A CONTROLLED STUDY OF THE EFFECT OF MEPHENESIN ON PSYCHIATRIC OUT-PATIENTS

By

P. A. L. SCOTT, M.B., Ch.B., B.Sc.

Registrar in the Department of Psychiatry
Manchester Royal Infirmary

INTRODUCTION

THE chemical compound 3–ortho–toloxy–1,2–propanediol, known as mephenesin, Myanesin or Tolserol, was shown by Berger and Bradley in 1946 to depress reflex excitability of the spinal cord and to have a depressant action at higher levels of the central nervous system in higher dosage. Other investigators confirmed this and the drug has been found effective for the spasticity and tremor of some neurological conditions.

The use of mephenesin in psychiatric conditions has been reviewed recently in this journal (Ewing and Mendenhall, 1953). In brief, there have been many reports of benefit in neuroses and psychoses with anxiety, tension and agitation; but results have been inconstant and their proper assessment made difficult by the absence, with two exceptions, of controls. Both studies in which controls were used were limited to alcoholic or post-alcoholic states; in one (Herman and Effron, 1951) it was reported that myanesin was of decided benefit; in the other (Ewing and Mendenhall) it was found to be of little value.

PROCEDURE

The present study was carried out with 24 out-patients, 17 women and 7 men. Their ages ranged from 18 to 57 but a large majority were in their thirties or early forties.

Criteria for selection of these patients were as follows:

(*a*) Anxiety present with some manifestation of somatic motor tension such as tremor, restlessness, subjective complaint of tension.

(*b*) No other treatment of any kind being received.

(*c*) Patients living within convenient travelling distance of the hospital.

(*d*) Patients with very low intelligence excluded.

(*e*) Women with pre-menstrual tension states excluded.

(*f*) Patients with obvious exogenous variables, such as intermittent domestic discord, excluded.

(*g*) Patients with prominent hysterical features such as exaggeration or exploitation of symptoms excluded.

None of the group had any psychotic features. In most, the basic personality was anankastic (i.e. strong affects, ambivalence, over-conscientiousness and scrupulousness, obsessive rumination, etc.); this probably contributed to these patients' co-operativeness and reliability as witnesses.

Three substances were given to each patient, all in the form of powder in

https://doi.org/10.1192/bjp.101.422.163 Published online by Cambridge University Press

gelatine capsules which looked identical. These were amytal (gr. 1/3 per capsule), lactose (gr. 7½ per capsule) and mephenesin (0·5 G. per capsule). Two capsules were taken four times a day before food so that the daily dose of amytal was 2⅔ gr. and of mephenesin 4 G.; this dose of mephenesin is about twice that given in most other therapeutic experiments.

The study of each patient was divided into 6 periods over 3 weeks; the periods were Monday–Tuesday–Wednesday and Thursday–Friday–Saturday; on Sundays sodium amytal gr. 1 t.i.d., a.c., was given in tablet form. Each substance was given for two periods.

The boxes of capsules were marked A, B, C by a hospital dispenser who alone knew which was which. The order of administration varied for different patients and, being fixed by other members of the staff, was unknown to the assessing psychiatrist. The orders were so arranged that each substance was given once in the first three periods and once in the last three. No substance was given for two contiguous periods. Not all the orders were regular (e.g. CABCAB) lest later assessments be biassed by the pattern of the patient's earlier responses. The orders were so arranged that in the total of 24 first periods there were 8 administrations of amytal, 8 of lactose and 8 of myanesin; and so for all the other periods, lest a difference in response to the various substances be complicated by a difference in response at various stages of the three weeks' investigation.

All patients were told in the beginning that they were to be given a new medicine, but one which was an improvement on older treatments in only a minority of patients. They were told that the most suitable dose varied for different patients and that 6 different doses were being given to see which, if any, helped them. They were warned that they might feel better in none or only one or two of the periods and much as usual during most periods. No possible side-effects were mentioned. The patients were told that it was most important that doses be taken regularly; if one was missed, they were to double the next dose. At every interview they were reminded that no steady improvement was to be expected.

This routine seemed best suited to produce a discriminating attitude in the patient. They were not told that there were 3 different substances of which one at least was ineffective lest they objected to the idea of being "experimented on" or introduced experimental variations of their own. The explanation given also justified repeating the same form of enquiry at each interview.

All assessments were made by the same psychiatrist at the same time on Wednesdays and Saturdays. At each visit the next period's supply of capsules was given. The patient was asked for a general comment on how he or she had felt for the previous couple of days and that day. A brief enquiry was then made about each of the following items:

Physical Symptoms: headaches, dizziness, visual disturbances, palpitation, sweating, loss of appetite, dyspepsia (nausea, vomiting, epigastric pain), bowel and bladder symptoms, trembling, physical tension symptoms.

