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Review of the literature of four new non-narcotic, non-barbiturate hypnotics : dormison, valmid, placidy, doriden

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A REVIEW OF THE LITERATURE OF FOUR NEW NON-BARBITURATE NON-NARCOTIC HYPNOTICS: DORMISON; VALMID; PLACIDYL; DORIDEN

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INTRODUCTION

In 1951 Batterson (2) listed ten criteria for the "ideal" sedative-hypnotic. They are as follows:

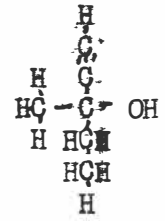
1. Induced sleep should be produced in a reasonable period of time, occur gradually, and merge into natural sleep.
2. The likelihood of induced sleep should be high with the usual therapeutic dose.
3. The induced sleep should not be preceded or replaced by cerebral stimulation.
4. The sleep should not be followed by a hangover or other manifestations of prolonged effect.
5. Therapeutic doses should not influence the cardiovascular, pulmonary, or respiratory systems or depress any vital function of the body.
6. Idiosyncrasies unrelated to pharmacologic effect should be rare or nonexistent.
7. Undue care should not be required because of the diseased state, the patient's age, or the functional capacity of the organs of excretion.
8. The preparation should be easily administered and well tolerated and should not cause gastrointestinal irritation, or if injected, local irritation.
9. Tolerance and cumulation should be minimal.

10. Habit and addiction liability should be small or preferably nonexistent.

Recently there has appeared on the market many new non-barbiturate hypnotics that claim to fulfill the above requirements. This paper is a review of the literature of four of these new drugs: DORMISON produced by Schering Laboratories, VALMID produced by Lilly, PLACIDYL produced by Abbott Laboratories, and DORIDEN produced by Ciba.

DORMISON

Dormison is pure 3-methyl-pentyne-ol-3, an unsaturated aliphatic carbinol that possesses high activity and desirable short duration of action. This simple tertiary alcohol occurs as a volatile liquid and has the following structural formula:



In published studies there have been no observations reported of action suggestive of a toxic effect on the liver, kidney, or blood forming organs. Dormison has no analgesic and no anesthetic effects, nor does it produce respiratory depression, or alter blood pressure or pulse rate. Deep hypnosis from overdosage is readily counteracted by administration of caffeine.(10,17)

This drug has been used in electroencephalography and

electric shock therapy. In these procedures, in which patient co-operation is difficult to obtain because of severe apprehension, Dormison has been a successful aid. (4,19)

Baer and Ludwig (1) have shown Dormison to be useful in asthma and allergies because it lets the patient rest without respiratory depression.

Chevalley (5) gave 134 hospitalized patients Dormison daily in dosages from 100 to 400 mg. These elderly patients suffered from a wide range of clinical entities including diabetes, hepatic, renal and cardiac diseases. The majority had been receiving barbiturates to induce sleep. He noted soporific effect with Dormison in 91.9 percent of patients within one hour.

A series reported by Hirsh and Orsinger (13) was made up of 276 patients whose ages ranged from twenty to eighty-three years. Patients suffering from hypertension, arteriosclerosis, cardiovascular-renal disease, arthritis, portal cirrhosis, acute hepatitis and diabetes, as well as 81 patients with acute alcoholism or disturbed personalities were included. At an average 500mg. dosage of Dormison, 92 percent of patients reported satisfactory onset, duration and quality of sleep. In 58 patients it was possible to compare effects of the drug with commonly used barbiturates. Dormison compared favorably or superiorly in 48 cases. Although patients with a variety of diseases were included,

no deleterious effects on the course of any disease were noted. Improvement frequently was undoubtedly facilitated by adequate sleep.

Moravec and Moravec, in a study quoted by Bedell (3), evaluated chronic insomniacs ranging in age from 28 to 78 years on a Dormison regimen of 100 to 600 mg. Those in whom there was barbiturate tolerance were not treated until five days had elapsed in order to eliminate withdrawal symptoms. The Moravecs concluded that since all patients had previously required various hypnotics routinely for sleep and yet 80.8 per cent obtained restful sleep during this investigation this study provides substantiation of the hypnotic properties of Dormison.

