EVALUATION OF PLEXONAL* AS A PREOPERATIVE HYPNOTIC†

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THE SUCCESS of an operative procedure depends upon many factors. It begins with the preoperative preparation of the patient and is not complete until the patient has recovered to the maximum degree possible from the condition for which he was admitted to hospital. One of the many steps involved is to provide satisfactory sleep for the patient during the night preceding operation so that he may arrive in the operating room in a rested state. The patient who is worn out by a restless night of tossing and turning and of worrying about the impending ordeal may be physically and mentally exhausted despite preoperative medication. This exhaustion will have repercussions upon the whole progress of his recovery. In an attempt to provide this sleep, we are constantly searching among new drugs to find one which is predictable, non-toxic, non-depressing and which will leave no hangover.

Plexonal is a new agent and it has been studied with these requirements in mind.

COMPOSITION OF PLEXONAL AND REVIEW OF LITERATURE

Plexonal is a combination of five drugs and has the following formula

Sodium diethyl barbiturate (Barbital®), 45 mg

Sodium phenylethyl barbiturate (Phenobarbital®), 15 mg

Sodium allylisobutyl barbiturate (Sandoptal®), 25 mg

Scopolamine hydrochloride, 0.08 mg.

Dihydroergotamine methanesulphonate, 0.16 mg

From the above composition it will be seen that none of the ingredients is present in quantities which are usually considered active and its effectiveness is therefore derived from the well-known effect of mutual potentiation and synergism. Plexonal is also available as "Plexonal Forte," in which each of the five ingredients is present in triple the amount found in ordinary Plexonal.

The formula contains three barbiturates, which differ in onset of action, duration, and in mode of elimination. They belong to the long and intermediate acting group of barbiturates. Scopolamine hydrochloride is added because of its parasympatholytic action and because its central sedative effects tend to enhance the barbiturates. Dihydroergotamine is an anti-adrenergic agent and its presence makes possible the reduction of the amount of scopolamine to one-fifth of the usual dose. Rothlin has stated that ergotamine has a central sedative effect and that it enhances the effects of barbiturates (1).

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The effects of Plexonal have been studied by a number of investigators. Kadish (4) comments on the prompt onset of action of the drug and states that it produces six to eight hours of refreshing sleep. Plexonal has been used widely in the treatment of anxiety and depressive states and in insomnia (2, 3, 4, 5, 6). In these conditions it has proved to be a reliable hypnotic-sedative and all authors agree on the absence of undesirable side effects.

PRESENT STUDY

In order to evaluate the usefulness of Plexonal in preoperative night sedation 250 patients were studied. They were divided into two groups: Group I (150 patients) received Plexonal the night before operation, Group II (100 patients) was submitted to a double blind study.

To obtain the information required a worksheet was drawn up. Each patient was interviewed by the same investigator. Special emphasis was laid on ascertaining the time the patient usually retired and usually fell asleep and the usual time of waking. The patient was also asked about delay in onset of sleep, whether sleep was broken, and what the causes for broken sleep were. Each was asked about insomnia or dreams. All the patients were checked for possible thyroid disease. Weight, age, and sex were noted as well as the fact that some patients were in multiple bed wards and others in single rooms. An attempt was made to assess the degree of apprehension of each patient for the impending operation.

The double blind study was carried out using placebo tablets which were the exact replica of the original drug. The nursing stations taking part in the study were supplied with coded vials of Plexonal and placebo tablets. Neither patient, physician, nor nurses were aware whether Plexonal or placebo was being given. Effects were recorded in the usual manner. The code was broken only after the study had been completed.

After a pilot study it was decided to give one tablet for each 50 pounds body weight. Further allowance was made for the presence of apprehension and the dosage increased by one tablet.

RESULTS

Apprehension

Determination of the degree of apprehension is frequently difficult since many patients succeed in suppressing their true emotions. Besides the information obtained from interviewing the patient, the opinions of the attending nurses and doctors were taken into account on various occasions.

TABLE I
APPREHENSION

Category	None	Slight	Severe	Totals
Straight Plexonal	157	9	2	168
Plexonal D B S	35	5	1	41
Placebo	32	9	2	43
TOTALS	67	14	3	84
$\chi^2 = 1.604$	Degrees of freedom = 2		Not significant	

In Study I, 157 patients out of a total of 168 studied (93 per cent) were free from apprehension after the administration of Plexonal. In the double blind study, 35 out of 41 (85 per cent) were free from apprehension after Plexonal, but 32 out of 43 individuals (74 per cent) also experienced no apprehension following the placebo. The difference between Plexonal and placebo is statistically not significant.