Psychic Symptoms: anxiety, self-consciousness, depression, morbid thoughts (phobias, aggressive urges, rumination), feelings of unreality or depersonalization, poor concentration.

These items were scored as 0, +, ++, +++, ++++ for none, slight, moderate, severe, very severe. This method is too subjective to allow item comparison between one patient and another but at each interview the record forms of previous interviews were so arranged that earlier comment on each item could be seen at a glance and discussed with the patient if need be. The

emphasis was always on comparison with previous periods. The patient was then asked to do a Serial Sevens test and finally to sum up his or her condition for that period on a five-point scale:

Very good / good / so-so / bad / very bad

The doctor's impression was recorded separately on a similar scale. Such interviews generally took 10–15 minutes; discussion in any other form was evaded as tactfully as possible, lest it should have a cathartic effect.

Results

The composition of the capsules and the orders of administration were made known to the assessing doctor only after the last interview of the last patient.

For each patient the six periods were ranked from best to worst (I–VI) by various criteria. The distributions for the total of 24 patients are given below.

Firstly, on each record form, the patient's and doctor's summings-up were given a quantitative value by rating "very bad" as four points, "bad" as three points, and so on; this gave Tables Ia and Ib:

Table Ia

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	3	10	2	3	2	4
II	4	5	1	7	4	3
III	7	5	4	2	2	4
IV	1	2	5	3	8	5
V	7	2	7	5	1	2
VI	2	0	5	4	7	6

This may be condensed to:

Table Ib

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	34	19	19
Worst (IV–VI) Periods	14	29	29

Secondly the pluses for all symptom items, physical and psychic, were added on each record form, and, for each patient, the 6 periods were given another ranking from best to worst (I–VI) on these scores; this gave Tables IIa and IIb:

Table IIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	5	12	2	2	1	2
II	4	4	2	5	3	6
III	5	5	3	3	6	2
IV	3	1	6	3	6	5
V	5	2	6	7	1	3
VI	2	0	5	4	7	6

https://doi.org/10.1192/bjp.101.422.163 Published online by Cambridge University Press

This may be condensed to:

TABLE IIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	35	17	20
Worst (IV–VI) Periods	13	31	28

Thirdly rankings in order of clinical benefit were made by using pluses from "autonomic" items only; dizziness, visual disturbances, palpitations, sweating, loss of appetite, dyspepsia, bowel and bladder disturbances. This gave Tables IIIa and IIIb:

TABLE IIIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	6	9	1	3	2	3
II	6	7	2	3	4	2
III	3	6	5	6	1	3
IV	5	2	3	3	4	7
V	3	0	7	4	6	4
VI	1	0	6	5	7	5

This may be condensed to:

TABLE IIIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	37	20	15
Worst (IV–VI) Periods	11	28	33

Fourthly rankings in order of clinical benefit were made by using pluses from "psychiatric" items alone; self-consciousness, depression, morbid thoughts, unreality, depersonalization and poor concentration; anxiety was not included here as its reporting might have been more contaminated by autonomic symptoms. This gave Tables IVa and IVb:

TABLE IVa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	3	11	4	2	2	2
II	6	6	2	6	2	2
III	3	1	2	5	7	6
IV	5	1	4	6	5	3
V	5	3	6	1	1	8
VI	2	2	6	4	7	3

This may be condensed to:

TABLE IVb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	30	21	21
Worst (IV–VI) Periods	18	27	27

Fifthly a ranking in order of clinical benefit was made for each patient using the pluses for "tremor" and "tension" alone, since these items might be

expected to reflect best the known pharmacological effect of myanesin; this gave Tables Va and Vb:

TABLE Va

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	5	9	0	2	4	4
II	7	6	4	3	2	2
III	2	1	6	4	4	7
IV	3	5	3	5	6	2
V	6	3	4	4	4	3
VI	1	0	7	6	4	6

This may be condensed to:

TABLE Vb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	30	19	23
Worst (IV–VI) Periods	18	29	25

Sixthly, on each record form, the Serial Sevens performance was given a quantitative value by the formula:

$$X = \frac{\text{Number of seconds taken}}{\text{Number of correct responses—number of mistakes}}$$

A ranking was then made from best to worst (I–VI) performance and this gave Tables VIa and VIb:

TABLE VIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	2	5	3	4	1	0
II	2	3	3	4	1	2
III	2	2	2	0	5	4
IV	4	1	2	3	1	4
V	1	1	4	3	3	3
VI	4	3	1	1	4	2

This may be condensed to:

TABLE VIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	16	16	13
Worst (IV–VI) Periods	14	14	17

