CLINICAL TRIAL OF METHYPRYLONE, A PIPERIDINE HYPNOTIC

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Few of those who have spent their illnesses in more secluded places realize how much noise there can be in a hospital ward at night. The usual practice in the ear, nose, and throat department of this hospital is therefore to offer adult patients a hypnotic such as amylobarbitone sodium or butobarbitone.

Methypylone ("noludar," 2,4-dioxo-3,3-diethyl-5-methyl-piperidine) has been found to be a safe and effective sedative-hypnotic in doses of 200–400 mg., with a fairly prompt onset, short duration of action, and no side-effects (Cass *et al.*, 1955). It is well tolerated by older patients in whom barbiturates are apt to produce confusion and sometimes delirium (Schmitt, 1955). This has been confirmed by Kemper (1955) in elderly psychiatric patients. Brandman *et al.* (1955), using methypylone in doses of 250 mg., reported occasional drowsiness, dizziness, and headache.

Present Investigation

The object of the trial was to compare the hypnotic effects of amylobarbitone sodium, butobarbitone, methypylone, and a control tablet in patients admitted to the ear, nose, and throat wards. The results were assessed objectively by the nursing staff (speed of onset and duration of action) and subjectively by the patients (speed of onset, quality of sleep, and nature of after-effects).

Four sets of tablets were prepared in equivalent doses—amylobarbitone sodium (1½ gr., or approximately 100 mg.), butobarbitone (1½ gr., or approximately 100 mg.), methypylone (200 mg.), and a control (lactose, starch, and a trace of infusion of quassia). All were identical in appearance and very closely similar in taste. The slight differences in taste could be detected only by chewing the tablets, an unlikely practice in view of their bitterly repellent flavour.

The bulk containers were labelled A, B, C, and D so that the tablets could not be identified. As it was thought that the control tablet might still be recognized by its lower scores, a random permutation of these letters was used to allot the tablets from their lettered containers to packets labelled 1, 2, 3, and 4 for first, second, third, and fourth nights, one tablet per packet. A set of four packets (containing one tablet of each type) for each patient was placed in a numbered box by a dispenser who did not know the key to the letters A, B, C, and D. On the wards the tablets were known only by their box and packet numbers until after the trial had been completed.

Since many of the patients stayed less than eight nights in the ward and there were four types of tablet to be tested, it was decided to give patients a different tablet on each of their first four nights, omitting the night of the operation. Administration of the tablets on these nights followed the usual sedative routine for the patients' first few nights in hospital, so that the conditions of the trial were the same as those of everyday practice. The tablets were given at 9.30 p.m. by the night nurse, who then made half-hourly rounds from 10 p.m. till 6 a.m. to determine whether the patients were sound asleep, dozing lightly, or awake, giving 2, 1, and 0 marks respectively. She recorded these results on a chart, along with any relevant remarks. The highest possible score was 34, representing between 8 and 8½ hours' sleep (see footnote to Table I). At 9 a.m. I asked each patient the following questions, marking the answers as shown: (a) Did you get to sleep quickly (1) or slowly (0)? (b) Was your night's sleep sound (3), fair (2), poor (1), or bad (0)? (c) Did you wake fully refreshed (3), reasonably

clear in the head (2), stale and drowsy (1), or "drugged" and confused (0)?

Scores were recorded separately for each of the three questions and a note was made of any side-effects (for example, headache) which seemed attributable to the tablets. The questions were designed to be answered in an even number of ways (2, 4, 4). With an odd number of possible answers (for instance, "Was your night's sleep good, fair, or bad?") there is a tendency towards the middle one, which is apt to mask a positive finding.

The experiment, including a preliminary pilot trial, had to be completed within three months. For the purpose of convenience it was intended to use the first 100 patients to complete the trial. Ideally, with a balanced design, each type of tablet would have been given an equal number of times on the four nights. In anticipation, however, of the inevitable withdrawals for such reasons as deterioration in clinical condition, a random allocation of tablets was used rather than a balanced design. Each type of tablet would ideally have been given 25 times on each of the four nights; the random allocation produced no greater discrepancy than that among the control tablets, which were given 28 times on the second and 22 times on the fourth nights. As will be shown, this had no material effect on the results.

Subjects

In order to minimize the selection of cases, all patients over 21 admitted to the ear, nose, and throat wards were included in the trial if they were willing to take part, except for those who were (1) acutely or seriously ill, (2) in more pain than could be relieved by tab. codein. co., (3) admitted for a major operation (one likely to last more than two hours), (4) suffering from any condition in which barbiturates were contraindicated, or (5) habituated to hypnotics. Patients were removed from the trial only if they subsequently developed illness or pain as described above.

