The hypnotic efficacy of doxylamine

The efficacy of doxylamine succinate as a nighttime hypnotic was compared with that of placebo and a standard drug, secobarbital sodium, using a double-blind, randomized block design and replicate observations. The study was performed in 22 hospitalized patients with chronic disease who were accustomed to taking nightly hypnotics. Doxylamine, in doses of 25 and 50 mg., was found to be an effective hypnotic drug, with little difference in the performance of the two doses. Doxylamine performed generally better than secobarbital, 100 mg., but was somewhat inferior to secobarbital, 200 mg. Although the active treatments were significantly better than placebo, 50 per cent of the patients reported satisfactory sleep on dummy medication. Side effects were mild with little difference between the different drugs and placebo except for "hangover," which occurred more often after doxylamine and secobarbital.

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Doxylamine (2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine) succinate[1] is one of the older antihistaminic drugs and is prescribed clinically in oral dosage of 12.5 or 25 mg. three or four times daily for adults. Under such conditions, its use has occasionally been associated with such complaints as epigastric pain, diarrhea, nervousness, irritability, palpitation, headache, and vertigo.[2, 3, 7, 9] At these doses, more than 30 per cent of patients have experienced drowsiness, but no serious toxicity or deaths have been attributed to the compound, even when it has been given in a daily oral dose as high as 1,600 mg.† Because of the possibility that doxylamine succinate (Decapryn) might possess significant hypnotic activity with a wider margin of safety than that provided by the barbiturates, it was decided to compare the efficacy of doxylamine as a nighttime hypnotic with that of placebo and of a standard drug, secobarbital sodium.

Methods

Twenty-four subjects on the chronic disease wards of the Baltimore City Hospitals participated in the study, having had fully explained to them the purposes and plan of the experiment. Of the 24 original volunteers, 2 dropped out after the first night, 1 because the placebo failed to produce an adequate hypnotic effect, and 1 because doxylamine in a dosage of 50 mg. was followed by excessive sedation (these subjects are not included in the subsequent analyses). Some relevant data on the experimental population are summarized in

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Table 1. Of the subjects, 15 were men, ranging in age from 40 to 89 with a mean age of 64 years, and 7 were women, ranging in age from 51 to 89 with a mean age of 63 years. Thirteen subjects were accustomed to taking chloral hydrate in liquid form at night. Three others took nightly chloral hydrate plus phenobarbital, and the others used phenobarbital, pentobarbital, or both. All stated that they required a hypnotic to fall asleep and to maintain sleep, an opinion concurred in by the ward personnel. Patients with sleep-disturbing pain, a history of epilepsy, or obvious impairment of mental, hepatic, or renal function were not included.

The treatments were: placebo, 100 mg. of secobarbital sodium, 200 mg. of secobarbital sodium, 25 mg. of doxylamine succinate, and 50 mg. of doxylamine succinate. These preparations were dispensed as identical-appearing capsules and were taken with a glass of water. Drugs were administered at the patient's usual time of retiring for the night and had to be swallowed in the presence of the attending nurse.

The various medications were administered double blind in a randomized block design such that each treatment was given once to each patient within each sequence of five treatments. Each sequence of treatments was completed during 5 consecutive days (Monday through Friday) and then a new randomized block sequence was repeated each week for the next 2 weeks if the subjects were willing and able to continue treatment. Three of the 22 subjects did not go on after the first week, one because she did not wish to participate further, and 2 because of medical problems unrelated to the trial. Of the 19 subjects who completed two sequences, 3 did not

Table I. *Clinical data on the experimental population*

Patient	*Sex*	*Race*	*Age*	*Time in hospital (years)*	*Normal sleeping medication**	*Onset of sleep† (hours)*	*Duration of sleep† (hours)*	*Diagnosis*
A	M	W	68	2	c	0.5	7.5	Alcoholism; arthritis
B	M	W	43	4	ph	0.5	6.75	Alcoholism
C	M	W	40	2	c	0.1	9.0	Multiple sclerosis; schizophrenia
D	M	W	64	3	c	1.0	8.5	Amputation, traumatic
E	M	W	89	3	p	0.3	4.5	Osteoarthritis
F	M	N	57	6	c	0.15	9.0	Paraplegia, traumatic
G	M	N	47	1	c	1.25	6.5	Diabetes mellitus
H	M	W	62	0.3	c	0.5	11.0	Parkinsonism
J	F	W	89	12	p	0.5	8.0	Arthritis; cardiac failure
K	M	W	66	5	c and ph	0.5	7.5	Hypertension
L	M	N	40	0.8	c	1.25	7.75	Alcoholism
M	F	W	58	18	c and ph	0.75	10.0	Tuberculosis
N	F	W	51	1	c	0.5	7.0	Bronchiectasis
P	F	W	55	8	p	1.75	6.0	Alcoholism; bronchitis
Q	F	W	52	7	c	0.33	6.0	Alcoholism
R	M	W	82	0.3	c	0.15	8.0	Tuberculosis
S	M	W	80	5	c	1.5	4.0	Alcoholism
T	M	W	85	0.8	c	0.5	6.0	Cataracts; vascular insufficiency
U	M	W	78	0.3	p	1.5	7.0	Pulmonary fibrosis
V	M	W	65	0.2	c	0.25	7.5	Emphysema
W	F	W	67	0.3	p and ph	0.5	10.0	Osteoporosis
X	F	W	71	8	c and ph	0.5	8.0	Diabetes mellitus

