PAPERS AND ORIGINALS

Long-Term Study of Disodium Cromoglycate in Treatment of Severe Extrinsic or Intrinsic Bronchial Asthma in Adults

Brompton Hospital/Medical Research Council Collaborative Trial

British Medical Journal, 1972, 4, 383-388

Summary

The results are reported here of a long-term double-blind controlled clinical trial of disodium cromoglycate (D.S.C.G.) and isoprenaline, D.S.C.G. alone, isoprenaline alone, and a placebo given as a powder for inhalation in the treatment of severe bronchial asthma.

At the end of one year 16 out of 20 patients on D.S.C.G.-isoprenaline remained on the allocated capsules, compared with 10 out of 15 on D.S.C.G., 5 out of 20 on isoprenaline, and 3 out of 19 taking the placebo. The differences between each of the D.S.C.G.-isoprenaline and D.S.C.G. regimens compared with the isoprenaline and placebo regimens were statistically significant. After eight weeks on four capsules a day the patients in each group were allocated at random so that half continued on full dosage and half on a reducing regimen. At the end of the year there was no significant difference in the failure rate between patients allocated the full dosage and the patients on the reducing dosage. The capsules were well tolerated and toxicity to D.S.C.G. was not observed.

Introduction

In 1965 disodium cromoglycate (D.S.C.G.) was isolated and found to be among the most active of the synthetic bichromones in its ability to inhibit certain anaphylactic reactions in animals and bronchial reactions to inhaled allergens in man (Altounyan, 1967; Cox, 1967). It has no direct bronchodilator action and has no antihistamine, anti-inflammatory, or steroid-like properties (Cox, 1967).

When given intradermally with an antigen D.S.C.G. inhibits passive cutaneous anaphylaxis in monkeys sensitized with human reaginic serum (Cox, 1967). It also reduces the amount of histamine and slow reacting substance A released from passively sensitized chopped lung after challenge with the appropriate antigen (Cox, 1967). D.S.C.G. does not appear to prevent interaction between antigen and cell-bound antibody but apparently prevents release of vasoactive mediators of anaphylaxis from mast cells (Goose and Blair, 1969). It also inhibits histamine release caused by phospholipase A, a substance not concerned with reaginic mast-cell degranulation (Orr and Cox, 1969). In man previous inhalation of D.S.C.G. but not placebo suppresses the immediate reaginic bronchial reaction to inhalation challenge with allergen and will also prevent the late (four to six hours) increase in airways obstruction, especially in those instances where a dual (immediate and late) bronchial reaction can be shown (Altounyan, 1967; Pepys *et al.*, 1968; Minette, 1970; Orie *et al.*, 1970). In contrast exercise asthma may be inhibited by both D.S.C.G. and placebo (Davies, 1968, 1970; Muittari and Kreis, 1969; Ward *et al.*, 1969; Blackhall and Jones, 1970; Poppius *et al.*, 1970).

When the present study was planned several short-term trials of various designs had indicated a definite superiority of D.S.C.G. over placebo in the suppression of asthmatic symptoms as reported by the patient (Howell and Altounyan, 1967; Kennedy, 1967; Bruce and Hansell, 1968; Moran *et al.*, 1968; Morrison-Smith and Devey, 1968; Altounyan and Howell, 1969; Chen *et al.*, 1969; Lopez *et al.*, 1969; Munro Ford, 1969; Williams and Kane, 1969). In only one trial was no difference found (Grant *et al.*, 1967). In some trials, however (Campbell and Tandon, 1969; Lane, 1969; Robertson *et al.*, 1969), in which a difference was found the clinical improvement was not always reflected in the changes in the forced expiratory volume in one second (FEV₁).

The purpose of the present trial was to study the effects of D.S.C.G. used as in clinical practice continuously over a

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prolonged period of time both in "extrinsic" and "intrinsic" asthma and to obtain information on its efficacy and toxicity. In addition two different dosage schedules were studied. In one a standard daily dosage was maintained throughout the first 12 months of the trial, and in the other the daily dosage was reduced but not stopped when the patient became and remained free of symptoms. This report gives the results of the first year of the study.

