹⁻³ The frequency of local reactions reported in prior studies has ranged from 26% to 82% in patients during a course of immunotherapy, with a 0.7% to 4.0% local reaction rate per 100 injections.⁴⁻⁶ Supported by a single peer-reviewed study,⁴ both the 1998 World Health Organization position paper on allergen immunotherapy¹ and the allergy textbook edited by Middleton et al² state that local reactions after immunotherapy are not predictive of subsequent systemic reactions. Nevertheless, many allergists continue to recommend immunotherapy dose reductions in response to local reactions, presumably in an effort to prevent future systemic reactions. Such dose adjustments for local reactions may delay progression to maintenance therapy, increase dosing errors, and introduce additional injections and patient visits, all of which may potentially hamper patient compliance and increase the costs of allergen immunotherapy. The goal of this study was to determine whether dose adjustment versus no adjustment for local reactions during allergen immunotherapy influenced the occurrence of subsequent systemic reactions.

METHODS

In our single-site allergy clinic, we undertook a retrospective study over a total 18-month period. Before October 1, 1997, local reactions after allergen vaccine injection resulted in adjustment of the subsequent dose to be administered as follows: (1) immediate 15- to 19-mm swelling: repeat the same dose; (2) immediate 20- to 25-mm swelling: repeat the last dose that caused no reaction; (3) immediate greater than 25-mm swelling or any swelling persisting longer than 12 hours: decrease dose by 50%. After October 1, 1997, no dose adjustments were made for immediate and late local reactions unless the reaction was larger than the palm of the patient's hand (adult, 8-10 cm) or caused the patient significant discomfort. In these cases any dose reduction was individualized.

Each suspected systemic reaction^{1,2} after immunotherapy, as well as the subsequent treatment, was documented by using a standard format and reviewed as part of an ongoing quality assurance program. Rates of systemic reactions were calculated monthly. Systemic reaction rates were then compared for the same 9-month period before (October 1996-June 1997) and after (October 1997-June 1998) the change in local reaction dose-adjustment policy. During this 18-month period, all other policies and procedures associated with administration of immunotherapy remained unchanged.

The immunotherapy injection record of each patient who had experienced a systemic reaction during either of the two 9-month periods was reviewed retrospectively. For each patient, the local reactions occurring during the 10 vaccine injections preceding the

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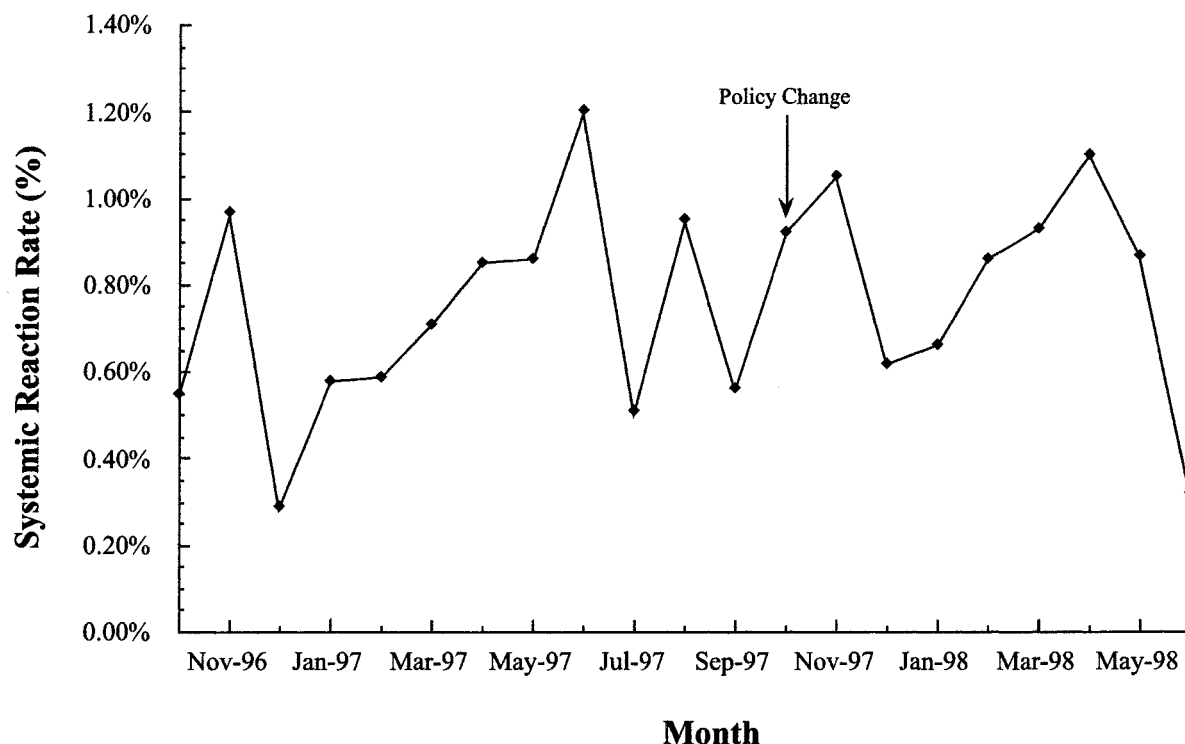