*Code: c, chloral hydrate; p, pentobarbital; ph, phenobarbital.

†Patient's estimate of "usual" performance of normal sleeping medication.

go on to the third week, 2 because they expressed a desire not to continue the study, and one because of intervening disease. Of the 16 patients who expressed a willingness to continue on a third week of treatment, 2 were not able to participate, one because of discharge from the hospital, and one because of intervening disease.

Evaluation was by subjective reports of the patients elicited early in the morning by a physician (F. S.) with the aid of a questionnaire containing the following questions: (1) How long did it take you to fall asleep? (2) How long did you stay asleep? (3) Did you sleep excellently, well, poorly, or not at all? (4) Did you sleep better than usual, worse than usual, or the same as usual? and (5) How do you feel this morning?

Because a plotting of the responses in regard to estimates of the time required for onset of sleep, and of total time spent in sleep during the night, suggested a non-normal distribution of responses, and because the responses to questions 3 and 4 seemed inappropriate for the usual kinds of parametric analyses, a nonparametric rank test[7] was used to compare treatments. The 1964 revision of *Some Rapid Approximate Statistical Procedures* by Wilcoxon and Wilcox[8] was utilized, employing the tables both for "comparisons of all possible pairs of treatments" and for "comparison of several treatments with a control." In the presentation of results, unless specifically stated otherwise the probability values are derived from the two-sided table for comparison of all possible pairs of treatments.

Table II. *Mean values for induction and duration of sleep*

	Induction of sleep (minutes)		*Duration of sleep (hours)*	
Medication	*Week 1*	*3 weeks pooled*	*Week 1*	*3 weeks pooled*
Placebo	116	123	5.99	5.63
Secobarbital, 100 mg.	78	76	6.94	6.97
Secobarbital, 200 mg.	41	47	8.42	7.97
Doxylamine, 25 mg.	56	63	7.91	7.41
Doxylamine, 50 mg.	49	67	7.73	7.27

Results

Induction of sleep. The mean values for induction of sleep during the first week are shown in Table II. When analyzed statistically by the rank test described above, secobarbital, 200 mg., and the two dose levels of doxylamine were each significantly better than placebo at the 5 per cent level, and secobarbital, 200 mg., was significantly better than secobarbital, 100 mg., at the 5 per cent level.

When all the data accumulated during the 3 week experimental period were used to calculate a mean score for each subject, regardless of how many replicates were involved for a given patient (Table II), the two doses of doxylamine and the higher dose of secobarbital were significantly better than placebo, but now at the 1 per cent level of confidence. In this analysis secobarbital, 100 mg., was significantly better than placebo at the 5 per cent level of confidence when a two-sided test for comparing treatments with control was used.

Another way of looking at the data is to ask how many subjects fell asleep within one hour after taking medication. During the first week, 13 of the 22 subjects took more than one hour to fall asleep when on placebo, whereas only 6 took this long after 100 mg. of secobarbital sodium, one after 200 mg. of secobarbital sodium, and 4 on each of the dose levels of doxylamine. A comparable situation was obtained for the data representing the averages over the 3 week period.

Duration of sleep. For the first week's data, the means for the total time asleep per night are also shown in Table II. By rank test, secobarbital, 200 mg., was significantly better than placebo and secobar-

bital, 100 mg., at the 5 per cent level. Doxylamine, 25 mg., was significantly better than placebo at the 5 per cent level, and doxylamine, 50 mg., was significantly better than placebo at the 5 per cent level in a two-sided comparison of treatments with control. During this first week, none of the patients slept for more than 8 hours after placebo, whereas 3 did so after 100 mg. of secobarbital, 11 after 200 mg. of secobarbital, and 12 and 9, respectively, after 25 and 50 mg. doses of doxylamine.