Patients and Methods

Asthmatic patients were admitted to the trial if they: (1) were aged 15 years or over; (2) had had variable dyspnoea and wheeze for more than three months; (3) had wheeze most days or nights; (4) had sufficiently severe symptoms to cause difficulty with their everyday routine; (5) had not had previous treatment with D.S.C.G.; (6) had not received corticosteroid treatment during the previous three months; (7) were suitable for pretrial treatment with a standard panel of drugs; (8) were willing to enter the trial, to have a period of pretrial assessment, to keep a daily diary of symptoms, and to attend regularly; and (9) were suitable for corticosteroid therapy if this became necessary.

Patients were admitted only if they had symptoms on most days sufficiently severe to interfere with their normal lives and not controlled by the pretreatment trial period of two weeks with drugs from the standard panel set out below.

TREATMENT REGIMENS

Four types of capsule were made up for inhalation via a Spinhaler. The contents of a capsule of each type were as follows. (1) D.S.C.G.-isoprenaline: D.S.C.G. 20 mg, isoprenaline sulphate B.P. 0.1 mg, lactose B.P. 20 mg; (2) D.S.C.G.: D.S.C.G. 20 mg, lactose 20 mg; (3) isoprenaline: isoprenaline sulphate 0.1 mg, anhydrous sodium sulphate B.P.S. 5 mg, lactose 35 mg; (4) placebo: anhydrous sodium sulphate B.P.S. 5 mg, lactose 35 mg.

The capsules were identical in appearance and similar in taste. Patients were allocated at random to receive one of the four types of capsule and also to receive either (a) full dosage—that is, four capsules a day for one year—or (b) the reducing dosage—that is, after eight weeks on four capsules a day if free of symptoms the dosage of capsules was to be reduced to three a day for a week, then two a day for a week, down to a minimum of one daily, which was to be maintained for the rest of the year. If wheeze returned the patient was to increase the daily dosage to the lowest number of capsules which kept him free of wheeze, the number being recorded daily on the diary card. The random allocation included stratification for physician and for eosinophilia.

The study was conducted double blind; none of the medical staff concerned or the patients knew the contents of any individual capsules.

MAIN PARTICIPANTS IN TRIAL

The roles of the physician in charge and of the clinical co-ordinator are summarized in Table I (a) at the pretrial assessment two weeks before the patient's possible admission to the study, (b) on the day of admission, and (c) at the subsequent attendances for follow-up. Each physician assessed new patients attending their outpatient clinic, and the patients were considered eligible for the trial if they satisfied the criteria outlined above. The referring physician remained responsible for the regular clinical assessment of the patient during the whole trial period and for the management (which included the use of the standard panel of drugs as well as the trial capsules). He could withdraw a patient from the trial

if at any time progress was clearly unsatisfactory and was then free to start known D.S.C.G., corticosteroids, or any other treatment. When a patient was withdrawn from the trial the physician was requested not to ask the patient's trial regimen unless this information was essential for further management.

The Medical Research Council Tuberculosis and Chest Diseases Unit participated in the planning and undertook the random allocation, the interim, and the final analyses of the results.

PATIENT ATTENDANCES

First Attendance.—In addition to assessing eligibility the physician prescribed treatment from a standard panel of drugs—namely, Franol* 2-4 tablets daily, orciprenaline 40-80 mg daily, salbutamol 4-8 mg daily, aminophylline suppositories 1 nightly, promethazine 10-25 mg nightly, nitrazepam 5-10 mg nightly, isoprenaline inhaler up to 10 puffs in 24 hours, salbutamol inhaler up to 6 puffs in 24 hours. The object of using a standard panel of "background" drugs was to limit to some extent the range of therapy used. The patient was instructed to keep a daily diary of symptoms, recording the severity of the asthma (severe, moderate, slight, or nil) and cough (severe, moderate, slight, or nil) and the amount of sputum (a lot, occasional blobs, or none). There was also space to record the treatment actually taken from the standard panel of drugs. This gave a record of baseline symptoms for a fortnight before the trial capsules were started.

