INDOLE EXCRETION PATTERNS DURING TREATMENT WITH RESERPINE

By

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RESERPINE was first used extensively in psychiatric practice in the U.S.A. where many favourable reports on its use were published in 1954 and 1955 (Kline, 1954; Hollister *et al.*, 1955; Kline and Stanley, 1955). Subsequently a series of reports appeared in the U.K. (Foote, 1955; Davies and Shepherd, 1955; Shepherd and Watt, 1955). These reports were more critical and sought to establish more precise indications for the use of the drug. It soon became apparent that the drug was of most value in schizophrenia and the organic hyperkinetic states. The value of reserpine in psychoneuroses is limited (Folkson and May, 1955) but that it is going to have a more than temporary place in the treatment of schizophrenia is suggested by the continued appearance of favourable reports (Moore and Martin, 1957). These last authors emphasize that not only is the drug an effective sedative but also that it does appear, in some places, to induce genuine remissions. The present difficulty is to predict which patients will respond in this way.

Meanwhile the physiologists and pharmacologists have shown an equivalent interest in reserpine (Shaw and Woolley, 1953; Gaddum, 1953; Shore *et al.*, 1955). The interesting fact emerging from the researches of these and many other workers is that reserpine appears to release serotonin (5-hydroxy-tryptamine) in the body. It has been suggested that the central action of reserpine is mediated through such a mechanism, the serotonin which is normally in a bound form being liberated from the brain cells by the action of the reserpine (Brodie *et al.*, 1955). Shore *et al.* (1955) were able to show a quantitative increase in the urinary excretion of 5-hydroxy-indole-acetic acid, a breakdown product of serotonin, in dogs following the administration of massive doses of reserpine. The response was maximal at 4 hours and had returned to the base-line by 8 hours. Meanwhile the same authors had shown that serotonin potentiates the hypnotic action of hexobarbital on mice and that this effect was antagonized by lysergic acid diethylamide, a potent hallucinogen.

The investigation reported here consisted of a controlled clinical trial of reserpine linked with serial examination of the urinary indole excretion patterns in twelve chronic schizophrenic patients.

MATERIALS AND METHODS

The criteria for admission to the trial were that the diagnosis must be schizophrenia, that the illness be of long standing and that the patients be sufficiently co-operative to take the tablets prescribed. For convenience the twelve patients were selected from one ward and this determined that they were of the same sex, female. The mean age was 38·9 years and the range 35 to 46 years. The mean length of illness was 13·8 years and the range 4½ to 28 years. The diagnoses were Hebephrenia (10 cases), Paranoid Schizophrenia

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(1 case) and Catatonic Schizophrenia (1 case). Both these latter cases had previously been subjected to prefrontal leucotomy. Of the twelve patients five had had previous E.C.T. and six had had previous treatment with reserpine. All drugs were discontinued four weeks before the trial commenced. The trial was run on the double blind principle. The pharmacist made up two bottles containing reserpine (1 mg.) and identical placebo tablets. The bottles were labelled PQR and XYZ and the pharmacist kept the key. The patients were then allocated PQR or XYZ (tablets 1 t.d.s.) using a series of random numbers (obtained from the tables in Bradford Hill's "Medical Statistics"). After six weeks all drugs were withheld for seven days and were then re-introduced for a period of four weeks with the order reversed and the dosage doubled (tablets 2 t.d.s.).

Methods of Assessment

The patients were examined physically and interviewed prior to the trial. It should be emphasized that they were all in a relatively "non-productive" stage of their illness and were not very informative at interview. In six patients an attempt was made using I/V sodium amytal to get further information about their mental content. This attempt was not, however, attended by any degree of success. Nevertheless an assessment of the mental state of each patient was made by the author (A.F.) before the trial began. The other observers were the ward sister (M.R.) and the senior occupational therapist (H.M.). The patients were well known to them and they were asked to make a base-line assessment of the patients' behaviour in the two weeks before the trial commenced. At the end of six weeks each observer had to record whether each patient was much improved, improved, the same or worse (+2 to −1). The criteria were those of behaviour in the observed situation, i.e. ward, O.T. Department or interview. This assessment recorded any change compared with the pre-trial base-line. A second assessment at eleven weeks recorded any change as compared with the six weeks level.