The total figures are smaller here as one or more performances of the test in 9 cases was invalidated by interruptions or background noise.

https://doi.org/10.1192/bjp.101.422.163 Published online by Cambridge University Press

The P levels of significance for the differences in the above condensed Tables were:

TABLE VII

	Amytal/Lactose			Amytal/Mephenesin			Lactose/Mephenesin		
	All Periods	First 3 Periods	Last 3 Periods	All Periods	First 3 Periods	Last 3 Periods	All Periods	First 3 Periods	Last 3 Periods
Summings-up	<0·01	<0·05	<0·02	<0·01	N.S.	<0·01	N.S.	N.S.	N.S.
All symptom items	<0·001	<0·05	<0·001	<0·01	N.S.	<0·001	N.S.	N.S.	N.S.
"Autonomic" items	<0·001	<0·05	<0·01	<0·001	0·02	<0·001	N.S.	N.S.	N.S.
"Psychiatric" items	N.S.	N.S.	N.S.	N.S.	N.S.	0·02	N.S.	N.S.	N.S.
"Tension" and "Tremor" ..	<0·05	N.S.	<0·05	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Serial Sevens	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S.=not significant at the P=0·05 level.

It will be noted that the levels of significance of differences are consistently higher in the last 3 administrations as compared with the first 3. In two distributions the first amytal periods are better than the second amytal periods above the P=0·05 level; there are no significant differences between the first and second lactose periods, or between the first and second mephenesin periods.

When the orders of clinical benefit (I–VI) based on the summings-up are plotted against the chronological orders of periods (1–6), this gives the distributions shown in Tables VIIIa and VIIIb:

TABLE VIIIa

	First Periods	Second Periods	Third Periods	Fourth Periods	Fifth Periods	Sixth Periods
I ..	0	5	2	5	6	6
II ..	2	4	3	2	7	6
III ..	8	4	1	5	4	2
IV ..	2	2	10	4	3	3
V ..	5	5	5	4	3	2
VI ..	7	4	3	4	1	5

This may be condensed to:

TABLE VIIIb

	First 2 Periods	Middle 2 Periods	Last 2 Periods
Best (I–III) Periods	23	18	31
Worst (IV–VI) Periods	25	30	17

The overall differences in the smaller table are significant at the P=<0·05 level; the last 2 periods show an improvement over the middle 2 periods significant at the P=<0·01 level. When similar distributions were drawn up using all symptom items, "autonomic" items and "psychiatric" items as the basis for the best to worst ranking, all showed a tendency, significant or bordering on

https://doi.org/10.1192/bjp.101.422.163 Published online by Cambridge University Press

significance, to improvement in the last 2 periods as compared with the first 2 or first 4. This tendency was minimal in the distributions based on "tension" and "tremor" items and the Serial Sevens performances.

No significant differences were found when the 24 patients were grouped according to age, sex, intelligence (Mill Hill Vocabulary Scale in 20 patients), total score of pluses and range of response on pluses. Such differences as did exist suggested that older patients, those of higher intelligence and those complaining most were more sensitive to the relative effectiveness of amytal.

The order of benefit of the lactose and mephenesin periods did not seem at all dependent on whether or not they followed an amytal period.

The 144 record forms were finally grouped into amytal periods, lactose periods and mephenesin periods and for each group the pluses for each symptom item were added. This gave Table IX:

TABLE IX

	Amytal Periods	Lactose Periods	Myanesin Periods
Headaches	33	42	44
Dizziness	8	13	16
Visual disturbance	13	15	18
Palpitations	27	39	30
Sweating	18	29	30
Loss of appetite	23	30	30
Dyspepsia	22	26	33
Bowel symptoms	7	8	9
Bladder symptoms	11	12	13
Tremor	23	39	30
Tension	77	101	91
Anxiety	68	83	86
Self-consciousness	38	46	47
Depression	60	72	63
Morbid thoughts	62	66	70
Unreality	11	15	15
Depersonalization	22	29	23
Loss of concentration	45	46	46
Totals	685	841	821

For the column totals the amytal/lactose and amytal/myanesin differences are significant at well beyond the $P=0\cdot001$ level; the lactose/myanesin difference is not significant.

Amytal produced the smallest plus score for every one of the 18 items; it seems to have been most effective for tremor, tension, sweating, palpitations and anxiety but only the first reaches the $P=0\cdot05$ level of significant difference. There are no significant differences between lactose and myanesin either for individual item scores or in their overall distribution between middle and highest plus scores.

