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CLINICAL RESULTS OF TREATMENT WITH ANTI-SEROTONIN IN ALLERGIC PATIENTS

By

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During the last years interests have been focused on the clinical effect of anti-serotonin preparations in allergic diseases. There has been some discussion whether or not serotonin is a major factor in the allergic reaction in man, and if there is, in man, a clinical effect of anti-serotonin preparations. Such an effect *may* be due to the simultaneous anti-*histaminic* effect of the various anti-serotonin drugs and not to a specific anti-serotonin effect *per se*. This question has not been definitely clarified yet.

Several papers on the clinical value of a serotonin antagonist in allergic diseases in man have already appeared (*Miller & Fishman*, *Welsh & Mitchell*, *Baily*), but the reports are not uniform. *Miller & Fishman* stated good results in various allergic manifestations, but did not find the results superior to those obtained with anti-histaminic agents. On the other hand they admit the anti-serotonin preparations (cyproheptadine = Periactin) to have a place in the symptomatic treatment "by effecting relief to a limited group of patients that were not benefited to other anti-allergic drugs". *Baily* obtained in cases of chronic urticaria results far better than with anti-histamines. *Tibor Bodi et alii* stated improvement in 78 per

cent of patients with various allergic diseases. Most authors agree that the results in bronchial asthma are disappointing.¹

In Copenhagen, our interest in anti-serotonin treatment was aroused by the experiments of *Klaus Jensen* who demonstrated (1960) that even a very short treatment with anti-serotonin will remarkably diminish the intradermal reaction to pollen extracts in pollen-allergic patients. Both the allergic wheal and the erythema around the wheal was diminished, particularly the erythema.

In the hay fever season 1960 the anti-serotonin preparation cyproheptadine, made by *Merck Sharp & Dohme* under the name of *Periactin*, was administered as a supplementary treatment to specific hyposensitization of hay fever patients and the results were highly promising. Therefore, in 1961 it was decided to treat hay fever patients with even record numbers with *Periactin* only and those with uneven record numbers with the classical pre-seasonal hyposensitization only.

TABLE I
*Clinical results in 117 hay fever patients, 65 treated with periactin,
52 with specific hyposensitization.*

	Periactin	Specific Hyposensitization
Free of symptoms	8 = 12 %	8 = 15 %
Almost symptom-free	22 = 33 %	28 = 54 %
Improved	14 = 22 %	12 = 23 %
Not improved	21 = 33 %	4 = 8 %
Number of patients	65	52 117 Patients

Legend to the tables: Free of symptoms means complete relief (a 100 % relief). Almost symptom-free means about 90% relief (occasionally and seldom, slight symptoms). Improved means at least 50 % relief. Not improved means slight or doubtful improvement or no improvement at all.

¹ Added to the proof: Recently *M. Hajos* reports good results in bronchial asthma if the anti-serotonin drug is administered with an aerosol-spray.

117 hay fever sufferers were included in this series, 65 of whom were treated with Periactin, and 52 underwent specific hyposensitization with grass pollen extracts.

The clinical results are seen in table 1. Although the results are better in the group of hyposensitization they must be said to be rather good in the group of patients treated with Periactin, too. There is, however, one point which must be taken into consideration: It is a well-known fact that hay fever patients, if they have been hyposensitized the year before, may during the pollen season of the next year, benefit from the hyposensitization treatment which they had the year before, even if they are not hyposensitized before the *present* season. There is an overlapping effect from one season to the next one.

Therefore, to obtain a real evaluation of the effect of the two forms of treatment one should compare the results in two groups of patients who have had no previous hyposensitization.

TABLE 2

Clinical results in 42 hay fever patients not previously treated with specific hyposensitization. 24 patients were treated with periactin alone, and 18 underwent specific hyposensitization

	Periactin	Specific Hyposensitization
Free of symptoms	1 = 4 %	3 = 17 %
Almost symptom-free	5 = 21 %	8 = 44 %
Improved	5 = 21 %	5 = 28 %
Not improved	13 = 54 %	2 = 11 %
Number of patients	24	18 42 Patients

This experiment was performed in a group of 42 patients, all of them hay fever sufferers, who in 1961 attended the Allergy Clinic for the first time, and who had never had specific hyposensitization treatment. 24 of the patients (even re-

cord numbers) were treated with Periactin only, and 18 (uneven record numbers) with specific hyposensitization only.