On analysis of the pooled 3 week data, both doses of doxylamine and the 200 mg. dose of secobarbital were significantly better than placebo at the 1 per cent level; secobarbital, 100 mg., was significantly better than placebo at the 5 per cent level, and secobarbital, 200 mg., was significantly better than secobarbital, 100 mg., at the 5 per cent level.

Comparison of sleep with usual sleep pattern. In comparison of sleep during the study with the usual sleep pattern, a response of "better than usual" was given a score of 1, "same as usual" was given a score 0, and "worse than usual" was given a score of -1. ("Usual" performance is indicated in Table I.*) The mean scores are shown in Table III. Statistical analysis of the data for the first week revealed only the higher dose of secobarbital to be significantly better than placebo at the 5 per cent level. With this treatment (i.e., 200 mg. secobarbital), 14 patients slept better than usual, and only one worse than usual, in contrast to the 4 patients who slept better than usual, and 8 worse than usual, after placebo.

On analysis of the pooled 3 week data (Table III), secobarbital, 100 mg., was significantly better than placebo at the 5 per cent level when a two-sided test for comparison of several treatments with control was used, whereas the lower dose of doxylamine was not significantly different from placebo. The 200 mg. dose of secobarbital was significantly better than placebo at the 1 per cent level of confidence. The higher dose of doxylamine was significantly better than placebo at the 5 per cent level of confidence only when a one-sided test for comparison of several treatments with control was used.

Table III. *Mean scores for comparison with usual sleep pattern and for over-all evaluation of sleep*

	*Comparison with usual sleep**		*Over-all sleep pattern*†	
Medication	*Week 1*	*3 weeks pooled*	*Week 1*	*3 weeks pooled*
Placebo	-0.18	-0.28	1.48	1.48
Secobarbital, 100 mg.	+0.09	+0.10	1.75	1.87
Secobarbital, 200 mg.	+0.59	+0.42	2.30	2.27
Doxylamine, 25 mg.	+0.32	+0.02	2.14	1.99
Doxylamine, 50 mg.	+0.23	-0.10	2.09	1.99

*Scoring: 1, better than usual; 0, same as usual; -1, worse than usual.

†Scoring: 3, excellent; 2, good; 1, poor; 0, none at all.

Over-all evaluation of sleep. Responses categorizing sleep as excellent, good, poor, or none at all were assigned scores of 3, 2, 1, and 0, respectively. The means for the first week's data and for the pooled 3 week scores are shown in Table III. For the first week, the lower dose of secobarbital did not differ significantly from the placebo, whereas the higher dose did so at the 5 per cent level of confidence. The lower dose of doxylamine was significantly different from placebo at the 5 per cent level in a two-sided test for comparison of treatments with control. The higher dose of doxylamine was significantly different from placebo at the 5 per cent level only if a one-sided test for a comparison of treatments with control was used. Only one subject rated his sleep as "excellent" on placebo, as did one subject for 100 mg. of secobarbital. In contrast, 25 mg. of doxylamine produced 5 "excellent" responses, 50

*The data were simply the responses to the fourth question described above, however.

mg. of doxylamine, 4, and 200 mg. of secobarbital was followed by an "excellent" night's sleep in 9 of the 22 subjects.

On analysis of the pooled 3 week data, secobarbital, 100 mg., was significantly better than placebo at the 5 per cent level when a one-sided test for comparison of treatments with control was used. Doxylamine, 25 mg., was significantly better than placebo at the 5 per cent level of confidence, and secobarbital, 200 mg., was significantly better than placebo at the 1 per cent level. The higher dose of doxylamine was significantly better than placebo at the 5 per cent level in a two-sided test for comparison of treatments with control.

Predictability of response. It was not possible to predict subsequent response accurately on the basis of initial response to placebo. For example, 8 subjects said they slept worse than usual on their first exposure to placebo, but on subsequent exposures to placebo approximately half of the responses were "worse than usual" while the rest were "the same as usual." Of the 10 subjects who slept "the same as usual" on their first placebo night, approximately half of the responses were "worse than usual" and half "the same as usual" on subsequent exposures to placebo. A similar pattern was seen for the 4 subjects who slept "better than usual" on the first night of placebo treatment.