While the trial was in progress 156 adults were admitted to the wards. Of these, 105 were eligible for inclusion on the above conditions, none declining to take part. Five were unable to complete the trial and have not been included in the analyses. Two of these were withdrawn because of pain, two because of radical change in treatment, and one because she was later found to be in the habit of taking hypnotics (with which she secretly supplemented her trial tablets). The 100 who completed the trial included 56 men and 44 women, their ages varying from 21 to 71 (average 39). Most of them stayed in hospital for a week to ten days and had their operation on the second day; 41 had tonsillectomy by dissection, 15 had no operation during the trial, 12 had submucous resection of the nasal septum, 10 had examinations under anaesthesia, 9 had polyps removed from ear, nose, or vocal cords, and 13 had other operations.

All patients eligible for the trial were interviewed personally on the day of admission. The outlines of the trial were explained, but the control tablet was mentioned only when patients asked specifically about this, as they did on several occasions.

Results

It is clear from Table I that there is no significant difference between the mean scores for the three drugs. Only for the control is the score significantly lower, but not greatly lower, than for the other three. [An analysis of variance shows that there is a difference between the four groups, disregarding the nights, which is significant at 1% ($P < 0.01$).] The night with the lowest score is the second night of the trial. For the 72 patients who had their operation on the second day this was the night of the day after operation, but the difference between this score and the first night's score is small. Figures for the onset of sleep derived from the night nurses' scores are not given because it was found that onset, as judged by the nurses, varied much more with the particular night than with any other factor. For instance, often on quiet nights every patient was asleep

by 10 p.m., and on noisier nights several were still awake at 10.30 p.m.

It has been said that each tablet was not given an equal number of times on the four nights. Accordingly separate figures are given for each tablet on each night. Without any formal tests of significance it can be seen that this fact has not materially affected the results. For instance, the figures for the control are the lowest on three of the four nights.

TABLE I.—Objective Assessment by Night Nurses*

Tablets	Nights. Hours of Sleep and Mean Scores				Hours of Sleep and Mean Scores for Tablets	Standard Error of Mean Scores for Tablets
	1st	2nd	3rd	4th		
Amylobarbitone sodium	6½ 27.2	6½ 26.7	7 29.4	6½ 28.2	6½ 27.9	0.40
Butobarbitone	6½ 27.8	6½ 28.1	6½ 27.3	7 28.7	6½ 28.0	0.38
Methypyrlylone	6½ 27.2	6½ 27.8	6½ 28.2	6½ 27.7	6½ 27.7	0.37
Control	6½ 26.4	5½ 24.0	6½ 26.9	6½ 28.4	6½ 26.3	0.43
Hours of sleep and mean scores for nights	6½ 27.1	6½ 26.6	6½ 28.0	6½ 28.2		

*Calculation of Approximate Duration of Sleep from Mean Score.—On the basis that the night nurse gave a patient 2 marks each half-hour he was asleep (see text), duration of sleep may be estimated in hours by dividing the night's score by 4. This, however, implies that the patient has been asleep for half an hour when the first 2 marks are given. If an average time of a quarter of an hour is allowed for him to get to sleep after the tablet or the last half-hourly observation, then 1 mark, representing nearly a quarter of an hour's sleep, is subtracted from the score before dividing by 4. The formula Hours of sleep = $\frac{(\text{score} - 1)}{4}$ probably gives too generous an estimate, as it does not allow for waking between observations, but the mean scores would be open to the same objection if taken as absolute values. Their translation into hours of sleep is given for the sake of convenience. (Maximum possible score: 34 marks, representing 8½ hours' sleep.)

TABLE II.—Onset of Sleep

Tablets	Did You Get to Sleep		Total	Mean Scores of 1 and 0
	Quickly ? (1)	Slowly ? (0)		
Amylobarbitone sodium	64	36	100	0.64
Butobarbitone	79	21	100	0.79
Methypyrlylone	74	26	100	0.74
Control	56	44	100	0.56

$\chi^2 = 15.73$. D.F. = 3. $P < 0.01$.

TABLE III.—Quality of Sleep

Tablets	Was Your Night's Sleep				Total	Mean Scores of 3, 2, 1 and 0
	Sound ? (3)	Fair ? (2)	Poor ? (1)	Bad ? (0)		
Amylobarbitone sodium	41	40	18	1	100	2.2
Butobarbitone	46	42	11	1	100	2.3
Methypyrlylone	48	43	7	2	100	2.4
Control	26	47	24	3	100	2.0

$\chi^2 = 13.90$. D.F. = 6 (third and fourth columns taken together). $P < 0.05$.