The clinical results appear from table 2. As anticipated, the figures of table 2 indicate that much of the beneficial effect of Periactin in the first mentioned material apparently is due, not to Periactin, but to a previous hyposensitization. Even with this reservation one must admit that Periactin seems to be a valuable symptomatic drug for hay fever patients; the question which arises is whether an anti-serotonin preparation has an effect superior to that of an anti-histaminic drug. This problem will be dealt with later on — first it has been attempted to obtain a rough estimation of the value of treatment with Periactin in various allergic diseases (table 3).

TABLE 3
Symptomatic effect of periactin in various allergic diseases.

	Hay fever	Vasomotor rhinitis	Urticaria	Bronchial asthma	Circum- scribed oedema
Free of symptoms ..	8 = 12 %	7 = 14 %	7 = 54 %	0	0
Almost symptom-free	22 = 33 %	21 = 42 %	5 = 38 %	1	1
Improved	14 = 22 %	5 = 10 %	0	4	0
Not improved	21 = 33 %	17 = 34 %	1 = 8 %	25 = 84 %	6 = 85 %
Number of patients ..	65	50	13	30	7
					Total 165 Patients

A total of 165 allergic patients are included in this series. Of these, 65 patients belong to the hay fever group, already accounted for in table I. The remaining 100 patients were all suffering from *chronic* allergic diseases with symptoms so frequently (several times a day, daily, or at least several times each week) that a real estimation of the effect of Periactin should be possible.

It appears from table 3 that the beneficial effect of Periactin lies within the more "exudative group" of the allergic diseases: hay fever, vasomotor rhinitis, and urticaria. In bron-

chial asthma and in circumscribed allergic oedema there does not seem to be any effect at all. Special mention should be made of the effect in urticaria. The series comprises 13 cases who all had a long history with frequent attacks during *years*. They had all been treated previously with various anti-histaminic drugs with little or no effect. While in hay fever and in vasomotor rhinitis the clinical effect of Periactin is a pure symptomatic one, there seems in cases of urticaria to be a more special effect in many cases. 7 out of 13 patients were completely relieved in spite of a history of a very long duration. 5 others were almost free of symptoms. What seems interesting is that the seven patients who had a complete relief have remained free of symptoms for 12–14 months *after cessation of the treatment*. It seems as if a vicious circle has been broken.

As the grass hay fever season in Denmark is rather short – about 6–8 weeks – it will be impossible to make reliable controlled experiments during the season. In these patients it will not be possible to carry through a general observation of the effect of Periactin compared with other drugs. To obtain an estimation of the effect of Periactin in comparison with the action of other anti-allergic drugs 50 patients suffering from chronic vasomotor rhinitis were selected. These patients all had a long history (more than a year), and were all suffering from daily attacks of sneezing accompanied or followed by watery nasal discharge and nasal obstruction.

It was intended to compare the effect of Periactin with that of placebo treatment and also with other forms of symptomatic treatment. Therefore, these patients were treated first with Periactin for two weeks, placebo treatment for two weeks, an anti-histamine (thephorin, Roche) for two weeks, tofranil for two weeks, and tofranil plus anti-histamine (nisorex, Geigy) for two weeks – and then back again through the whole series. Very often the drugs must be re-tested several times with the same patient to obtain a reliable judgment of their effect. In this way the experiment for each patient may last a year or more.

When tofranil is included in the experiment it is because of its chemical relationship to Periactin (fig. 1).

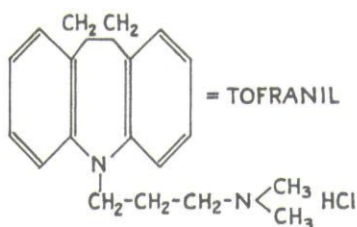
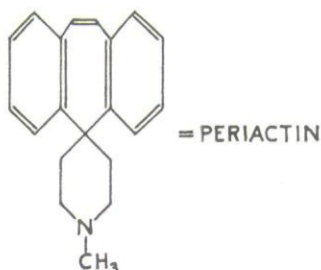


Fig. 1.

