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THE ORALLY ADMINISTERED ANTI-ALLERGIC AGENT, SODIUM NIVIMEDONE (BRL 10833); EFFICACY IN BRONCHIAL ASTHMA AND EFFECTS ON IgE, COMPLEMENT AND EOSINOPHILS

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1 Sodium nivimedone (BRL 10833) which acts similarly to disodium cromoglycate (DSCG), given at an oral dose of 200 mg thrice daily, was compared, after a preliminary standardization week, with placebo in a 6-week double-blind cross-over trial. Twenty-four non-smoking, atopic, asthmatic outpatients aged between 16 and 32 years, who were not taking corticosteroids took part. Subjects recorded symptoms and bronchodilator use each day and measured peak expiratory flow rate (PEFR) thrice daily.

2 Data was analysed separately for the twelve subjects who received placebo followed by sodium nivimedone (Group I) and those who took the treatments in the reverse order (Group II).

3 In Group I subjects, with sodium nivimedone, bronchodilator use decreased, symptom scores improved and there was a significant improvement in overall PEFR as well as the separated morning and evening values. When symptom scores were expressed as a percentage of the placebo disability index, wheezing, chest tightness, cough and asthma on activity showed significant improvement.

4 Subjects in Group II showed no improvement in any of these variables when drug was compared to placebo.

5 Sodium nivimedone did not appear to have any effect on circulating eosinophil levels, and concentrations of serum IgE, C3 and C4.

6 There was no clinical or laboratory evidence that sodium nivimedone had any untoward effect in the doses given.

7 Sodium nivimedone appeared to be of benefit in the subjects studied. The importance of appreciating the order of treatments and the value of frequent serial objective and subjective measures of disability backed up by appropriate data processing is stressed.

Introduction

A number of studies have shown that disodium cromoglycate (DSCG) is of value in the treatment of bronchial asthma (Brogden, Speight & Avery, 1974). It is generally agreed that the patients most likely to respond are young atopic individuals whose symptoms may or may not be accentuated by exposure to specific allergens. DSCG requires to be administered as a powder by inhalation. This has prompted the search for a compound with similar activity which can be taken orally. Since individuals with extrinsic (or allergic) asthma often have concomitant atopic dermatitis or allergic rhinitis, an orally administered anti-allergic agent may also be of benefit in these associated conditions.

Sodium nivimedone (BRL 10833) is an orally active anti-allergic agent with similar properties to DSCG. Chemically, sodium nivimedone is one of a novel series of 2-nitroindane-1,3-diones showing anti-allergic activity (Figure 1). The compound inhibited IgE-mediated passive cutaneous anaphylactic (PCA) reactions in the rat (Spicer, Ross & Smith, 1975) and the antigen-induced release of histamine from human lung passively sensitized with atopic serum (Coulson, Ford, Marshall, Walker, Wooldridge, Bowden & Coombs, 1977). The pharmacological potency of sodium nivimedone when compared to DSCG was 42 times greater in the human lung system and approximately ten times greater in rat PCA (Coulson *et al.*, 1977). In addition, single doses of sodium nivimedone given by mouth inhibited antigen-induced bronchoconstriction in man (Pauwels, Lamont & Van der Straeten, 1976). This has

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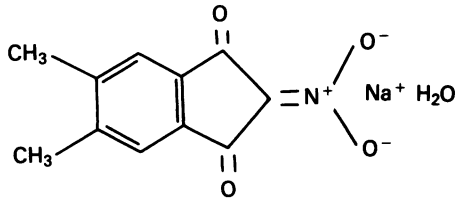


Figure 1 The structural formula of sodium nivimedone (BRL 10833), sodium 2-nitro-5,6-dimethylindane-1,3 dione monohydrate). The compound was administered in the form of its neutral sodium salt monohydrate.

prompted us to study the effects of sodium nivimedone by repeated oral administration in asthmatic subjects. Because of the variable nature of asthma and previous difficulties in assessing the efficacy of similar anti-allergic agents (Grant, Channell & Drever, 1967) we have undertaken frequent objective and subjective measurements and administered the agent using a placebo-controlled, double-blind cross-over design.

