TRANQUILLIZERS, A LATIN SQUARE TRIAL

By

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THIS study is an attempt to assess the value of certain drugs commonly used in psychiatric practice in decreasing the hyperactivity of patients. It is one of a series investigating tranquillizers and mental disorder in mental deficiency practice (Craft 1958).

Six drugs were used. Amylobarbitone was included as a sedative whose action was well known. Amphetamine is said by Bradley (1950) to be effective in behaviour disturbances associated with epilepsy, whilst promazine has been found effectively to sedate aggressive epileptic defectives by Bergin and Bergin (1958). The sedative properties of promethazine have recently been noted (Erwin, 1957) and encouraging reports of reduction of hyperactivity by prochlorperazine have been given (Lecomte *et al.*, 1957). Acetyl promazine, the sixth drug used, has been found of distinct value by Collard and Maggs (1958) in disturbed schizophrenic patients.

A Latin square trial with tranquillizers has previously been reported by Raymond *et al.* (1957) who based his study on work by Williams (1949). Raymond compared a placebo with amylobarbitone, meprobamate, chlorpromazine, benactyzine and sedaltine and found amylobarbitone significantly superior to the others in terms of patients' assessment of their own improvement.

Although the design of the present study was based on that of the foregoing authors, there were important differences. The present trial involved 18 patients only, and they were mental defectives. The patients were selected on account of their outstanding hyperactivity, aggression and socially bad habits. They had needed tranquillizers during the previous winter and the rating scales developed in preceding trials were used again (Craft, 1957–8). These scales consisted of daily ratings by nurses on three dimensions; activity, graded from destructive of any article (+6), through normal (0) to stuporose (−6); aggression, ranging from actual injury to others (+6), through normal (0) to actual injury to self (−6); and social behaviour, spitting and shouting (+6) through normal to (0) to eating excreta (−6). This trial was an attempt to assess the true taming or tranquillizing effect of these drugs, for one wished to see the hyperactivity reduced without excessive sleep inducement, and both injury to others and to self reduced.

Clinically the majority of patients appeared brain injured, ten being epileptics, although three had schizophrenia. All patients were below I.Q. 34, some being imbeciles, the majority being high grade idiots. Ages ranged from 15 to 44, average 25·2 years old.

The Chief Pharmacist of the hospital ensured that the administration of drugs would follow the design set out below, and that the experiment was blind from the medical and nursing point of view. Despite the tablets looking similar the nursing staff knew from previous trials that it was essential for patients to take their individually labelled tablets. The experiment was spread over a period

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of 165 days, being a preliminary period of 39 days followed by 6 equal periods of 21 days, during each of which one of the drugs was administered. It was felt that a period of a fortnight on each drug, as used by Raymond, was too short for an adequate assessment, for many of the tranquillizing drugs need time for effective action.

During the first week of each three-week period a stepwise increase in dosage of drugs was arranged by the pharmacist so that one tablet was taken the first and six on the final day. A similar stepwise decrease occurred during the third week. During the second week each patient took six tablets of the appropriate drug daily, i.e. amylobarbitone gr. 6; amphetamine sulphate 30 mg.; promethazine hydrochloride 150 mg.; acetyl promazine 150 mg.; promazine hydrochloride 600 mg.; and prochlorperazine 150 mg.

Of the 18 patients involved in this experiment, 6 were from one ward and 12 from the adjacent ward. These were divided into three groups of 6. In each group of six the drugs were administered according to the following experimental design, each symbol standing for a drug.

TABLE I

	Three Week Period					
	1	2	3	4	5	6
Patient 1	A	C	B	E	F	D
Patient 2	B	D	C	F	A	E
Patient 3	C	E	D	A	B	F
Patient 4	D	F	E	B	C	A
Patient 5	E	A	F	C	D	B
Patient 6	F	B	A	D	E	C

This design ensured that each patient received each drug during one period of the experiment, and that during any period all 6 patients in any group were receiving a different drug. Also each drug is followed by every other drug once only in each group. Following Williams (1949) this enables the residual effect to be estimated, that is the effect of the drug after it has been discontinued. In fact the analysis here mainly follows that suggested by Williams.

During the whole period of 165 days the behaviour of the patients was recorded on three counts; there being no losses of patients or of observations during the trial. Since the purpose of the tranquillizers is to make a patient more normal, the absolute value of any observation can be used in the assessment of drug action, i.e. ignoring plus or minus signs. These can be taken into account if more detailed analysis is required later.