TABLE IV.—After-effects

Tablets	Did You Wake				Total	Mean Scores of 3, 2, 1, and 0
	Fully Refreshed ? (3)	Reasonably Clear in the Head ? (2)	Stale and Drowsy ? (1)	"Drugged" and Confused ? (0)		
Amylobarbitone sodium	16	50	33	1	100	1.8
Butobarbitone	25	48	25	2	100	2.0
Methypyrlylone	16	53	28	3	100	1.8
Control	11	64	25	0	100	1.9

$\chi^2 = 10.51$. D.F. = 6 (third and fourth columns taken together). $P > 0.05$.

The distribution of answers to the three questions is shown in Tables II-IV. Analysis of the answers relating to onset and quality of sleep (Tables II and III) shows a significant difference between the forms of treatment (see χ^2 tests at the foot of each table), which is clearly attributable to the lower score of the control. This is not so for the answers to the question on after-effects (Table IV). In none of the tables are there any demonstrable differences between the three drugs. A similar analysis shows that there is no significant difference between the four nights in any of the questions.

The only side-effect recorded was headache, which occurred twice after each drug and once after the control. Patients sometimes volunteered that a particular night was the best they had had for a long time. They did this five times after amylobarbitone sodium, five after butobarbitone, six after methypyrlylone, and twice after the control.

Discussion

Standards of comparison for hypnotics, such as onset and duration of action, quality of sleep, and nature of after- and side-effects are generally accepted, but reports of controlled trials are comparatively infrequent. In hospital it is possible to supplement the patients' own impressions with objective observations. Even the quality of sleep, although usually best judged by the patients themselves, can be assessed with considerable accuracy by a nurse looking after a reasonable number of patients.

An obvious criticism of this trial is that each drug was tried once only on each patient. This raises the question of whether one patient will respond fairly consistently to one hypnotic. If this is so, more information will be gained by studying the effects of each tablet on every patient than by using the available time in any other way. Hare (1955) has made a detailed study of the comparative efficacy of hypnotics in a neurosis unit. He observed 30 female patients for an average time of three to four weeks each. His results show that each patient responded fairly consistently to any one hypnotic, although great variation was found between different patients. This confirms strong clinical impressions from the routine use of hypnotics in the wards.

The investigation of after-effects remains the least satisfactory part of the trial. Many patients found it difficult to distinguish between waking heavy-headed as a result of excessive sedation and waking tired as a result of lack of sleep. On other points the patients proved reliable witnesses. With a few notable exceptions, their impressions corresponded well with the nurses' observations.

As equivalent doses of the three drugs were deliberately chosen it is not surprising that the results were similar, but the high figures for the control are interesting. It would probably have been worth while to include a fifth night without any tablet, but co-operation for this might sometimes have been more difficult to enlist, especially on the day after the operation, when the wide difference between the control and the drugs (Table I) would seem to show that a hypnotic is a valuable part of treatment at this time.

The present trial has shown methypyrlylone to be a reliable hypnotic of comparable efficacy and onset and duration of action to amylobarbitone sodium and butobarbitone. If subsequent investigation confirms the rarity of side-effects found by previous workers, methypyrlylone should prove a valuable addition to the non-barbiturate hypnotics.

Summary

Methypyrlylone, a piperidine hypnotic, was investigated in 100 patients in the ear, nose, and throat wards of a general hospital. The onset and duration of action, quality of sleep, and nature of after-effects were compared with those of amylobarbitone sodium, butobarbitone, and a control. Nurses' observations supplemented and were usually consistent with patients' impressions. No significant difference was found between the three

drugs. The score of the control was not greatly lower, but the difference was statistically significant.

Methypyrone is a reliable non-barbiturate hypnotic of comparable effect to amylobarbitone sodium and butobarbitone.

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TOXIC EFFECTS AND SIDE-EFFECTS OF METHYLPENTYNOL

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Novelty has all the appeal of invention, and it is common experience that newly introduced drugs pass through a phase during which they are esteemed too highly. Methylpentynol ("oblivon") has been no exception, for early reports were unanimous in emphasizing its distinct paucity of toxic complications (Allen and Krongold, 1951; Hirsh and Orsinger, 1952; Malone *et al.*, 1952).

