Effects of doxylamine and acetaminophen on postoperative sleep

The separate and combined effects of doxylamine succinate (25 mg) and acetaminophen (1 gm) on sleep were studied by interview procedures and information from medical records of 2,931 postoperative patients. The sample contained 1,617 patients with mild or moderate pain and 1,314 who were free of pain. Each received either doxylamine alone (S), acetaminophen alone (A), a combination of both drugs (C), or placebo (P). Drug treatment was double blind and randomized separately for the pain and pain-free subsamples. Twelve measures of sleep were determined. C was more beneficial than S or A, and S and A were each superior to P. For all 12 sleep measures, the effect of the combination (C − P) approximated or exceeded the sum of the two separate effects (S − P) + (A − P). The presence of either drug tended to enhance the sleep benefit of the other. The sedative and analgesic benefits to sleep were at least additive, and some outcome measures suggested synergism. In the total sample, the contributions of sedative and analgesic were similar. Among patients with pain, contributions of the analgesic surpassed those of the sedative. For patients free of pain, the sedative was better, but even pain-free patients had enhanced sleep after the analgesic. The analgesic, but not the sedative, reduced pain; the analgesic induced the feeling of being well rested and not tired; the sedative induced a feeling of being drugged. Nondrug variables (e.g., pain, sex, age, and sleep expectations) influenced sleep outcome at least as much as drugs, but randomization and the large sample prevented those extraneous variables from biasing drug comparisons. (CLIN PHARMACOL THER 37:549-557, 1985.)

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A recent report of a Consensus Conference on Drugs and Insomnia[6] cites evidence that one third of the American population experiences some degree of insomnia, but the report recommends a very cautious approach to pharmacologic treatment of sleep problems, especially when the difficulty is transient (a few days) or short term (a few weeks). The practitioner is advised to prescribe modest doses of comparatively safe drugs (e.g., benzodiazepines) for as briefly as practicable. As an alternative to barbiturates and tranquilizers, antihistamines have frequently been proposed as nighttime sleep aids. Drowsiness as a side effect of antihistamines has been recognized for decades,[8,13,15,22] and sleep facilitation by antihistamines has been shown in various types of subjects, including normal subjects, subjects with insomnia, nursing home residents, and hospitalized patients who customarily sleep well at home but who might have temporary sleep difficulty because of pain and other circumstances associated with hospitalization.[5,7-9,11,12,14,16-19,22,24,25] Some studies, however, have not found sleep facilitation with antihistamines.[1-4] Not surprisingly, the various antihistamines appear to differ in the degree of sedative effect,[17] and a given antihistamine may be efficacious at one dose but not at another.[11,13,25] Studies of the sedative effects of certain analgesic/sedative combinations (e.g., aspirin or acetaminophen combined with an antihistamine) have also shown promise,[20,21,23,26] but, as noted in a Food and Drug Administration report,[11] evidence is needed to clarify the separate and possibly interactive contributions of the components of such combinations to the sedative effect.

Our main purpose was to seek answers to three questions: (1) What is the extent and dependability of the contribution to sleep of an antihistamine (doxylamine) alone and in combination with a mild oral analgesic (acetaminophen)? (2) Which component in the two-drug combination contributes more to sleep and how is the contribution of each related to the presence or absence of nighttime pain? (3) Is the combined effect of the two drugs additive, synergistic, or less than additive? Our investigation, which is a factorial study of the separate and combined effects on sleep of 25 mg

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doxylamine succinate and 1 gm acetaminophen, was designed to address those and related questions.

METHODS

The 2,931 subjects who participated in this study were male (51%) and female (49%) postoperative patients at the Massachusetts Eye and Ear Infirmary who were studied at least 24 hours after their operation. They ranged in age from 17 to 92 years, but most (98%) were between 18 and 80 years (one was 17 years old and 83 were over 80 years old). Sixty-three percent reported that they anticipated having sleep difficulty. Forty-five percent reported having no pain at the time the sleep medication was given, 42% reported slight pain, and 13% reported having moderate pain. Subjects reporting severe pain were excluded from study. Potential participants were also excluded if they had received tranquilizers, narcotics, nonnarcotic analgesics, or muscle relaxants within 4 hours of the scheduled test medication; were receiving anticoagulants; had a history of drug abuse; had severe communication problems (e.g., foreign language, deafness); had notations in their medical records indicating severe anxiety, depression, or hostility; had relevant drug allergies; or had any other medically disqualifying problems.