RESULTS

The average behaviour for patients on each drug are given in Table IIa, Table IIb showing the residual effects adjusted for treatment effects. It should

TABLE IIa

Average Behaviour Away from Normal on Rating Scales

Average for All Patients	No Drug	Amylo-barb.	Amphet-amine	Pro-methazine	Acetyl Pro-mazine	Pro-mazine HCl	Prochlor-perazine
Aggression	0·67	1·03	1·16	0·80	1·36	1·27	1·01
Activity ..	2·21	2·82	2·50	2·53	2·42	2·18	1·68
Social behaviour	2·50	3·21	2·78	3·16	2·76	2·89	2·51

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TABLE IIb

Average Behaviour Away from Normal on Rating Scales

Residual Effects (adjusted for treatment effects)	Amylo-barb.	Amphet-amine	Pro-methazine HCl	Acetyl Pro-mazine	Pro-mazine HCl	Prochlor-perazine
Aggression ..	−0·194	0·143	−0·180	0·042	0·069	0·120
Activity	0·319	−0·049	−0·282	−0·121	0·277	−0·144
Social behaviour	0·047	0·185	−0·042	−0·043	0·048	−0·195

TABLE III

Difference in Average Deviation

(a) *Aggression*

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Significance
Patients	177·096:	17:	10·417	30·60	p<0·001
Between orders of treatment	34·697	5	6·939	0·58	
Within orders of treatment	142·399	12	11·867		
Between periods ..	1·679:	5:	0·336	0·99	—
Linear regression ..	1·560	1	1·560	4·58	0·025<p<0·05
Higher terms ..	0·119	4	0·030	0·09	—
Treatments:					
Direct effects ..	*0·453* | 0·352	5	0·091	0·27	—
Effect of preceding treatment	1·456 | *1·557*	5	0·311	0·91	—
Error	25·529	75	0·340	—	—

(b) *Activity*

Patients	211·841:	17:	12·461	45·43	p<0·001
Between orders of treatment	43·710	5	8·742	0·62	
Within orders of treatment	168·131	12	14·011		—
Between periods ..	3·292:	5:	0·658	2·95	0·01<p<0·025
Linear regression ..	1·519	1	1·519	5·54	0·01<p<0·025
Higher terms ..	1·773	4	0·443	1·62	—
Treatments:					
Direct effect ..	*3·133* | 2·020	5	0·627	2·28	—
Effect of preceding treatment	3·031 | *4·144*	5	0·829	3·02	0·01 p 0·025
Error	20·574	75	0·274	—	—

TABLE IV

Difference in Average Behaviour for Activity Only

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Significance
Patients	258·269:	17:	15·192	15·51	p<0·001
Between orders of treatment	83·504	5	16·701	1·15	
Within orders of treatment	174·764	12	14·564		—
Between periods ..	6·949:	5:	1·390	1·42	—
Linear regression ..	0·007	1	0·007	0·01	—
Higher terms ..	6·941	4	1·735	1·77	—
Treatments:					
Direct effects ..	*16·379* | 13·607	5	3·276	3·34	0·001<p<0·01
Effects of preceding treatment	8·187 | *10·958*	5	2·192	2·24	—
Error	73·475	75	0·980	—	—

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be noted that the average for the preliminary period (no drug) is for 39 observations, whereas the averages for the drugs are derived from 21 observations. The preliminary period also differs in occurring for all patients at the same time, and during a fine weather period. It has previously been noted (Craft, 1957a, page 856) that rating scores mount when hyperactive patients are confined indoors during bad weather.

Table III gives the Analysis of Variance for the Latin square for deviation, and Table IV for behaviour respectively. These analyses represent a comparison of the six drugs and do not include any information from the preliminary period.

Discussion of Results

(a) *Aggression*

From Table III it may be seen that the mean square due to variation between patients compared with the error mean square gives a value for the variance ratio of 30·60. This corresponds to $p+0·001$ from the F-tables, indicating a highly significant difference between patients. Breaking this down into variation between orders of treatment (that is, within the groups of six patients) and within orders of treatment between groups of six shows that there is no evidence that the patients in different groups differed more than those in the same group, although in both cases there is still a significant difference when compared with the error mean square. That is merely saying that the 18 patients are not a particularly homogeneous group as far as their deviation from normality in aggression is concerned. However, because of the design of the experiment this lack of homogeneity, which might have masked any possible treatment effects, may be separated from the rest of the analysis. The fact that the variation between orders of treatment is comparable with that within orders of treatment suggests that there is no difference in rating between the nursing staff on the two villas.