Margolin *et al.* (1951) studied the acute toxicity of the drug with animals and found that the LD₅₀ ranged from 600 to 900 mg. per kg., whereas chronic toxicity experiments disclosed no gross or microscopical changes following the daily oral administration of 200–300 mg. of methylpentynol, an equivalent of seventy times the recommended human dose. The drug has also been given daily by mouth to human subjects in a dose ranging from 0.1 to 1.5 g. for six months without any undesirable side-effects (Chevalley *et al.*, 1952), although Schaffarzick and Brown (1952) reported that two out of six epileptics given the substance developed a strongly positive cephalin flocculation reaction. As a corollary, it was noted that the livers of rats given methylpentynol in their drinking-water exhibited a diminution of hepatic-cell cytoplasmic basophilia.

The effect of single doses of methylpentynol has been assessed by Trotter (1954), who found that speed of reaction, concentration, and co-ordination were either unimpaired or enhanced after 500 mg. of the drug. Sinton (1954) was also unable to detect any deleterious result from 1 g. of methylpentynol, although Macdonald (1955), using half this dose, noted an 8% deterioration on a numerical test.

In view of these predominantly eulogistic appraisals, it is hardly surprising that a wide field of application has been found for methylpentynol: for example, as a

hypnotic for elderly patients (Simpson, 1954), as a pre-operative sedative for tonsillectomy (Simmons, 1954; Gusterson, 1955), for allaying apprehension before dental operations (Trotter, 1953), as a prophylactic against nocturnal attacks of asthma (Bendkowski, 1955), and for reducing anxiety at childbirth (Bourne, 1954).

Recently attention has been directed to the drug's potential toxicity. May and Ebaugh (1953) noted drowsiness, ataxia, and slurred speech in five patients who had ingested between 3.89 and 10.16 g. of methylpentynol during periods ranging from two to six days. They also described a confusional episode in a woman who had swallowed at least 10 g. of the drug. Glatt (1955a) referred briefly to the appearance of a "confused and highly emotional state with slurring of speech and ataxia" in alcoholics after taking up to 20 capsules (each of 250 mg.) daily for two to three days. He amplified this subsequently (Glatt, 1955b), describing the cases of 15 patients who after excessive doses of methylpentynol presented a picture of "gradually increasing confusion with lack of concentration and attention, tearfulness, depression, speech difficulties, and ataxia." Diplopia, nystagmus, and slight ptosis were each seen separately in three patients, while visual hallucinations were also encountered. Cares *et al.* (1953) reported a death after a dose of 4.5–6 g., and it is also on record following 2.25 g. of methylpentynol in conjunction with 20 pentobarbitone sodium ("nembutal") tablets (*British Medical Journal*, 1955). Recovery after 8.75 g. and 10 g. of methylpentynol has been noted respectively by Lemere (1952) and Brown and Ellis (1955); and Lovelace and Roith (1955) documented an attempted suicide with a combination of methylpentynol and "persomnia" (carbromal and bromvaletone). Recently, two youths who had each taken 0.75–1 g. of the substance were involved in a motor accident associated with a fatality (*Lancet*, 1955).

Case Histories

Eight brief illustrative case histories of toxic reactions to methylpentynol are described, followed by a synopsis of the side-effects—as distinct from toxic phenomena—noted in two groups each of 15 patients, the one given therapeutic doses of methylpentynol (0.5–2 g. a day) for one to six weeks, and the other receiving larger doses of methylpentynol (approximately 5 g.) during labour.

Case 1

An unmarried woman aged 24, suffering from an anxiety state, had taken eight capsules of methylpentynol (2 g.) daily for four days. She now complained of feeling cold and shivery, of declining appetite, and of being unsteady on her feet.

On examination the positive abnormalities consisted of unsustained nystagmoid jerks on conjugate lateral deviation of the eyes, loss of tone in the facial musculature, dysarthria, and tremor of the protruded tongue. The gait was ataxic and Romberg's sign positive. There was a static tremor of the hands, with cerebellar defects in both upper and lower limbs, including ataxia on the finger–nose, heel–shin tests, and dysidiadokokinesis. The tendon reflexes were diminished, and were associated with an overall reduction of tone. The urine was normal.

Her mood was one of depression and, although denying hallucinations, she appeared to be hallucinated one evening, insisting there was a woman standing beside her bed. Orientation was correct, but she performed only moderately at serial sevens (the subtraction of serial sevens from 100), the digit span (number of correctly repeated non-consecutive digits in same or reverse order as given by the examiner) being seven forwards and six backwards. She