

A METHOD FOR THE EVALUATION OF HYPNOTICS IN MAN

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IN THIS study, the principle of using a physiological fluid load to produce a disturbance in the sleep of normal subjects has been utilized both for the evaluation of the non-barbiturate hypnotic, ethchlorvynol ('Arvynol': Pfizer) and to compare its hypnotic effect with glutethimide ('Doriden': Ciba). The technique, which is based on the work of Isaacs (1957 a,b.) and Condouris, Costa and Bonnycastle (1960), has been adapted to provide a simple reproducible method for evaluating and comparing hypnotics in man.

Ethchlorvynol, ethyl- β -chlorovinyl ethinyl carbinol, has been shown to produce hypnotic effects in animals (P'An, Kodet, Gardocki, McLamore and Bavley, 1955) and to be as effective as glutethimide (Cuthbert, 1963) thalidomide, butobarbitone (Woodd-Walker, 1963) and dichloralphenazone (Tsapogas, Modle & Wheeler, 1962) in clinical trial. In addition, when compared with an equivalent dose of thalidomide in rabbits, ethchlorvynol produced no teratogenic effects whereas thalidomide in the same experiment produced either stillbirth or teratogenic effects in the great majority of the offspring (Reinert, 1962). No effect on the human fetus has been noted in the U.S.A. where this hypnotic has been available for over 6 years.

Methods

This study was carried out in four phases on healthy adult subjects of both sexes with no history of insomnia or recent disease.

In the first phase each subject was given one of five treatments on each of five different nights in a randomized order. These treatments were a placebo, 250 mg. glutethimide, 500 mg. glutethimide, 200mg. ethchlorvynol and 500 mg. ethchlorvynol. Each subject was instructed to take the hypnotic and a water load (1½ pints) on retiring and note this time and the time of first waking. However, after the first night of the experiment it became apparent that 1½ pints of water produced a disturbance of sleep irrespective of whether the subjects received either a hypnotic or a placebo. Therefore, for the following four nights the water load was reduced to ¾ pint but this amount was later found to be inadequate.

Further experiments (phase 2) demonstrated that 1 pint of milk produced a more consistent disturbing effect on sleep. In our experience the majority of subjects prefer milk to water and the use of a one-pint bottle ensures the correct volume being taken.

In phase 3 ethchlorvynol was compared with a placebo and in the final phase with both glutethimide and a placebo.

Results

The results of the water-load experiment can be seen in Table 1, which shows the mean sleeping time obtained following a 1½-pint water load (1st night only); a ¾-pint water load (nights 2-5 inclusive); and the effects over all five nights. In this phase, 71 subjects participated.

As these preliminary trials demonstrated that the technique in this form was not suitable for our purpose phase 2 was carried out as a small pilot review, with six subjects only (all males) with an intermediate fluid load of 1 pint of milk. This second investigation was organized as a cross-over trial on two nights only with a placebo and 500 mg. ethchlorvynol. The results (Table 2) show no difference between sleeping times for the hypnotic and placebo which suggested that this modified procedure was more suitable and that with larger numbers, statistically valid results could be obtained.

Phase 3 was organized as a cross-over study with 500 mg. ethchlorvynol and a placebo in 24 subjects (12 male and 12 female). On the first night half each group received the placebo and the other half the active tablet, the alternate treatment being given on the second night. It was also decided to take the difference in time between retiring to bed and actually getting up to empty the bladder rather than the time of first waking, since previous experience had shown that some subjects were minimally roused but did not get out of bed. The results of the phase and a combined analysis of sleeping times for phases 2 and 3 together, are shown in Table 3. A further analysis demonstrated that the average duration of sleep on the second night both with the hypnotic and with the placebo was significantly longer than on the first night. It can also be seen that irrespective of night or treatment, females had a significantly longer sleeping time than males (Table 4).

Utilizing the experience and results obtained from the first three phases of this investigation, the

TABLE I
PHASE I: WATER LOAD EXPERIMENTS

No. of subjects: 71	1st night only (1½-pint water load)		Nights 2-5 inclusive (¾-pint Water load)		Over all five nights	
	Mean sleeping time hrs. mins.	Difference mins.	Mean sleeping time hrs. mins.	Difference mins.	Mean sleeping time hrs. mins.	Difference mins.
1. Placebo	4 46	—	6 18	—	6 3	—
2. 250 mgm. glutethimide	4 46	—	6 11	- 7	5 58	- 5
3. 500 mgm. glutethimide	4 57	+ 11	6 27	+ 9	6 7	+ 4
4. 200 mgm. ethchlorvynol	4 49	+ 3	6 6	-12	5 52	-11
5. 500 mgm. ethchlorvynol	5 21	+ 35	6 23	+ 5	6 12	+ 9
significant difference (P = .05)		127		41		40

TABLE 2
PHASE 2: CROSS OVER STUDY WITH 6 SUBJECTS FOR 2 NIGHTS

Treatment	Mean sleeping time hrs. mins.
500 mgm. ethchlorvynol	6 50
Placebo	4 37
Difference	2 13
Significant difference (P = .05)	2 51

TABLE 3
PHASE 3: CROSS OVER STUDY WITH HYPNOTIC AND PLACEBO

Treatment	24 subjects: phase 3 only	30 subjects: phases 2 and 3
	Mean sleeping time hrs. mins.	Mean sleeping time hrs. mins.
500 mgm. ethchlorvynol	7 23	7 16
Placebo	6 30	6 8
Difference	53*	1 8*
Significant difference (P = .05)	50	47

*These differences are significant

final experiment was carried out as follows: 60 volunteer subjects were given a one-pint fluid load in the form of milk together with a placebo on retiring. The time at which they retired was noted and also the time at which they were sufficiently disturbed to get up and empty their bladders. From this information 30 subjects were selected who were obviously disturbed by this fluid load: the remaining 30 did not show any appreciable effect.

