Br. J. clin. Pharmac. (1980), **10**, 473–476

A COMPARISON OF THE EFFICACY OF KETOTIFEN (HC 20-511) WITH SODIUM CROMOGLYCATE (SCG) IN SKIN TEST POSITIVE ASTHMA

C.W. CLARKE† & C.S. MAY*

The Respiratory Investigation Unit,
The Prince Charles Hospital, Rode Road,
Chermside, Qld. 4032. Australia.

1 Ketotifen (HC 20-511 Sandoz) 1 mg twice daily for 12 weeks was found to be equivalent to sodium cromoglycate (SCG) 20 mg four times daily for 12 weeks in 35 skin test positive asthmatic patients in a randomised double-blind cross-over study.

2 No statistically significant difference between the two drugs in mean values for daily peak flow rates, diary card scores and spirometry at monthly visits was demonstrated.

3 Treatment failures as judged by severe asthma requiring withdrawal from the trial or addition of short courses of prednisone occurred in three patients on each drug.

4 Sedation was noted by 10 patients on HC 20-511 and 5 on SCG.

5 Weight loss was noted in those patients on SCG, but not those on HC 20-511.

Introduction

Ketotifen (HC 20-511: Sandoz) is a benzocycloheptathiophene derivative that has been shown to possess anti-histaminic and anti-anaphylactic properties (Martin & Römer, 1978). It has been demonstrated that it can block *in vitro* release of mediators from rat peritoneal mast cells (Martin & Römer, 1978). *In vitro* studies have yielded conflicting results at the present time, particularly its efficacy in blocking bronchoconstriction following inhalation of antigen (Pauwels, Lamont & Van Der Straeten, 1978; Craps, Greenwood & Radielovic, 1978; Wells & Taylor, 1979). Clinical trials have suggested that it may be effective orally in skin test positive asthma (Craps *et al.*, 1978; Weheba, 1978). It is well tolerated when given over long periods (Weheba, 1978).

Sodium cromoglycate (SCG) now has an established place in the treatment of skin test positive asthma (Brompton Hospital/Medical Research Council Collaborative Trial, 1972) but a major disadvantage is its lack of absorption from the gastrointestinal tract. As a result, it is administered as an inhalation of dry powder, a number of patients find this inconvenient and occasionally transient bronchospasm results.

The paper presents the results of a study that compared the efficacy of HC 20-511 to SCG in a group of skin test positive asthmatic patients the majority of whom had been well controlled on SCG.

Methods

Patients between the ages of 15–65 years with skin test positive asthma and who were inadequately controlled on bronchodilators alone were selected for study. The study had the approval of the hospital ethics committee and all gave informed consent. Exclusions for entry were hepatic or renal insufficiency, pregnant or lactating women, inability to co-operate fully over the study period and therapy with oral or inhaled steroids in the 3 months prior to commencement of the trial. Previous therapy with SCG was not an exclusion.

Trial design

The study was a double-blind crossover with double dummy technique with 3 months on each therapy. Prior to a 2 week run-in period during which routine therapy was maintained, each patient was randomly entered in blocks of six into either Group I or Group II. Group I was given SCG active 20 mg four times daily via a spinhaler plus HC 20-511 placebo capsule orally twice daily for 12 weeks changing to SCG placebo 1 capsule four times daily plus HC 20-511 active 1 mg twice daily for 12 weeks. Group II commenced with active HC 20-511 changing to active SCG after 12 weeks.

Present addresses: *Dr C.S. May, Suite 1, 9th Floor, Qantas House, London Circuit, Canberra City. 2601. Australia. †Dr C.W. Clarke, P.O. Box 310, Eastwood 2122, Australia

0306–5251/80/050473–04 $01.00

Trial procedure

The first visit was regarded as week −2. A full history was taken with emphasis on duration of asthma, number of episodes of wheeze per week, presence of associated cough and sputum, previous therapy for asthma including duration of and response to SCG. Physical examination included measurement of supine and standing pulse rate and blood pressure (BP), weighing and urinalysis. Baseline forced expiratory volume in one second (FEV_1) and vital capacity (VC) was measured using a dry spirometer (Vitalograph Ltd, Bucks, England) and peak flow rate (PFR) with a Mini-Wright Peak Flow Meter (Clement Clarke Int. Ltd, London, England). The patient was instructed in the correct operation of the meter and asked to perform the manoeuvre before therapy in the morning and again in the evening prior to night-time medications. A diary card was provided and the patient was finally warned about possible sedative effects of HC 20-511 in the initial stages of therapy and interaction with alcohol.