The sample composition, classified by operative category, was as follows: cataract, 915 patients; retina, 338; vitrectomy, 79; squint, 61; eye plastic, 83; eye major miscellaneous, 201; eye minor miscellaneous, 80; stapedectomy, 155; tympanoplasty, 110; ear major miscellaneous, 144; ear minor miscellaneous, 36; submucous resection and rhinoplasty, 267; nose major miscellaneous, 127; nose minor miscellaneous, 34; laryngoscopy, 148; neck mass, 65; throat major miscellaneous, 30; throat minor miscellaneous, 33; cosmetic major, 15; and cosmetic minor, 10. Information about operative category, age, height, weight, and other potentially relevant matters was taken from the subject's medical record.

Each subject accepted for participation in the study was interviewed by one of three nurse investigators who explained its purpose and recorded pertinent information about the subject and his or her typical sleep habits. Subjects were told that our objective was to compare various medications designed to facilitate sleep; that each subject would be studied only once; and that his/her responsibility was to evaluate how well the medication worked. The interviewer imparted a positive expectation by stating that our purpose was to determine which of several effective sleep medications was most beneficial.

At bedtime the nurse investigator who had recruited the subject earlier that evening returned with the experimental medication, which had been selected on a predetermined randomized basis; interviewed the subject and recorded information such as degree of pain, drowsiness, readiness for sleep, and anticipated sleep difficulty; observed the subject take the medication; and informed the subject that she or another nurse investigator would return the following morning to discuss the subject's evaluation of the medication. Each subject received one of the following: 25 mg doxylamine succinate (S), 1 gm acetaminophen (A), the combination of 25 mg doxylamine succinate plus 1 gm acetaminophen (C) or placebo (P). To maintain the double-blind control, each treatment (which consisted of two tablets) was packaged in an individual plastic vial inserted into an envelope identified by subject number (i.e., 1 to 3,000). The treatment given to each subject was determined by breaking a sealed code (relating treatment to subject number) at the time of statistical analysis. All tablets were indistinguishable except by chemical analysis. The pain and pain-free samples had separate randomizations for drug. Our goal was to have equal sample sizes for the three active treatments and a sample half that large for placebo (e.g., 840, 840, 840, and 420 subjects). Through error, the final batch of medications used (13% of the total) was prepared with equal numbers of the four treatments. Consequently, the actual sample sizes were 824, 827, 822, and 458 for S, A, C, and P.

Arrangements were made for the ward nurse to give additional nonexperimental sleep or pain medication on subject request after a minimum of 60 minutes following the experimental treatment. To avoid an effect of negative suggestion, subjects were not informed of this back-up plan unless they specifically asked about the possibility of receiving additional medication. Ward nurses were asked not to volunteer additional medication and not to discuss with the subject the effectiveness of the experimental medications or any aspects of the study itself.

On the morning after nighttime dosing, the subject was interviewed by one of the three nurse investigators. The schedule of questions asked is reproduced as Fig. 1. In addition to obtaining answers to those questions, the morning interviewer examined the subject's medical record to determine whether additional sedative or analgesic medication had been given after the experimental treatment.