FIG 1. Monthly rates of systemic reactions after allergen vaccination. Dose adjustment for local reactions was discontinued on October 1, 1997.

systemic reaction were identified and characterized. Being the local reactions on which the dose-adjustment assumption rests, local reactions associated with the injection immediately preceding the injection that caused the systemic reaction were also catalogued and characterized separately.

The local and systemic reaction rates for the 9-month periods before and after the dose-adjustment policy change were analyzed by using the χ^2 test or the Fisher exact test. An α significance level of .05 was chosen for all comparisons. The sample size provided a power of 80% to detect a difference in systemic reaction rates as small as 0.6%.

RESULTS

Over 18 months, a total of 12,926 immunotherapy injections were given. Monthly rates of systemic reactions are shown in Fig 1. For the 9-month period (October 1996-June 1997) before the local reaction policy change, 65 systemic reactions occurred among the 8076 injections administered, for a systemic reaction rate of 0.80%. For the comparable period (Oct 1997-June 1998) subsequent to the policy change, 49 systemic reactions occurred among the 4850 injections administered (fewer injections during this period were a result of temporary extract shortages, which temporarily delayed the initiation of immunotherapy by some patients), for a systemic reaction rate of 1.01% (Table I). These systemic reaction rates were not statistically different ($P = .24$).

To evaluate the rate of local reactions immediately preceding a systemic reaction, a retrospective chart review was conducted among patients who experienced

systemic reactions during each of the two study periods (Table II). For the period before the policy change, 73.8% (48/65 systemic reactions) of the patient immunotherapy records were located. These records revealed an 18.8% (9/48) rate of local reactions immediately preceding systemic reactions. For the period after the policy change, 77.6% (38/49 systemic reactions) of the patient immunotherapy records were available for review. During this time, local reactions immediately preceded systemic reactions at a rate of only 10.5% (4/38). Although the percentage of systemic reactions after local reactions was decreased after the policy change, the difference did not reach statistical significance ($P = .37$). For the entire 18-month period, the sizes of local reactions that preceded systemic reactions (69% [1], 23% [2], and 8% [3], as described in the "Methods" section) were not as large as those that did not precede systemic reactions (51% [1], 33% [2], and 16% [3]).

By using the same immunotherapy injection records located for those patients experiencing systemic reactions, a total local reaction rate for each 9-month period was calculated (Table III). For the 9-month period before the policy change, the 48 patients under review experienced 50 local reactions over a total of 685 injections, for a local reaction rate of 7.3%. During the 9-month period after the policy change, the set of 38 patients had 25 local reactions over a total of 531 injections, for a local reaction rate of 4.7%. The local reaction rates during these two periods were not statistically different ($P = .07$). During the 18-month period, no local reactions were larger than

TABLE I. Systemic reaction rates per immunotherapy injection

	Oct 1996-June 1997 (dose adjustment)	Oct 1997-June 1998 (no dose adjustment)
Systemic reactions	65	49
Injections*	8076	4850
Systemic reaction rate†	0.80%	1.01%

*Injection counts were not adjusted for counting multiple injections at one clinic visit as a single injection, which was true for approximately 35% of patients receiving immunotherapy. Such an adjustment would decrease reaction rates proportionally.

† $P = .24$.

TABLE II. Systemic reactions preceded by a local reaction at the previous immunotherapy injection

	Oct 1996-June 1997 (dose adjustment)	Oct 1997-June 1998 (no dose adjustment)
Local reaction associated with injection previous to systemic reaction	9	4
Systemic reactions*	48	38
Systemic reaction with preceding local reaction†	18.8%	10.5%

*Retrospective data available for 48 (73.8%) of 65 and 38 (77.6%) of 49 systemic reactions.

† $P = .37$.

TABLE III. Local reaction rates per immunotherapy injection in patients experiencing a systemic reaction*

	Oct 1996-June 1997 (dose adjustment)	Oct 1997-June 1998 (no dose adjustment)
Local reactions	50	25
Injections	685	531
Local reaction rate†	7.3%	4.7%

*Retrospective data available for 48 (73.8%) of 65 and 38 (77.6%) of 49 systemic reactions.