Investigations

Each week samples of urine from each patient were examined starting two weeks before the trial and continuing throughout the eleven weeks of the trial. The urine was examined for indoles using a two-way ascending chromatographic technique based on that described by Jepson (1955). The solvent for the first run was isopropanol–ammonia and the papers were held in an aluminium frame (supplied by Shandon Ltd.). Whatman No. 4 paper was used and the run was continued for about 8 hours. The papers were then dried (using a hair-dryer), the frame rotated through 90 degrees and the second run, using butanol-acetic acid, continued for about 7 hours. They were then dried and developed using an Ehrlich hydrochloric-acid-acetone dip. Spots were outlined in pencil as they appeared and numbered in order of appearance. Confirmatory tests for serotonin (5-H.T.), 5-hydroxy-acetic acid (5-H.I.A.A.) and indole-acetic acid (I.A.S.) were the same as those suggested by Jepson. With each batch of papers a standard solution containing serotonin, creatinine sulphate, tryptamine, urea and tryptophane (of each 1 mg./ml.) was "run" for location purposes. The only difference between the technique employed in this investigation and that advocated by Jepson was that the papers were smaller (20 by 20 cm.). This gave shorter "runs" which was convenient but resulted in a lesser degree of separation of the "spots". In fact examinations

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using larger (12 in. × 12 in.) and "slower" papers (No. 20 Whatman paper) have been performed on all the patients at various times during the trial. The "spots" using this latter technique were better defined and more clearly separated but were not different as regards their relative positions.

Other Measurements

The patients were weighed at the start of the trial and then at weekly intervals. Their blood pressure was recorded at the start of the trial (mean of two readings in the supine position), at six weeks and at the end of the trial. The weights were known to M.R. but not to A.F. and vice-versa for the blood pressure readings. It was recognized that this information might bias these two observers but it was not found practicable to involve yet another observer.

Results

Clinical Trial: The ratings given by the three observers at six and eleven weeks were summed and are shown in Table I (maximum score +6, minimum score −3).

Table I

Comparison of Placebo With Drug Period for Each Patient

Patient	First Period of 6 Weeks		Second Period of 4 Weeks	
	Medication	End Rating	Medication	End Rating
E.B. ..	Placebo	0	Reserpine	+1
A.B. ..	Reserpine	+2	Placeho	+1
M.C. ..	Reserpine	+2	Placebo	−5
C.C. ..	Reserpine	+1	Placebo	+1
R.D. ..	Placebo	0	Reserpine	0
M.G. ..	Placebo	+1	Reserpine	+2
G.H. ..	Reserpine	0	Placebo	0
J.K. ..	Placebo	+2	Reserpine	+1
M.L. ..	Placebo	0	Reserpine	+2
M.M. ..	Reserpine	+3	Placebo	0
M.McD. ..	Placebo	0	Reserpine	+2
I.M. ..	Reserpine	+3	Placebo	+1

It should be noted here that one patient (M.C.) had to be withdrawn from the trial during the 9th week on account of disturbed behaviour. Her ratings have been included in Table I as the deterioration during the second part had been matched by a very noticeable improvement during the first part. The mean scores for the drug periods and placebo periods are shown in Table II; the difference between these scores is thought to be significant.

However it should be noted that when the number of patients improving on placebo and reserpine are compared the difference is not significant ($\chi^2 = 1 \cdot 45$ P 0·3 0·2).

Table II

No. of Patients	Drug or Placebo	Mean Score	Per cent. of Maximum Score
12	Drug	+1·7	26·4
12	Placebo	+0·08	1·39

The blood pressure readings have not been included in Table III as they are not thought to be significant; the differences noted were of the order of ±20 mm. systolic and ±10 mm. diastolic pressure. One point of interest was

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that five patients showed a rise of blood pressure after their period on reserpine (mean rise: 14 mm. systolic, 7 mm. diastolic). The weight changes are shown in Table III.

