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References

- Fahy, A., and Marshall, M. (1969). *British Journal of Anaesthesia*, 41, 433.
 Thomas, E. (1963). *British Journal of Anaesthesia*, 35, 327.
 Hannington-Kiff, J. G. (1969). *British Journal of Anaesthesia*, 41, 401.
 Tyrrell, M. F., and Feldman, S. A. (1968). *British Journal of Anaesthesia*, 40, 99.

Multicentre, Short-term Therapeutic Trial of Disodium Cromoglycate, With and Without Prednisone, in Adults with Asthma*

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Summary

A total of 117 asthmatic patients were studied in a double-blind, cross-over trial with half-periods of three weeks in which disodium cromoglycate (D.S.C.G.) was compared with an inactive preparation. D.S.C.G. improved spirometric measurements, at a very high level of statistical significance, more than did placebo. The mean advantage of D.S.C.G. was less than 10% after three weeks. Symptomatic improvement by D.S.C.G. was small though significant; it was not correlated with spirometric improvement. A history of chronic cough was the only clinical characteristic associated with a better-than-average spirometric response to D.S.C.G.

Introduction

The effects of disodium cromoglycate (D.S.C.G.) on the respiratory manifestations of antigen-antibody reactions, both in animals and in man, have been striking (Altounyan, 1968; Pepys *et al.*, 1968). In contrast the use of D.S.C.G. in the treatment of adult patients with asthma has produced less convincing results (Grant *et al.*, 1967; Kennedy, 1967; Altounyan and Howell, 1969; Gianoutsos and O'Donnell, 1969; Bernstein *et al.*, 1971). In particular, objective evidence of improvement has been poorly related to symptomatic improvement, although in many trials the individual patient's potential capacity for spirometric improvement has not been clearly indicated. On the other hand, there is evidence (Read and Rebuck, 1969) that in patients receiving continuous treatment with a corticosteroid drug, its dose can be reduced when D.S.C.G. is administered.

In the clinical trial reported below the effect of D.S.C.G. was compared with that of an inactive preparation before and after a three-day course of prednisone in adult patients with chronic asthma.

Patients and Methods

The general criterion for inclusion in the trial was chronic asthma of moderate severity. "Chronic asthma" was defined by clinical and spirometric evidence of wheeze and airways obstruction of fluctuating degree for at least six months. "Moderate severity" demanded evidence that at some time during the three months before the trial the forced expiratory volume in 1 second (FEV₁) had increased by at least 20% in response to an adequate dose of isoprenaline, orciprenaline, or salbutamol aerosol. Patients with chronic bronchitis (defined as a productive cough for at least three consecutive months for at least two successive years (Medical Research Council, 1965), were not excluded, but an attempt was made to include a reasonable number of patients who did not give such a history. Previous treatment with D.S.C.G. was no bar to inclusion, provided that no such treatment had been given for at least eight weeks before the trial began. Otherwise, all patients continued to take their usual treatment according to previously established indications throughout the trial. In 58 of the 117 patients selected asthma had been thought to be of such severity that continuing corticosteroid therapy had been prescribed.

DESIGN OF TRIAL

The trial was preceded by one week during which preliminary history-taking and examination were completed, and in which the procedure was explained to the patients, and spirometric manoeuvres were practised by them.

The trial itself was conducted simultaneously in all eight centres during the six weeks from 1 March to 7 April 1971, just past the peak of the summer season in the South Pacific area. During the first three weeks either 20 mg disodium cromoglycate (D.S.C.G.) or an inactive control substance (15 mg lactose, 5 mg sodium sulphate) was given by Spinhaler at 07.00, 12.00, 17.00, and 22.00 hours. During the second three weeks the alternative substance was given at these hours, the order for each patient being randomly determined. The days of the trial will be referred to as D.S.C.G. 1 to 21 and placebo 1 to 21, irrespective of the order in which the preparations were given. On days D.S.C.G. 10, 11, and 12, and placebo 10, 11, and 12, prednisone was administered (10 mg given by mouth every eight hours). The patients were not aware of the activity of the preparations they received. Many patients detected a difference between D.S.C.G. and the placebo, but all were told that the purpose of the trial was "to compare two drugs." The observers were not aware of whether D.S.C.G. or the placebo was being taken, but knew that on days 10, 11, and 12 an active steroid drug was being given.