Second Attendance.—A fortnight after the first attendance the patient's progress was revived and the diary card inspected to ensure that the recordings were adequate. If asthmatic symptoms were still present on most days of the week in spite of treatment with full doses of standard panel drugs the patient was admitted to the trial and started on four trial capsules daily.

Subsequent Attendances.—The patient attended fortnightly for the first eight weeks and then monthly up to a year to enable continuing assessments of progress to be made by the physician and co-ordinator. The patient's diary was checked regularly for completeness by the co-ordinator but it was not made available to the physician in charge. In order to detect possible toxic effects samples of blood and urine were obtained each month and examined by the same tests as at the first attendance (Table I).

TABLE I—Roles of Physician in Charge and Clinical Co-ordinator

	Pre-trial Assessment (2 weeks Before Admission)	Assessments for Admission to Trial	Follow-up Assessments (2-weekly to 8 Weeks, 4-weekly Thereafter)
Physician in charge	Criteria of eligibility checked	Review of progress and of clinical management	Review of progress and of clinical management
Clinical co-ordinator	Allergic history taken Skin testing to 22 allergens Spirometry (FEV ₁ , FVC) Blood specimens taken* Urine specimens collected†	Patient's diary checked Spirometry (FEV ₁ , FVC) Blood specimens taken* Urine specimens collected†	Patient's diary checked Spirometry (FEV ₁ , FVC) Blood specimens taken* Urine specimens collected

*For haemoglobin, white cell count, wet eosinophil count, E.S.R. (Westergren), blood urea, and serum aspartate and alanine aminotransferases.

†For examination for sugar and albumin.

WITHDRAWAL FROM TRIAL

If the physician was not satisfied with the patient's progress the patient could be withdrawn from the trial as a "treatment

* Franol tablets contain ephedrine hydrochloride 11 mg, phenobarbitone 8 mg, and theophylline 120 mg.

failure," the reasons being categorized as one or more of the following: acute attack, inadequate general control, no improvement since starting capsules, intolerance to the capsules.

Results

A total of 103 patients was admitted to the study—26 on the D.S.C.G.-isoprenaline regimen, 24 on D.S.C.G., 26 on isoprenaline, and 27 on the placebo. Two patients in the placebo group were withdrawn from the trial, one because she became pregnant and the other, who had late onset extrinsic asthma due to cedar wood dust, because he lost all his symptoms when removed from exposure. Three patients (one on each of the D.S.C.G.-isoprenaline, isoprenaline, and placebo regimens) were withdrawn because of intolerance to the capsules. A further 18 patients (four on D.S.C.G.-isoprenaline, six on D.S.C.G., four on isoprenaline, four on placebo) who were making satisfactory progress but did not complete 36 weeks because they stopped attending for a variety of non-medical reasons were excluded from the analyses at a year. There remained in the main analyses 80 patients (21 on D.S.C.G.-isoprenaline, 18 on D.S.C.G., 21 on isoprenaline, 20 on placebo), of whom six (three on D.S.C.G. and one in each of the other treatment groups) stopped attending between 36 and 52 weeks. (These six patients are excluded from Table IV onwards.)

PRETREATMENT CONDITION

A pretreatment analysis of the patients in the main study is summarized in Table II. More men than women were admitted to the trial. The numbers of patients aged less than 35 and 35 or more were similar. A history of known allergy was obtained in 64% and positive skin tests to one or more allergens were obtained in 69% of the patients. Of the 55 positive reactors 16 (29%) showed single positive skin tests, the commonest allergen being house dust to which 82% of the 55 patients reacted. About half of the patients tested had a blood eosinophil count of 500 or more per mm³.

The distributions of these factors within the treatment

TABLE II—Pretreatment (Time of Admission to Study) Status of Patients in Analysis