TABLE III

Weight Changes on Placebo and Reserpine

Patient	Placebo		Reserpine	
	Initial Weight	Change in Weight	Change in Weight	Final Weight
B.B. ..	8 st. 4 lbs.	+4 lbs.	+6 lbs.	9 st. 0 lbs.
A.B. ..	7 st. 5 lbs.	−4 lbs.	+9 lbs.	7 st. 10 lbs.
M.C. ..	8 st. 7 lbs.	−4 lbs.	0 lbs.	8 st. 3 lbs.
C.C. ..	10 st. 0 lbs.	−1 lbs.	+5 lbs.	10 st. 4 lbs.
R.D. ..	7 st. 0 lbs.	+4 lbs.	0 lbs.	7 st. 4 lbs.
M.G. ..	7 st. 3 lbs.	+3 lbs.	+5 lbs.	7 st. 11 lbs.
G.H. ..	9 st. 7 lbs.	−3 lbs.	+7 lbs.	9 st. 11 lbs.
J.K. ..	7 st. 6 lbs.	+3 lbs.	0 lbs.	7 st. 9 lbs.
M.L. ..	7 st. 5 lbs.	+3 lbs.	+3 lbs.	7 st. 11 lbs.
M.M. ..	8 st. 10 lbs.	+2 lbs.	+12 lbs.	9 st. 10 lbs.
M.McD. ..	9 st. 0 lbs.	+2 lbs.	+4 lbs.	9 st. 6 lbs.
I.M. ..	8 st. 0 lbs.	−3 lbs.	+7 lbs.	8 st. 4 lbs.

The results of the chromatographic studies are shown in Table IV. Urea, tryptophane and indoxyl sulphate were present in all urines and have not been included in the table. Similarly indole acetic acid and indole lactic acid were found in some of the urines but for the sake of simplicity of presentation these also have been left out of the table. The technique employed is essentially qualitative and the results have therefore been tabulated as absent (−), trace (±) and present (+). The results for serotonin (5-hydroxytryptamine) and 5-hydroxy-indole-acetic acid, using this method of scoring, are shown in Table IV; the findings for the twelve patients over a period of 13 weeks have been recorded. There are some blanks and these are due to unavoidable difficulties in collecting the urine samples.

TABLE IV

Indole Excretion During Reserpine and Placebo Periods

Patient	Placebo									Reserpine				Indoles
	1	2	3	4	5	6	7	8	9	10	11	12	13	
	(Time in Weeks)													
E.B. ..		−	−	−	+	+	−	+	+	−		−	−	5-H.I.A.A.
		+	−	−	±	±	−	−	±	−		−	−	5-H.T.
R.D. ..	−	+	+	−	+	−	+	+	+	−	−	−	−	5-H.I.A.A.
	−	+	−	+	+	+	+	+	+	+	−	+	+	5-H.T.
M.G. ..		−	−	−	−	−	−	−	−	−	−	−	−	5-H.I.A.A.
		−	+	+	+	±	±	−	+	+	+	±	±	5-H.T.
J.K. ..		−	−	−	+	−	+	+	+		−	−	−	5-H.I.A.A.
		+	+	+	+	+	+	+	+		−	+	±	5-H.T.
M.L. ..	−	−	−	−	−	+	−	+	+	−	−	−	−	5-H.I.A.A.
	+	−	+	+	+	+	+	+	+	−	−	±	±	5-H.T.
M.McD.	−	+	+	−	−	+	+	+	−	−	−	−	−	5-H.I.A.A.
	+	+	+	+	±	+	+	+	+	+	−	±	+	5-H.T.

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TABLE IV—*continued*

Patient		Reserpine (Time in Weeks) 1	2	3	4	5	6	7	8	Placebo 9	10	11	12	13	Indoles
A.B.	..	+	−	−	−	−	−	−	−	+	−	−	−	+	5-H.I.A.A.
		−	+	+	+	+	+	+	+	+	+	+	+	+	5-H.T.
M.C.	..	−	−	+	−	−	−	−	+	+					5-H.I.A.A.
		−	+	+	+	+	±	+	+	+					5-H.T.
C.C.	..	−	−	−	−	−	−	−	+	−	−	−	−	−	5-H.I.A.A.
		+	+	−	−	+	+	+	±	+	+	−	+	+	5-H.T.
G.H.	..	−	−	−	−	−	−	−	−	+	−	−	−	−	5-H.I.A.A.
		−	−	−	−	−	−	−	−	−	−	−	−	+	5-H.T.
M.M.	..	−	−		−	−	−	+	+	+	−	+			5-H.I.A.A.
		+	+		−	±	±	±	±	±	+	+			5-H.T.
I.M.	..	−	−	+	−	−	−	−	+	+	+	−	−	−	5-H.I.A.A.
		+	+	+	+	±	±	+	−	+	+	−	+	+	5-H.T.