Lemere (14) reported a case with overdosage with suicidal intent. This patient ingested Nembutal gr. 6 and Dormison, 35 capsules. Her survival, remarked Lemere, confirms the low toxicity of the hypnotic Dormison. Sufficient time (seven hours) had elapsed between overdosage and administration of stimulants for death to have ensued. Within five minutes after metrazol, 2cc. intravenously and caffeine sodium benzoate Gm. 0.5, the patient was sufficiently awake to get out of bed. Urine and blood chemical determinations were normal upon admission to the hospital. Electroconvulsive therapy was instituted. There were no sequelae noticeable of the drug overdosage.

In studies covering 1300 patients, quoted by Bedell (3),

side actions are mentioned in only 42 patients, and incidence of 3 percent. Of the 12 hangovers, the authors have in seven instances noted that they existed without objective symptoms or that patients previously claimed hangover without medication. Nausea is noted 16 times, with side notes that these were cases of a terminal nature in which patients vomited spontaneously, or were nauseated from intractable pain.

Schering Laboratories (9) report that animal experimentation with the drug showed no histologic changes in the liver, spleen, heart, lungs, testes, and kidneys of rats who had been given oral doses of 250 mg./Kg./day for 12 weeks.

Carefully controlled clinical studies were made, as reported by Schering Laboratories (9), in which blood chemistry and liver function tests were done on a group of more than 30 patients before the drug was administered. Dormison was then given daily for varying periods--in some cases exceeding 100 days--at which time liver function tests and blood studies were repeated. In no case was there any derangement of the liver or blood forming organs. There have been a few isolated reports, however, of increased cephalin flocculation time following Dormison. An occasional elevated thymol turbidity determination has been noted but, for the most part, liver function studies following long-term usage of Dormison have been negative. However, when the drug is used continuously in large doses for prolonged periods, the possibility of liver damage should

be kept in mind.

The following dosage and aministration schedule is recommended by the Schering Corporation:

Adults: Hypnosis: One or, on occasion, two 500mg. capsules at bedtime. The capsules should be taken just before the patient is ready for sleep. For the most successful result, the environment should be conducive to normal sleep.

Sedation: One 250 mg. capsule one or two times daily. More frequent administration may be required in some instances but, as with all drugs, it should be the objective to use the minimum quantity that will provide the desired result.

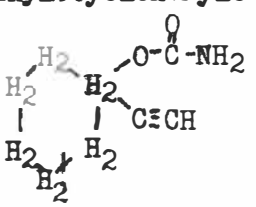
Children: Hypnosis: One or two 250 mg. capsules at bedtime.

Sedation: One 250 mg. capsule one or two times daily. The capsules are especially useful for this purpose immediately preceding daytime rest periods.

Dormison is supplied in capsules of 250 and 500 mg.

VALMID

Valmid is described by Gruber (12) as a non-irritant, colorless, odorless, faintly bitter, stable, crystalline powder. It is relatively insoluble in water but is quite soluble in many alcohols and oils. It produces central nervous system depression in man and animals without convulsions. The chemical name is 1-ethinyl-cyclohexylcarbamate. Its structural formula is:



Studies of chronic usage of the drug have showed no toxicity, tachyphylaxis, tolerance or physical dependence.

