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ANTI-ASTHMATIC PROPERTIES OF A NEW PERORAL DRUG (HC 20-511)

By

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The discovery of disodium cromoglycate (2) represents a remarkable progress in the management of asthma. However, due to its poor solubility and inability to be reabsorbed, the galenic form of this agent is one of its major disadvantages in clinical practice. This has stimulated numerous efforts to find active and well-tolerated peroral therapeutical agents.

A new therapeutical agent (HC 20-511), which belongs chemically to the cycloheptathiophene group of substances, was shown to exhibit several pharmacological properties in the field of anti-allergic activity (6).

This substance proved to have a very low level of toxicity and, furthermore, was rapidly and completely absorbed through the gut (7).

We report clinical trials, testing the effect of HC 20-511 on two groups of asthma patients.

PATIENTS AND METHODS

This study comprised 24 asthma patients divided into two groups; ages 18-52, half men and half women. All patients were thoroughly investigated before the trial to determine the aetiological agents responsible for their disease. All cases had perennial asthma. According to the classical criteria, 18 patients could be classified as extrinsic asthma, six as intrinsic asthma. In all cases inhalation provocation tests were performed, according to a published procedure (4), several weeks before the start of the trial.

Criteria for the selection of patients: Patients under permanent corticoids or

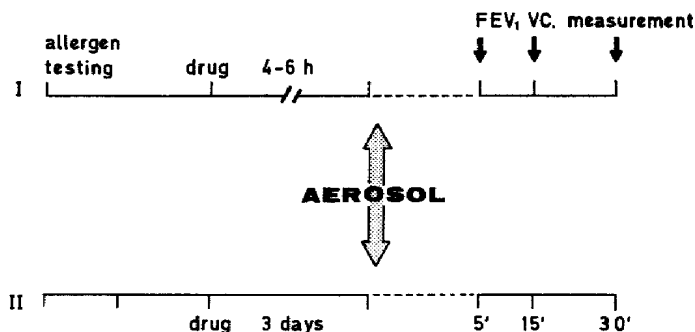


Fig. 1.

Protocol of the two clinical assays using HC 20-511.

disodium cromoglycate therapy were excluded, or, when possible, controlled with short-term therapy (β -stimulating agents, aminophyllin).

Pregnant women and patients with intrinsic asthma which was evidently infectious were also excluded.

The study protocol: The first group of 12 patients was given at random HC 20-511 or a placebo. The drug was administered 4-6 h before the antigen provocation test was done with a previously tested allergen, giving at least a 20 per cent reduction of the respiratory parameters. FEV₁ and VC were registered before and 5, 15, and 30 min following the provocation test. The respiratory parameters were measured with the aid of a Vitalograph.

The second group of 12 patients was administered 1.0 mg HC 20-511 twice a day, or 1.0 mg clemastin (Tavegil®) twice a day for 3 days before the challenge, in a cross-over double-blind study. The provocation tests were done 4-6 h after the last tablet was taken, following the schedule mentioned earlier, Fig. 1.

The patient's impression and all side effects were registered.

RESULTS

First Trial

In Fig. 2, the mean values of FEV₁ at 0, and 5, 15, and 30 min following the challenge with the antigen are illustrated. Results for both HC 20-511 and placebo treatment are illustrated. *T*-test analysis of difference among the two groups demonstrates a significant difference at 5, 15, and 30 min.

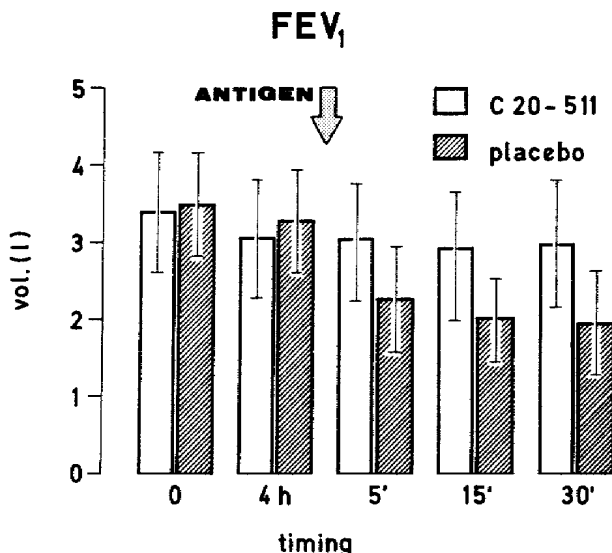


Fig. 2.