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RECORDING OF INFORMATION

During the preliminary week the following inquiries and examinations were undertaken: full history and clinical examination; age, height, and weight; chest radiography; haemoglobin concentration, total and differential leucocyte count; sputum examination for purulence and eosinophils; and FEV₁ and vital capacity (VC) before and 20 minutes after the inhalation of two carefully supervised puffs of salbutamol aerosol (average total dose 0.2 mg). The spirometric procedure set out by Cotes (1966) was followed; each recorded VC and FEV₁ was the mean of three technically satisfactory measurements.

During the trial the patients were asked to attend at the same time (between 10.00 and 16.00 hours) on each of days 0, 9, 13, 19, and 21 for each half of the study, making nine visits in all. In making comparisons, day 0 for the first half was also taken as day 0 for the second half. Patients were asked not to use an inhaler for at least six hours before attendance. On each occasion the chest was examined, spirometric measurements were made before and after salbutamol aerosol inhalation, and the patient's own daily record card was checked for completeness.

Each patient was given a record card on which he was asked to enter daily and nightly scores for nasal congestion, wheeze, breathlessness, tightness in the chest, cough, sputum, and number of attacks of asthma (or, during the night, the number of times he was awakened by asthma). Scores were allotted as follows: no symptoms 1, mild 2-3, moderate 4-5, severe 6, and intolerable 7. For sputum the scores were 1 to 6 for "no sputum" to "more than two eggcupfuls" a day.

Results

CLINICAL FEATURES OF PATIENTS

One hundred and seventeen patients completed the trial, 13 to 17 in each of the eight centres. Three patients withdrew from the trial; one lost interest, another found the travelling too expensive, and a third withdrew when his asthma deteriorated over the first two weeks. He was receiving placebo at that time. Forty-five per cent. were male; one centre produced only 11% males, but the others agreed well with the overall sex distribution. Twelve per cent. were under 20 years old, 19% were 20 to 29, 32% were 30 to 39, 32% were 40 to 49, and 5% were over 50 years old.

The age of onset of asthma was ascertained in only 88 patients. In 63 of these (30 male and 33 female) asthma began during the first 15 years of life, and in only nine (five male and four female) after 30 years of age. Blood eosinophilia greater than 6% of the white cell count was found in 56 patients. Of 85 patients in whom sputum was available and examined, 22 showed pronounced and 21 showed minor sputum eosinophilia. A personal history of hay fever and/or skin rashes was given by 75 patients, a family history of asthma or allergic conditions by 87, and of both conditions by 59. Seventy-two patients gave a history of cough (with or without sputum) between asthmatic attacks. These patients fulfilled the criteria for a diagnosis of associated chronic bronchitis, which is so commonly found in adult asthmatic patients. Sixteen patients had received D.S.C.G. as treatment previously but none within eight weeks of the start of the trial. Abnormalities in the chest radiograph, other than evidence of hyperinflation, were seen in 22 patients; they consisted of increased lung markings or small linear opacities, and no gross changes were reported.

SPIROMETRY

The statistical significance of the changes in FEV₁, VC, and FEV₁/VC ratio associated with D.S.C.G. at different stages of the trial are shown in Table I. The spirometric data were

TABLE I—Significance of Spirometric Differences between D.S.C.G. and Placebo on Corresponding Days

Day:	9	13	19	21
FEV ₁ (D.S.C.G./placebo): Before salbutamol	N.S.	N.S.	0.001 < 2P < 0.01	2P < 0.001
After salbutamol	N.S.	N.S.	2P < 0.001	2P < 0.001
VC (D.S.C.G./placebo): Before salbutamol	0.01 < 2P < 0.02	N.S.	0.001 < 2P < 0.01	0.001 < 2P < 0.01
After salbutamol	0.01 < 2P < 0.02	N.S.	0.02 < 2P < 0.05	0.001 < 2P < 0.01
FEV ₁ /VC (D.S.C.G./placebo): Before salbutamol	N.S.	N.S.	N.S.	0.001 < 2P < 0.01
After salbutamol	N.S.	N.S.	0.001 < 2P < 0.01	2P < 0.001

N.S. = Not significant.

taken for each patient, before and after salbutamol, and each value for a D.S.C.G. day was listed alongside the corresponding value for the same control day. A comparison was then made by paired *t* test. Significant differences were all in favour of D.S.C.G. and the significance increased as the trial progressed. At day 21 the improvement of FEV₁ for D.S.C.G. over placebo was highly significant (2P < 0.001).

