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Topical treatment of seasonal allergic rhinitis with a β-adrenoceptor stimulant (KWD 2131)

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SUMMARY

During 4 weeks of the grass pollen season in the south of Sweden 27 patients with seasonal allergic rhinitis were treated topically with a β-adrenoceptor stimulant, KWD 2131, which in an earlier rhinomanometric study had shown a prophylactic effect at nasal allergen provocations in hay-fever patients.

A clinical effect of KWD 2131 could not be documented in this randomized placebo-controlled, double-blind comparative study. The results contribute to conclusions in the clinical implications of rhinomanometric data.

INTRODUCTION

An antiallergic effect in animal as well as in man has been attributed to sympathomimetic amines (Holroyde et al., 1977; Sörenby, 1977; Strandberg et al., 1979; Martin et al., 1980). A new β-adrenoceptor stimulant, KWD 2131, was recently shown to have a prophylactic effect on allergen-provoked nasal obstruction in hay-fever patients - out of season - studied rhinomanometrically (Svensson, 1980). In a prior study (Svensson et al., 1981) KWD 2131 did not block the action of histamine in the nasal tissue. Probably, the drug acts as a mast-cell stabilizer. The present report deals with the clinical use of KWD 2131 during the hay-faver season.

MATERIAL AND METHODS

Altogether 27 patients, 23 males and 4 females, aged between 14 and 52 years (average 27 years), were included in the trial, all of them being sensitive to grass pollen, as shown by positive skin test or positive provocation test (Löfkvist and Svensson, 1975). All had suffered from hay fever during at least the last two seasons, and prior medication with antihistamines or disodium cromoglycate or beclomethasone dipropionate or hyposensitization had been insufficient for required relief of the allergic symptoms. No subject currently on a hyposensitization course was included. The characteristics of the patients are provided in Table 1.

Table 1. Patients' characteristics.

variable		value or frequency for KWD 2131-placebo	placebo-KWD 2131
age	mean	28	25
	range	14–52	15–41
sex	male	11	12
	female	3	1
duration	mean	10	8
	range	2–20	2–17
treatment previous years:			
antihistamine		14	13
disodium cromoglycate		5	5
nasal applic. of steroids		4	6
general adm. of steroids		5	6
hyposensitization		5	4

The trial was conducted over a 4-week period between mid-June and mid-July during the summer of 1979.

The study was of a randomized, placebo-controlled, double-blind type and the design made cross-over evaluations as well as comparisons of parallel groups possible.

Fourteen patients started with a 2-week treatment period with 1-(3,5-dihydroxyphenyl)-2-/(1,1-dimethyl-2-hydroxyethyl)-amino/ethanol sulphate (KWD 2131, AB Draco, subsidiary of AB Astra, Sweden), followed by 2 weeks' placebo (saline solution) treatment. The other 13 patients were treated in the reverse order. KWD 2131 and placebo were distributed in identically equal packings, and were administered as nose drops. The dosage was 3 drops to each nasal cavity, repeated after 2 minutes, 3 times daily during both the placebo period and the KWD 2131 period. Six drops (3 × 2) of the active substance corresponds to 5 mg KWD 2131, which means a total dose of 30 mg in a 24-hour period. The dosage was based on experiences from prior investigations (Svensson, 1980; Svensson et al., 1980). A supply of tablets containing antihistamine and sympathomimetic substance (brompheniramine + phenylpropanolamine - Lunerine® mite/AB Draco, Sweden) was issued to each patient with instructions to use them only if symptoms were so severe as to make the medication indispensable. Treatment with other drugs was not allowed.

Each subject recorded the following symptoms on a daily diary card: nasal blocking, running, itching and eye symptoms, on a scale 0–3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms). The number of sneezing attacks were also recorded on a 0–3 scale (0 = no attacks, 1 = 1–5 attacks, 2 = 6–15 attacks, 3 = more than 15 attacks in a 24-hour period). If it was

necessary to take Lunerin® mite tablets, the number was entered on the diary card too. The patients were also requested to enter suspected and convincing side effects on the diary card.

Each patient was interviewed and medically examined (routine ENT examination) before entry into the trial and on the last day of both the KWD 2131 and the placebo period. The condition of the nose was recorded as to the presence of oedema and secretion, again on a 0–3 scale.