DISCUSSION

This clinical trial of reserpine in chronic schizophrenic patients confirms the work of other workers such as Wing (1956) and Moore and Martin (1957) that the drug is of real value in this illness. It is perhaps worth emphasizing that the twelve patients reside in an active ward where they are not permitted to "deteriorate" in a psychiatric sense. They were all in a "non-productive" phase of their illness and seldom required sedatives with the exception of patients G.H. and C.M. The former has hostile outbursts from time to time while the latter had constantly tried to escape in her disturbed phases. In view of these factors the improvement was particularly impressive. Although this trial was technically a "controlled" trial, yet the ward sister (M.R.) was able, during the second part of the trial, to forecast which patients were on placebo and which were on reserpine. She based her forecast on their appetites and on their behaviour but did not impart her knowledge to the other observers. When the key was opened she was proved to be correct. Another point worth stressing is that comparing the post-trial with the pre-trial period eleven patients showed gain in weight and eleven patients showed some degree of improvement in their mental state, though in some cases the improvement was not of sufficient magnitude to warrant a plus rating. This only confirms what is already recognized in mental hospital work, that the interest aroused by a drug trial is good for the staff and therefore good for the patients (Houston, 1956; Wing, 1956).

The results of the investigation into urinary indole excretion patterns are difficult to interpret. The normal range of excretion of serotonin is still undecided, differing figures being reported by Rodnight (1956), Boyland *et al.* (1956) and Haverback *et al.* (1956). The last authors also examined the urine from four schizophrenic patients and found 5-H.I.A.A. in amounts similar to that for the normals (the range was 2·2 to 6·7 mg./24 hours). As part of another investigation carried out in this hospital urine from sixty medical patients has been examined using the same technique. Serotonin was detected in 20 patients (33·3 per cent.). Urine from thirty schizophrenic patients has similarly been examined and serotonin was detected in 22 cases (73·3 per cent.). Clearly

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further work on this subject is required before any inferences can be drawn. However, the known effect of reserpine on brain and platelet serotonin suggested that the administration of reserpine would be associated with changes in the indole excretion pattern and the absence of any such correlation in this present investigation was unexpected. Admittedly the dose was small; Shore *et al.* (1955) in their experiments on dogs used 3 mg./kilo body weight. Also early morning urine samples were examined in this investigation as opposed to 24-hour samples; the reason for this was simply the difficulty of collecting 24-hour specimens from schizophrenic patients who are up and about. In fact this negative observation confirms that made by Haverback *et al.* (1956) regarding 5-H.I.A.A. They examined the urine of six patients before and after reserpine (1–6 mg. daily) using a quantitative test. The differences in the amounts of 5-H.I.A.A. excreted were not significant. These authors point out that the largest depot of serotonin in the body lies in the gastro-intestinal tract and that while reserpine has been shown to lower the brain and platelet serotonin content, it has (in therapeutic doses) little effect on the gastro-intestinal depot. They go on to argue that therefore there may well be changes in brain serotonin content without changes in urinary excretion of 5-H.I.A.A. It may be that further complicating factors are the time relationships involved. Thus Shore *et al.* (1955) found in their dogs that the maximum rise in excretion of 5-H.I.A.A. was at 2–4 hours and that the excretion had returned to normal by 8 hours. This might well happen in human subjects given comparably large doses, but even then it would be difficult to correlate that with the accepted fact that the effects of reserpine (as regards the mental state) do not appear for several days. Another point of interest arising from this investigation was that serotonin was more commonly detected in the urine than 5-H.I.A.A. It seems to have been accepted in the various reports in the literature that 5-H.I.A.A. is the normal excretion product of serotonin. This was not found to be the case in the twelve schizophrenic patients investigated in this trial.

Conclusions

1. A controlled trial of reserpine in 12 (female) schizophrenic patients revealed a significantly greater improvement during the period when the patients were receiving reserpine.

2. These results have been discussed in relation to the non-specific effects resulting from the enthusiasm engendered by the trial itself.

3. The urinary indoles excreted by these 12 patients were examined weekly during the trial, using a paper chromatographic technique. There was no correlation found between the administration of reserpine and the excretion of serotonin or 5-hydroxy-indole-acetic acid. These results have been discussed in relation to present knowledge regarding the range of excretion of these indoles in "normal" and schizophrenic subjects.

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