A comparison was made between the mean increase in FEV₁ between days placebo 21 and D.S.C.G. 21 and the mean increase in FEV₁ due to salbutamol on day 0 (Table II).

TABLE II—Change in FEV₁ Due to Salbutamol and D.S.C.G.

	Day 21		Day 0
	Before Salbutamol	After Salbutamol	Salbutamol
(1) Mean control FEV ₁ (l.)	1.72 (Placebo)	2.16 (Placebo)	1.65
(2) Mean test FEV ₁ (l.)	1.88 (D.S.C.G.)	2.33 (D.S.C.G.)	2.03
(3) Mean difference 2-1 (l.)	0.16	0.17	0.38
(4) 3 as percentage of 1	9	8	23
(5) 68% limits of 3 (l.)	-0.30 to 0.63	-0.22 to 0.56	0.01 to 0.75
(6) 5 as percentage of 1	-17 to 37	-10 to 26	1 to 45

"Control" FEV₁ is that during placebo on day 21 or before salbutamol on day 0. "Test" FEV₁ is that during D.S.C.G. on day 21 or after salbutamol on day 0. D.S.C.G. was associated with a rise of 9% in the mean FEV₁ before salbutamol and an 8% further rise in the mean FEV₁ after salbutamol. The mean increase after salbutamol on day 0 was 23%.

The change in FEV₁ was rather variable, as shown in Table II by the 68% confidence limits of the difference (± 1 S.D.). About 16% of patients responded very favourably and showed an increase in FEV₁ of more than 45% of the mean control value after salbutamol alone, of more than 37% after D.S.C.G. alone, and of more than 26% after D.S.C.G. after salbutamol. On the other hand, about 16% actually showed a fall of greater than 17 and 10%, before and after salbutamol respectively, in association with the administration of D.S.C.G.

No significant improvement of FEV₁ was apparent when, instead of comparing the FEV₁ changes for the three-week trial periods, a comparison was made of changes in FEV₁ over the shorter intervals preceding or after the three days of prednisone. In Table III, the FEV₁ on day 13 was taken as showing the maximal effect of prednisone, and this was compared with the FEV₁ on days 0, 9, and 21. When the D.S.C.G. period is considered alone, the mean FEV₁ on day 13 is seen to be significantly greater than on the other three days; the difference between day 13 and day 9 was probably due mainly to the prednisone. However, as shown in Table III, the dif-

TABLE III—Effect of Prednisone on FEV₁, before Salbutamol

	Mean Increase in FEV ₁ on D.S.C.G.			Mean D.S.C.G.-Placebo Difference in FEV ₁ Increase		
	(l.)	(%)	Significance	(l.)	(%)	Significance
Day 13-Day 0	0.38	41	2P < 0.001	0.10	0.04	N.S.
Day 13-Day 9	0.19	14	2P < 0.001	-0.04	-0.04	N.S.
Day 13-Day 21	0.13	10	0.01 < 2P < 0.02	-0.06	-0.07	N.S.

ferences in FEV₁ over these intervals were not significantly affected by whether the patient received placebo or D.S.C.G. One may conclude that the effect of prednisone was the same whether or not D.S.C.G. was given (day 13-day 9), and that there was no significant difference in the trend of FEV₁, during those intervals not so markedly influenced by prednisone (day 13-day 0 and day 13-day 21), between D.S.C.G. and placebo. The interval day 9-day 0, not at all influenced by prednisone, was tested with the same result.

SYMPTOMS

The mean daily symptom score was calculated for each patient, each symptom (seven by day and seven by night), each week in each half of the trial, and the placebo-D.S.C.G. difference calculated for corresponding scores; a paired *t* test was then carried out for each symptom and each week. In every case the advantage lay with D.S.C.G., and in many instances the difference was statistically significant (Table IV). The differences were, however, always small—as shown in Table V in which the six most highly significant differences (2P < 0.001) from Table IV are shown in more detail. The mean “numbers of attacks” in Table V imply that a mean incidence of 14 attacks a week was reduced to 10 attacks a week during the administration of D.S.C.G. The mean placebo-D.S.C.G. difference for the remaining symptoms is 0.286, equivalent to a difference of one grade on two days a week.