Considering the variation between the six 3-week periods the mean square of 0·336 due to this cause corresponds to a variance ratio of 0·99, which would seem to indicate that there is no difference between the periods. If, however, we consider the possibility that the deviation in aggression may steadily increase (or decrease) over the 18 weeks under consideration we find that there is, in fact, a significant increase during this time indicating a steady increase in aggression ($F=4·58$, $0·025<p<0·05$).

It is in considering the possibility of a steady increase that this analysis differs from that of Raymond. This extra analysis merely involves breaking down the sum of squares due to the difference in periods into five parts due to linear variation, quadratic variation and so on up to quintic variation, each with one degree of freedom. None of the terms higher than the linear were here significantly different from zero.

It may be noted here that it is possible that had Raymond *et al.* analysed their results in this way, they might have obtained a similar result. Their sum of squares due to variation between periods is large enough to provide a significant linear term, but it would need the original data to enable this sum of squares to be broken down in the appropriate manner.

Continuing the interpretation of Table III the remaining two variance ratios indicate no significant difference between treatments or between their residual effects. This is not to say that the drugs themselves have either no direct or no residual effect. This is almost certainly not the case, since otherwise

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a steady increase with time would be unlikely. The analysis merely says that the drugs appear to act in a similar way.

Comparing the average deviation for the whole period during which drugs were administered (2·007) with that for the preliminary period (1·591) there is a difference of 0·416. Because these preliminary observations are additional to the main design, it is not possible to eliminate the difference between patients as was done in the main analysis. These patient differences inflate the standard error of the averages to such an extent that a real difference of this order would be difficult to detect, and it is only possible here to say that although there appears to be no difference between the drugs themselves, there has been a steady increase in aggression over the whole 165 days of observation. This is possibly due to the cumulative effect of the drugs, also possibly due to external circumstances such as weather, a cumulative effect of confinement indoors, or even to a steady shift in the standards of judgment of the nursing staff.

(b) *Activity*

The analysis in Table III of the deviations in activity shows a pattern similar to that of the deviations in aggression, with one exception. As before there is, as might be expected a considerable difference between patients generally ($F=45\cdot43$, p $0\cdot<001$), but not between patients in the different groups of six. In this case, however, there is also a significant difference between periods, but since this is entirely due to a linear trend ($F=5\cdot56$, $0\cdot01<p<0\cdot025$) the conclusion is similar to that for aggression. The linear trend is here negative, indicating a steady decrease in deviation from normality during the experimental period. Reference to Table IV shows that this effect disappears when the behaviour of the patients is considered indicating that this is a true tranquillizing effect.

Further analysis shows that the drugs show a significant difference between themselves with respect to residual effects (Table IIb). Application of the test for extreme values (see for example, Pearson and Hartley, 1954, p. 49–51 and p. 173) to the second row of Table IIb shows that the drugs may be divided up into two classes; amylobarbitone with promazine, and the others. Amylobarbitone and promazine have a greater *positive* residual effect than the remainder of the drugs. Since, however, the general effect of the drugs as indicated by the period difference seems to be in reducing activity, this is equivalent to saying that amylobarbitone and promazine appear to be *less* effective in their residual effect than the others used.

The analysis of the average behaviour of the patients in Table IV exhibits one notable difference from the analysis of average deviation. The significance of the residual effects is no longer apparent, although the value of 2·24 for the variance ratio is fairly close to the appropriate 5 per cent. significance level of 2·35. There is, however, a fairly significant treatment difference ($F=3\cdot34$, $0\cdot01<p<0\cdot025$), which is largely due to the effect of prochlorperazine. Using the extreme value technique already referred to, the value of $-0\cdot780$ found for prochlorperazine is significantly lower than the other treatment effects. It would appear, therefore, that this drug has a useful tranquillizing effect compared with the other five drugs. It may be noticed that it also has a strong negative residual effect.

There is some evidence that the average deviations for the periods during the administration of the drugs are different from the average deviation during the preliminary period, though an accurate comparison is not possible

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here. It may be concluded that there is some prima facie evidence that all the drugs have a similar small effect in decreasing activity with reservation for amylobarbitone and promazine noted above.

(c) *Social Behaviour*

The analysis does not reveal any significant differences between the drugs or periods, although there is, as might be expected, a difference between patients. Although a strict comparison with the preliminary period is not possible, it appears unlikely that any real difference between this period and the drug administration periods exists.