A study reported by Gruber, Kohlstaedt, Moore, and Peck (12) comparing Valmid with seconal was done with twenty three hospital patients. These patients received either Valmid or Seconal Sodium in the morning 30 minutes before breakfast. An initial dose of 1500 mg. of Valmid or 300 mg. of Seconal Sodium was given and if obvious central nervous system depression was not present at the end of one hour, a second dose of 500 mg. or 100mg. respectively, was given. It was found necessary to give this second dose of Valmid to four patients. One of these four patients received a second dose of Seconal Sodium. Each patient received Valmid once and Seconal Sodium once. Seconal Sodium was the initial medication in fourteen patients whereas Valmid was given first nine times. Most of the patients received this sedation test on successive days. During the tests they were isolated in a relatively quiet room. Prior to the administration of the initial dose, tests were made which were repeated while the patient was under the influence of the sedative in an attmept to estimate the depth of depression, the degree of ataxia, and the effect of the drugs on the autonomic nervous system. These tests consisted of an estimation of mental state (that is normal, lethargic, stuporous, or comatose), determination of the presence or absence of Romberg's sign and of positive heel-to-knee-to-toe test bilaterally,

	Onset in Minutes	Duration in Hours				Blood Pressure			Pulse			Respiratory Rate		
		Lethargy	Stupor	Ataxia	Speech	Control	Maximum	Minimum	Control	Maximum	Minimum	Control	Maximum	Minimum
Seconal Sodium	37	4.5	2.8	4.5	4.5	145/81	142/84	131/75	82	86	77	20	21	18
Valmid	31	2.5	1.6	2.6	2.5	138/80	134/80	130/74	82	82	78	20	20	19

TABLE ONE

From a report by Gruber, Kohlstaedt, Moore, and Peck (12)

observation as to the development of slurred speech, and determination of the blood pressure, pulse and respiratory rates at one to two hour intervals. The patients had the usual diseases seen on medical services. Among the principal diagnoses were diabetes, hypertension, cirrhosis, and opiate addiction. The patients were selected on the basis of their willingness to co-operate and apparent ability to undergo the test safely and satisfactorily.

A summary of the results obtained are given in Table One. Valmid apparently has a shorter duration of action than does Seconal Sodium. The depression produced by this dose of Valmid may have been slightly less intense than that produced by Seconal. Four patients required a second dose of Valmid and only one required a second dose of the barbiturate. There were three patients who, when given Valmid, were not observed to be stuporous at any time during the period of sedation; this was true of only one after Secondal Sodium was given. In general, however, there was no great difference in the depth of sedation and it is believed that Valmid is definitely of a shorter duration of action than Seconal Sodium in its cerebral depressive effects. Ataxia, is not more marked with Valmid than with Seconal Sodium. The unresponsiveness of the blood pressure, pulse, and respiration to Valmid was, if anything, more consistent than that to Seconal Sodium. No significant change was noted with either drug, except in the patients with

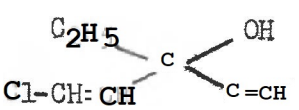
hypertension. Some fall in blood pressure was observed with both drugs. This fall was no greater than that usually obtained when sedation tests are performed on labile hypertensive patients. This certainly suggests that the vital centers of the brain are spared when hypnotic doses of these drugs are given. This adds to the evidence that Valmid and Seconal Sodium have wide margins of safety.

In animal studies, as reported by Lilly laboratories (8), no pathologic changes in the blood, liver, and kidneys were observed following prolonged administration. Lethal doses of the drug caused death in deep narcosis, with temperature drop and respiratory failure but without convulsions. Valmid was absorbed promptly and almost completely by the gastrointestinal tract. Only a small portion of the drug was recovered in the urine.

Administrations and dosage schedule is as follows. Valmid is taken by mouth about twenty minutes before retiring. Usually 0.5 Gm. will suffice. At times 1 Gm will be necessary. Valmid is supplied in 0.5 Gm. tablets.

PLACIDYL

Placidyl is a beta-chlorovinyl ethyl ethynyl carbinol. It has the following structural formula:



It is supplied in 500 mg. capsules. The recommended dosage is

500 mg. at bedtime for insomnia, according to Abbott laboratories (6).