TABLE IV—Mean Daily Symptom Scores showing Comparison of D.S.C.G. with Placebo

	Week	Significance of Placebo Score minus D.S.C.G. Score	
		Day	Night
Nasal “stiffness”	1	N.S.	0.01 < 2P < 0.02
	2	0.02 < 2P < 0.05	N.S.
	3	N.S.	N.S.
Wheeze	1	0.02 < 2P < 0.05	0.001 < 2P < 0.01
	2	0.01 < 2P < 0.02	0.001 < 2P < 0.01
	3	0.001 < 2P < 0.01	N.S.
Breathlessness	1	0.01 < 2P < 0.02	2P < 0.001
	2	N.S.	0.01 < 2P < 0.02
	3	0.001 < 2P < 0.01	0.02 < 2P < 0.05
Tightness in chest	1	2P < 0.001	2P < 0.001
	2	0.01 < 2P < 0.02	2P < 0.001
	3	0.001 < 2P < 0.01	0.001 < 2P < 0.01
Cough	1	N.S.	N.S.
	2	N.S.	N.S.
	3	N.S.	0.02 < 2P < 0.05
Sputum	1	N.S.	N.S.
	2	N.S.	N.S.
	3	N.S.	0.02 < 2P < 0.05
No. of attacks	1	2P < 0.001	2P < 0.001
	2	N.S.	N.S.
	3	0.02 < 2P < 0.05	0.02 < 2P < 0.05

N.S. = Not significant.

TABLE V—Mean Daily Symptom Scores where 2P < 0.001

	Week	Day		Night	
		D.S.C.G.	Placebo	D.S.C.G.	Placebo
Breathlessness ..	1			1.679	1.993
Tightness in chest	1	1.672	1.945	1.585	1.939
No. of attacks ..	2			1.473	1.675
	1	0.741	1.045	0.652	0.937

CORRELATION OF SPIROMETRY WITH SYMPTOMS

Those patients who showed the biggest D.S.C.G.-placebo differences in FEV₁ on day 19 and/or day 21, and before and/or after salbutamol, were identified. The criterion by which they were chosen was a D.S.C.G.-placebo difference bigger than the mean of the whole series plus 1 S.D. Similarly, for each recorded symptom, those with a D.S.C.G.-placebo advantage better than the mean plus 1 S.D. were identified; the basis for this selection was the last three days' score minus the first three days' score. Two questions were then asked: (1) Were

the FEV₁ improvers and the symptomatic improvers the same people? (2) Were the clinical characteristics of those whose FEV₁ improved most on D.S.C.G. different from those of the whole series of 117 patients?

Improvement in FEV₁ and in Symptoms

There were 14 symptom categories, seven during the day and seven for the night. In each category the patients showing a good response (as defined above) were listed. For each patient the number of symptom categories in which such a response occurred was then determined. The same procedure was followed for the 32 patients who showed the best response in FEV₁. The result is shown in Table VI. A χ^2 test showed

TABLE VI—Distribution of “Best” Symptom Improvement on D.S.C.G.

No. of Symptom Categories Showing Good Improvement (Maximum = 14)	Whole Series (117 Patients)		FEV ₁ Improvers (32 Patients)			
	No. of Patients	%	Day 19 or 21	Day 19 and 21	Total	%
0	48	41	9	5	14	44
1	22	19	7	0	7	22
2	14	12	2	0	2	6
3	13	11	2	0	2	6
4	9	8	3	0	3	9
5	7	6	2	0	2	6
6	2	2	0	1	1	3
7	0	0	0	0	0	0
8	1	1	1	0	1	3
9	0	0	0	0	0	0
10	0	0	0	0	0	0
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	0	0	0	0	0	0
14	1	1	0	0	0	0
Total	117	101	26	6	32	99

no significant difference between the two distributions, indicating that improvement in FEV₁ was not associated with either a better or a worse response in symptoms than the average.

Clinical Characteristics of Patients Showing the Best Improvement in FEV₁

The 32 patients showing “best” improvement, as previously defined, in FEV₁ due to D.S.C.G. on day 19 or day 21, or on both days, and before and/or after salbutamol, were compared with the remainder in respect of clinical features by means of appropriate χ^2 tests.