Onset of Sleep

TABLE II
ONSET OF SLEEP

Category	Minutes					Totals
	1-15	16-30	31-45	46-60	61-90	
Plexonal D B S	0	18	6	15	5	44
Placebo	1	14	11	18	3	47
TOTALS	1	32	17	33	8	91
$\chi^2 = 3.652$ Degrees of freedom = 4 Not significant						

No significant statistical difference exists between Plexonal and the placebo with regard to the onset of sleep

Length of Sleep

TABLE III
A NORMAL SLEEP LENGTH SLEEP LENGTH

Category	Hours														Totals
	2½	3	4	5½	6	6½	7	7½	8	8½	9	9½	10	10½	
Plexonal D B S	1	1	1	1	4	3	3	6	11	4	6	2	2	1	46
Placebo	0	0	0	0	1	1	7	9	5	10	9	4	6	2	54
TOTALS	1	1	1	1	5	4	10	15	16	14	15	6	8	3	100
$\chi^2 = 16.889$ Degrees of freedom = 13 Not significant															

B SLEEP LENGTH AFTER DRUGS

Category	Hours											Totals
	3½	4	5	5½	6	6½	7	7½	8	8½	9	
Plexonal D B S	1	1	0	0	3	6	14	8	7	2	4	46
Placebo	0	1	2	2	3	4	9	9	14	8	2	54
TOTALS	1	2	2	2	6	10	23	17	21	10	6	100
x² = 12.589 Degrees of freedom = 10 Not significant												

There is no significant difference in the usual length of sleep between the individuals who were to receive Plexonal and those who were to receive the placebo. Similarly after administration of the drug the difference between the two groups is statistically not significant.

Dreams

Patients who dream, particularly those who dream frequently or vividly, are usually under some degree of tension and therefore sleep may be relatively light. Therefore, a patient who has no dreams, but who usually does dream, might be said to be well sedated.

TABLE IV

A BEFORE PLEXONAL

DREAMS

Category	None	Present	Vivid	Totals
Plexonal D B S	15	26	5	46
Placebo	16	31	7	54
TOTALS	31	57	12	100

$\chi^2 = 0.23$ Degrees of freedom = 3 Not significant

B AFTER PLEXONAL

Category	None	Present	Vivid	Totals
Straight Plexonal	166	23	2	191
Plexonal D B S	38	6	1	45
Placebo	39	11	3	53
TOTALS	77	17	4	98

$\chi^2 = 1.844$ Degrees of freedom = 2 Not significant

There is no statistical significance between the usual dream pattern of the patients who later were to receive either Plexonal or the placebo.

After the administration of Plexonal in Group I the great majority of patients were free from dreams. The same applied to those undergoing the Double Blind Study and again the difference between Plexonal and the placebo is statistically not significant

Patient's Opinion

TABLE
PATIENT'S OPINION

Category	Less good	Normal	Better	Totals
Straight Plexonal	9	46	36	91
Plexonal D B S	6	25	15	46
Placebo	15	31	4	50
TOTALS	21	56	19	96

$\chi^2 = 10.723$ Degrees of freedom = 2 Highly significant

The vast majority of patients receiving Plexonal in Study I thought that they slept as well as usual or better. In the Double Blind Study a similar result was obtained with individuals receiving Plexonal, whereas, for those receiving the placebo the relationship was reversed, a relatively large number thought they did not sleep as well after the placebo and only 4 out of 50 thought they slept better. Here the difference between Plexonal and the placebo is highly significant.

Nurses' Opinion

It is notorious in hospital practice that the patients' and the nurses' opinion regarding duration and depth of sleep do not coincide. The nurses thought that of those receiving Plexonal in Group I the large majority slept well. In the

TABLE VI
NURSES' OPINION

Category	Poor	Fair	Good	Totals
Straight Plexonal	4	8	62	74
Plexonal D B S	2	4	29	35
Placebo	4	5	21	30
TOTALS	6	9	50	65

 $\chi^2 = 1.682$

Degrees of freedom = 2

Not significant

Double Blind Study the same opinion was expressed irrespective of whether Plexonal or the placebo had been administered. The difference is statistically not significant.

Hangover

The presence of hangover in the morning is indicative of the continuing effect of a drug. The large majority of patients receiving Plexonal in Study I had no

TABLE VII
HANGOVER

Category	None	Slight	Severe	Headache	Totals
Straight Plexonal	149	9	9	7	174
Plexonal D B S	28	4	8	3	43
Placebo	43	6	0	2	51
TOTALS	71	10	8	5	94

 $\chi^2 = 11.186$

Degrees of freedom = 3

Significant but not highly significant
(dubious)

hangover. In the Double Blind Study more patients had no hangover after the placebo than after Plexonal. The difference in the two groups is significant from a statistical point of view but not highly so. The statistician considered this difference a rather dubious one.