	No. (%) of Patients	Treatment Group			
		D.S.C.G.-Iso-prenaline	D.S.C.G.	Iso-prenaline	Placebo
Males	46 (58)	8	14	14	10
Females	34 (42)	13	4	7	10
Age in years:					
Less than 35 ..	42 (52)	9	12	12	9
35 or more ..	38 (48)	12	6	9	11
Previous history of allergy:					
None	29 (36)	6	8	8	7
Known history ..	51 (64)	15	10	13	13
Allergy to:					
House dust ..	41 (51)	14	7	9	11
Seasonal allergens ..	15 (19)	3	5	3	4
Pollens	22 (28)	3	6	5	8
Animals	19 (24)	5	4	7	3
Foods	16 (20)	3	5	1	5
1 Group only ..	16 (20)	8	2	1	5
2 Groups	17 (21)	4	3	7	3
3-5 Groups ..	18 (23)	3	5	5	5
Skin tests:					
No positive result ..	25 (31)	7	5	7	6
Positive results ..	55 (69)	14	13	14	14
Positive to:					
Dusts	45 (56)	12	10	13	10
Fungi	12 (15)	3	2	2	5
Plants	33 (41)	7	8	9	9
Foods	13 (16)	3	3	4	3
Animals	21 (26)	6	4	7	4
1 Group only ..	16 (20)	3	6	1	6
2 Groups	19 (24)	6	3	7	3
3-5 Groups ..	20 (25)	5	4	6	5
Blood eosinophilia:					
Less than 500/mm ³ ..	39 (49)	9	11	10	9
500/mm ³ or more ..	34 (42)	9	6	10	9
Not available ..	7 (9)	3	1	1	2
Total	80 (100)	21	18	21	20

groups were broadly similar but with the following exceptions. There were substantially fewer female patients on the D.S.C.G. and isoprenaline regimens than on the others. The D.S.C.G. group contained a higher proportion of patients aged under 35 years. Histories of allergy to a single group of allergens were commoner in the D.S.C.G.-isoprenaline and placebo groups than in the D.S.C.G. and isoprenaline groups. Positive skin tests to a single group of allergens were obtained more frequently in the D.S.C.G. and placebo groups. In summary, there was little evidence on the small numbers available of noteworthy differences between the four treatment groups.

RESULTS DURING YEAR

The available results of treatment at intervals of four weeks up to a year are set out in the Chart for the patients who completed at least 36 weeks in the study. It is also seen from Table III that in the first four weeks none of the patients in the D.S.C.G.-isoprenaline or D.S.C.G. groups were treatment failures, compared with four of the 21 on isoprenaline and five of the 20 on the placebo. By eight weeks the number of failures on the placebo regimen had increased to 10; two had failed on the D.S.C.G.-isoprenaline regimen and one on the D.S.C.G. regimen. The proportion of treatment failures on the isoprenaline regimen increased so that by 16 weeks it was nine out of 21, compared with 12 out of 20 on the placebo regimen, findings clearly different from the two failures among the 21 patients on D.S.C.G.-isoprenaline and two among the

Results of treatment up to one year for patients completing at least 36 weeks in the trial.

TABLE III—Results of Treatment

Week of Observation	Treatment Group	No. of Patients Assessed	Treatment Failure	Patients Continuing on Capsules as Allocated	
				No.	%
4	D.S.C.G.-Isoprenaline	21	0	21	100
	D.S.C.G.	18	0	18	100
	Isoprenaline	21	4	17	81
	Placebo	20	5	15	75
8	D.S.C.G.-Isoprenaline	21	2	19	90
	D.S.C.G.	18	1	17	94
	Isoprenaline	21	5	16	76
	Placebo	20	10	10	50
12	D.S.C.G.-Isoprenaline	21	2	19	90
	D.S.C.G.	18	2	16	89
	Isoprenaline	21	7	14	67
	Placebo	20	12	8	40
16	D.S.C.G.-Isoprenaline	21	2	19	90
	D.S.C.G.	18	2	16	89
	Isoprenaline	21	9	12	57
	Placebo	20	12	8	40
24	D.S.C.G.-Isoprenaline	21	2	19	90
	D.S.C.G.	18	3	15	83
	Isoprenaline	21	11	10	48
	Placebo	20	13	7	35
52	D.S.C.G.-Isoprenaline	20	4	16	80
	D.S.C.G.	15	5	10	67
	Isoprenaline	20	15	5	25
	Placebo	19	16	3	16

All the percentages are based on less than 25 observations.