Follow-up visits were at week 0 and then at a maximum of four-weekly intervals till week 24. At week 0, the run-up diary card was returned and checked, respiratory function, physical examination, urinalysis and weighing was carried out as for week −2. Blood was collected for estimation of full blood count, serum electrolytes, urea, creatinine and liver function tests. The patient was supplied with a new diary card, advised to cease taking regular SCG therapy and commenced on the study regimen. The procedure at the follow-up visits was similar; at these visits the patients were asked specifically for any change in symptoms and change in medications. Unused trial drugs were returned at these visits.

Statistical methods

Verification of the randomisation procedure for treatment order was made on baseline parameters using the two tailed *t*-test or Mann-Whitney two sample test, as appropriate.

To allow for possible carryover effects from previous treatment or gradual build up of effects of the current treatment, the analysis of results was concentrated on the last 4 weeks of treatment in each phase. The two tailed *t*-paired test was used to compare the results for each patient on each treatment. Point estimates and 95% confidence intervals were also calculated for the population mean difference and indicated that significant differences would have been detected had they been present.

Results

Thirty-five patients; 23 males, 12 females with a mean age of 28.3 years (s.d. ± 12.4 years) and a mean duration of asthma of 17.9 years (s.d. ± 10.9 years) entered the trial. The mean number of wheezing episodes per week was 3.9 (s.d. ± 2.8). Thirty-two had had previous SCG, duration of therapy ranged from 0.1–8.0 years. The mean percentage PFR observed/PFR predicted was 74% with a range of 40–105%.

Thirty patients completed the study. There was no significant difference in baseline parameters between the patients admitted into Group I (15) and Group II (15). The mean values for FEV_1 for each group were respectively 3.03l and 2.84l, VC4.33l and 3.86l and PFR 439l/s and 442 l/min. Of the five patients who did not complete the study, one dropped out at 1 week for family reasons, one did not return after week 0, two completed the trial but records were too incomplete for analysis and one patient was withdrawn after 6 weeks because of increasing severity of asthma. She proved to be on HC 20-511. Prior to the study she had been well controlled on SCG and improved once this was resumed.

Compliance was checked by a capsule count at each visit. This showed that for SCG, the mean daily dose was 3.2 capsules (80% of prescribed dose) and for HC 20-511, 1.8 capsules (91%).

A composite asthma score was calculated by adding the diary score the patient gave for night asthma (graded 1 = none, 4 = most severe), daytime asthma with activity (1–4), daytime asthma at rest (1–4), cough—day (1–4), sputum amount—day (1–3) plus the number of bronchodilator puffs used during the night and day and the number of tablets of theophylline or its salts taken daily. Thus, the

Table 1 Spirometry and peak flow rate (mean ± s.d.) at each clinic visit

Regimen	*Run-in period*		*HC 20-511*			*Sodium cromoglycate*		
Week number	−2	0	4	8	12	4	8	12
FEV_1(l)	2.92 (±0.85)	2.93 (±0.92)	3.03 (±0.92)	3.2 (±0.89)	2.95 (±0.9)	3.18 (±0.84)	3.05 (±0.84)	3.05 (±0.82)
VC(l)	4.17 (±1.03)	4.1 (±1.01)	4.17 (±1.14)	4.41 (±1.03)	4.09 (±1.12)	4.39 (±1.06)	4.31 (±1.1)	4.26 (±1.01)
PFR (l/min)	400 (±115)	441 (±96)	419 (±108)	431 (±95)	414 (±105)	449 (±110)	429 (±77)	404 (±105)

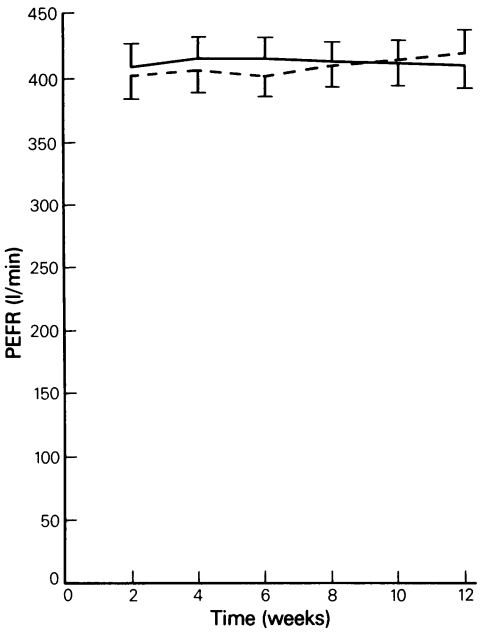

Figure 1 Peak flow rates on ketotifen (HC 20-511) (----) and sodium cromoglycate (——) (mean ± s.e. mean) over the fortnight ending at week number shown.

minimum possible score was 5. A mean daily score over the last 4 weeks on each therapy was calculated for 28 patients in whom full details were available. For HC 20-511 the mean score was 12.47 (s.d. ± 5.33), for SCG it was 11.97 (± 5.21). The difference was not significant, $P>0.05$.