Age and sex, separately and combined, showed no association with FEV₁ improvement.

Age of onset, where known and grouped above and below 15 years of age, showed no association with FEV₁ improvement.

Duration and frequency of attacks were not associated with FEV₁ response.

Duration of asthma—only 14 patients gave a history of five years or less, giving “expected” numbers too small to test. No association with FEV₁ response was obvious.

Eosinophils in blood and sputum, separately and in combination, showed no association.

Personal history of allergy and/or family history of allergy (including asthma) were not associated with the response of FEV₁ to D.S.C.G.

Seasonal incidence, “warmer” or “colder” or either, was not associated.

Previous treatment with steroids, classified as “never,” “when severe,” or “regularly,” showed no association with the FEV₁ response.

Cough—seventy-two patients gave a history of cough (with or without sputum) between asthmatic attacks. Of the group of 32 patients with “best” responses in FEV₁, 29 gave such a history. The difference was highly significant (2P < 0.001).

Discussion

SPIROMETRY

Woolcock and Read (1966) showed that relief of overinflation of the lungs in asthmatic patients may occur without significant change in FEV_1 . This observation provides an explanation of how symptomatic relief may sometimes occur without an increase in FEV_1 . As Tocker and O'Donnell (1972) have shown, however, this phenomenon is uncommon. We believe that it cannot be invoked whenever a supposed remedy for asthma fails to increase the FEV_1 and that, as with bronchodilator amines and steroids, an effective drug should induce in most cases a clearly demonstrable effect on the forced expiratory spirogram. This trial provides good evidence that D.S.C.G. given for three weeks to an unselected series of patients with moderately severe bronchial asthma significantly increased FEV_1 , VC, and FEV_1/VC ratio, and is the first to have shown such a highly significant mean change in FEV_1 in adult patients. The difference between D.S.C.G. and the inactive preparation increased as the trial progressed (Table I). This could have been due to a cumulative effect of D.S.C.G., and if so the difference might have become bigger had the trial lasted longer. Alternatively, a carry-over effect in the patients who received placebo second could have biased the result against placebo.

The mean increase in FEV_1 ascribable to D.S.C.G. was, however, less than 10%. The immediate increase of 23% after salbutamol on day 0 provides an indication of the potential for prompt improvement in these patients. A mean value conceals high and low values, and as shown in Table II the FEV_1 increased in a few patients on D.S.C.G. almost as much as after salbutamol. However, when assessing the overall improvement by comparing the effect of D.S.C.G. with the acute and more transient benefit after salbutamol, the mean increase in FEV_1 provides a more reliable guide.

The patients showing the best responses in FEV_1 did not show a symptomatic improvement better than the remainder (Table VI). This supported the view that the benefit due to D.S.C.G. was small. While it may be argued that symptoms may genuinely improve without change in FEV_1 , it is extremely unlikely that a major increase in FEV_1 would not be accompanied by symptomatic relief.

EFFECT OF PREDNISONE

Much of the improvement from the high dosage of prednisone (30 mg daily) used in this trial would be expected to occur within 72 hours except in patients recovering from a severe exacerbation of asthma. The chief aim of the administration of prednisone was to provide an indication of the potential capacity for improvement in the patients under study. The degree of improvement on the prednisone would indicate the best that could be hoped for from D.S.C.G. To achieve maximum co-operation from the eight centres engaged in this trial it had to be completed within a seven-week period before Easter. The administration of prednisone had to be limited to three days in order not to interfere with the primary task of comparing D.S.C.G. and placebo. As expected, the mean FEV_1 during the D.S.C.G. period was greatest on day 13 after the three days of prednisone. By day 21 the mean FEV_1 for those on D.S.C.G. was 10% less than on day 13. This was an improvement on the FEV_1 at day 9 on D.S.C.G. but before the prednisone (Table III).

In spite of the improvement in FEV_1 at day 21 for those on D.S.C.G. there was no significant difference between the maximum value for FEV_1 on day 13 after the prednisone and the FEV_1 at the 9-day or 21-day stages of the trial whether the patient was on D.S.C.G. or placebo (Table III). This confirmed our conclusion that the significant improvement of FEV_1 on D.S.C.G. was not a large one.