In a study reported to Abbott Laboratories by Rosenlof and Grissom (18) 500 mg. of Placidyl was compared to 50 mg. of secobarbital sodium. The study included 24 patients selected from several medical wards. In all cases there was 24 hour intervals between the administration of barbiturate and Placidyl. The majority of these patients had been on other hypnotics as adjuncts to therapy in hypertension. The age of the male patients ranged from 35 to 75 and the age of the female patients ranged from 15 to 77. These patients reported satisfactory onset and duration of sleep with Placidyl 81per cent of the time, as contrasted with 66 per cent reported similarly for secobarbital sodium. There was no difference in time required to fall asleep between Placidyl and the barbiturates. No hangover or untoward effects were noted with Placidyl.

In a blind study reported by Fostvedt (11) Placidyl was compared with a related carbinol and a placebo. The subjects varied in age from 31 to 93 years and had a wide variety of diseases. It was found that Placidyl was an effective inhibitor of undesirable psychomotor responses such as anxiety, excitement, agitation, adverse moods and adverse disposition. Placidyl produced sound normal sleep in patients with simple insomnia in dosages of 300-600 mg. There were no abberrant central nervous system manisfestations such as ataxia, nervousness, vertigo, drowsiness or hangover. Patients were alert and

mentally clear on awakening. Urinalysis and routine blood counts revealed no significant toxicity when Placidyl was used for 12 to 15 day periods.

Some of the original work on the hypnotic and anticonvulsant properties of a number of tertiary acetylenic carbinols was done by Margolin, Perlman, Villani, and McGavack (15). They did metabolic studies on the carbinols. They found that no drug was found in the urine of three humans during a 60 hour period after a single dose of 100 mg. They estimated that no more than 8 per cent of the total dose could have been in the four hour specimen. They did analysis of rat tissues (the brain, kidney, spleen, adipose tissue, muscles, and liver) and found these tissues contained 20 per cent of the dose while the effect of the drug was manifest. None of the drug was found in the tissue after the effect of the drug was no longer manifest.

Placidyl was administered to dogs and rats in doses up to 50 mg/Kg/day for a period of over a year, in a study reported by Abbott Laboratories (6), and there was no evidence of toxicity or development of tolerance. Gross and histopathologic study of the tissue from both groups of animals revealed no abnormalities attributed to Placidyl administration. All of the dogs underwent the following tests during the study: red, white and differential cell count, hemoglobin and cell volume determinations, prothrombin times determinations, blood sugar,

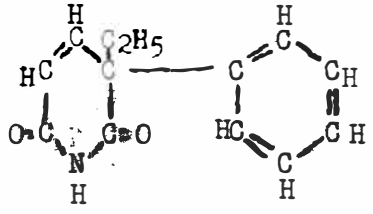
non-protein nitrogen, urea, total serum protein, albumin and globulin, CO_2 combining power, sodium, potassium and chloride determinations. All determinations remained in the normal range.

In 1953 S. Y. P'an, et al (16) reported that the effect of acetylenic carbinols as hypnotic and anticonvulsant agents was affected by halogenation. It was found that the most active compound was a chlorinated carbinol namely chlorovinyl ethyl ethynyl carbinol (Placidyl).

In clinical studies of approximately 1,200 cases Placidyl has been remarkably free of side effects. Mild hangover occurred in 1.67%; mild excitation in 0.33%; and vomiting in 0.58%. Doses of Placidyl up to 1,000 mg. produced no observable effect on pulse, blood pressure, respiration, blood, or urine.

DORIDEN

Chemically Doriden is alpha-ethyl-alpha-phenyl-glutarimide. Its structural formula is:



It comes in tablets 0.25 and 0.5 gm.

Clinical evidence indicates that Doriden is not habit forming and produces rapid onset of sleep in 15-30 minutes that lasts four to eight hours. It has been found that there is relatively

low incidence of excitation or morning hangover. It has been found to produce an excellent depth of hypnosis with a physiologic dreamless sleep with no respiratory depression. It does not impair psychomotor performance, and it has minimal side effects, according to Ciba Laboratories (7).

Alex has reported in a communication to Ciba Laboratories, a study in which Doriden was compared to phenobarbital. He gave 19 patients the following type of medication three times a day for fourteen days in a series: a placebo, one-half grain of phenobarbital and 0.25 Gm. of Doriden. Doriden gave the desired sedation to every patient. Two patients had no sedative effect from the phenobarbital and four obtained only slight sedation. A few patients said they had sedative effect from placebos, as might be expected.