TABLE 4
PHASE 3: ANALYSIS OF ORDER OF TREATMENT AND SEX DIFFERENCE

No of subjects: 24	Mean sleeping time hrs. mins.	Mean sleeping time hrs. mins.	
		Males	Females
1st night	6 31	6 3	6 3
2nd night	7 22	7 50	7 50
Difference	51*	1 47*	1 47*
Significant difference (P = .05)	50	50	50

* These differences are significant

TABLE 5
PHASE 4: 30 SUBJECTS IN A 3-NIGHT CROSS-OVER STUDY

Treatment	Mean sleeping time hrs. mins.	Difference hrs. mins.
Placebo	5 21	—
500 mgm. ethchlorvynol	6 43	1 22*
500 mgm. glutethimide	6 52	1 31*
Significant difference (P = .05)		1 5

* These differences are significant

The 30 subjects selected for further study were then given one of three treatments together with a pint of milk at night in a random order. These treatments were a placebo, 500 mg. ethchlorvynol and 500 mg. glutethimide. On the second and third nights they received the other treatments. The results (Table 5) demonstrate that ethchlorvynol 500 mg. and glutethimide 500 mg. have an equal hypnotic action which is significantly greater than that of the placebo.

Side effects were encountered on only a small proportion of subjects (ethchlorvynol 10%: glutethimide 13%: placebo 7%), and consisted of slight headache or dry mouth on waking. There was no significant difference between the incidence of these side effects with ethchlorvynol, glutethimide or the placebo. This compares with the findings of Goldstein (1953). Similarly drowsiness of a transient nature was noted in some subjects, but again occurred in the same proportion of each group.

Discussion

The experience and results obtained from the early phases of this investigation led to the final experiment which showed that both glutethimide and ethchlorvynol produce the same hypnotic effect at a dose of 500 mg. In addition, both produce a statistically significant increase in sleeping time when compared with a placebo. Side effects were minimal and there was no difference between the incidence with ethchlorvynol, glutethimide or the placebo.

The method which we finally evolved is simple to operate and causes less inconvenience to the subjects than similar techniques which necessitate urine collection. In addition, it gives reproducible results and allows a comparison to be made between the duration of action of different hypnotics.

In the original work by Isaacs, (1957 b.) all subjects were asked to collect and measure the urine passed on waking. Within certain limits it was suggested that the depth of sleep could be estimated from the product of the log of the sleeping time and the log of the urine volume passed on first waking. However, this scheme has two drawbacks; first, there is no clear correlation between volume of urine voided and the duration of sleep (Condouris and others 1960) and, second, subjects often do not complete the course of an experiment, if it requires the collection and measurement of urine. Indeed, Isaacs (1957 b.) found that of 109 students in his investigation only 9 submitted a complete record. In contrast, by employing our modified technique we obtained complete returns from 131 subjects out of a total of 150.

The results of the water-load experiments did not show statistically significant differences between hypnotic and placebo. We consider there are two reasons for this finding which were overcome by modifying the technique. There are many people who are unaffected by the fluid-load stimulation irrespective of whether they receive a hypnotic or a placebo. Since disturbance of sleep is the basis of this technique all subjects were given a placebo on the first night, and it was noticed

whether or not the fluid-load stimulation disturbed sleep. Approximately half can be described as 'fluid load responders' and this agrees with the findings of Condouris and Bonnycastle (1961). Only these selected subjects in whom sleep was disturbed were then included in the remainder of the experiment. In the initial experiments a water load of either $1\frac{1}{2}$ pints or $\frac{3}{4}$ pint was used. The larger volume produced sleep disturbance in nearly all subjects, irrespective of whether they had received a hypnotic or a placebo, but the smaller volume proved inadequate. Further work demonstrated that the ideal compromise was a pint of milk which the subjects found more palatable, and in addition this enabled the exact volume of fluid to be taken on each occasion.

Further analysis of the earlier experiments employing a water load showed a statistically significant difference between the first and second nights, the second night showing an increase in sleeping time irrespective of treatment. This was found also by Condouris and others (1960). To overcome this, all subjects were given, unknown to them, a placebo on the first night of the study, as well as a placebo during the trial, in a random order with the test hypnotics. It is considered that this difference is an exaggerated placebo response in subjects many of whom were taking a hypnotic for the first time.

Our studies showed that, again irrespective of treatment, females slept longer than males, and the difference was statistically significant. This is in direct contrast to the findings of Lasagna (1954) who found that males slept longer than females. None of the males in our series had symptoms of prostatic enlargement and we are unable to explain this difference between the sexes.

The quality of the sleep cannot readily be determined with this technique as the only means of analysis is a subjective assessment the next day. It is felt that quality can best be estimated from trials in hospital patients who can be observed during sleep, (Cuthbert, 1963). However, as assessed subjectively in our series, no differences could be detected between the quality of sleep following ethchlorvynol, glutethimide or a placebo.

The evaluation of hypnotics by this method does presume that the test compounds have no diuretic action. In our experience this modified technique is a useful and reproducible method for the comparative evaluation of hypnotics and, in particular, their duration of action. Furthermore, the duration of hypnotic effect found in these experiments correlates with that observed in patients (Cuthbert, 1963).

Summary

A technique is described for the evaluation and

comparison of hypnotics in normal subjects. This method employs a physiological fluid load to produce a disturbance of sleep, the hypnotic effect being measured as the duration of sleep between retiring and waking to empty the bladder.

Using this technique ethchlorvynol 500 mg. and glutethimide 500 mg. were found to produce a comparable hypnotic effect and the duration of

sleep was comparable to that produced by the same dose of these hypnotics in hospital patients.

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