THALIDOMIDE—A NEW NONBARBITURATE SLEEP-INDUCING DRUG

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THALIDOMIDE* is the generic name for N-phthalyl-glutamic acid imide, a compound which has been employed in Europe for several years as a sedative-hypnotic. It is chemically related to glutethimide (Doriden), another sedative-hypnotic, and to bemegride (Megimide), a convulsant analeptic.

Unpublished data supplied by the Scientific Division of The William S. Merrell Company indicate that thalidomide is a central nervous system depressant in mice, reducing spontaneous motor activity slightly in doses of 30 mg. per kilogram and to a considerable degree in doses of 100 mg. per kilogram. Thalidomide at doses of 100 mg. per kilogram, orally or intraperitoneally, does not produce loss of righting reflexes in mice, rats, cats, dogs, or monkeys. Large quantities of drug (up to 4 Gm. per kilogram), by mouth or intraperitoneally, failed to produce death in mice over a 72-hour observation period. This lack of toxicity of large doses is most likely related to the insolubility of the compound and a consequent limitation in absorption.

Uncontrolled German trials[1-4] have reported thalidomide to be an effective hypnotic drug when administered in doses of 50 to 200 mg. In a controlled English trial by Salter, Lodge-Patch, and Hare,[5] 50 or 100 mg. of drug has been reported to produce sleep as quickly as 200 mg. of secobarbital, and the duration of sleep after 100 mg. of the thalidomide was found to be significantly greater than that after 200 mg. of secobarbital. The latter drug in turn produced significantly longer sleep on the average than did 50 mg. of thalidomide. No placebo treatment was included in the English trial. The authors reported that "moderately severe" hangover could occur after thalidomide, especially with the 100-mg. dosage.

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METHODS

The present study compares two doses of thalidomide with placebo in a group of medical and surgical ward patients at the Johns Hopkins Hospital. Medical patients were chosen for study if they were considered by the nursing and house staff to present a sleep problem. Surgical patients were studied on their first night in the hospital; patients admitted for elective surgery, free of pain, and not requiring other medication were used exclusively.

Patients were interviewed during the day to elicit information about their underlying disease, the nature of their sleep problems and past exposure to hypnotic drugs, the presence or absence of pain, and their usual subjective state on awakening in the morning. (This last bit of data was utilized as a base line against which to assess any postdrug complaints by a patient on the morning after the actual experiment. Certain patients complain of headache, tiredness, sleepiness, dizziness,

TABLE I. MEAN SLEEP INDUCTION TIME (MINUTES)

PATIENT GROUP	PLACEBO (POOLED)	THALIDOMIDE	
		100 MG.	200 MG.
Those whose usual induction time was less than 30 minutes	26 (N = 17)	32 (N = 15)	11 (N = 10)
Those whose usual induction time was 30 minutes or more	81 (N = 24)	100 (N = 10)	30 (N = 15)
All patients	58 ± 10.3 (N = 41)	59 ± 16.8 (N = 25)	23* ± 4.9 (N = 25)

*Significantly different from placebo and 100 mg. of thalidomide at 0.05 level.

etc., on awakening, whether or not a drug has been given, so that the true incidence of drug-related hangover may be overestimated if this precaution is not taken. The data on side effects to be reported therefore include only complaints clearly distinguishable from the normal subjective state without drug.)

Patients suitable for study were given, at bedtime, in randomized fashion, either placebo (single capsule), placebo (two capsules), 100 mg. of thalidomide (one capsule), or 200 mg. of thalidomide (two capsules). The next morning, patients were interviewed again and asked how long they estimated it had taken them to fall asleep, how long they had slept, and how they felt on awakening. Any spontaneous reports regarding the occurrence of untoward effects at other times were also recorded. If a patient failed to sleep at all or had to be given another sleeping medication during the night to induce sleep, the induction time of such a patient was arbitrarily called 240 minutes and the duration of sleep zero hours, to allow computation of means. The high correlation between "subjective" patient reports and "objective" reports by nurses or technicians has been described in previous papers.[6-8]

RESULTS

Previous studies in this laboratory have revealed a relationship between sleep performance under drugs (or placebo) and "usual" sleep habits without drugs; patients who ordinarily sleep poorly are more likely to sleep poorly under drugs than patients who ordinarily sleep well. The data are therefore presented in Tables I and II both as total mean scores and as subgroup scores. The patients are stratified for the sleep induction analysis into those who claimed to fall asleep usually in less than 30 minutes and those who claimed to require 30 minutes or more. For the duration of sleep analysis, the stratification is on the basis of usual sleep duration without drugs of less than 7 hours versus usual duration of 7 hours or more. These dividing points were chosen in both cases because they were convenient for dividing the groups into two roughly equal parts. Because the means for the two placebo groups did not differ significantly either in regard to induction or duration of sleep, the placebo data were pooled.

TABLE II. MEAN TOTAL DURATION OF SLEEP (HOURS)

PATIENT GROUP	PLACEBO (POOLED)	THALIDOMIDE	
		100 MG.	200 MG.
Those whose usual duration of sleep was 7 hours or more	6.7 (N = 24)	7.2 (N = 13)	7.6 (N = 14)
Those whose usual duration of sleep was less than 7 hours	5.1 (N = 17)	4.5 (N = 12)	7.1 (N = 11)
All patients	6.1 ± 0 .35 (N = 41)	6.2 ± 0.50 (N = 25)	7.4* ± 0.20 (N = 25)

*Significantly different from placebo and 100 mg. of thalidomide at 0.05 level.

