

HYPOSENSITIZATION THERAPY INCLUDING REPOSITORY: A DOUBLE-BLIND STUDY

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THE recent controversies over the efficacy of repository therapy for pollinosis have led to general re-evaluation of specific hyposensitization therapy of both the conventional aqueous type and the newer emulsion methods. Over the past two years we have attempted to evaluate these methods of therapy in a double-blind fashion only in previously untreated ragweed-sensitive patients. The experimental design and clinical results of these studies will be described.

METHODS

All patients from the Allergy Clinics of the Buffalo General and Children's Hospitals who had previously never received any injection treatments for their ragweed hay fever or asthma were chosen. Sensitivity to ragweed was established by strongly positive skin tests with a correlating history of symptoms during the pollinating season. These patients were then randomly divided into 3 groups known only to one of the authors.

Group I was composed of patients who were given injections of aqueous short ragweed pollen extract at weekly intervals, according to a predetermined schedule, and 2 saline placebo emulsions 8 and 4 weeks prior to the pollen season. The actual maximum dosage attained by aqueous injections just prior to the season varied from 2000 to 10,000 protein nitrogen units (PNU).

Group II received weekly placebo aqueous injections and also placebo emulsions at the same times as group I.

Group III received placebo aqueous injections weekly plus emulsions of whole ragweed extract 8 and 4 weeks prior to the onset of the ragweed pollen season. In 1961, the first repository dose was 500 PNU and the second 2500 PNU. In 1962, the first dose was also 500 PNU, and the second dose was 4000 PNU. All emulsions were made in a Brown Emulsor.* In 1961, a 1:9:10 ratio of Arlcel A, Drakeol VR6, and ragweed extract was used. In 1962 a 3.5:6.5:10

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*Manufactured by Andonian Associates, Waltham, Mass.

ratio was used. All emulsions were checked microscopically and by centrifugation before use. One-half milliliter of the emulsion was injected deep subcutaneously.

All injections were ordered by other physicians in the clinic, who did not know in which group each patient belonged. Each patient's extracts were in individual vials. Reactions of a local or systemic nature were noted and the subsequent dosage lowered if deemed necessary. All of the emulsions, placebo and ragweed, were given on the same days.

Other allergens were given as indicated during this time.

Each patient was given a symptom card on which he was instructed to record his daily symptoms and the amount of medication taken each day. Patients were seen each week prior to and during the pollen season. They were examined and their cards reviewed. Evaluation was done without knowledge of the type of therapy received.

Blood samples were obtained from each patient before the onset of treatment, prior to the first and second repository injections, and again just prior to the ragweed pollen season.

Hemagglutination antibody titers were determined by the tanned cell technique¹ with a "purified"* fraction of ragweed pollen as the coating antigen² and reagin titers obtained by the standard passive transfer technique.

RESULTS

We had available for final evaluation 20 untreated ragweed-sensitive patients in 1961 and 39 previously untreated ragweed-sensitive patients in 1962. There was a total of 41 children (under age 16) and 18 adults. The clinical response was divided simply as satisfactory or unsatisfactory. This was based upon the physician's judgment following interviews and examinations of the patients and review of the symptom cards. It will be noted from comparing 1961 and 1962 in Table I that there were only slight changes in the general results. Aqueous therapy appeared to be quite effective, with good results obtained in about 75 per cent of the patients. These clinical results could not be correlated with the amount of aqueous extract received. The placebo and repository groups were comparable, and the totals for the 2 years came out exactly the same. Eleven of 19 patients in both groups responded satisfactorily. There was no essential difference in the results occurring in patients with hay-fever or asthma.

There was a good correlation between the evaluation of the clinical response by the examining physicians and the patients' records of symptoms and medication as kept on the daily symptom card. For example, in the 1962 group, 31 of the 39 patients returned their cards. In only one instance was there disagreement between the clinical impression and the recorded results.

In 1961, 2 patients complained of local soreness and swelling following placebo emulsions. Another patient stated that she had a generalized rash and swelling of her hands for 3 days following placebo repository administration.

*The "purified" fraction "pool C" was obtained through the courtesy of Dr. A. R. Goldfarb.

TABLE I. CLINICAL RESPONSE OF PATIENTS IN THE DOUBLE-BLIND STUDY

THERAPY	CLINICAL RESPONSE	
	SATISFACTORY	UNSATISFACTORY
Repository	11	8
1961	3	3
1962	8	5
Aqueous	16	5
1961	6	1
1962	10	4
Placebo	11	8
1961	4	3
1962	7	5

TABLE II. EFFECT OF THERAPY UPON THE TANNED CELL HEMAGGLUTINATION TITER. TITERS COMPARED PRIOR TO TREATMENT AND JUST PRIOR TO POLLEN SEASON, FOLLOWING FULL COURSE OF THERAPY

THERAPY	HEMAGGLUTINATION TITER	
	INCREASE*	SAME
Repository	8	5
Aqueous	7	8
Placebo	2	11

*At least a fourfold increase.

Following ragweed repository injections in 1961, there were 2 systemic reactions, 1 mild local reaction, and 2 local abscesses. One of these abscesses developed several weeks after the emulsion administration, but the other occurred about 3 months later, after the study had been completed. There were no reactions, either local or systemic, following aqueous therapy during that year. In 1962, following ragweed emulsion administration, there were only 1 systemic reaction and 3 mild local reactions. One patient claimed to wheeze for 1 week after placebo emulsion and aqueous injections. Two other patients had systemic reactions following aqueous placebo administration along with other pollen allergens. Therefore, it was only in a few instances that the examining physicians were aware of the type of therapy administered. The evaluation of the clinical results, however, was determined by one of us (C. E. A.) who did not have the information regarding systemic or local reactions.