SYMPTOMS

The trial provided convincing evidence of symptomatic improvement due to D.S.C.G. (Table IV) but, again, the mean improvement noted was small (Table V). As in the case of spirometric measurements it is necessary to consider to what extent mean differences may conceal genuine and substantial improvement in a small number of patients. So far as symptoms are concerned, detailed analysis of this aspect is as likely to mislead as to instruct; the scoring of symptoms is entirely subjective, and as has been shown (Table VI) those patients who reported the biggest symptomatic improvement did not have the biggest increase in FEV_1 . It would thus be hazardous to suppose, and impossible to prove, that the extremes of response, both good and bad, represented more than random scatter.

Table VI was compiled from the most significant placebo-D.S.C.G. differences. A drug which reduces the mean number of attacks from 14 to 10 a week, and makes a difference in other symptoms of from moderate to mild or intolerable to severe on two days a week may certainly have a place in the treatment of asthma, but it can hardly be regarded as impressive.

SELECTION OF PATIENTS FOR TREATMENT

It would be helpful in practice to be able to identify those patients who are likely to show good responses after D.S.C.G. We have been unable to identify any clinical characteristic by which a good response may be predicted, save one. This was a history of cough, given much more frequently by those who responded better to D.S.C.G. The chosen criterion of response was exceeded by 44% of those who gave such a history, and by less than 7% of those who did not.

The criterion used for "cough" was similar to that adopted for chronic bronchitis by the Medical Research Council (1965). It is, however, difficult to say exactly what it means when applied to patients with chronic asthma. Cough is a common symptom of the asthmatic attack, and in many patients it is a somewhat arbitrary exercise to define the absence of an attack. There have been previous reports of favourable responses to D.S.C.G. in patients with a chronic cough (Cayley, 1970; Marshall and Birtwistle, 1970) but the explanation is at present wholly conjectural.

Comment

In this trial D.S.C.G. produced evidence of symptomatic and functional improvement in a group of unselected adult asthmatic patients. The results are less striking than some optimistic assessments—for example, Howell and Altounyan, 1967—made previously on the basis of controlled trials in adults, or the subjective clinical impressions on which current opinion of this drug still widely rests. The present results tend rather to support the assessment of Grant *et al.* (1967).

Grant (1968) pointed out that the conclusions to be drawn from trials of D.S.C.G. greatly depend on the importance attached to FEV_1 . In the present trial neither FEV_1 nor symptoms showed striking improvement due to the drug. Another possible source of discrepancy lies in the selection of patients; Howell and Altounyan (1967) apparently selected their 10 patients with "allergic bronchial asthma" solely on the basis of eosinophilia of the sputum. Many patients in the present series could have been selected on this basis, yet neither this nor other stigmata of allergy were associated with a better-than-average response to D.S.C.G.

The contrast between the effects of D.S.C.G. in bronchial provocation studies (Pepys *et al.*, 1968) and in the treatment of clinical asthma raises an important question concerning their relation in most patients.

Participants in the trial: G. S. Kellaway, Auckland (Convenor); T. Gebbie, Wellington; A. C. Hayton, New Plymouth; P. E. Holst, Dunedin; A. R. Kirk, Nelson; M. Kirk, Palmerston North; J. A. McLeod, Christchurch; T. V. O'Donnell, Dunedin; J. J. O'Hagan, Invercargill; and R. G. P. Rothwell, Hamilton.

References

- Altounyan, R. E. C. (1968). *Acta Allergica*, 22, 487.
 Altounyan, R. E. C., and Howell, J. B. L. (1969). *Respiration*, 26, Suppl. No. 131.
 Bernstein, L., et al. (1971). *Journal of Allergy*, 47, 95.
 Cayley, F. E. (1970). *Disodium Cromoglycate in Allergic Airways Disease*, p. 44. London, Butterworths.
 Cotes, J. E. (1966). I.L.O. Occupational Safety and Health Series, No. 6.
 Gianoutsos, P., and O'Donnell, T. V. (1969). *New Zealand Medical Journal*, 70, 311.
 Grant, I. W. B. (1968). *Lancet*, 2, 282.
 Grant, I. W. B., Channell, S., and Drever, J. C. (1967). *Lancet*, 2, 673.
 Howell, J. B. L., and Altounyan, R. E. C. (1967). *Lancet*, 2, 539.
 Kennedy, M. C. S. (1967). *Lancet*, 2, 838.
 Marshall, J. S., and Birtwistle, I. H. (1970). *Disodium Cromoglycate in Allergic Airways Disease*, p. 173. London, Butterworths.
 Medical Research Council (1965). *Lancet*, 1, 776.
 Pepys, J., Chan, M., Hargreave, F. E., and McCarthy, D. S. (1968). *Lancet*, 2, 134.
 Read, J., and Rebuck, A. S. (1969). *Medical Journal of Australia*, 1, 566.
 Tocker, D., and O'Donnell, T. V. (1972). *New Zealand Medical Journal*. In press.
 Woolcock, A. J., and Read, J. (1966). *American Journal of Medicine*, 41, 259.