18 on D.S.C.G. Thereafter there were relatively few treatment failures, and by 52 weeks there were four failures among 20 D.S.C.G.-isoprenaline patients and five among 15 D.S.C.G., 15 among 20 isoprenaline, and 16 among 19 placebo patients. At four weeks the difference between the placebo and each of the D.S.C.G. regimens first attained statistical significance ($P=0.05$) and remained significant thereafter. Correspondingly, at 16 weeks the differences between the isoprenaline and each of the D.S.C.G. regimens also attained significance at the 5% level and remained significant thereafter. None of the differences between the two D.S.C.G. regimens or between the isoprenaline and placebo regimens attained statistical significance. Thus patients on the placebo or isoprenaline fared badly, the failures on the placebo in particular tending to occur earlier in treatment, while the two D.S.C.G. series fared substantially and significantly better.

Of the patients who failed none of the four on D.S.C.G.-isoprenaline, three out of five on D.S.C.G., six out of 15 on isoprenaline, and five out of 16 on placebo did so with acute attacks of asthma. Of the rest a substantial proportion—namely, two, one, seven, and 10 respectively—were regarded as having “inadequate general control” of the asthma, and two, one, two, and one respectively had no improvement since starting the capsules. There was some overlap between the three categories.

FULL AND REDUCING DOSAGE

As described above, having completed eight weeks on four capsules daily patients were then continued at random either on four capsules (full dosage) or the reducing regimen. The results at 52 weeks are set out in Table IV for the four

TABLE IV—Results at One Year with the Full and Reducing Dosage Schedules*

Treatment Group	Subgroup	No. of Patients Assessed	Treatment Failure	Patients Continuing on Capsules as Allocated	
				No.	%
D.S.C.G.-Isoprenaline ..	Full	9	1	8	89
	Reducing	9	1	8	89
D.S.C.G. ..	Full	7	1	6	86
	Reducing	7	3	4	57
Isoprenaline ..	Full	10	6	4	40
	Reducing	5	4	1	20
Placebo ..	Full	5	4	1	20
	Reducing	4	2	2	50

*This table does not include the 18 patients who failed in the first 8 weeks (see Table III). All the percentages are based on less than 25 observations.

treatment groups. There was little evidence of any difference between patients on the full reducing dosage, although the numbers of patients for comparison were very small. (Analyses at 24 and at 36 weeks, when larger numbers were available, led to the same conclusions.)

Dosage of Capsules Received.—As stated above, the aim in the reducing dosage was to drop to a maintenance dose of one

a day, provided the asthma remained under adequate control. In the event 27 out of 30 patients in all four treatment groups on full dosage recorded that they had inhaled throughout the year an average of 25 or more capsules a week.

Of those allocated to the reducing regimen six out of nine receiving D.S.C.G.-isoprenaline, three out of seven on D.S.C.G., none of the five on isoprenaline, and three out of four taking the placebo recorded that they had reduced their capsules to an average of 18 or fewer a week.

Of the 21 patients with records available who failed on their allocated treatment all but four had, in fact, increased their capsules to 25 or more a week before the physician's decision to withdraw them.

SPIROMETRY

In order to study changes of ventilation on the four regimens an analysis was made of the change of the FEV₁ in each patient from pretreatment to the time of failure or at 24 or 52 weeks (Table V). Among those who failed there was no evidence of any change in the FEV₁ in any of the treatment groups. By contrast those who continued on their prescribed regimens of D.S.C.G.-isoprenaline, D.S.C.G., or isoprenaline showed statistically—significant improvements in the FEV₁ at both 24 and 52 weeks. No improvement was seen in the FEV₁ at either of those times among the patients on the placebo.

PROGNOSTIC IMPORTANCE OF FACTORS IN PRETREATMENT STATE

A multiple regression analysis (not tabulated here) was undertaken for each regimen separately, the following factors being included in the regression: age, sex, height, percentage of predicted normal FEV₁, percentage of predicted normal forced vital capacity, wheeze, general state, eosinophilia, history of any allergy, history of allergy to house dust, all skin test results, and the results of the skin test to house dust. The only pretreatment factors shown to be significantly associated with response in the D.S.C.G.-isoprenaline group were the general state and sex, the females responding better than the males, and none of the factors studied was significantly associated in the patients on the other three regimens.