Dosage: The dosage of the various drugs was as follows:

- Periactin: 1 tablet of 4 mg twice daily for two weeks
- Placebo: 1 tablet twice daily for two weeks
- Thephorin: 25 mg twice daily for two weeks
- Tofranil: 10 mg three times daily for two weeks
- Nisorex (each tablet containing 10 mg of tofranil and 10 mg of synopen):
1 tablet twice daily for two weeks

Table 4 elucidates that, in chronic vasomotor rhinitis, Periactin has a better symptomatic effect than the other drugs examined. It is also shown that nisorex (a combination of tofranil and an anti-histamin) has an effect which seems superior to the effect of each of the two components when given

TABLE 4
50 patients with chronic vasomotor rhinitis treated with peractin. Controlled experiments
with placebo and with drugs with anti-histaminic action.

	Cyproheptadine (Peractin)	Placebo	Antihistamine	Tofranil	Tofranil + anti- histamine (Synopen)
Free of symptoms	7 = 14%	0	4 = 8%	3 = 6%	7 = 14%
Almost symptom-free	21 = 42%	5 = 10%	5 = 10%	11 = 23%	10 = 21%
Improved	5 = 10%	6 = 12%	12 = 24%	9 = 19%	10 = 21%
Not improved	17 = 34%	39 = 78%	29 = 58%	25 = 52%	21 = 44%
Numbers of patients ...	50	50	50	48*	48*

* In spite of several attempts in two patients it was impossible to obtain a real evaluation of the clinical effect of tofranil and tofranil + synopen.

separately. Finally, the table shows that in chronic vasomotor rhinitis placebo treatment has no value. 22 per cent stated improvement with placebo, but this figure lies within the spontaneous variations of the disease or may be due to psychological factors which always play a role in chronic allergic patients (*Bruun*, 1949). No patient had a perfect relief with placebo.

As to side-effects of Periacin they have generally been mild and transient (table 5). Only in 13 patients out of 165 (i.e. 8 per cent) they have been disturbing, and in 7 cases so heavy that treatment had to be interrupted.

TABLE 5
Side-effects of periacin in 56 out of 165 patients.

	Slight, transient	Moderate, persistent	Heavy, treatment interrupted
Drowsiness weakness	29	3	5
Hunger, gain of weight	2		
Dryness of mucus membranes ...	7		
Influenza-feeling	1	1	
Nausea, "intoxication"	3	2	2
Mental depression	1		
Number of patients	43	6	7

Side-effects in 56 patients = 34%, but only disturbing in 13 patients = 8%.

It should be noticed that with the combination of tofranil and synopen (nisorex, Geigy) very few side-effect were seen, and they did not cause interruption of the treatment in any case. In a recent publication *Fagerberg et alii* (1962) arrived at the same conclusion.

SUMMARY

165 patients suffering from various allergic diseases have been treated with an anti-serotonin preparation (Periacin, Merck Sharp & Dohme). The series comprises 65 patients suffering from hay fever, 50 patients with chronic vasomotor

rhinitis, 13 cases of chronic urticaria, 30 asthmatics, and 7 cases of circumscribed oedema.

In hay fever patients the clinical effect of Periactin was compared to that of specific hyposensitization with aqueous pollenextracts. In chronic vasomotor rhinitis the effect of Periactin was controlled with placebo experiments and compared to the effect of anti-histaminics and to that of tofranil.

It is concluded:

1. that the effect of treatment with Periactin is inferior to the effect of specific hyposensitization;
2. that the symptomatic effect of Periactin is superior to that of the anti-histaminic drugs applied in the control series;
3. that among the studied allergic diseases, Periactin seems to give good symptomatic relief in cases of hay fever, vasomotor rhinitis and urticaria, but is without effect in bronchial asthma and circumscribed oedema.
4. Tofranil appears to have at least as good an effect in vasomotor rhinitis as the examined anti-histaminics.
5. A combination of tofranil and an anti-histamine ("Nisorex", Geigy) seems to have a better effect than either of the two components applied independently. There seems to be an additive effect.

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