Conventional β-adrenocepter stimulants are shown to increase the content of glucose in blood, be metabolized to a varying degree in the liver and excreted in urine in different forms. Therefore haematological analysis (haemoglobin, leucocyte count) and examination of protein (Albustix®) and glucose (Clinistix®) in urine as well as estimations of serum enzymes (alkaline phosphatase, glutamyltransferase, aspartate amino transferase, alanine amino transferase) and bilirubin/s were also carried out on these occasions.

On the last day the both treatment periods, the patients', subjective evaluation of the therapeutic effect was recorded as answers to the following questions:

1. Were your nasal symptoms adequately controlled?
2. Do you regard the treatment with the nose drops as a success or a failure?
3. Have you experienced any side effects of the treatment?

At the last examination, the patients' opinion as to which of the treatment periods had given the least nasal trouble, or whether they had found no difference between the two periods, were entered on the protocol.

Data on pollen counts were obtained by means of a Burkard® slit sampler, placed at the ENT Clinic, Malmö General Hospital. The identification of the pollen was performed at the Botanical Institution, University of Göteborg.

Statistical methods

The data obtained from the diary cards and medical examinations were subjected to statistical analysis with t-test.

The study was approved by the Ethical Committee of the University of Lund and informed consent was obtained form all patients.

RESULTS

The summer of 1979 may be regarded as medium-good with respect to the weather. During the first part of the investigation, it was warm and sunny, but during the second part the weather changed to lower temperature and cloudiness, mostly without rain (Ehde, 1979). The grass pollen season began at about the normal time.

A couple of days before the start of this trial the pollen count showed a peak with about 30 grass pollen/m^3 air. During the first week the count reached 8 grass

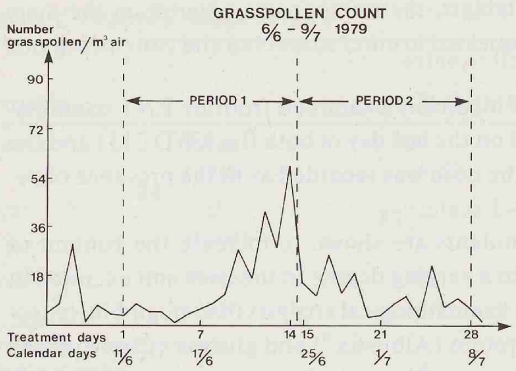

Figure 1. Grass-pollen count before and during the investigation.

pollen/m^3 (Figure 1). The highest grass pollen content (about 30–60 grass pollen/m^3 air) was recorded during the second week of the trial. A marked decrease took place on passing to week 3, i.e. at the same time as the patients shifted medication from placebo to KWD 2131 or vice versa. During the third and fourth weeks the pollen count was low with 3 small peaks (26, 19, 22 grass pollen/m^3 air, respectively). The total count of grass pollen during each week was 31, 194, 90 and 66 grass pollen/m^3 air, respectively.

Figure 2 shows the mean scoring as far as the different symptoms are concerned. The patients experienced the symptoms as mild with the exception of rather intense nasal obstruction and secretion during the second week. Generally, the scores were higher during the first part of the trial and especially during the second week.

All patients participating in the trial completed the treatment with three exceptions. One patient left the investigation due to insufficient effect of the treatment, the second patient due to intervening illness, and the third due to side effect (tremor).

The patients' subjective evaluation of the treatment with placebo and KWD 2131 after each treatment period did not reveal any certain difference between the two forms of medication. Eighteen patients out of 24 experienced the treatment during the second period as more successful than during the first period, independently of the type of medication. Two patients did not find any differences between the periods and four patients preferred the first period. These six patients were all treated with KWD 2131 during the first part of the study.

Analysis of the notes on the diary cards with the patients arranged in parallel groups did not reveal any certain difference in symptom-relieving capacity between KWD 2131 and placebo. Special attention was paid to days with different amounts of grass pollen. During the days with the highest pollen count, i.e. day 10–14 (average 35 grass pollen/m^3 air) as well as during days with 29–20, 19–10

and 9-0 grass pollen/m^3, no significant differences were documented between treatment with KWD 2131 and placebo.

At the rhinoscopic examination no differences as regards oedema and secretion were observed. The use of Lunerin® mite was low (Figure 2) and without significant differences during both periods.