The response at eight, 24, and 52 weeks for the patients who had a history of allergy and one or more positive skin tests

TABLE VI—Response at eight, 24, and 52 Weeks Related to Type of Asthma*

Treatment Group	Type†	No. of Patients Assessed	No. of Failures by:		
			8 Weeks	24 Weeks	52 Weeks
D.S.C.G.-isoprenaline	Extrinsic	13	0	0	1 (8%)
	Intrinsic	4	1	1	2 (50%)
D.S.C.G. ..	Extrinsic	7	1	2	2 (29%)
	Intrinsic	5	0	1	2 (40%)
Isoprenaline	Extrinsic	11	2	5	8 (73%)
	Intrinsic	6	1	3	4 (67%)
Placebo ..	Extrinsic	12	7	7	9 (75%)
	Intrinsic	6	3	5	6 (100%)

*This table excludes patients who were non-attenders after 36 weeks.
†See text for definitions.

TABLE V—Percentage of Predicted Normal for FEV₁ Comparison of Pretreatment Means with Means at Week of failure or at 24 or 52 Weeks

Status	Week	D.S.C.G.-isoprenaline		D.S.C.G.		Isoprenaline		Placebo	
		No. of Patients Assessed at Both Periods	Means	No. of Patients Assessed at Both Periods	Means	No. of Patients Assessed at Both Periods	Means	No. of Patients Assessed at Both Periods	Means
Failed before 24 weeks ..	{ 0 Week of failure	2	{ 17.35 19.00	3	{ 58.17 64.17	9	{ 54.52 46.18	8	{ 49.79 51.56
Continuing at 24 weeks ..	{ 0 24	15	{ 47.38 62.07	11	{ 47.42 66.16	8	{ 59.10 75.68	7	{ 56.11 57.90
Failed before 52 weeks ..	{ 0 Week of failure	4	{ 23.88 32.92	4	{ 50.80 67.10	12	{ 55.83 52.87	11	{ 51.81 53.98
Continuing at 52 weeks ..	{ 0 52	13	{ 50.63 71.98	10	{ 45.00 62.01	5	{ 58.70 72.62	3	{ 57.57 56.40

(commonly termed extrinsic asthma) is compared in Table VI with the response of patients with *both* a negative history *and* negative skin tests (commonly termed intrinsic asthma). There were three (15%) failures among the 20 patients with extrinsic asthma who were receiving one or other of the D.S.C.G. regimens compared with four (44%) of the nine patients with intrinsic asthma, a difference which is not significant ($P=0.2$) on these small numbers.

Of the 35 patients receiving a D.S.C.G. regimen there were nine who failed—only one showed multiple skin reactions, four showed weak responses to single allergens, and four were skin-test negative. This compares with 13 multiple skin reactions in the 26 patients on the D.S.C.G. regimens who were successes of therapy at 52 weeks, a single positive in six, and negative skin tests in seven. Again the difference was not significant ($P=0.1$) on these small numbers.

TOXICITY

No evidence of clinical toxicity to D.S.C.G. was encountered. No changes of clinical significance in haemoglobin, white blood count, eosinophil count, ESR, blood urea, serum aspartate or alanine aminotransferase or urine analysis were seen in individual patients over the whole year for any of the regimens. No appreciable change in each group was seen when mean values pretreatment and during treatment were compared.

Discussion

This appears to be the first long-term (one year) double-blind investigation, based on random allocation, of the use of D.S.C.G. in the treatment of bronchial asthma in adults, though a favourable long-term response in paediatric practice has recently been reported (Silverman *et al.*, 1972). The study also has other special features. All the patients had severe asthma in that they had had wheezing on most days for more than 12 weeks immediately preceding the study. None had had D.S.C.G. or D.S.C.G.-isoprenaline at any time or corticosteroids or corticotrophin during the preceding three months. Furthermore, the asthma was not controlled by the use of a specified group of bronchodilator, antihistamine, and sedative drugs which were tried for an assessment period of two weeks immediately before admission to the study. These drugs were then continued while the trial therapy, which included two dosage schedules, was introduced. Nearly all other controlled trials of D.S.C.G. have included mild asthmatics and have not attempted to standardize bronchodilator treatment in this way; most have been short-term cross-over investigations, and none have assessed different dosage schedules.