Mean ± s.e. mean values for morning PFRs for each 2 weeks of daily readings are presented in Figure 1. No significant difference could be demonstrated between the two drugs. Analysis of this data separately for Group I and Group II showed that treatment order did not cause a significant change in morning PFRs.

Additional therapy during the study consisted either of short courses of prednisone or antibiotics that were prescribed by other medical officers for symptoms of an exacerbation. Two patients on HC 20-511 were given prednisone at 6 and 8 weeks of treatment; three patients on SCG required four courses at weeks 2 and 4 (patient number 31), 7 and 10. Patient number 31 who had HC 20-511 first required prednisone on both therapies, after 8 weeks on HC 20-511 and at 2 and 4 weeks of SCG.

Five patients had courses of antibiotics while taking HC 20-511; one after 6 weeks of treatment and four after 8 weeks. Antibiotics were also prescribed for five patients on SCG; three after 2 weeks of therapy, one at 4 weeks and one at the twelfth week.

Table 1 shows mean FEV_1 VC and PFR (± s.d.) recorded at each clinic visit. There was again no statistical difference between the two drugs.

Side-effects

Sedation occurred in ten patients with HC 20-511. This persisted to 12 weeks in (1), 8 weeks (2), 4 weeks (5) and 2 weeks (1). The therapeutic failure on HC 20-511 also complained of sedation. Five patients complained of sedation on SCG, four of these had SCG first.

There was a significant difference between HC 20-511 and SCG in weight at the end of 3 months ($P<0.05$). There was a mean loss of 1.4 ± 0.8 kg in patients receiving SCG in the second half of the trial. These patients gained 0.1 kg while on HC 20-511 in the first half.

No significant change was detected at anytime in BP, pulse rate, urinalysis, blood counts, serum electrolytes, urea, creatinine or liver function tests on either drug.

The first patient was commenced on therapy in May 1978 (end of Autumn) and the last patient completed the study in February 1979 (end of Summer).

Discussion

The results of this study suggest that HC 20-511 was comparable to SCG in the control of asthma in these patients. There was one treatment failure on HC 20-511 while a further two patients required short courses of prednisone. No patients had to be withdrawn while on SCG but three patients required four short courses of prednisone. Thirty-two of the 35 patients entered into the study had been well controlled on SCG prior to the study being commenced. Because of this we were reluctant to cease their therapy for any period of time to consider a placebo on its own at this stage.

The only index in which a statistical difference could be detected between treatments was weight. Those patients in Group II had a significant weight loss, the clinical relevance of this is not known. Sedation was reported more frequently in those on HC 20-511 but in all except three patients it had ceased to be a problem at the end of week 4. Patient compliance with HC 20-511 was marginally better, 91% of doses being taken compared to 80% for SCG. This could prove to be useful in some patients.

The clinical response of the patients was encouraging and further work is now warranted in larger groups to determine the place of HC 20-511 in the management of asthma and related disorders.

Sandoz Australia Pty. Ltd for providing supplies of ketotifen and placebo capsules and to Fisons Clinical Trials Department, Loughborough for supplies of SCG active and placebo capsules and spinhalers.

References

BROMPTON HOSPITAL/MEDICAL RESEARCH COUNCIL COLLABORATIVE TRIAL (1972). Long-term study of disodium cromoglycate in treatment of severe extrinsic or intrinsic bronchial asthma in adults. *Br. med. J.*, **4**, 383–388.

CRAPS, L., GREENWOOD, C. & RADIELOVIC, P. (1978). Clinical investigation of agents with prophylactic and antiallergic effects in bronchial asthma. *Clin. Allergy*, **8**, 373–382.

MARTIN, U. & RÖMER, D. (1978). The pharmacological properties of a new, orally active anti-anaphylactic compound: ketotifen, a benzocycloheptathiophene. *Arzneim. Forsch/Drug Res.*, **28**, 770–782.

PAUWELS, R., LAMONT, H. & VAN DER STRAETEN, M. (1978). Comparison between ketotifen and DSCG in bronchial challenge. *Clin. Allergy*, **8**, 289–293.

WEHEBA, A.S. (1978). Clinical assessment of the efficacy and tolerance of ketotifen in bronchial asthma. *Pharmatherapeutica*, **2**, 85–90.

WELLS, A. & TAYLOR, B. (1979). A placebo-controlled trial of ketotifen (HC 20-511, Sandoz) in allergen induced asthma and comparison with disodium cromoglycate. *Clin. Allergy*, **9**, 237–240.

(Received March 3, 1980)