Assay No. 1: Measurement of FEV₁ values before and after antigen challenge (arrow) in subjects treated with HC 20-511 (open column) and placebo (hatched column).

Following treatment with HC 20-511 the decrease of FEV₁ never exceeded 20 per cent whereas during placebo therapy this value fell in all cases from 20 to 50 per cent.

In Fig. 3, the mean values of VC at 0, 5, 15, and 30 min following the challenge are represented. *T*-test analysis revealed also a significant difference between the two types of treatment.

Three of the patients under placebo developed a late asthma attack (after 4–6 h), which was not observed among the same patients when they received HC 20-511.

Tolerance to HC 20-511 was excellent. Only two patients complained of slight fatigue lasting 1–2 h after having taken the active substance.

VC

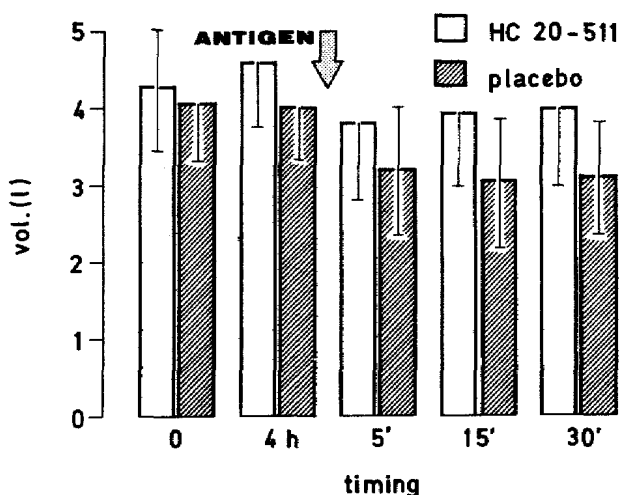


Fig. 3.

Assay No. 1: Measurements of VC values before and after antigen challenge in subjects treated with HC 20-511 and placebo.

Second Trial

In this second trial HC 20-511 was compared with a well-established antihistaminic agent, clemastin.

Fig. 4 illustrates the comparative results of the FEV₁ values among the two treated groups. Using the Wilcoxon matched pairs signed rank test, a significant difference in favour of HC 20-511 could be shown after 3 days of treatment, but also following the provocation test, at 5, 15, and 30 min. All patients receiving HC 20-511 exhibited a decrease of FEV₁ values between 0 and 20 per cent whereas in all cases receiving clemastin, this change was between 20-50 per cent.

Fig. 5 illustrates the results of the VC values among the two groups of treated patients. Using the same Wilcoxon

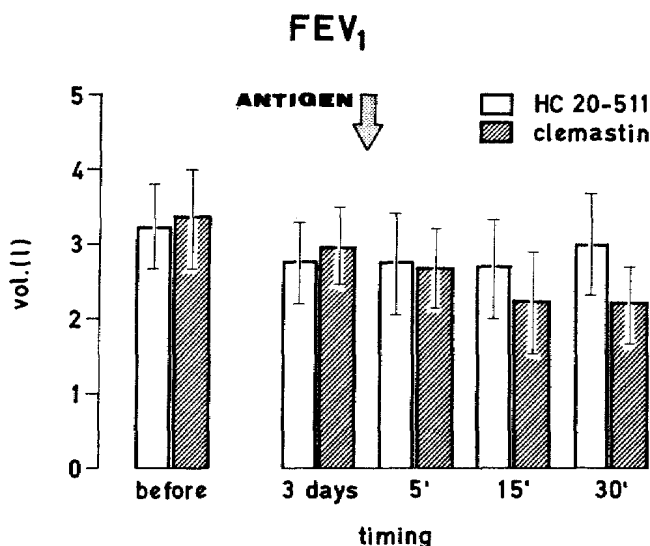


Fig. 4.

Assay No. 2: Measurement of FEV₁ in non-treated patients, during treatment with HC 20-511 and clemastin and following challenge with antigen.

matched pairs signed rank test, a significant difference could be ascertained in favour of HC 20-511.

Table 1 illustrates the number of increases or decreases in FEV₁ and VC tests following therapy with HC 20-511 and clemastin.

TABLE 1

Number of Changes in FEV₁ and VC Following Treatment with HC 20-511 and Clemastin.