† $P = .07$.

the palm of the patient's hand. It is of interest that in both study groups, individuals with systemic reactions had preceding local reactions at about twice their total local reaction rate (18.8% vs 7.3% before and 10.5% vs 4.7% after the policy change), and both differences were near significance ($P = .03$ and $.09$, respectively).

The percentage of all local reactions that were followed by a subsequent systemic reaction did not increase with the change from a dose-adjustment (9/50 [18%]) to a no-adjustment policy (4/25 [16%], $P = .85$). Overall, the sensitivity of a local reaction predicting a systemic reaction at the next dose was 15%, and the specificity of the absence of a local reaction predicting the absence of a systemic reaction was 95%. The positive predictive value of a local reaction for a subsequent systemic reaction was only 17%.

DISCUSSION

The frequency of systemic reactions was statistically unchanged after discontinuation of dose adjustment for local reactions after allergen vaccination (Fig 1 and Table I). Mean systemic reaction rates with and without the dose-adjustment policy were comparable with the clinic's historical systemic reaction rates, which have shown random variation but no seasonal trends in past years (data not shown). During the 2 years after the study periods, the systemic reaction rates under the no-adjustment policy remained stable at 0.96% (1998-1999) and 0.86% (1999-2000).

With or without dose adjustment, the frequency of local reactions among individuals with systemic reactions was unchanged (Table III). During the 18-month study period, a sample of 15 patients without systemic reactions had 41 local reactions during 449 allergen vaccine injections, for a local reaction rate of 9.1%. This rate is slightly greater but similar to that of the study group (Table III). Local reaction rates were similar to those reported previously by other investigators.^{4,7} In addition, the frequency of a local reaction preceding a systemic reaction was no greater without dose adjustment than with a dose-adjustment policy (Table II). Although local reactions preceding a systemic reaction occurred with slightly greater frequency than the overall rate of local reactions, they did not predict subsequent systemic reactions. The sensitivity of an immediately preceding local reaction as a predictor of a systemic reaction was only 15%, and the positive predictive value was only 17%. These conclusions contradict the underlying presumption for dose adjustment that a local reaction after immunotherapy injection requires a dose adjustment to avoid an increased risk of a subsequent systemic reaction.^{3,4}

Our results are in agreement with the most recent recommendations that local reactions to immunotherapy are not predictive of subsequent systemic reactions.^{1,2} In 1986, in the only prior study addressing this issue, Nelson et al⁴ described a prospective study of 416 patients who received 26,645 pollen vaccine injections. In this study the sensitivity of a local reaction at any time during therapy as a predictor of systemic reactions was 64%, the specificity was 1.2%, the positive predictive value was 12%, and the negative predictive value was 14%. Nelson et al concluded that local reactions were not predictive of patients having systemic reactions. This study differed from our current study in two respects: (1) during the study, a consistent dose-adjustment policy for local reactions was applied; and (2) statistical associations were calculated for any local reaction during therapy predicting a systemic reaction at any time during therapy rather than at the very next dose.

A dose-adjustment policy presumes the association of a local reaction with an increased risk of a subsequent systemic reaction at the next dose. By decreasing the next dose, it is assumed that the patient will be less likely to have a systemic reaction with that dose. By discon-

tinuing this policy, the current study was able to test this basic assumption for the dose-adjustment policy and found it to be false. After discontinuance, increases were not seen in either the systemic reaction rate or the frequency of local reactions preceding systemic reactions. An unstated corollary of the dose-adjustment policy is that dose adjustment will decrease the incidence of local reactions. This, too, proved to be false. In summary, a local reaction was a very insensitive predictor of a systemic reaction at the next injection of allergen vaccine.

A no-adjustment policy should result in fewer patient visits to achieve maintenance vaccine doses and thereby result in monetary savings, as well as increased patient compliance and satisfaction. Decreasing the emphasis on dose adjustment for local reactions should also result in fewer dosing errors in the subset of patients receiving two or more vaccines (35% of our patient population). Under a dose-adjustment policy, a local reaction often prompts dosing changes in only one of the vaccines. Thereafter, the patient would receive dissimilar doses, increasing the chance of a subsequent dosing error. Dissimilar doses, with their potential for error, are less likely to occur when adjustments are not made for local reactions to individual mixes.

In conclusion, in this 18-month evaluation, no difference was found in either systemic or local reaction rates when comparing dose adjustment to no adjustment for local reactions. Our findings suggest that allergen vaccine immunotherapy does not require dosing changes for most local reactions. This conclusion is in agreement with the 1998 World Health Organization guidelines for immunotherapy.

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