Methods

Patients

Twenty-four asthmatic out-patients with ages between 16 and 32 years (mean 22.9 years) took part in the study. Treatment at the time of entering the study, together with some clinical features and laboratory investigations, are given in Tables 1 and 2. All subjects had evidence of airway obstruction which reversed, either spontaneously or as a result of treatment, by more than 40% of either (i) the initial forced expiratory volume in one second (FEV_1) or (ii) the peak expiratory flow rate (PEFR). In addition, all the volunteers gave a personal history of asthma and all except one (no. 16) gave a weal of more than 3 mm in diameter on skin ('prick') testing to at least one common allergen (Bencard). All subjects had either associated allergic rhinitis or eczema or exercise-induced asthma or a family history of atopic disease.

The majority of subjects were taking DSCG prior to entering the study. It was not considered justifiable to ask them to discontinue this preparation before the start of week 1. However, some subjects having stopped taking DSCG had to postpone their date of entry into the 7-week study for a variety of personal reasons. In these situations they were asked not to recommence DSCG if their symptoms were controlled by inhalation of salbutamol.

All subjects were non-smokers, had not taken oral or inhaled corticosteroids during the previous 3 months and there were no individuals in whom clinical observations or laboratory tests suggested abnormal renal, hepatic or cardiac function. At the commencement of the study, female subjects were advised not to become pregnant during the trial and were warned that there was no guarantee that the drug did not have an adverse effect on pregnancy. The consent of the family doctor and the written consent of the subject were obtained in all cases. The study was approved by the Physicians Advisory Ethical Committee of the South Lothian District, Scotland.

Design of trial

The study lasted 7 weeks. At the preliminary visit all suitable subjects were instructed in the use of a pressurized salbutamol inhaler and were told to use this as often as necessary. Those taking bronchodilator preparations, or DSCG, prior to the study were asked to discontinue these treatments. The subjects were also instructed how to use a Wright peak flow meter—Airmed, Harlow (previously checked against a rotameter).

The patients made daily subjective assessment of symptoms on diary cards on a visual analogue scale 50 mm long; those recorded were wheezing, chest tightness, cough, sputum, daytime asthma at rest, daytime asthma on activity, night-time asthma, hay fever and eczema. Each day they also recorded duplicate readings of PEFR in the morning, at midday, in the evening and at night if woken by asthma with the exact time of readings. The dose and exact timing of inhaler usage were also noted. The subjects maintained a record of measurements of PEFR, subjective symptoms and inhaler usage on diary cards throughout the 7-week study period. The first week was a standardization period to allow the subjects to become accustomed to recording data on the daily diary cards.

Weeks two to seven were the 'double-blind' part of the study during which subjects received sodium nivimedone 200 mg three times a day (approx. 8 mg kg^{-1} day^{-1}) before meals for three consecutive weeks and placebo, identical in appearance, for the other three weeks. The order of the two treatments followed a balanced randomized block design so that half the subjects received placebo first, followed by sodium nivimedone (Group I) and half were given these agents in the reverse order (Group II).

Each week the subjects attended a clinic where they were assessed by a physician and asked to report any unusual signs and symptoms. The diary cards were checked and a further week's cards and tablets were issued. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured and a urine sample was obtained. At the preliminary clinic visit and at the beginning and end of each of the two treatment periods haemoglobin, red cell count, packed cell volume, platelets, white cell

Table 1 Details of clinical features, some allergy-associated laboratory tests and the treatment prior to entering the study in group I subjects