Substances	FEV ₁	VC
HC 20-511	9 < · 3 >	8 < · 4 >
Clemastin	2 < · 10 >	1 < · 11 >

VC

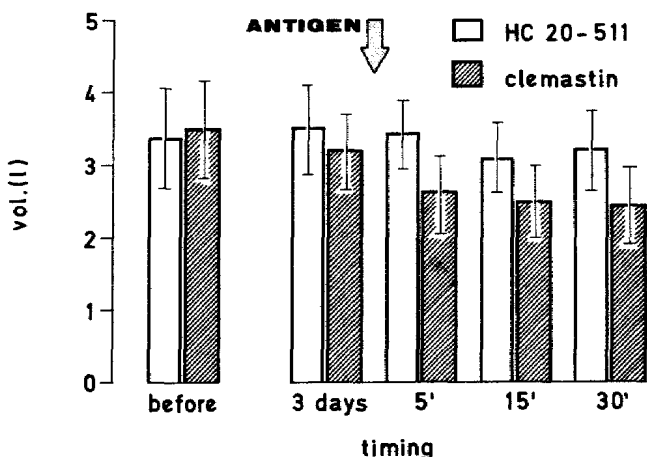


Fig. 5.

Assay No. 2: Measurement of VC in non-treated patients, during treatment with HC 20-511 and clemastin and following challenge with antigen.

Three patients developed a late asthma attack when receiving clemastin, whereas the same patients failed to do so when receiving HC 20-511.

Concerning the side effects, three patients receiving HC 20-511 complained of slight and short-lasting fatigue, whereas under clemastin therapy, three patients complained of sleepiness, three of fatigue and one of dryness of the mouth.

DISCUSSION

This clinical trial demonstrates unequivocally the beneficial therapeutical effect of a new substance derived from the cycloheptothiophene group in the management of asthma. In a rather low dosage, as far as pharmacological properties are concerned, this agent seems able to protect most asthma pa-

tients against an aerosolized allergen to which they show specific hypersensitivity (3). This effect is immediate, unlike the group of β -stimulating agents, which rapidly release the spasm of bronchial muscles. Protection is still present 4–6 h after ingestion of 1.0 mg of the substance. Therefore it may be acting as a mastocyte-protecting agent in the same way as disodium cromoglycate (1).

Tolerance, as far as we can judge, seems to be excellent. No side effects were noticed by our patients, such as sleepiness and gastro-intestinal symptoms, with the exception of a short-lasting, slight fatigue claimed by three patients. Further assays are required with this substance, using higher dosages over a longer period of time, in order to establish the true features of its clinical activity and safety.

This trial also demonstrates a fact well known by physicians, that pure antihistaminic drugs such as clemastin fail to protect, at least in the recommended dosages, against allergenic bronchospasms (5).

As far as we can tell, within the limits of our protocol, HC 20-511 may offer promising therapeutical properties for the management of asthma.

SUMMARY

A clinical trial was performed with a new substance (HC 20-511) derived from the cycloheptothiophene group used in the management of asthma. Twenty-four asthma patients were treated at random, with HC 20-511 or placebo or the antihistaminic substance, clemastin (Tavegil®).

A statistical evaluation of the results unequivocally demonstrates good protection with a single dose of 2.0 mg or two times 1.0 mg for 3 days against a challenging antigen, compared with the placebo or the antihistaminic agent.

Tolerance was excellent.

ACKNOWLEDGEMENTS

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REFERENCES

1. Altounyan, R. E. C., Cox, J. S. G. & Orr, T. S. C. (1971): Biological and pharmacological basis of disodium cromoglycate therapy. In *New concepts in allergy and clinical immunology*, p. 377. Proc. VIIth Int. Congress of Allergology. Florence 1970. Excerpta Med. (Amst.).
2. Altounyan, R. E. C. & Howell, J. B. L. (1969): Treatment of asthma with disodium cromoglycate. *Respiration* 26, Suppl. 131.
3. Debelic, M., Wüthrich, B. & Radjelovic, P. (1976): Protective drug effect in antigen-induced bronchial asthma. *Pneumologie*. S. Karger, Basel. In press.
4. Girard, J. P., Horvat, L. & Didisheim, J. C. (1973): Inhalation tests as a routine diagnostic procedure in allergic asthma. *Ann. Allergy* 31, 596.
5. Henderson, L. L. (1968): Clinical use of anti-allergic agents: non-steroid drugs. In *"Allergology"*. Montreal, 1967. Excerpta Med. (Amst.).
6. Sandoz Ltd., Basel (1975): Personal communication.
7. Waldvogel, E., Schwarb, G., Bartian, J. M. & Bourquin, J. P. (1976): Untersuchungen über synthetische Arzneimittel 9-10-Oxo-Derivate von 9,10 Dihydro-4H-benzo (4,5) cyclohepta (1,2-6) thiophenen. *Helv. chim. Acta* 59, 866.

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