(d) *Toxic reactions*

Toxic reactions occurred with several drugs. Undue sedation with staggering gait was reported among six patients with promazine, acetyl promazine, promethazine, and prochlorperazine. Two unpleasant hypotensive reactions among patients on promazine hydrochloride necessitated a reduction of dose to a maximum of 300 mg. early in the trial. Two further patients had hypotensive episodes on acetyl promazine some hours after grand mal fits. Four instances of parkinsonism occurred in the eighteen patients on prochlorperazine, each recovering with alteration of dose, but suggesting that a dose of 150 mg. daily was near the upper limit for this group of patients. None of these toxic reactions occurred among the adolescents and none lasted more than two days.

Conclusions

A detailed statistical analysis shows that during the trial there was a steady increase in the deviation from the normal on the rating scale for aggression. This might possibly be due to the cumulative effect of the drugs, but more probably is due to continuing confinement in winter months. The activity rating scale showed a steady decrease in activity perhaps due to the cumulative effects of the drugs. Prochlorperazine appeared to have a significant effect in reducing activity where $0{\cdot}001 < p < 0{\cdot}01$, an absence of undue sedation, with a return towards normally acceptable behaviour. However, at the dose used, 150 mg. daily, there were four parkinsonism reactions among eighteen patients. A further analysis of the scale of activity suggested that there was some evidence that amphetamine, promethazine and acetyl promazine had a similar, small effect in decreasing activity. Since toxic reactions of varying degree occurred among four of the six drugs used, there is evidence to suggest that dosage with these drugs was at least adequate. Amphetamine, promethazine, acetyl promazine and prochlorperazine were found to have a definite residual effect after discontinuation of the drug, and this should be borne in mind in the planning and analysis of other trials. The Latin square type of trial seems to be relatively efficient in assessing a number of drugs over a short period of time with the same patients, also in enabling one to compare drugs with similar actions fairly stringently against each other. One considerable disadvantage of such trials is the need to balance the experiment; if one or two of the patients had been transferred or lost from this trial, much of the statistical analysis would have been impossible. It is probable that under the circumstances the significant effect of prochlorperazine would not have been uncovered.

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Summary

A Latin square trial is reported, assessing the effect of six tranquillizing agents among mental defectives, using three rating scales. Statistical analysis suggested that all agents used had some slight effect in decreasing the hyperactivity shown by these predominantly brain-injured patients during winter months. A significant ($0{\cdot}001 < p < 0{\cdot}01$) reduction on the activity scale was shown by prochlorperazine at 150 mg. daily, but at this dosage four parkinsonian syndromes resulted among eighteen patients. Within the limits of this study the drug appears to be the most effective tranquillizer and deserves further investigation.

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References

Bergin, J. T. F., and Bergin, M. M., "The use of Sparine in low-grade mental defectives", *J. Irish Med. Ass.*, 1958, **42,** 29.

Bradley, C., "Benzedrine and Dexedrine in the treatment of Children's Behaviour Disorders", *Pediatrics*, 1950, **5,** 24.

Collard, J. F., and Maggs, R., "Clinical trial of Acepromazine Maleate in Chronic Schizophrenia", *Brit. med. J.*, 1958, *i*, 1452.

Craft, M. J., "Tranquillizers in Mental Deficiency; Hydroxyzine", *J. Ment. Sci.*, 1957a, **103,** 855.

Idem, "Tranquillizers in Mental Deficiency; Chlorpromazine", *J. Ment. Def. Res.*, 1957b, **1,** 91.

Idem, "Tranquillizers in Mental Deficiency; Meprobamate", *ibid.*, 1958a, **2,** 17.

Idem, "Mental disorder in the defective", 1958b, the Royal Institution, Starcross, Devon.

Idem, "Mental disorder in the defective; the use of tranquillizers", 1959. In press. *Amer. J. Ment. Def.*

Erwin, H. J., *Amer. J. Psychiat.*, 1957, **113,** 783.

Lecomte, G., Certoux, A., and Garrabe, J., "Efficacy of prochlorperazine in moderate dosage in states of excitement", *Ann. Méd. Psychol.*, 1957, **50,** 922.

Pearson, E. S., and Hartley, H. O., *Biometrika Tables for Statisticians*, 1954. Vol. I. Cambridge University Press.

Raymond, M. J., *et al.*, "A Trial of five tranquillizing drugs in psychoneurosis", *Brit. med. J.*, 1957, No. 5036, p. 63.

Williams, E. J., "Experimental designs balanced for estimation of residual effects of treatments", *Aust. J. Sci. Res.*, 1949, **2,** 149.

https://doi.org/10.1192/bjp.105.439.482 Published online by Cambridge University Press