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CLINICAL EVALUATION OF AN ORAL COMBINED ANTIHISTAMINIC SYMPATHOMIMETIC PREPARATION

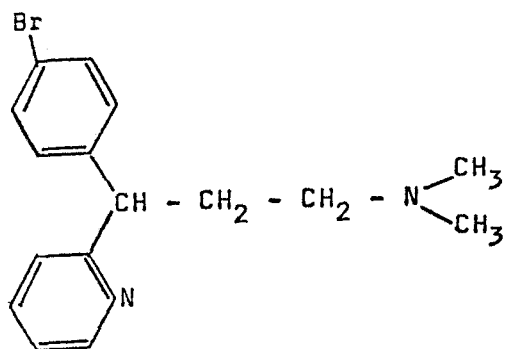
By

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Allergic conditions affecting the nose in the form of seasonal or perennial rhinitis constitute a great problem on account of the marked discomfort associated with the condition and on account of the prolonged, often extensive investigations which must be carried out to ascertain the cause of the allergy. In certain cases the patient presents with acute, intensive symptoms of allergic rhinitis. It is therefore desirable to be able to offer immediate symptomatic treatment with suitable drugs while awaiting the allergological investigation. On many occasions symptomatic, medical treatment must also be added to causal therapy, for example, desensitisation.

Since 1942 (9) antihistamines have been used with varying success in the symptomatic treatment of allergic rhinitis. A very large number of substances with antihistaminic action have been described, but the effect has been variable. Due to sedative side-effects and short duration of action, no preparation can be regarded as ideal. A compound with good clinical effect, and which to a large extent lacks these disadvantages is brompheniramine, which has been used in the USA for about a decade. A new preparation containing brompheniramine, is now available on the Swedish market under the name

Brompheniramine



Phenylpropanolamine

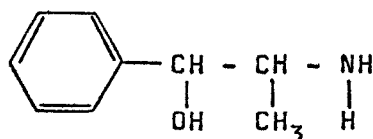


Fig. 1.

Lunerin®*. In this preparation brompheniramine is combined with a sympathomimetic agent, phenylpropanolamine, which exerts a vasoconstrictive effect in the nasal airway.

The purpose of the present investigation was to compare the effect of Lunerin and a placebo on a clinically well-defined series of patients with perennial allergic rhinitis.

Pharmacology and Dosage

Lunerin contains 12 mg brompheniramine and 50 mg phenylpropanolamine.

Brompheniramine is an antihistamine which belongs to the alkylamine group. Chemically, it is related to chlorpheniramine with the difference that chlorine is exchanged for bromine in the phenyl group (See formula). Experimental studies in animal, including mice, rats, guinea pigs, cats and dogs, have shown the substance to be a strong histamine antagonist (11, 20) with low toxicity and low sedative effect. It has been used in the USA since 1958 and has been tested in different allergic conditions in several investigations, in which it was compared partly with a placebo and partly with other antihistamines, particularly chlorpheniramine and tripelenamine (8, 15, 21). Uncontrolled trials of the preparation have also been pub-

* Draco, subsidiary to AB Astra, Sweden.

lished (5, 6, 7, 16, 25) with reports of good effect in allergic diseases. In none of the reported controlled investigations brompheniramine was inferior to the reference preparations; on the contrary it had a clearly lower frequency of side-effects. The most common side-effect was sedation.

Phenylpropanolamine is a sympathomimetic agent belonging to the ephedrine group. Its predominant effect is vasoconstriction, while the effect on the heart is weak; blood pressure and pulse are unaffected (2, 17). In contrast to ephedrine the effect on the CNS is minimal (12, 22). It is almost exclusively excreted unchanged via the kidneys (1, 10). No serious side-effects have been reported, and prostatic hypertrophy is no contraindication (4). Clinically, the preparation is used in a pure form in allergic rhinitis, where it diminishes nasal obstruction by virtue of its vasoconstrictor effect and gives good symptomatic relief. It has given equally good effect when administered orally or locally in the nose (3, 4, 18, 23). Both compounds, brompheniramine and phenylpropanolamine, are released successively from the Lunerin tablet, which forms a porous plastic matrix. This gives an even serum concentration curve and a long duration of effect (13, 19). The placebo tablets used in the present investigation consisted of the same basic constituents as Lunerin tablets and the appearance was identical. To avoid any possibility of the tablets being distinguished by taste 0.27 mg quinine was added to the placebo.

The dosage during the trial was 1 tablet morning and evening.

PATIENT MATERIAL

The material comprised 27 out-patients with perennial (non-seasonal) allergic rhinitis. Perennial allergic rhinitis was defined as a condition with watery secretion from the nose, sneezing attacks, nasal obstruction and irritation, unconnected with any particular season or time of year. Of the 27 patients, 9 were men and 18 women. The ages varied between 20 and 53 years (mean 35 years). Besides the anamnesis, the diagnosis was verified by a positive intradermal test and positive provocation test. Hereditary allergy, diseases with allergic connections, symptoms and laboratory results are shown in Table 1.