	Clinical features								*Laboratory tests*		*Treatment*		
Number	*Age (years)*	*Sex*	*Age at onset (years)*	*Rhinitis*	*Eczema (+) infantile*	*Exercise induced asthma*	*Family history*	*Skin prick tests positive/ total*	*Blood eosinophils × 10^9 l5'1)*	*Serum IgE (IU ml^{-1}) (highest recorded value)*	*DSCG dosage (spin-caps/ week)*	*Weeks since stopping DSCG*	*Salbutamol dosage (puffs/ week)*
2	30	M	<1	+	0	+	+	10/13	0.400	1650 (>4400)	2	4	14
3	32	F	26	+	0	+	+	18/27	0.290	115 (2350)	21	0	1
5	19	F	8	+	0	+	+	3/4	0..865	138 (403)	21	0	0
8	21	F	<1	+	0	+	+	3/4	0.378	>2000 (>2000)	28	0	1
11	18	F	3	+	0	0	0	2/10	0.817	83 (374)	14	2	0
12	29	F	7	+	+	+	+	10/10	1.395	1320 (>4400)	28	2	1
13	18	F	16	+	+	0	0	4/5	0.297	341 (>4000)	21	1	0
16	26	M	18	0	+	+	+	0/4	0.144	23 (95)	21	5 years	3
19	16	M	11	0	0	0	+	2/3	0.775*	170 (200)	21	0	1
20	16	F	8	+	0	+	+	4/17	0.120	550 (650)	28	2	6
21	26	F	5	+	+	+	+	3/10	0.152	264 (475)	0	NA	21
23	22	M	14	0	(+)	+	+	5/8	—	203 (250)	0	NA	21

* Week 2 (Placebo)
NA = not applicable (i.e. patient had never taken DSCG)

Table 2 Group II subjects. Details as in Table 1.

	Clinical features								*Laboratory tests*		*Treatment*		
Number	*Age (years)*	*Sex*	*Age at (onset (years)*	*Rhinitis*	*Eczema (+) infantile*	*Exercise induced asthma*	*Family history*	*Skin prick tests positive/ total*	*Blood eosinophils × 10^9 l^{-1}*	*Serum IgE (IU ml^{-1}) (highest recorded value)*	*DSCG dosage (spin-caps/ week)*	*Weeks since stopping DSCG*	*Salbutamol dosage (puffs/ week)*
1	24	M	8	0	+	+	0	11/21	0.135	3960 (>4400)	2	0	14
4	22	F	11	0	0	0	+	11/24	0.111	220 (550)	7	0	0
6	25	M	21	+	0	+	+	4/4	1.184	102 (975)	21	2	28
7	16	F	2	+	0	0	+	7/14	0.259	475 (1265)	21	0	0
9	16	M	3	0	0	+	+	2/12	0.385	1540 (1980)	21	0	14
10	26	M	7	+	+	+	+	15/18	0.366	300 (420)	28	0	7
14	25	F	13	+	0	+	+	3/7	0.780	58 (120)	21	3	28
15	29	M	21	0	+	+	0	9/18	0.043	143 (190)	21	0	0
17	28	M	10	0	0	+	+	1/2	0.435‡	66 (350)	21	0	21
18	16	F	10	0	(+)	+	+	4/4	0.126	450 (1000)	21	0	0
22	19	M	3	+	0	+	0	2/4	0.667	450 (700)	0	NA	14
24	30	F	16	+	0	+	+	2/5	<0.040	120 (120)	0	NA	42