At the Veteran's Administration Center, Los Angeles, Seymour Pollack, as reported by Ciba (7), observed use of Doriden for insomnia in 25 men and women ages 20 to 85. Most of these patients had multiple diagnoses, seven had rheumatic fever or rheumatoid arthritis, four had arteriosclerotic heart disease or myocardial infarction, eight had serious neurological diseases, such as cerebral vascular accident and chronic brain syndrome. Most patients at this time had been receiving 1½ grains secobarbital sodium at bedtime; neuropsychiatric patients were frequently receiving two to four drams of chloral hydrate solution

with regular repeat doses. For comparison of Doriden with these hypnotics, a sleep chart was devised, recording the subjects sleep state for three nights prior to Doriden therapy. Dosage of Doriden ranged from 0.25gm. per night to 3.0gm. per night. Doriden was used for 5 to 41 nights. Average initial dose was 0.5 Gm. In 69 trials a nightly dose of 2.0 Grams was given. In this study Doriden was rated for time of onset of sleep and duration of sleep. The drug was considered good for onset of sleep if the patient went to sleep within one hour after the dose and poor if the onset was delayed over one hour. Doriden was rated good for duration of sleepp if the subject had five hours of uninterrupted sleep or a total of six hours of sleep during a night, and was rated poor if these standards were not met. If the drug produced good sleep in 75% or more of the trials it was rated good; if it produced g ood sleep in less than 50% of the trials it was considered poor. The findings in this trial were that Doriden proved to be effective in hypnotic doses of 0.25 Gm. for women and 0.5 Gm. for men. These doses compared favorably with the hypnotic effect of 1½ grains secobarbital sodium. Many of the patients said they slept well without side effects and preferred Doriden to their previous hypnotic. Thirteen of the 17 male patients stated that Doriden gave good sleep without hangover effects produced by many other hypnotics.

Doriden was studied in an experiment reported by Ciba (7),

to determine its effect on manual dexterity and mental acuity. For manual steadiness tests subjects were scored on their ability to put small nuts on bolts in two minutes; in the mental acuity tests, subjects were given an alphabetical decoding test. Approximately 220 seconds were needed to complete both tests. Before the tests, subjects breathed in either high or low oxygen mixtures for 2½ minutes. In the control run the only factor was the oxygen mixtures. In subsequent tests, the additional factors were Doriden alone, alcohol alone, then alcohol plus Doriden. The drug was given in doses up to 1.0 or 1.25 Gms. on an empty stomach. Two or Three Doriden tablets had so little effect on psychomotor performance as to be of doubtful significance. Effects on perception and manual dexterity were not clear cut until 1.0 to 1.25 gms. was taken in excess of the recommended dose.

In over 1000 cases studied, side actions of Doriden have been minimal. Occasional cases of nausea were noted. Skin rash occurred occasionally.

In animal experimentation, reported by Ciba (7), two groups of rats were given Doriden in 0.1 and 0.2% concentration in food for 60 days. Then the animals on the 0.1% concentration were raised to 0.4% for an additional 50 days. The animals remained in good condition throughout the study. When the blood was checked initially and again at three months it was found that total

erythrocytes and leukocytes, hemoglobin determinations, and differential leukocyte counts were within normal ranges. Autopsy showed no gross lesions.

No withdrawal symptoms have been reported following prolonged administrations of Doriden. In a study on dogs, according to Ciba Laboratories (7), 100 and 200 mg./Kg./day was given with no withdrawal syndrome. Since a profound withdrawal syndrome marked by convulsions had been reported in dogs on maximally tolerated doses of barbital, it is believed Doriden is non-addicting to dogs.

Recommended doses for Doriden are as follows:

Insomnia: 0.25 to 0.5 gm. one-half hour before bedtime.

Presurgery Sedation: 0.5 gm. the night before surgery.