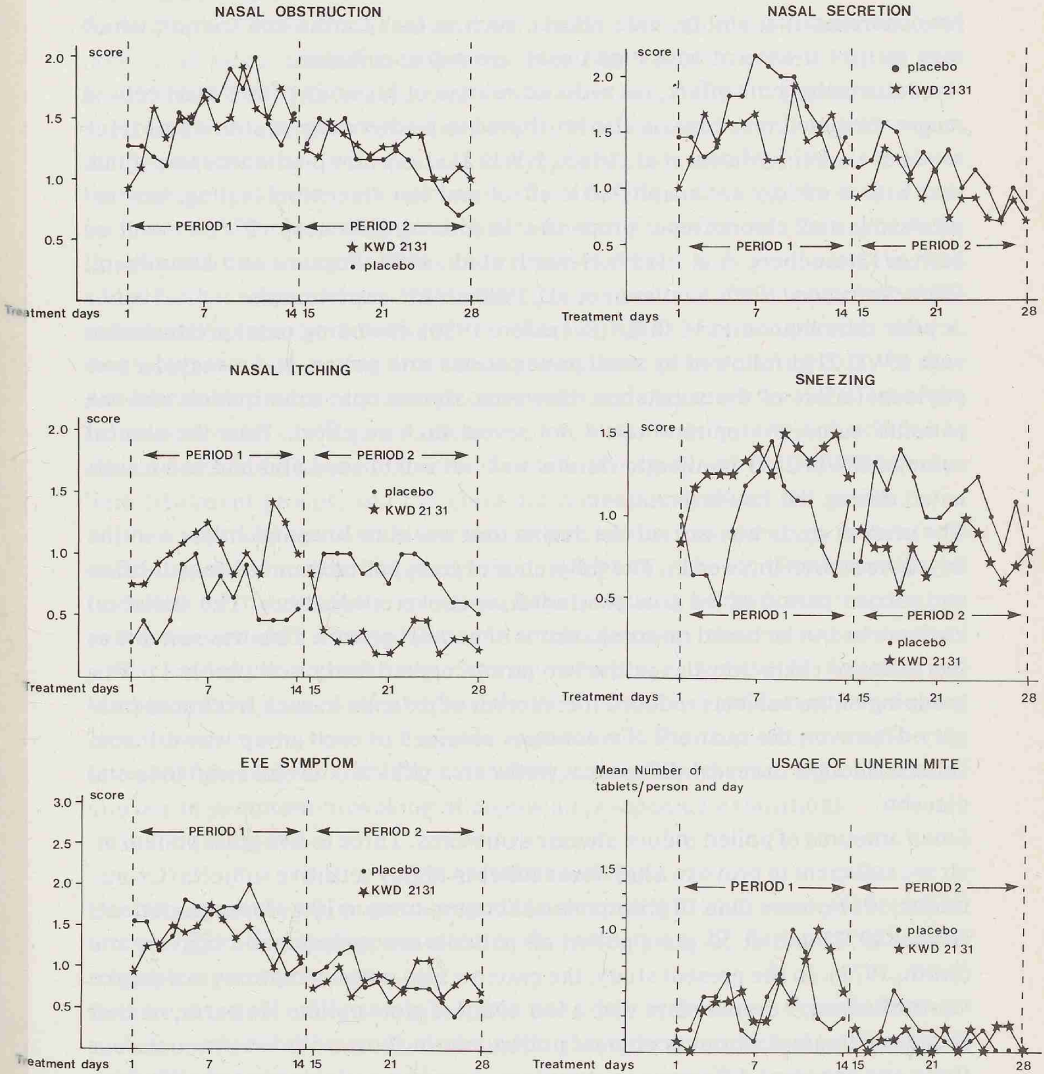

Figure 2. Mean symptom score as regards nasal obstruction, nasal secretion, nasal itching, sneezing and eye symptoms as well as the usage of Lunerin® mite during treatment with KWD 2131 and placebo in patients with seasonal allergic rhinitis.

No certain side effects were revealed except tremor in one patient on KWD 2131. All laboratory analyses (haemoglobin, white cell count as well as hepatic and renal function tests) were within normal limits before and after each period of treatment.

DISCUSSION

β-adrenoceptor stimulants are often used in the treatment of asthma due to their bronchorelaxating ability. Side effects, such as tachycardia and tremor, which may restrict treatment with high doses, are not uncommon.