TABLE I

<i>Hereditary allergy</i>	22/27 (81.5 %)
<i>Allergic disease</i>	
Eczema	13/27 (48.1 %)
Urticaria	4/27 (14.8 %)
Nasal polyps	7/27 (25.9 %)
<i>Symptoms</i>	
Sneezing	23/27 (85.2 %)
Nasal irritation	22/27 (81.5 %)
Nasal obstruction	21/27 (77.8 %)
Secretion (thin, profuse)	14/27 (51.9 %)
(thin, sparse)	9/27 (33.3 %)
(thick, profuse)	3/27 (11.1 %)
(thick, sparse)	1/27 (3.7 %)
Eye irritation	20/27 (74.1 %)
<i>Trouble worst</i>	
In the morning	23/27 (85.2 %)
During the day	1/27 (3.7 %)
In the evening	3/27 (11.1 %)
At night	3/27 (11.1 %)
In damp weather	6/27 (22.2 %)
In dry weather	1/27 (3.7 %)
<i>Number of sneezes per day</i>	appr. 0-100 (M appr. 16)
<i>Laboratory results</i>	
Eosinophils in diff.	3 % (0-16 %)

METHOD

At the time of the patient's first visit to the clinic any treatment with anti-histamines or nasal drops had been stopped one week before. A detailed history and nasal examination were recorded on a special case sheet. Following this, the trial was begun, comprising two 5-day-periods with a tablet-free interval of 2 days.

The trial was carried out with a randomised supply of the preparations and with a cross-over technique. Half the patients received Lunerin during the first period, and half placebo. During the second period those who had Lunerin during the first period received placebo, and vice-versa, all according to a special code, which was unknown to both doctor and patient. During both periods the dosage was one tablet morning and evening. To check that the

patients had followed the prescription they were requested to return the pack after each test period. After each trial period the patient returned to the clinic, the nasal status was evaluated, and the patient's symptoms and any side-effects of the preparation given were recorded. Special attention was paid to the symptoms of sneezing, nasal irritation, nasal obstruction and secretion. After the second trial period the patient was asked which preparation he preferred. During both periods the patients were provided with a "Sneeze card", for recording of sneeze attacks. Several sneezes immediately following one another were counted as one sneezing attack.

The trial was carried out between November 1970 and February 1971.

RESULTS

The mean number of sneezing attacks per day during the placebo period was 4.93 and during the Lunerin period 1.62, giving a t_0 -value of 5.16^{xxx}. The frequency of sneezing during the period with active preparation was significantly lower ($p < 0.001$) than with placebo.

TABLE 2
Nasal Symptoms.

	All day	Several times a day	Once or twice a day	Never
<i>Irritation</i>				
Without therapy	5	7	10	4
With Lunerin	1	1	8	16
With placebo	6	7	7	6
<i>Obstruction</i>				
Without therapy	11	7	5	3
With Lunerin	4	1	8	13
With placebo	7	7	8	4
<i>Secretion</i>				
Without therapy	6	10	6	3
With Lunerin	0	3	8	14
With placebo	9	10	3	3

Other related nasal symptoms, that is to say, nasal irritation, nasal obstruction and nasal secretion, were judged on 3 occasions and graded according to a 4-point scale. The symp-

toms were scored according to the following: All day = 4 p, Several times a day = 3 p, Once or twice a day = 2 p, and Never = 1 p. Table 2 shows the number of patients who had different grades of trouble during the respective periods.

The statistical analysis of the difference between the periods gives the t_0 -values 4.33^{xxx}, 4.05^{xxx}, and 5.87^{xxx} for the symptoms irritation, nasal obstruction and nasal secretion respectively. By all parameters Lunerin was thus significantly ($p < 0.001$) better than the placebo.

After the second test period the patients were asked to make an over-all judgement of period 2 compared with period 1, by use of the scale trouble-free, improved, not improved, and worse. The result is shown in Table 3. Trouble-free was given 4 points, improved 3, not improved 2, and worse 1 point, giving a t_{diff} -value of 5.00^{xxx}, that is to say, Lunerin was significantly better than the placebo.

TABLE 3

Over-all Judgement by the Patients of Lunerin and the Placebo After Period 2.

	Lunerin	Placebo
Trouble-free	2	1
Improved	9	1
Unimproved	1	4
Worse	0	8

At the end of the trial each patient was asked which preparation she/he preferred. 24 patients preferred Lunerin, 1 patient considered the preparations equally good, and 2 preferred the placebo.

Those patients who reported that they had become symptom-free or improved when questioned after the trial periods (after period 1, comparison was made with earlier therapy) were asked to assess the duration of improvement or freedom from symptoms according to one of the following alternatives: 2, 4, 6, 8 or 10 hours. 19 patients answered this question after

the period with Lunerin; 17 patients stated 10 hours or more, 1 patient 8 hours and 1 patient 4 hours.