‡ Follow up

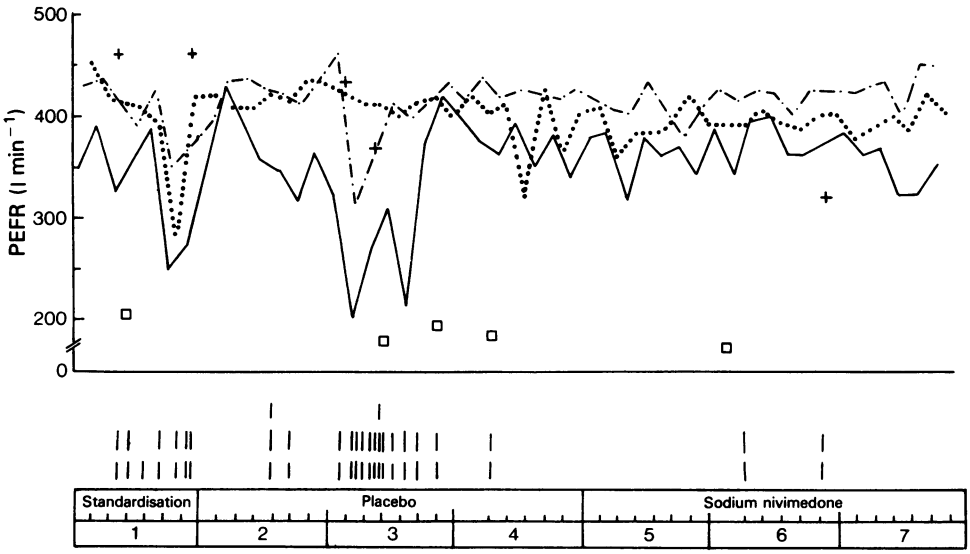


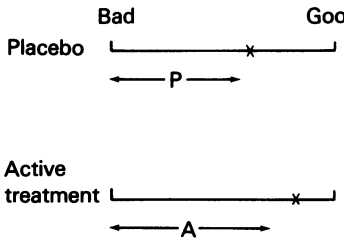
Figure 2 An example of inhaler usage and PEFR (—morning, -·-·- noon, ····· evenings) separated according to time of day for a subject in Group 1. + Values up to 4h after inhaler use; □ night values. The results were plotted by computer. Note the reduction in inhaler usage, less frequent night values and disappearance of low morning values during treatment with sodium nivimedone in this subject.

count, differential white cell count and one stage prothrombin time were measured in venous blood and a blood film examined; in addition urea, creatinine, alkaline phosphatase, bilirubin and alanine aminotransferase were measured in venous blood. (These haematological and biochemical measurements were considered necessary because sodium nivimedone is a new drug which had not previously been given to man on a continuous basis for 3 weeks.) The complement components C3 and C4 were measured by single radial immunodiffusion using mono-specific antisera and IgE by the radioimmunosorbent test (Phadebas, Pharmacia). Weekly urine samples and blood samples taken at the beginning and end of each treatment period were assayed for sodium nivimedone levels by extraction in *n*-butanol and absorbence at 350 nm (H. Smith, personal communication) to confirm adequacy of drug absorption and patient co-operation.

Data recorded daily on the diary cards were subjected to a system of computer storage, analysis and display (Clarkson, Lumb & McHardy, 1978). Computer programs permitted rapid calculation of the mean weekly values of PEFR, inhaler use and symptom scores for individual subjects as well as the overall mean values for the two groups. Output of these figures as a proportion of the standardization week or placebo period mean value was also possible. The weeks to be compared were then specified and the comparison was 'printed out' and examined for statistical significance. Information on the times of PEFR measurements and inhaler use allows those values of PEFR likely to have been influenced by prior inhaler use to be removed from subsequent analysis. In our study, readings up to 4 h after inhaler use were eliminated. This interval was chosen from knowledge of the time-course of action of inhaled salbutamol (Walker, Evans, Richards & Paterson, 1972) and represented a compromise between removal of the greatest effects of salbutamol and the desire to retain a reasonable number of peak flow values for analysis. The daily PEFR readings could be divided into those taken in the morning, at mid-day or in the evening; these could then be examined with or without removal of values likely to have been influenced by prior inhaler use. An example of computer displayed data for PEFR and inhaler usage for a patient in Group I is shown in Figure 2.

Statistics

The PEFR measurements and weekly inhaler usage followed a normal distribution and were analysed by the Student's *t*-test for paired observations. The symptom scores were analysed by a non-parametric test (Wilcoxon test of paired differences) and were also treated in the following manner: the mean score during the placebo period was converted to a placebo disability index (PDI) by subtracting it from a score of 50; the score which should be achieved in the entire absence of symptoms (Figure 3). The differences in



$$\text{Placebo disability index (PDI)} = \text{Max. score} - \text{Placebo score} = 50 - P$$

$$\text{Change in mean symptom score (\% PDI)} = \frac{A - P}{50 - P} \times 100$$

Figure 3 The method of calculating the placebo disability index. Nine symptoms were recorded on diary cards by marking a cross on a 50 mm line. The symptoms and cues at the left and right of each analogue scale were as follows. Wheezing (continuous—absent); chest tightness (severe—none); cough (frequent—absent); sputum (a lot—none); daytime asthma, at rest (severe—none); daytime asthma, on activity (hardly able to move at all—none); asthma last night (awake most of the night with asthma—none); hayfever (very bad—none); eczema (very bad—none).

mean score when on sodium nivimedone compared with placebo were expressed as a percentage of the PDI and were then analysed by the Wilcoxon test of paired differences.