Results were not significantly affected by age and sex of patients, or by whether the patients were in single rooms, or in double or four-patient wards.

DISCUSSION

If one considered the results of the straight Plexonal study (Study I) by themselves, one would have to conclude that this is indeed a very excellent agent for night sedation and is admirably suited as such to provide sleep and allay apprehension the night before operation. The figures obtained by themselves for Plexonal are most impressive.

However, if the figures obtained in the Double Blind Study are analysed, one finds to one's surprise that almost equally excellent results are obtained with the placebo. Indeed, this conclusion applies to all the factors investigated with the exception of the patient's own opinion. It seems that the patients themselves felt the absence of the sedative effect of the drug more correctly than any tests applied. Still the fact remains that even in this group the large majority, 25 out

of 46 patients, thought they slept no better than they did without sedation (54 per cent) which detracts somewhat from the value of the drug.

This does not mean that Plexonal in itself is not a useful agent. Rather it seems to imply that a majority of patients in our study did not require sedation the night before operation and that those who did require it needed an agent more potent than Plexonal. Moreover this study clearly re-emphasizes the great importance of the Double Blind Study when evaluating drugs of this kind (7, 8), since without it one would of necessity have concluded that this particular agent was excellent for preoperative night sedation

SUMMARY

The effectiveness of Plexonal for preoperative night sedation has been tested in 250 patients, 100 of whom underwent a Double Blind Study

The fallacy of relying on a straight study in the evaluation of these drugs has been demonstrated and the necessity of controlling results with a Double Blind Study has been emphasized. In the last resort it is the patient's subjective response to hypnotic medication which is of prime importance. In this respect Plexonal produced a mild but definite soporific effect

RÉSUMÉ

Nous avons étudié chez 250 malades l'efficacité du Plexonal comme sédatif la veille de l'opération, chez 100 de ces malades, nous avons fait cette étude en employant la technique aveugle, c'est-à-dire en employant des ampoules numérotées dont on ignore le contenu. Si l'on tient compte des résultats obtenus au cours de l'étude ordinaire du Plexonal, on en vient à la conclusion que ce médicament est excellent comme sédatif la veille de l'opération. Toutefois, en évaluant les résultats obtenus avec la technique aveugle, on se rend compte que le placebo a donné des résultats d'aussi bonne qualité. Dans cette conclusion, nous tenons compte de tous les facteurs étudiés à l'exception de l'opinion personnelle du malade

Cela ne veut pas dire que le Plexonal n'est pas un médicament utile. Au contraire, il faudrait croire que la majorité des malades étudiés n'avaient pas besoin d'un médicament ou en avaient besoin d'un plus puissant que le Plexonal. Les résultats obtenus plaident fortement en faveur d'une étude à technique aveugle quand quelqu'un veut étudier un médicament, car, sans cette technique, nous en serions venus à conclure nécessairement que le médicament en question était un excellent sédatif à employer la veille de l'opération

REFERENCES

- 1 ROTHLIN, E. The Pharmacology of the Natural and Dihydrogenated Alkaloids of Ergot. *Bull. schweiz. Akad. d. med. Wissensch.*, 2, 249-73 (1947)
- 2 KRAL, V. A. & KRAUSER, W. G. Psychiatric Experiences with Plexonal. *Canad. M. A. J.*, 70, 453-5 (April 1954).
- 3 SIMMS, L. M. Plexonal in Treatment of Anxiety and Insomnia. *Dis. Nerv. System*, 16(2), 54-6 (Feb. 1955)
- 4 KADISH, A. H. Plexonal. A New Hypnotic and Sedative. *Clin. Med.*, 2(4), 379-80 (March 1955)

5. BANKOFF, M. L., KOHRMAN, B. M. & HOOVER, A. W. Plexonal. A New Hypnotic-Sedative in Office Treatment of Depressive States *J. Indiana M. A.*, 48(6) 608-11 (June 1955).
6. BLOCK, C. The Evaluation of a New Sedative-Hypnotic *J. M. Soc. New Jersey*, 52 363-5 (July 1955)
7. BEECHER, H. K. Experimental Pharmacology and Measurement of the Subjective Response *Science*, 116(3007) 157-62 (August 15, 1952)
8. LASAGNA, L. A Comparison of Hypnotic Agents *J. Pharmacol. & Exper. Therap.*, 111(1) 9-20 (May 1954)