Nevertheless, there was a pattern of relative nondiscrimination between treatments shown by half of our experimental population, who were pooled retrospectively as having had at least a good or fair night's sleep after placebo. The mean induction time for these 11 subjects on placebo was 62 minutes, the mean duration of sleep 5.74 hours, and comparison of their sleep after placebo with their usual night's sleep produced a mean score of 0.09, i.e., essentially the same as usual. While the active treatments were all associated with shorter mean induction and longer duration times in this group, these differences from placebo were slight and were in no case significantly different at a statistical level of 0.05. In contrast, the other 11 patients (who slept poorly on nights they received placebo) not only showed significant differences between each active treatment and placebo (which is at least partially explainable by the obvious bias against placebo inherent in the method of identifying these subjects as nonresponsive to placebo) but also revealed significant interdrug differences, such as the anticipated dose-response relationship for secobarbital in regard to both induction and maintenance of sleep.

Side effects. Side-effect data were sought on 55 separate occasions for each treatment. For a variety of reported side effects on the morning-after interview, there seemed to be no important difference between placebo and active treatments. Thus, there were three gastrointestinal complaints after nights when placebo was given, two after 100 mg. of secobarbital, one after 200 mg. of secobarbital, and none after doxylamine at either dose level. There were three reports of headache after nights when placebo was given, four and three, respectively, for the lower and higher doses of secobarbital, and four each for the two dose levels of doxylamine. There were complaints of nervousness or shakiness on two occasions after placebo, three after 100 mg. of secobarbital, one after 200 mg. of secobarbital, and four after each of the two doses of doxylamine. For residual sedation and "hangover," however, there was an impressive difference between placebo and active treatments. Such reports occurred on only four occasions after placebo, whereas there were 10 such reports after secobarbital, 100 mg., 10 after secobarbital, 200 mg., 14 after 25 mg. of doxylamine, and 18 after 50 mg. of doxylamine.

Discussion

A decade ago, it was pointed out that there was little reliable information available in regard to the performance of antihistamines as hypnotic preparations.[4] The situation has not changed significantly since that time. Our own unpublished ex-

perience with methapyrilene, the "active" ingredient present in most over-the-counter hypnotics, suggests that this particular antihistamine is a very weak hypnotic, essentially indistinguishable at a dose of 50 mg. from placebo. We have also found that diphenhydramine and tripelennamine, in doses of 50 or 100 mg., do not provide hypnotic effect with sufficient consistency to substitute for secobarbital sodium in usual dosage (100 to 200 mg.).

In contrast, doxylamine seems to have impressive hypnotic properties at doses of 25 to 50 mg. Its performance in the present study was in general comparable to that of secobarbital given in doses ranging from 4 to 8 times those of doxylamine, although our data do suggest that 200 mg. of secobarbital was in most respects somewhat superior to either dose level of doxylamine used. This excellent performance of secobarbital, 200 mg., is in keeping with our past experience with this drug in controlled trials, as was the greater difficulty in distinguishing 100 mg. of secobarbital sodium from placebo.

While a dose-response relationship was apparent for secobarbital, it was not for the two doses of doxylamine chosen for study. In animals, doxylamine resembles other antihistamines in producing central nervous system stimulation at high doses.[1] Doxyl- pattern of acute toxicity different from that amine might, therefore, produce a clinical of barbiturates in accidental or suicidal overdosage, and which might possibly pose a different management problem from that now presented by patients poisoned with barbiturate and nonbarbiturate hypnotics. Unfortunately, little is known about certain aspects of doxylamine effect which would be extremely relevant to its use as a hypnotic. It would be interesting, for example, to know whether doxylamine is capable of producing tolerance and physical dependence in either animals or man. To our knowledge, there are no reports of abuse of this drug for purposes of addiction just as there are none of its implication in accidental deaths or suicide, but doxylamine is used much less widely than the popular barbiturate and nonbarbiturate hypnotics or certain other antihistamines.

From the standpoint of experimental design, our data are in keeping with the previously published data of Lasagna and coworkers[5] and of Liberman[6] in regard to the difficulties involved in predicting from the response after one exposure to placebo how a given subject will respond to subsequent doses. A great proportion of our subjects reported satisfying sleep on placebo despite a purposeful attempt by us to select patients who definitely needed hypnotic drugs to achieve a satisfactory night's sleep. Since subjects who respond to placebo increase the difficulties of detecting real differences between treatments, it would be desirable to avoid such subjects in clinical trials. "Screening" out subjects who react to placebo by an initial exposure of all study patients to placebo, however, is not usually feasible, both because of variability in response to placebo and because it involves the risk of creating an unfavorable attitude among the subjects to continuation of the trial.

The replicate data seemed to provide additional information over that available from the data collected during the first week of exposure. Whether the gains were due primarily to a diminution in the impact of irrelevant variables (such as a noisy night on the ward) or to the acquisition of subject means which provided more interindividual differences and thus fewer "tied pairs" in the rank tests than with single observations is not clear, but statistical gains were apparent in most of the analyses.

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