Results

The data for Groups I and II were analysed by comparing either the full three weeks on sodium nivimedone with placebo or the last week only on each treatment. Examination of the last week only revealed greater differences between sodium nivimedone and placebo and so these periods were used for all subsequent comparisons. The PEFR measurements and inhaler usage are shown in Figure 4. The total PEFR measurements and those taken in the morning and evening differed significantly in Group I subjects when sodium nivimedone was compared to placebo. No significant difference was found for the noon-time values in Group I subjects or for any of the PEFR measurements in Group II subjects. The magnitude of these changes was largely unaffected, and their significance unaltered, by removal of PEFR values likely to have been influenced by prior inhaler use. Inhaler usage in both Group I and Group II subjects showed no significant difference between sodium nivimedone and placebo.

Symptom scores were analysed by comparison of the mean scores during the final week on each treatment. In subjects in Group I the comparison favoured the active drug for all symptom scores. When analysed by the Wilcoxon test of paired differences only the score for wheezing proved to be statistically significant ($P < 0.05$). In contrast, subjects in Group II tended to show a slight deterioration in all scores (except hay fever and eczema) when the comparison was made. The symptom scores were further analysed in terms of PDI (see above) and the results are shown in Figures 5a and 5b. Significant changes in favour of sodium nivimedone were found in Group I subjects for wheezing, chest tightness, cough and asthma on activity. Sputum production, asthma at rest and asthma at night were not significantly affected. The number of subjects with hay fever and eczema was too small for statistical analysis. None of the symptom scores for subjects in Group II showed significant changes in this analysis.

The mean changes in the morning PEFR, inhaler usage and the symptom score for wheezing between the standardization week and the individual weeks for subjects in Group I or II are shown in Figure 6. Those in Group I showed only slight changes from the standardization week value whilst on placebo but tended to improve when on sodium nivimedone in a time-dependent manner, with the greatest improvement being found at the third week. Therefore, in this group, comparisons between the last week on placebo and the last week on sodium nivimedone showed the greatest differences. In contrast, Group II subjects (who received sodium nivimedone first) showed an improvement when the last week of active therapy was compared to the standardization week and this improvement tended to be maintained during the time they were on placebo. Therefore, in Group II subjects, comparisons between the last week on placebo and active preparations did not show appreciable differences, although they had improved whilst on sodium nivimedone.

The data for each subject were also examined separately to try to estimate the benefit from treatment in each individual. The criteria of benefit chosen were a 10% increase in PEFR irrespective of time of day, an increase in any symptom score of 5 mm or more or a reduction of inhaler use of at least 10 puffs per week. When the last weeks on sodium nivimedone and on placebo were compared, all the subjects in Group I and half of those in Group II showed an improvement in at least one of these variables whilst taking sodium nivimedone.

In general, an improvement in a subjective measurement in a given individual was associated with improvement in PEFR. An example is given in Figure 7 in which the change in wheezing symptom score is compared with the change in morning PEFR of subjects in Group I. Nine of the twelve subjects showed an improvement in both variables when sodium nivimedone was compared to placebo for the last week on either treatment.

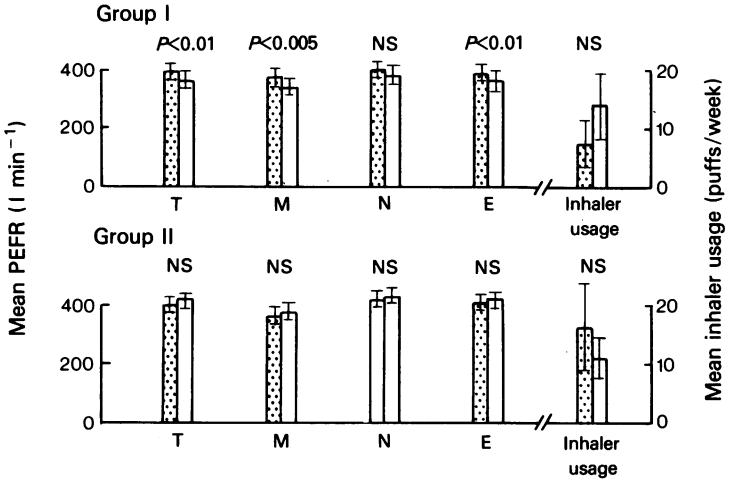


Figure 4 The effect of sodium nivimedone (▩) and placebo (□) on the PEFR and inhaler usage. The mean values for the last week on either treatment are shown together with the s.e. mean, and the significance of the difference between each pair of means is shown. T=total, M=morning, N=noon and E=evening.