An antianaphylactic effect, i.e. reduced release of histamine from mast cells at reagin-mediated reactions, is also attributed to β-adrenoceptor stimulants (Holroyde et al., 1977; Martin et al., 1980). KWD 2131 is a new β-adrenoceptor stimulant with a mainly antianaphylactic effect and low tracheorelaxating, tremor-producing and chronotropic properties in animal (Sörenby, 1977) as well as human (Strandberg et al., 1979; Hegardt et al., 1980; Pegelow and Strandberg, 1980; Svensson, 1980; Svensson et al., 1980, 1981) experiments.

A prior rhinomanometric study (Svensson, 1980), including nasal pretreatment with KWD 2131 followed by nasal provocations with pollen, had revealed a prophylactic effect of the substance. However, rhinoscopic examination and the patients' subjective opinion could not reveal such an effect. Thus the clinical value of KWD 2131 in allergic rhinitis was not established and had to be evaluated during the hay-fever season.

The present study was carried out during four weeks in June and July, i.e. at the hay-fever season in Sweden. The difference in grass pollen counts during the first and second period of the trial precluded cross-over evaluations. The statistical analyses had to be based on comparisons of parallel groups. This was suitable as the patients' characteristics in the two groups agreed fairly well (Table 1). This grouping of the subjects reduced the number of patients in each treatment category. However, the quantity of volunteers obtained in each group was still considered enough to reveal differences between a clinically useful substance and placebo.

Small amounts of pollen induce allergic symptoms. Three to five grass pollen/m^3 air are sufficient to provoke a hay-fever attack in highly sensitive subjects (Gronemeyer, 1967), more than 10 grass pollen elict symptoms in 10% of allergic patients (Hyde, 1972) and at 50 grass pollen all patients are symptomatic (Davies and Smith, 1973). In the present study, the patients also noted symptoms in a degree worth studying – even in days with a low count of grass pollen. However, neither in days with great amounts of grass pollen, nor in those with low amounts was there any apparent difference in symptoms between patients treated with 5 mg KWD 2131 three times a day and placebo. Higher doses of KWD 2131 would perhaps induce a more favourable relief of nasal symptoms, but such an increase of

the dose seems to be restricted. Already in the given dose, one patient left the trial due to a general side effect - tremor.

The sum of data collected in this study do not support a clinical effect of KWD 2131, i.e. a result contrary to that presented in a preceding rhinomanometric study (Svensson, 1980). An explanation of this disagreement may be a higher sensitivity in rhinomanometric examinations than in the patients' subjective evaluations.

According to Cohen (1978) patients with nasal congestion due to common cold note relief when treatment improves their flow/resistance values by at least 15–20%. KWD 2131 decreased nasal airway resistance by 20–30% at the nasal provocations with allergens (Svensson 1980), which seemed promising. However, the negative findings in the present study give rise to doubts about the validity of the statement of Cohen at recommendations for clinical testing of a drug. There seems to be a demand for higher figures for the improvement of nasal passage. For practical reasons rhinomanometry was not used and could scarcely have added further relevant data - rhinomanometry is a rather time-consuming examination and comparisons between the effect of KWD 2131 and placebo should, due to exposure of varying amount of pollen, have been performed day by day. Antihistamines reduce the allergic symptoms and may mask a weak effect of the substances to be investigated. However, antihistamines have to be used due to ethical demands. The use of Lunerin® mite in this study was limited and equal in both treatment groups, and therefore did not seriously affect the results.

A final comment deals with the second part of the trial, when in spite of low counts of pollen most patients had definite symptoms. The explanations might be threefold. Firstly, due to the selection our patients may be more sensitive to grass pollen than patients with hay fever as a whole. Secondly, the absolute amounts of pollen are representatively only of the counting place (Hyde, 1972; Solomon and Mathews, 1978; Leuschner and Boehm, 1979), and those patients who live about 20 km away might have had higher expositions. The third factor may be the so-called "priming effect" (Connell, 1969), i.e. increased reactivity of the nasal mucosa to symptom-provoking allergens after repeated expositions.

ZUSAMMENFASSUNG

Die beta-adrenorezeptor stimulierende Substanz KWD 2131 wurde während der vierwöchigen Graspollensaison in Südschweden an 27 Patienten mit Heuschnupfen getestet.

Die Applikation erfolgte lokal. KWD 2131 hat in früheren Provokationsversuchen an Patienten mit Heuschnupfen rhinomanometrisch eine prophylaktische Wirkung gezeigt.

In den vorliegenden randomisierten, plazebokontrollierten Doppel-Blind-Studien zeigt KWD 2131 keine klinische Wirkung.

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