CLINICAL STUDIES OF A NEW BARBITURATE (NEALBARBITONE)

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BRANDSTRÖM (1957) in Sweden, has recently resolved certain problems in the synthesis of barbiturates with a neopentyl group as one of the ring substituents and the resulting compound 5-allyl-5-neopentyl-barbituric acid* has been subjected to experimental studies which show it to be less hypnotic and anaesthetic than amylobarbitone or pentobarbitone sodium and yet protective to rats subjected to a stress situation after the technique of Jacobsen and Sonné (1955). The drug is rapidly absorbed after oral administration, and has a duration of action between that of amylobarbitone and phenobarbitone.

A preliminary clinical report by Ryde (1959) suggested it might be a useful sedative for the treatment of anxiety, and some comparison seemed, therefore, indicated between nealbarbitone and amylobarbitone sodium, which has already been shown to be effective in the symptomatic treatment of neurotic anxiety in a number of controlled trials (Raymond *et al.*, 1957; Scott, 1955; Robin, 1959).

When considering treatment by barbiturates it must be remembered that 447 suicides in England and Wales of a total of 4,754 in 1953 were caused by "poisoning by analgesic and soporific substances" (Registrar General, 1954), and in the United States, even in the mid-thirties, 6 per cent. of suicides and 18 per cent. of accidental deaths of Metropolitan Life Insurance policy-holders were caused by barbiturates (Curran, 1944).

Death in the greatest proportion of barbiturate intoxications follows a period of coma and some thought has been given to combining barbiturates with an antidote (Gershon and Shaw, 1957; Trautner *et al.*, 1957) in order to prevent or lighten the depth of coma. A barbiturate which retained therapeutic activity in the sedative sense but which made it more difficult for the uncooperative recipient to produce coma would clearly represent a major advance. The following trial was designed to examine the possibility that nealbarbitone is such a drug.

METHOD

The drug was examined to assess its therapeutic properties in comparison with amylobarbitone sodium and its hypnotic properties in comparison with amylobarbitone sodium or pentobarbitone.

* Now available in Great Britain as "Censedal" brand nealbarbitone.

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A "double blind" cross-over trial was conducted in out-patients diagnosed as suffering from anxiety states. Patients entered the trial in random order determined by the spin of a coin and received either amylobarbitone sodium grain 1 t.i.d. or nealbarbitone grain 1 t.i.d. for one week. The tablets were identical in appearance and only the pharmacist was aware of the actual drug used on any patient during the observation period.

At the end of a week the patients were changed over to the drug they had not received and continued this for a further week.

Each patient was examined at an initial interview and actuarial data, the diagnosis, prognosis rating (Davies and Shepherd, 1955), an impression of intellectual capacity, and symptom scores were recorded. Patients were re-examined at the end of a week and a fortnight. A note was made of any outstanding situational changes—beneficial or otherwise—and, in the case of premenopausal women, of the phase of the menstrual cycle.

At the third interview the patient was asked a sequential question: "In which of the last two weeks did you feel the better?" The trial was terminated on the basis of the results of the sequential test (Bross, 1952).

As far as the hypnotic effect of the drug is concerned, a trial was conducted in the EEG Department at Runwell Hospital and the attempt was made to produce sleep for sleep recording comparing in each patient on different days, sodium amylobarbitone or sodium pentobarbitone with nealbarbitone. A one to one dosage ratio was normally used when the comparison was with amylobarbitone and a two to one ratio when the comparison was with pentobarbitone. Thus grains 6 nealbarbitone was normally compared with grains 6 amylobarbitone sodium or grains 3 pentobarbitone. In a few cases a much higher ratio was used and as much as grains 18 nealbarbitone were administered. Assessment of sleep in these recording sessions was based on observation as well as on the appearances of EEG changes. A fuller study of the EEG effects of the drug is in preparation.

Group Matching in Out-Patient Trial

In this trial 20 patients were treated and the question arises whether these are typical anxiety states whose response to treatment might be predicted. In fact, the symptoms scored were the 23 most commonly reported in a previous trial (Robin, 1959) comparing pecazine and amylobarbitone in which a total of 51 symptoms were examined. It was thus possible to compare the symptom scores of the two groups of patients—21 from the first trial and 20 in this trial—and no significant differences were found in the distribution of symptoms (Table I) although the patients in the current trial showed slightly fewer symptoms. As the patients in the trial comparing amylobarbitone sodium and pecazine showed a good response to amylobarbitone as quite distinct from pecazine it might be expected that the patients in this trial would behave likewise. The actuarial and other data (Table II) however suggest that there were fewer patients above average intelligence in the present trial and that these patients also had a longer duration of illness. They might in general, therefore, respond less well and the prognosis rating also suggested this.