Criteria for failure were straightforward and clinically determined. Failure was defined as uncontrolled acute attacks of asthma or inadequate general control with persistent symptoms or worsening of asthma and wheeze and in all cases required, in the opinion of the physician in charge, the addition of known D.S.C.G. or corticosteroids to the standard panel of drugs. The criteria for failure did not include patient preferences or analyses of diaries.

The results show that both D.S.C.G. regimens were effective in the clinical control of most of the patients and that this effectiveness was maintained for one year under conditions of management feasible in routine clinical practice. Thus only four of the 20 patients treated with D.S.C.G.-isoprenaline and five of the 15 patients treated with D.S.C.G. alone failed during the year.

In contrast patients on isoprenaline alone or the placebo failed with significantly greater frequency than those in the D.S.C.G. groups. Patients in the isoprenaline group appeared to fail less rapidly than those in the placebo group. Indeed, at eight weeks there was an appreciable, although statistically non-significant superiority over the placebo, and this trend continued up to 16 weeks.

A multiple regression analysis of the clinical features found before treatment showed no significant factor from which a satisfactory response to D.S.C.G. might be predicted. Nevertheless, in those on the D.S.C.G. treatments there was only one failure among 14 patients with multiple skin reactions. On the other hand, the remaining eight failures on the D.S.C.G. regimens were from 21 patients who had weak single or absent prick skin test readings.

Altounyan and Howell (1969) reported a good response to D.S.C.G. in patients with a sputum eosinophilia. In the present study of 35 patients treated with the D.S.C.G. regimens 11 had no blood eosinophilia (defined as $500/\text{mm}^3$ or more) on any occasion throughout the study and three failed, a similar proportion to the failure rate in patients with blood eosinophilia—namely, six out of 24. Thus in this study there was no evidence of a correlation between the presence of blood eosinophilia and response to D.S.C.G. No other special features peculiar to the patients who failed were identified.

Failure occurred sporadically throughout the year in all four groups, in some patients a number of months after starting treatment. The success of some patients on placebo or isoprenaline for the whole year despite the initial severity is of interest. Presumably some patients had spontaneous remissions. The influence of the physician's desire to persist with the treatment is also likely to have had an influence on the progress of some patients. It is also possible that the placebo capsule exerted a real protective effect in some asthmatics. Placebo capsules have also been shown to block exercise-induced asthma in some patients (Silverman, 1972).

The ways in which patients failed were broadly similar for the four groups, the main reasons being inadequate general control and acute attacks of asthma. It is, however, worth noting that none of the four patients who failed on the D.S.C.G.-isoprenaline inhalant did so with an acute attack of asthma, whereas three of the five patients on D.S.C.G. alone did. The results achieved with D.S.C.G.-isoprenaline were not significantly better than with D.S.C.G. alone.

Another important feature of this study was the comparison of a full (four capsules daily for the whole year) and reducing schedule of capsules after an initial period of eight weeks on full treatment.

The experience gained in titrating the dose of D.S.C.G. in asthma is encouraging, and the data suggest that the adult patients in this trial adjusted the frequency of their dosage in a responsible way. Thus nearly all who failed either on the reducing or on the full schedule were actually on four capsules a day during the weeks before the time of failure, which was therefore unlikely to be due to inappropriate reduction in the frequency of their dosage. The stepwise and gradual reduction in dosage is important and in sharp contrast to the intermittent and irregular doses taken by some patients in attempts to alleviate their symptoms. Reduction in dosage has two important advantages—it makes treatment more convenient for the patient and also allows considerable economy, for expenditure on D.S.C.G. alone or with isoprenaline by the health services in England and Wales runs into several million pounds a year.

Intolerance of D.S.C.G. was not a problem, and only one patient was withdrawn for this reason. Clinical toxicity was not encountered. Further, there were no significant changes in the serial mean values for each treatment group for haemoglobin, white blood count, eosinophil count, blood urea, serum aspartate or alanine aminotransferase over the year. Also there was no evidence of any appreciable deviations of these values in any of the individual patients.