Tables I and II show that the smaller dose of thalidomide was not significantly different from placebo either in inducing sleep or in prolonging it, whereas 200 mg. of drug produced effects significantly better ($P < 0.05$) than either placebo or 100 mg. of drug for both parameters. Each treatment shows the differential effect alluded to before, i.e., better performance in the "low-challenge" groups than in the "high-challenge" groups, but the higher dose of thalidomide differs from the other two treatments in its impressive over-all performance.

Side effects were more common in the drug groups. Only one of the 41 patients given placebo described a side effect of any sort, a feeling of drowsiness on awakening in the morning. Of the 25 patients on the 100-mg. dose of thalidomide, 1 patient complained of having to urinate six to seven times during the night, another felt dizzy in the morning, another felt drowsy on awakening and went back to sleep for 1 hour, and the fourth patient complained of headache, drowiness, and "tiredness" on the morning after taking drug. Of the 25 patients

who received 200 mg. of thalidomide, 2 felt slightly drowsy on awakening, 1 felt dizzy and confused during the night and had headache and residual drowsiness in the morning, and the fourth woke up after 2 hours of sleep with severe nausea, went back to sleep after 1 hour, and had residual nausea in the morning.

DISCUSSION

Our data indicate thalidomide to be a potent hypnotic, and the mean figures for the 200-mg. dose are similar to what we have come to expect from an equal dose of secobarbital or pentobarbital in similar past studies. It is therefore somewhat disappointing to have failed to show even a trend in favor of the 100-mg. doses over placebo, particularly in the light of the report from Salter, Lodge-Patch, and Hare[5]; but sampling problems, the different populations and methods employed, and the relative imprecision of studies of this type may explain the discrepancies between the English study and the present one. Our data would not justify their conclusions that thalidomide is three times as "potent" as secobarbital in terms of amount of drug required to produce a given effect. Our own guess would be that the two drugs are about equipotent. We do agree, however, with their observation that the drug is capable of producing hangover and other side effects, with an incidence in our experience roughly comparable to that seen with equal doses of secobarbital or pentobarbital. Only further comparative trials of thalidomide and standard drugs will define the appropriate niche of this new agent in the treatment of insomnia, but the data reported so far suggest that thalidomide is a drug worth trying in patients whose therapeutic needs cannot be met by older drugs. The drug has not as yet been reported to produce euphoria, and there is one report in which it is stated that a patient has taken 2.1 Gm. of drug without suffering severe consequences.[9] A British report[10] on the ability of thalidomide to inhibit uptake of radioactive iodine by the thyroid has been denied by another group of investigators.[11] The evidence available to date is therefore encouraging and arouses hope that thalidomide may represent a significant advance in hypnotic therapy, but wider experience is needed to define precisely the addiction liability and safety margin of the drug in man.

SUMMARY

Thalidomide has been evaluated in the treatment of insomnia in medical and surgical inpatients. The performance of 100-mg. doses was not significantly different from that of placebo. Doses of 200 mg., however, proved effective in inducing and maintaining sleep in the majority of patients and were significantly better in these regards than either placebo or 100-mg. doses. Administration of drug was associated with a higher incidence of side effects than was administration of placebo.

REFERENCES

1. Esser, H., and Heinzler, F.: Klinische Erfahrungen mit einem neuen Sedativum und Hypnotikum, Therap. Gegenwart **95**:374, 1956.

2. Stärk, G.: Klinische Erfahrungen mit dem Sedativum K 17 in der Lungenheilstätte und der allgemeinen Praxis, Praxis **45**:966, 1956.
3. Jung, H.: Klinische Erfahrungen mit einem neuen Sedativum, Arzneimittel-Forsch. **6**:430, 1956.
4. Schober, W.: Action and Possible Uses of the Glutamic Acid Derivative, Contergan, Wien. med. Wchnschr. **108**:869, 1958.
5. Salter, C. E., Lodge-Patch, I. C., and Hare, E. M.: Thalidomide: Clinical Trial of a New Hypnotid Drug, J. Clin. & Exper. Psychopath. **20**:243, 1959.
6. Lasagna, L.: A Comparison of Hypnotic Agents, J. Pharmacol. & Exper. Therap. **111**:9, 1954.
7. Owens, A. H., Jr., and Coauthors: A Comparative Evaluation of the Hypnotic Potency of Chloral Hydrate and Trichloroethanol, Bull. Johns Hopkins Hosp. **96**:71, 1955.
8. Imboden, J., and Lasagna, L.: An Evaluation of Hypnotic Drugs in Psychiatric Patients, Bull. Johns Hopkins Hosp. **99**:91, 1956.
9. de Souza, L. P.: Correspondence Section, Brit. M. J. **2**:635, 1959.
10. Murdoch, J. M., and Campbell, G. D.: Antithyroid Activity of N-Phthalyl Glutamic Acid Imide (K17), Brit. M. J. **1**:84, 1958.
11. Greene, R., and Farran, H. E. A.: Correspondence Section, Brit. M. J. **2**:1355, 1958.