Results

Out-patient trial: The sequential test required 20 patients to show that, in general, the drugs—amylobarbitone sodium and nealbarbitone—were equally useful (Figure 1). In addition, four patients had withdrawn and one

TABLE I

Comparison of Symptoms in 41 Patients Before Treatment from a Previous Trial (Robin, 1959) and Current Study

	Trial 1 (Robin 59) No. of Patients	Trial 2 (Present study) No. of Patients
Total patients	21	20
Tremor	13	8
Fidgety	20	13
Muscle Twitching	8	7
Headache	14	13
Muzziness or Pressure	15	12
Tension, Strung Up, Anxious, Unrelaxed	21	20
Could Scream or Smash	16	14
Could Cry	20	16
Can't get off to sleep	13	11
Sleep broken or restless	15	9
Dreaming more	11	4
Poor Concentration	16	17
Loss of Interest	14	13
Loss of Pleasure	16	13
Fatigue: Lassitude	16	16
Irritable or Excitable	17	17
Worrying about trivialities	18	15
Ideas of reference	14	7
Phobias: Insanity	11	8
Dry mouth	14	14
Loss of Libido	12	16
Dyspepsia	11	7
Sweating	13	11

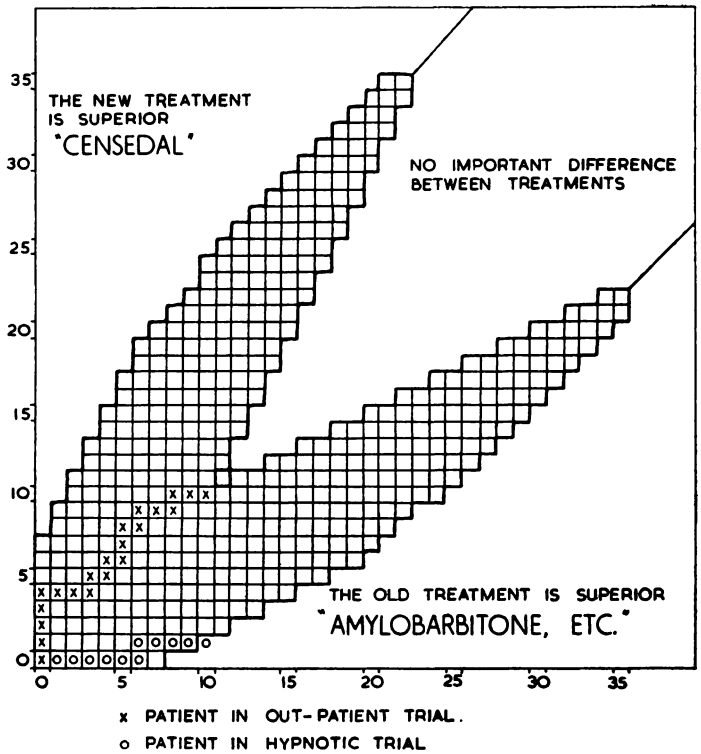

FIG. 1.—Sequential graph showing preferences in out-patient and hypnotic trials.

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TABLE II

Actuarial and Other Data on 41 Patients from a Previous Trial (Robin, 1959) and Current Study

	Trial 1	Trial 2
Sex:		
Female	15	12
Male	6	8
Age in years:		
<30	11	7
31–50	9	13
>50	1	0
Civil State:		
Married	19	18
Separated	—	1
Single	2	1
Precipitant:		
Domestic	11	9
Illness	2	7
Housing	1	2
Finance	2	1
Work	5	1
Prognosis:		
Rating 1	10	2
2	8	9
3	3	9
Duration of illness:		
<1 year	13	5
1–2 years	3	5
>2 years	5	9
Not stated	0	1
Clinical assessment of Intelligence:		
+	9	3
Average	10	13
−	2	4
Night sedation prescribed	12	8

been withdrawn from the trial. These were on amylobarbitone in four cases and nealbarbitone in one case.

The symptom scores appear to confirm the global assessment (Table III). The number of symptoms appearing one-third less frequently in the first week's treatment were 10 of 23 in the amylobarbitone treated patients and 8 of 23 in the nealbarbitone treated patients. Of 170 symptoms reported before nealbarbitone, 52 were not reported after it (31 per cent.) whereas of 119 before amylobarbitone, 46 were cleared (26 per cent.).

If the number of patients showing symptoms after one week's treatment with nealbarbitone or amylobarbitone (regardless as to whether this was in the first or second week of the trial) is recorded (Table IV) again the drugs are seen to be comparable, any advantage being with nealbarbitone.

Two factors were examined to see what influence they may have had on the results—the phase of the menstrual cycle, where this was applicable, and situational changes. The pre-menstrual and menstrual periods—the significance of which Dalton (1959) refers to, occurred in roughly equal numbers receiving nealbarbitone and amylobarbitone so that neither drug could be said to have suffered any disadvantage (Table V).