Side-effects

The distribution of reported side-effects is shown in Table 4. A total of 13 patients reported some kind of side-effects during the trial periods. Some patients reported several symptoms. Side-effects were noted during the period with Lunerin by 11 patients, during the period with the placebo by 7 patients. In all cases the side-effects were minimal and did not lead to discontinuation of the preparation.

TABLE 4

Symptoms	Lunerin	Placebo
Fatigue	5	5
Dryness in the nose	3	
Dryness in the mouth	1	
Headache		1
Nausea		1
Itching eyes		1
Palpitation	1	1
Feeling warm		1
Impaired sleep	1	
Visual "blurring"	1	
Anxiety	1	
Acid stomach		1

DISCUSSION

This investigation is a comparison between brompheniramine with phenylpropanolamine as a combined slow-release preparation, and a placebo. In order to eliminate the subjective element as far as practicable and to obtain as objective an estimation as possible the trial was carried out with a double blind, randomised supply of the preparations and with a cross-over technique. The patient was thus his own control. Allergic conditions in the nose are influenced however by factors such

as subclinical infection, psyche, weather etc. It was not possible to evaluate such variables, nor variations in exposure to allergens but their effect was diminished by limiting the trial periods to 5 days each. Furthermore, the patients were informed how essential it was that both trial periods be as similar as possible, e.g. they should not change their environment, start taking new drugs, get a pet animal, etc. between the trial periods. Both for checking this and for evaluation of the symptoms on a point basis, it was an advantage that the patient was seen by the same doctor on all three occasions.

On over-all consideration, the investigation shows with high significance that Lunerin is better than placebo. Thus during the second trial period 11 out of 12 patients in the Lunerin group were symptom-free or improved, compared with only 2 out of 14 in the placebo group. Statistical analysis of the basic symptoms: nasal irritation, nasal obstruction, secretion, and frequency of sneezing shows that even when these four parameters are concerned Lunerin is better than the placebo and that the difference is highly significant. Assessment of irritation and secretion was based on the patient's own subjective evaluation, as it is difficult to measure these symptoms objectively. Nasal obstruction can be measured by a rhinomanometric method, but for practical reasons the patient's subjective evaluation was thought preferable regarding these symptoms also. By asking the patient to record all sneezing during the trial periods a certain objective measurement of the effect was obtained.

From earlier investigations (27), it is known that the fewer times per day a drug needs to be taken, the greater is the chance that the patient takes the prescribed dose. From this viewpoint it may be an advantage that Lunerin needs only to be administered twice daily to obtain a good clinical effect. Besides, less frequent doses are of practical advantage to the patient. 17 out of 19 patients reported a duration of effect of Lunerin of 10 hours or longer, supporting clinically the pharmacokinetic studies carried out with Lunerin in man (13, 19). A consequence of prolonged duration of effect is that the

patients obtain an alleviation of symptoms also during the night and early hours of the morning. In this investigation 85 per cent of the patients reported most trouble during just these hours (Table 1).

During the Lunerin period 11 patients noted side-effects, half of these in the form of tiredness. However, all side-effects, including tiredness, were slight, and it did not become necessary to discontinue the drug. The patients were questioned thoroughly after each trial period about side-effects, and a certain degree of suggestion arising from this close scrutiny could not be excluded. It is noticable that both after Lunerin and placebo 5 patients reported tiredness as a side-effect. Earlier investigations with brompheniramine have shown a frequency of side-effects varying between 0 per cent (26) and 16.8 per cent (15), the most common side-effect being sedation. Only in exceptional cases has this sedation been pronounced enough to cause discontinuation of the drug, and in comparative investigations brompheniramine has a regularly lower frequency of sedation than reference preparations (8, 14, 15, 21, 24). The frequency of side-effects did not increase when the preparation was taken for a longer time (16).

CONCLUSION

The present investigation shows that the drug Lunerin must be considered a good addition to the arsenal of symptomatic agents for use in nose affections of an allergic nature. The drug had a good clinical effect, a long duration and a low incidence of side-effects.

SUMMARY

A new oral combination preparation (Lunerin®, Draco) for symptomatic treatment of allergic rhinitis has been tested in 27 patients with perennial (non-seasonal) allergic rhinitis. The preparation contains an antihistaminic (brompheniramine) and a sympathomimetic (phenylpropanolamine) agent. The

pharmacology of the compounds is briefly reported. Lunerin was compared with placebo in a double-blind study with a randomised supply and cross-over technique. By all studied parameters, frequency of sneezing, nasal irritation, nasal obstruction, and nasal secretion, Lunerin was highly significant better than placebo. The duration of effect of Lunerin was 10 hours or more in 17 out of 19 patients. The side-effects were neglectable and did not lead to discontinuation of the preparation.

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