The results of tanned cell hemagglutination studies are shown in Table II. Following repository therapy, 8 of 13 patients had a fourfold or greater increase in their hemagglutination titers. The titers of 7 of 15 patients receiving aqueous therapy also increased, and it is interesting to note that 2 of the patients who received placebo therapy also had an increase in their hemagglutination titers. In Table III the change in hemagglutination titer and the clinical response are compared, and it is evident that there is no correlation between these factors. Fifteen of 34 patients who had a satisfactory response had an increase in titer, and the other 19 remained the same. Seven of 17 patients who had an unsatisfactory clinical response also had an increase in hemagglutination

titer, while 10 patients whose response was unsatisfactory had no change in hemagglutination titer.

Reagin titers were determined in 20 patients divided equally among placebo, aqueous, and repository groups.

Following repository therapy, the reagin titer increased in 1 patient, decreased in 1 patient, and remained the same in 4 patients. Aqueous therapy resulted in an increased titer in 3 patients and no change in the titer of 4 others. Following placebo therapy, the reagin titer also increased in 3 patients and remained the same in 4 patients.

We were particularly interested in the relationship of a change in titer and the absolute reagin titer to the clinical response. In Table IV the results in the change of the reagin titer from pretreatment to preseason sera and the clinical response are shown. Three of 7 patients with an increase in reagin titer had a satisfactory response. One patient whose reagin titer decreased also had a satisfactory response, and 8 of 12 patients whose reagin titer remained the same had a satisfactory response.

The next table shows the absolute reagin titer just before the pollen season. Five of 8 patients with reagin titer of 100 or over had an unsatisfactory clinical response. Of 12 patients whose reagin titers were less than 100, only 3 responded poorly to therapy.

TABLE III. RELATIONSHIP OF CLINICAL RESPONSE TO CHANGE IN HEMAGGLUTINATION TITER

HEMAGGLUTINATION TITER	CLINICAL RESPONSE	
	SATISFACTORY	UNSATISFACTORY
Increase*	15	7 22
Same	19	10 29
	34	17

*At least a fourfold increase.

TABLE IV. RELATIONSHIP OF CLINICAL RESPONSE TO THERAPY AND CHANGE OF REAGIN TITER

REAGIN TITER (PRE-RX TO PRESEASON)	CLINICAL RESPONSE	
	SATISFACTORY	UNSATISFACTORY
Increase	3	4
Decrease	1	
Same	8	4

TABLE V. RELATIONSHIP OF ABSOLUTE PRESEASON REAGIN TITER AND CLINICAL RESPONSE

PRESEASON REAGIN TITER	SATISFACTORY	UNSATISFACTORY
0	4	2
10	3	0
50	2	1
100	1	1
200	1	3
800	1	1

DISCUSSION

In our hands, routine aqueous therapy has been more beneficial than repository therapy in the management of previously untreated ragweed-sensitive patients. Placebo therapy produced the same effects as did repository therapy. Certainly, the number of patients evaluated is small, and many more will have to be studied to see if these results can be confirmed. It must be pointed out, however, that in the treatment of patients who have received previous injection therapy, the results of our repository treatment are about as good as the results obtained with aqueous therapy.

There are several variables which certainly might influence therapeutic response. We arbitrarily chose the repository dosages of 500 and 4000 PNU. Perhaps certain patients may require larger amounts to obtain a beneficial response. On the other hand, it was quite interesting that in our aqueous-treated group there was no correlation between clinical response and the amount of aqueous therapy given. Other factors which might influence the clinical response include the number of injections, the time of therapy, and the composition and "purity" of the emulsion.

Our groups of patients each contained a comparable number of children and adults selected randomly. It may be that the results would be more meaningful if patients were matched in terms of severity of symptoms, number of years of symptoms, and response to symptomatic drugs in the past.

The rise in hemagglutinating antibody titers following specific therapy was similar to those results reported previously in a much larger group of patients.³ In the past, we have generally found no change in titer following placebo therapy, although in this particular series 2 of 11 patients did have a rise in titer. Thus, a rise in the hemagglutinating antibody titer usually occurs following therapy but does not reflect clinical response. The lack of correlation between the change in hemagglutination titer and the clinical response also verifies the findings in larger studies following both conventional aqueous and repository therapy.³⁻⁶

Recently, there has been evidence presented by Connell and Sherman suggesting that the serum reagin titer may be a very important indication of the successful response to specific therapy.⁷ There is some suggestion in our studies of this small group that patients whose reagin titers increase prior to the pollen season may have more symptoms. In addition, it would appear that those patients who have high preseason reagin titers may also have more difficulty. Certainly, our numbers are small and no definite statement of fact can be derived from them.

It was of some interest that following repository therapy only 1 of 6 patients had an increased reagin titer, whereas 3 of 7 patients following placebo therapy and 3 of 7 patients following aqueous therapy had increases in reagin titers. These studies are somewhat in contrast to those of Connell and Sherman,⁸ who felt that repository therapy is more likely than conventional aqueous therapy to stimulate an increased reagin titer.

SUMMARY

1. Ragweed-sensitive patients who had never received previous hyposensitization therapy were divided randomly into 3 groups. Either repository, placebo, or aqueous therapy was administered to each group. Following aqueous therapy, 16 of 21 patients responded satisfactorily. In both the repository and placebo groups, 11 of 19 patients had a satisfactory clinical response. The study was conducted in a double-blind manner.

2. There was no correlation between the clinical response and the change in hemagglutination titer.

3. There was a slight suggestion that patients with an elevated reagin titer or a rising reagin titer have a poorer therapeutic response to specific therapy.

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