During the standardization week the FEV_1, FVC and FEV_1/FVC were within the predicted range for the majority of subjects. These measurements fluctuated from week to week but appeared to be unrelated to treatment with sodium nivimedone or placebo even in those individuals whose initial values were below their predicted limits.

In Figure 8 the effects of sodium nivimedone and placebo on circulating eosinophil counts, and serum concentrations of IgE, C3 and C4 were compared in subjects in Group I and Group II. The compound did not have any significant effect on these indices of hypersensitivity. However, these variables exhibited marked variations in the majority of subjects.

Although occasional abnormal values of laboratory tests and signs and symptoms were noted, the pattern of these did not allow any interpretation in terms of the treatment with the drug or placebo and were not considered, clinically, to be 'side effects'.

Blood and urine levels of sodium nivimedone confirmed subject co-operation but these concentrations were not of value in determining the therapeutic outcome.

Discussion

The congruence of several methods of assessment, both objective and subjective, suggests that sodium nivimedone was of benefit in the asthmatic subjects studied although most of them had a mild form of the disease. Furthermore, these improvements were more easily appreciated in Group I subjects, since, with those in Group II, the effect of sodium nivimedone appeared to be sustained into the 'placebo period'. This may be due to the failure of the asthmatic subjects in Group II to deteriorate during the subsequent three weeks on placebo. The data do not allow us to distinguish between a 'carry-over' effect of an active drug (sodium nivimedone or DSCG treatment taken prior to the study) into the placebo period or a change in the pattern of asthma following a period of effective treatment. DSCG had a marked 'carry-over' effect in a previous double-blind cross-over trial in asthma (Bernstein, Siegel, Brandon, Brown, Evans, Feinberg, Friedlaender, Krumholz, Hadley, Handelman, Thurston & Yamate, 1972).

In the present study, exclusion of subjects taking oral or inhaled corticosteroids resulted in a group of mild asthmatics. Despite this we found (Figure 2) that during the study period all subjects showed variations of PEFR or FEV_1 of more than 40% of the initial value despite the fact that for the majority the preliminary spirometric measurements were within the normal range. Clark & Hetzel (1977) observed changes in PEFR of a similar magnitude and suggested that the diurnal variations might result from incomplete control of the subject's asthma during sleep.

A most important point, which was apparent from the present study, was that no consistent effect, beneficial or otherwise, was demonstrable by *weekly* spirometric measurements, i.e. FEV_1, FVC and FEV_1/FVC. In contrast, *thrice daily* measurements of the PEFR (using the portable Wright Peak Flow Meter) emphasized the variability of airway obstruction even in these mild asthmatics and also allowed the beneficial effect of sodium nivimedone to be assessed.