0.5 to 1.0 gm. one hour before surgery.

Daytime Sedation: 0.25 gms. 3 or 4 times daily after meals.

SUMMARY

In the past few years there has been an influx of new non-barbiturate non-narcotic hypnotics on the market. The preceding paper has been a review of the literature on four of these: Dormison, Doriden, Placidyl, and Valmid. Table Two, based on information compiled from all the references listed in the bibliography, summarizes some of the results obtained with these new drugs and compares them with some of the older hypnotics commonly used.

Hypnotic	Action begins in minutes	Duration of effect	Respiratory Depression	Miscellaneous effects	Contraindications
Barbiturates (short acting)	15-30	2-4 hrs.	Yes	dermatitis antidiuretic action decreased tone of G.I. tract habituation	hepatic and renal disease
Barbiturates (long acting)	30-60	4-8 hrs.	Yes	same as above	same as above
Bromides	Days	Days-Weeks	No	Not advised as hypnotic	Tuberculosis Advanced arteriosclerosis Cachexia Dehydration
Chloral Hydrate	30-60	5-8 hrs.	Yes	Irritant to G.I. tract	Hepatic, renal or cardiac disease
Paraldehyde	10-15	1-2 hrs.	No	Odor lasting as long as 24 hours	Bronchopulmonary disease Hepatic insufficiency Gastroenteritis
Dormison	5-30	1-2 hrs.	No	Negligible	None
Placidyl	15-30	5 hours	No	Negligible	None
Doriden	20-30	4-6 hrs.	No	Negligible	None
Valmid	15-25	4 hours	No	Negligible	None

TABLE TWO

CONCLUSION

In the introduction of this paper, ten criteria for an ideal sedative-hypnotic were listed. The information presented in the preceding discussion gives evidence that Placidyl, Valmid, Doriden, and Dormison fulfill, to some satisfaction, these criteria.

BIBLIOGRAPHY

1. Baer, R. L. and J. S. Ludwig; Postgrad. Med.; 12:41; 1952.

2. Batterman, R. C.; Mod. Med.; 19:59 (Dec. 15); 1951.

3. Bedell, Harold; American Practitioner and Digest of Treatment; Vol, 5 No. 7; July 1954.

4. Brinegar, W.C. and A. Sainz; Disease of Nervous System; 14:172; 1953.

5. Chevalley, J., N. Heminway, G. Meyer, R. Frankhauser, and T.H. McGavack; New York State J. Med.; 52:572; 1952.

6. Communication from ABBOTT; 1956.

7. Communication from CIBA; 1956.

8. Communication from LILLY; 1956.

9. Communication from SCHERING CORPORATION; 1956.

10. Drill, V. A.; PHARMACOLOGY IN MEDICINE; New York; Mc Graw Hill Book Co, Inc.; 1954; p. 13/12-13/13.

11. Fostvedt, G. A.; Communication to Abbott Laboratories; 1955.

12. Gruber, C. M and K. Kohlstaedt, B. Moore, R.B. Peck; The Journal of Pharmacology and Experimental Therapeutics; Vol. 112, No. 4; December 1954.

13. Hirsh, H. L. and W. H. Orsinger; Am. Pract. and Digest Treat.; 3:234; 1952.

14. Lemere, F.; Northwest. Med.; 51:778; 1952.

15. Margolin, S. et al.; Letters to the Editors; Science; 14:384; Oct. 12, 1951.

16. P'an, S.Y. et al., The Effect of Halogenation on the Hypnotic and Anticonvulsant Activities of Acetylenic Carbinols; J. Pharm. and Exper. Therap.; 109:268; November, 1953.

17. Perlman, P. L. and C. Johnson; J. Am. Pharm. A (Scient. Ed.); 41:13; 1952.

18. Rosenlof, R. and R.L. Grissom; Comm. to Abbott Lab.; 1955.

19. Tukel, K. and M. Tukel; Electroencephalog. and Clin. Neurophysiol. J.; 4:363; 1952.