In conclusion, D.S.C.G. alone or with isoprenaline has been shown to be highly effective and safe in the treatment of bronchial asthma for a period of one year. The frequency of inhalation can be regulated by the patient without impairment of effect and there are substantial financial savings to the Health Service to be made by adopting this practice.

This report was written by Professor Margaret Turner-Warwick, Dr. J. C. Batten, the co-ordinators, and the M.R.C. participants.

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Changes in Lung Capillary Permeability in Renal Failure

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British Medical Journal, 1972, 4, 388-390

Summary

Excess fluid in the lung can be quantified in chronic dialysis patients by using the double indicator dilution technique. The lung capillaries show an increased permeability to sodium when these patients develop pulmonary oedema.

Introduction

Pulmonary oedema is a common complication in patients with renal disease. Increased capillary pressure from a failing left ventricle, increased capillary flow due to the high cardiac output associated with anaemia, and a minor reduction in the plasma osmotic pressure secondary to low albumin concentration have been suggested as the main factors causing outflow of fluid from the capillaries into the extravascular lung tissue (Rendich *et al.*, 1941; Alwall *et al.*, 1953). Changes in the permeability of lung capillaries could also produce a similar effect. Thus far no quantitative means of measuring such a change in renal patients has been reported. We have applied the multiple indicator dilution technique to this problem and the results form the substance of this paper.

Patients and Methods

All the patients studied were members of a regular haemodialysis programme centred in Dulwich Hospital. The measurements were made with the subject propped up in bed. For the first study 27 patients were divided into three groups according to their clinical and radiological states. The lung water was measured independently, and became known only after this classification had been made.

Group 1.—"Normals." There were 12 patients in this group and all were regarded as free of excess fluid in their lungs.

They were all within 2 kg of their normal dialysing weight, there was no adventitious sounds in the chest, and chest radiographs showed no evidence of venous congestion or interstitial or alveolar oedema.

Groups 2.—"Overloads." There were seven patients in this group. They were at least 5 kg above their normal dialysing weight. They all had noticed increased breathlessness on exertion, and crepitations were audible on auscultation. Chest radiographs showed distended upper lobe veins, hilar accentuation with loss of outline of vessels, and lymphatic lines were present in two patients.

Group 3.—"Pulmonary oedema." There were eight patients in this group. All were breathless at rest, many crepitations were present in the chest, and radiographs showed varying degrees of opacification of the lung fields associated with pulmonary oedema. The clinical condition of these patients required urgent therapy to control their pulmonary symptoms.

An intravenous infusion drip was linked to the venous end of a Scribner shunt. A 1-ml bolus containing 2.5 μ Ci of ^{125} I-labelled human serum albumin (RISA), 2.5 μ Ci of ^{24} Na, and 150 μ Ci of tritiated water ($^3\text{H}_2\text{O}^+$) was injected into the venous line while the infusion flowed maximally. Thirty 1-ml samples of blood were collected in 30 seconds from the arterial line using an automated fraction collector and pump (Crosbie and Wyatt, 1971). The amount of labelled albumin, tritiated water, and ^{24} Na recovered in each sample was measured. The $^{24}\text{Na}^+$ count rate was measured within two hours of collection using a gamma spectrometer and well counter. The radioactivity of the ^{125}I albumin was counted three weeks later in an automated well counter when the radioactivity due to the ^{24}Na had decayed. In both instances the sample was counted sufficiently long to give a total count of the modal value, a value at least five times that of background. Standards were prepared by serial dilutions of the injectate and measured in a manner identical to that of the samples. The tritium ($^3\text{H}^+$) was measured by liquid scintillation counting of the beta activity: 0.5 ml of the blood collected in each sample was added to 4.5 ml of absolute alcohol and left for three weeks in a refrigerator; 1 ml of the supernatant was then added to 10 ml of scintillation fluid (P.P.O. 4 g, Dm-P.O.P.O.P. 0.2 g, naphthalene 60.0 g, dioxan 1 l.) and counted in a Tri-carb Packard automated scintillation counter. Again, serial dilutions of the injectate were treated in a similar manner to provide standards.

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