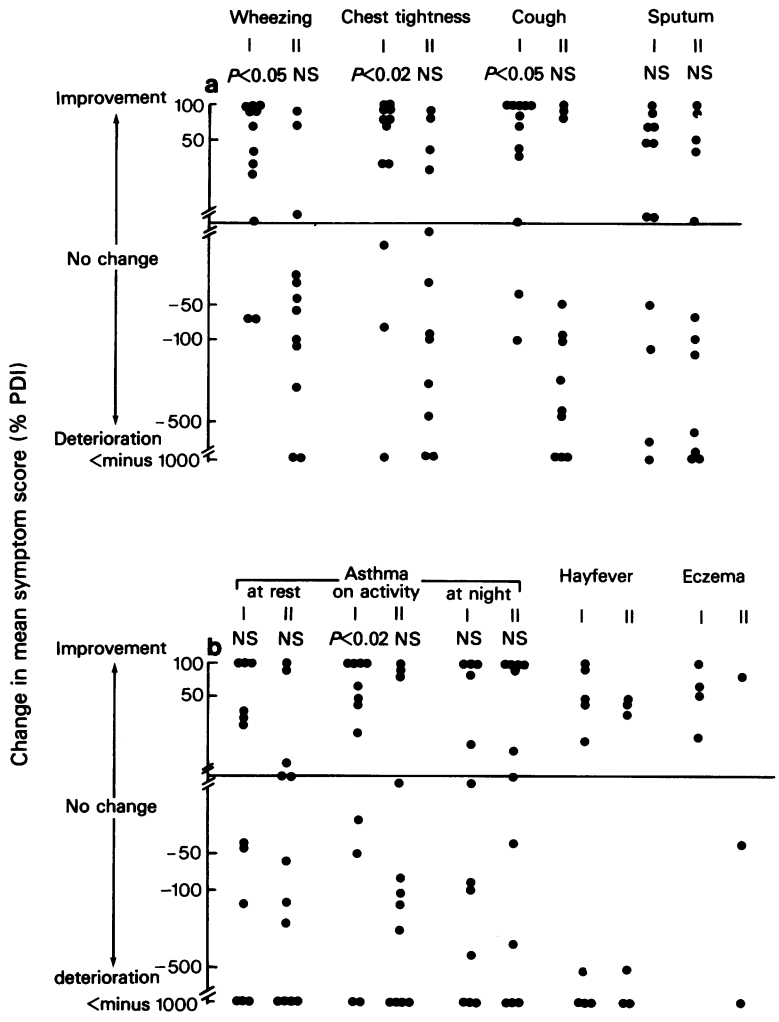


Figure 5a and b Changes in subjective symptom scores, expressed as % PDI (for explanation see text), obtained from diary cards for subjects in Groups I and II for the last week on either treatment. Note breaks in the ordinate scale. Statistical significance was assessed using the Wilcoxon test. The number of subjects with hayfever and eczema was too small for statistical analysis.

Many subjects had symptom scores of close to the maximum of 50 which should only have been achieved in the complete absence of symptoms. This could be partly due to freedom from symptoms in those with mild asthma. We noted, however, that some individuals were stoical; despite marked daily fluctuations in PEFR (which was often considerably lower than the predicted value) these individuals considered themselves almost free from symptoms. Nevertheless, in the majority of subjects changes even in consistently high symptom scores were related to objective measures of disability. Because of this phenomenon we feel it is justifiable to analyse subjective improvement not only in terms of symptom scores alone but also in terms of changes in the derived PDI. A similar manipulation of symptom scores was used in a study of DSCG in asthma (Scherrer & Wyss, 1970).

Consideration of entire groups of subjects, whilst allowing the significance of objective and subjective measures to be assessed, may also mask individual improvements. Examination of an individual's weekly data indicated that the majority of subjects derived some benefit from sodium nivimedone. The benefit might be more accurately assessed by analysis of the daily fluctuations in objective and subjective measures that occur as a result of the episodic nature of asthma.

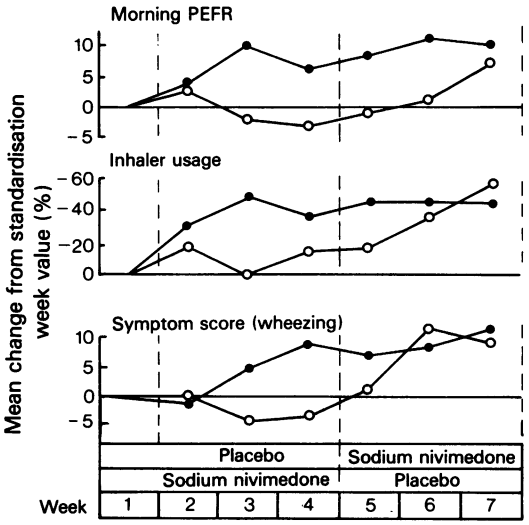


Figure 6 Mean weekly values of selected objective and subjective indices of asthma during the study for subjects in Groups I (○) and II (●). Week 1 was for standardization.