Patients had not been warned of specific side-effects but note was made of spontaneous comment on any symptom that a patient regarded as new. During amytal periods, 5 patients complained of drowsiness and 2 of mild griping pains. During lactose periods, 1 patient complained of tiredness. During myanesin periods, 4 patients mentioned drowsiness, 1 dizziness and 1 nausea and headache; 3 others were the only patients who had symptoms severe enough to make them stop taking that lot of capsules; one complained of irritability and forgetfulness; another complained of confusion, dizziness, trembling, loss of appetite and nausea; the other complained of nausea and severe griping pains.

Discussion

Mephenesin seems to give no clinical benefit in cases with anxiety and tension and the fact that the more troublesome side-effects were limited to periods when it was used indicates that it would probably be impracticable to give higher doses.

Table VIa shows that only 4 of the best 2 performances of Serial Sevens were during mephenesin periods as against 14 during lactose periods. This difference is significant at about the $P=0{\cdot}02$ level and suggests a retardation effect which may be worth investigating further.

While amytal is shown to be superior to lactose and mephenesin, it should be noted that the condition of the patients in the aggregate was, in general terms, only about 20 per cent. better while they were having amytal than while they were having lactose. Even this estimate may be artificially high, as it is likely that patients interviewed while benefited by amytal would view their condition over the previous two days more tolerantly; this is suggested by the fact that every symptom and not just a majority of symptoms was improved during the amytal periods. It is not clear why the second amytal administration should have been so much more effective than the first. A probable factor was a more hopefully expectant attitude on the part of the patients, it being found that, whatever the criteria for assessing the clinical condition, there was always a tendency, sometimes statistically significant, to improvement in the later stages despite the patients being warned that this was not to be expected. There is little doubt that, if the patients had been encouraged to hope for cumulative improvement, the majority would have reported that the course as a whole gave decided benefit. It is interesting to consider this effect of suggestion in relation to the response of out-patients who attend twice a week for six or more electrical convulsive treatments. Many psychiatrists justify the use of E.C.T. in patients whose presenting symptoms are very largely "neurotic" by quoting an improvement rate of 70 per cent. or more and postulating that this is evidence of an underlying endogenous depression in such cases. Fifteen of the 24 patients in this experiment had been given such a provisional diagnosis initially and had had a course of E.C.T. within the previous six months. Seven had experienced no benefit and 8 had reported slight to moderate benefit, usually for a matter of weeks only. When the clinical orders of benefit (on summings-up) are compared with the chronological order of periods it is found that, for the 7 patients who had felt no benefit from E.C.T., there was no significant relationship; for the 8 patients who had benefited temporarily from E.C.T. there was an improvement in the last three periods significant at the $P=0{\cdot}02$ level approximately. This suggests that a patient's report of improvement at the end of a course of E.C.T. is no certain indication that it has been a specific remedy for an occult endogenous depressive process.

Summary

The procedure for a controlled administration of mephenesin, amytal and lactose to 24 psychiatric out-patients is described.

Mephenesin is found to be ineffective for anxiety and tension symptoms. Amytal was found to be significantly superior but limited in its effect.

Some comparisons are made with the response of out-patients to E.C.T.

Acknowledgments

My thanks are due to Professor E. W. Anderson for suggesting this study, to Mr. J. C. Kenna for his comments on the statistics, to Miss B. W. Clegg and Mr. J. B. Lloyd for the dispensary work involved and to Miss P. M. Lockwood and Dr. K. Rawnsley for arranging the courses.

References

BERGER, F. M., *Brit. J. Pharmacol.*, 1947, **2**, 241.
Idem and BRADLEY, W., *ibid.*, 1946, **1**, 265.
Idem, *Lancet*, 1947, *i*, 97.
BLOCK, S. L., *Arch. Neurol. and Psychiat.*, 1953, **69**, 727.
DINENBERG, S., and HECKER, A. O., *Dis. Nerv. Syst.*, 1950, **11**, 58.
DIXON, H. H., DICKEL, H. A., COEN, R. A., and HAUGEN, G. B., *Amer. J. Med. Sci.*, **1950, 220**, 23.
EWING, J. A., and MENDENHALL, J. H., *J. Ment. Sci.*, 1953, **99**, 464.
Idem, *ibid.*, 1954, **100**, 262.
FREUDENBERG, R. K., *J. Ment. Sci.*, 1950, **96**, 751.
HECKER, A. O., MERCER, M., and GRIFFIN, M. A., *Dis. Nerv. Syst.*, **1951, 12, 99.**
HOLT, W. E., *J. Nerv. Ment. Dis.*, 1952, **115**, 343.
PAUL, L., *Psychosom. Med.*, 1952, **14**, 378.
SCHLAN, L. S., and UNNA, K., *J.A.M.A.*, 1949, **140**, 672.

https://doi.org/10.1192/bjp.101.422.163 Published online by Cambridge University Press