Effects of Four Commonly-used Tranquillizers on Low-speed Driving Performance Tests

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Summary

A double-blind controlled comparison of four commonly-used tranquillizing drugs (haloperidol, amylobarbitone sodium, chlorthalidoxepoxide, and trifluoperazine) against placebo was made in their effects on the performance of volunteers during three low speed vehicle-handling tests. The drugs (with the exception of haloperidol) significantly altered driving behaviour though they did not seem to interact significantly with alcohol. There is, therefore, a strong possibility that such drugs will similarly alter driving performance in patients taking them for therapeutic purposes. Since, as these experiments also show, those affected may be subjectively unaware of it, and routine clinical screening is not sensitive enough to detect them, physicians should warn patients of the probability that their driving performance will be affected by such drugs, particularly during the first few days that they are taken.

Introduction

Road accidents are a leading cause of death and morbidity, particularly in young people. Alcohol is directly involved in many of these accidents, and there is growing concern that the large amount of psychotropic medication currently prescribed in the Western hemisphere may also be involved. Several authors have recently reviewed the large amount of literature that reflects the growing interest in this problem (Havard, 1970; Kibrick and Smart, 1970; Waller, 1971; Milner, 1972), though evaluation of the effect of psychotropic drugs on driving performance is much more difficult and has many more methodological problems than studying the effect of alcohol on driving.

This is largely due to the unique pharmacological properties of alcohol. Unlike alcohol, however, the absorption of psycho-

tropic drugs may be erratic, their metabolism is often complex (the effects of a drug may be difficult to distinguish from those of its related metabolites), and excretion is slow—indeed a patient may still be excreting the drug in the urine several weeks after he has taken his last dose. Blood levels of the drug may have little relation to drug effect, and may not correlate with urine levels of the drug. Dose response relations are more complex than those of alcohol, and the amount of idiosyncratic response or individual variation in response is probably much greater than with alcohol. There is a strong placebo element in drug response.

Psychotropic medication is taken by patients suffering from emotional symptoms or illnesses (which have their own complex effects on performance), and the medication has to be taken regularly. It is unrealistic, therefore, to study the effects of a single dose of a drug on driving performance (as can be done legitimately with alcohol). The use of normal subjects in such experiments also has a slightly limited value.

The direct causal involvement of drugs in road accidents has been examined by determining whether psychotropic drugs were present in the body tissues, blood, or urine of drivers killed or injured in road accidents or involved in traffic violations (reviewed by Havard, 1970). However, no properly controlled study of psychotropic drugs in accident situations has been carried out to compare with the classic study of Borkenstein *et al.* (1964) on the involvement of alcohol in road accidents, and in the present state of the art we doubt if it could be.

Most studies of the interaction between psychotropic drugs and driving behaviour have been in the laboratory, mostly involving driving simulators (devices of varying complexity in which a number of skills resembling driving can be tested simultaneously). Unfortunately, a simulator needs to be extremely sophisticated to match the demands of an actual driving situation. In addition the attitude and "set" of a subject "driving" in a simulator are likely to be different from his attitude to real driving. Different models (each with their own method of measurement) have been used in the various studies undertaken, and replication experiments have not been done.

In many simulator studies little allowance has been made for practice effects and little pretest training has usually been given. Sometimes sufficient time has not been allowed for absorption and metabolism of the drug before testing.

Most experimenters have used single doses or once repeated doses of the drug under test though some chronic experiments have been done with meprobamate (Kelly *et al.*, 1958a, 1958b).

The results of many simulator studies are now partly irrele-

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