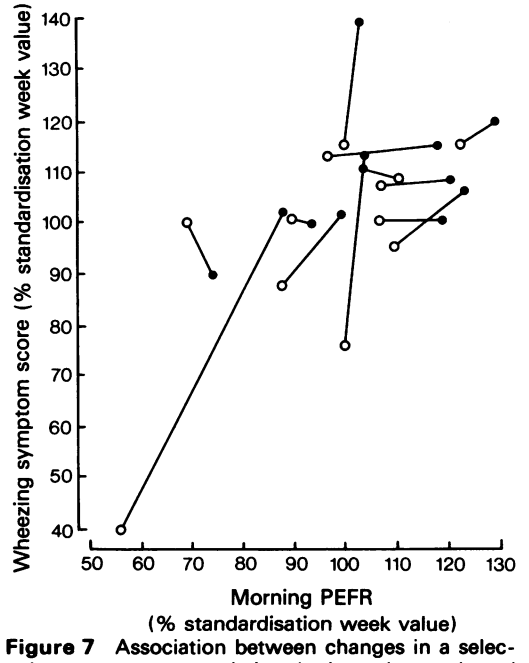


Figure 7 Association between changes in a selected symptom score (wheezing) and a selected objective measurement (morning PEFR) for the last week on placebo (○) and the last week on sodium nivimedone (●) in Group I subjects.

The possible contribution of type I hypersensitivity to the symptomatology in these subjects was estimated from circulating IgE concentrations and the numbers of circulating eosinophils. Since complement-derived peptides (anaphylatoxins) are

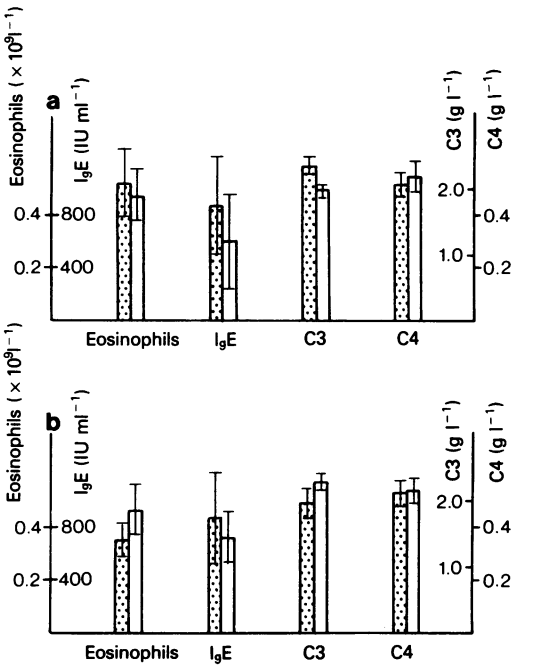


Figure 8 The effect of sodium nivimedone (▨) and placebo (□) on IgE, C3 and C4 serum concentrations and blood eosinophils in (a) Group I and (b) Group II. The mean values for the last week on either treatment are shown together with the s.e. mean.

known to release histamine from mast cells the concentrations of circulating C3 and C4 were also measured but were unaltered by the drug. The finding with eosinophils is in contrast to those of Easton (1973) who showed a fall in peripheral eosinophilia after 3 weeks' treatment with DSCG in children; however, his patients were selected on the basis of an initial eosinophil count of more than 500 cells per mm^3 whereas ours were not.

We believe that the design of this study has certain advantages in the assessment of the effectiveness of oral drugs in the treatment of asthma. Both subjective and objective measurements are needed, previous trials having been criticized on these grounds (Howell, 1978). Infrequent simple objective measurements proved to be of no value in this study and infrequent complex tests are unlikely to be any better. We stress the value of serial measurements of PEFR at several times of day, especially when backed up by appropriate data processing facilities.

After this trial was completed the results of some chronic toxicity studies in the rat became available. Forty of these animals who had received high doses of sodium nivimedone for 16 months (equivalent to some 30 years in man) were autopsied. The bladder mucosa showed hypertrophy in six animals and definite malignant change in three. All the animals

showing this effect came from the medium and high dose levels used in the test. No such abnormalities were seen in animals from the low dose and control groups. Further clinical trials on sodium nivimedone have been halted until the results of more extensive toxicity data are available.

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