TABLE III

Group Symptom Scores in 20 Out-Patients Treated with Amylobarbitone and Nealbarbitone

Week	0	1	2	0	1	2
Drug*	Nil	N	A	Nil	N	A
Number of Patients	12	12	12	8	8	8
Tremor	5	3	5	3	4	4
Fidgety	8	6	9	5	5	4
Muscle Twitching	2	2	2	5	3	3
Headache	9	7	9	4	5	6
Muzziness or Pressure	6	8	5	6	7	6
Tension, Strung Up, Anxious, Unrelaxed	12	8	10	8	6	6
Could Scream or Smash	8	7	5	6	2	2
Could Cry	9	6	8	5	5	6
Can't get off to sleep	7	3	5	4	1	1
Sleep broken or restless	5	4	6	4	5	3
Dreaming more	1	2	2	3	3	2
Poor Concentration	11	6	7	6	4	3
Loss of Interest	8	7	7	5	4	3
Loss of Pleasure	7	6	8	6	3	7
Fatigue: Lassitude	9	8	9	7	6	5
Irritable or Excitable	10	8	9	7	4	3
Worrying about trivialities	9	8	8	6	5	6
Ideas of reference	4	4	3	3	2	1
Phobias: Insanity	5	2	4	3	2	2
Dry mouth	8	5	7	6	5	6
Loss of Libido	8	8	9	8	5	7
Dyspepsia	3	4	3	4	3	3
Sweating	6	3	5	5	3	4

* N=Nealbarbitone.
A=Amylobarbitone.

TABLE IV

Group Symptom Scores After One Week's Treatment with Amylobarbitone and Nealbarbitone

	Before treatment	After neal-barbitone	After amylo-barbitone
Total number of points	20	20	20
Tremor	8	7	9
Fidgety	13	11	13
Muscle Twitching	7	5	5
Headache	13	12	15
Muzziness or Pressure	12	15	11
Tension, Strung Up, Anxious, Relaxed	20	14	16
Could Scream or Smash	14	9	7
Could Cry	16	11	14
Can't get off to sleep	11	4	6
Sleep broken or restless	9	9	9
Dreaming more	4	5	4
Poor Concentration	17	10	10
Loss of Interest	13	11	10
Loss of Pleasure	13	9	15
Fatigue: Lassitude	16	14	14
Irritable or Excitable	17	12	12
Worrying about trivialities	15	13	14
Ideas of reference	7	6	4
Phobias: Insanity	8	4	6
Dry mouth	14	10	13
Loss of Libido	16	13	16
Dyspepsia	7	7	7
Sweating	11	7	8

TABLE V

Phase of Menstrual Cycle During Trial

Week of cycle	Nealbarbitone treatment period	Amylobarbitone treatment period	First week of trial	Second week of trial
1	2	4	2	4
2	3	2	3	2
3	4	5	6	3
4	6	4	4	6

All the positive situational changes occurred in the first week of the trial and distributed equally among both drug groups. The disadvantages appeared later and again the distribution was to both drugs (Table VI).

TABLE VI

Situational Changes During Trial

	Nealbarbitone treatment period	Amylobarbitone treatment period	First week of trial	Second week of trial
Situational Changes:				
Advantageous	2	2	4	0
Disadvantageous	2	1	1	2

As was anticipated the effect of the drugs is not as marked as that of amylobarbitone in the first trial where the mean symptom score was reduced from 16·2 to 10·8 in two weeks. Here the reduction for the whole trial was from 13·9 to 11·9. Nevertheless, using the Wilcoxon Matched-Pairs Signed-Ranks Test (Seigel, 1956) on the differences in each individual patient's total symptom score before and after one week's treatment with nealbarbitone shows these to be significant at the 1 per cent. level of confidence (N=19; T=26; at P=0·01; T=32). Amylobarbitone produces differences which just fail to be significant at the 5 per cent. level of confidence with the two tail test (N=20; 2=52·5; at P=·05; T=52) but *are* significant with the one tail test which would apply in this case.

No major toxic symptoms were observed. Side-effects of the drugs might be included in symptoms which were not reported before the particular drug was administered but reported thereafter. In the first week the 12 nealbarbitone treated patients reported 13 such symptoms and the 8 amylobarbitone patients 17. Considering the whole trial 35 new symptoms were reported after nealbarbitone and 57 after amylobarbitone. Four individual symptoms appeared more frequently in the amylobarbitone group—including tremor which was reported in the last trial—and only one, muzziness, in the nealbarbitone group.

EEG DEPARTMENT TRIAL

The sequential test required twelve patients to show that amylobarbitone or pentobarbitone were significantly (P=0·01) more hypnotic than nealbarbitone in the doses used (Figure 1). In one case grains 18 of the latter drug failed to produce any evident change of awareness, in one case grains 15 failed to produce any change and in a further case grains 15 produced only drowsiness; grains 9 was used on three occasions producing sleep, drowsiness and no change respectively. Grains 6 of the drug produced sleep on only one occasion.

Conclusion

In a small group of anxiety states treated as out-patients nealbarbitone is shown to be comparable in therapeutic activity to amylobarbitone sodium in the same dosage and to be therapeutically effective. The group as a whole were, although comparable in symptoms, of poorer outlook than a previously treated group and responded less well to treatment. No major toxic symptoms were observed and fewer new symptoms (possible side-effects) followed nealbarbitone than amylobarbitone. A trial with the drugs and pentobarbitone used as hypnotics by day, with observers present, and with EEG records of sleep showed that nealbarbitone is significantly less hypnotic than the other drugs.

It is thus suggested that nealbarbitone is a therapeutically active sedative drug with low hypnotic activity. It seems desirable to repeat and attempt to confirm these results on a larger scale.

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