Some of the sleep criterion measures are continuously distributed (e.g., number of minutes to get to sleep), while some have categorically ordered responses (e.g., overall amount of help), and still others have dichotomous responses (e.g., did you awaken during the night?). To obtain an omnibus comparison of the effects

1. How was your sleep last night?
   terrible_____ poor_____ fair_____ good_____ excellent_____
2. Did the medication relieve your pain?
   yes_____ no_____ had none_____
3. Did the medication help you get to sleep?
   yes_____ not sure_____ no_____
4. How long (in minutes) do you estimate that it took you to fall asleep last night? _____
5. Did the medication help you stay asleep?
   yes_____ not sure_____ no_____
6. *Did you awaken last night or sleep straight through the night?*
   awoke_____ did not awaken_____ did not sleep at all last night_____
7. If you awoke last night, please estimate the number of times.* _____
8. If you awoke, how much trouble did you have getting back to sleep?
   none_____ some_____ a lot_____
9. Altogether, how many hours do you estimate that you slept last night? _____
10. Compared with your usual sleep at home, was the number of hours you slept last night:
    less than average_____ average_____ more than average_____
11. Did you lose needed sleep because you awoke too early this morning?
    yes_____ no_____
12. How did you feel when you woke up this morning?

drugged	yes_____	no_____
well rested	yes_____	no_____
hung over	yes_____	no_____
tired	yes_____	no_____
alert	yes_____	no_____
energetic	yes_____	no_____

13. Since taking our medication last night, did you experience any unpleasant dryness of the mouth or nose, severe thirst, or difficulty swallowing?
    yes_____ no_____
14. Overall, how much do you think the medication we gave you last night helped?
    not at all_____ a little_____ some_____ a lot_____ it was terrific_____

*This measure has a Poisson distribution. To stabilize its variance, a square root transformation was used.

Fig. 1. Interview schedule.

of the four treatments (S, A, C, P) on continuously distributed variables and on the categorically ordered variable concerning the number of nighttime awakenings, F values were computed with one-way ANOVA; categorically ordered variables with either three or five response options were analyzed by chi-square as well as by ANOVA; and dichotomous variables were analyzed by chi-square. Where chi-square values are reported, the frequency distributions associated with them are also included. The numeric values assigned to alternative responses on the categorically ordered variables are shown in the tables. For each of the 12 outcome measures, t tests were performed for each of the six treatment contrasts (S − P, A − P, C − P, C − S, C − A, and S − A). For the three outcome measures calling for a yes or no response, chi-square tests were also performed.

Effects of the sedative alone and of the analgesic alone were evaluated by the S − P and A − P contrasts. The factorial structure of the study also provided measures of the sedative and analgesic effects that are more stable and have more generality of meaning than the S − P and A − P contrasts. Because S − P is an evaluation of the sedative effect when the analgesic is absent, and C − A is an evaluation of the sedative effect when the analgesic is present, (C + S − A − P)/2 measures the average sedative effect in the presence and absence of the analgesic. Similarly, (C + A − S − P)/2 measures the average analgesic effect in the presence and absence of the sedative. The logic and analytic efficiency of the factorial approach was first described by Fisher.[10]

RESULTS

Tables I, II, and III deal with measures of sleep onset, maintenance, and duration, and Table IV lists two measures of overall sleep benefit. All 12 measures reported in these four tables show significant differences among

Table I. Comparison of four treatment groups on two measures of latency of sleep onset

			Drug treatment				
	Scoring		*S*	*A*	*C*	*P*	*Statistical parameters*
Did medication help you get to sleep?	Yes = 2		436	458	512	220	$\chi^2 = 43.41$; P = 0.0001
	Not sure = 1		216	209	199	113	
	No = 0		171	160	111	125	
		$\bar{X}$	1.32	1.36	1.49	1.21	F = 13.81; P = 0.0001;
		SD	0.80	0.79	0.72	0.84	df = 3 and 2,926
Minutes needed to fall asleep		$\bar{X}$	46.0	43.9	37.3	53.9	F = 11.21; P = 0.0001;
		SD	53.4	48.0	41.5	61.2	df = 3 and 2,925

Table II. Comparison of four treatment groups on five measures of sleep maintenance

			Drug treatment				
	Scoring		*S*	*A*	*C*	*P*	*Statistical parameters*
Did medication help you stay asleep?	Yes = 2		353	340	404	161	$\chi^2 = 30.03$; P = 0.0001
	Not sure = 1		72	65	78	44	
	No = 0		398	421	340	253	
		$\bar{X}$	0.95	0.90	1.08	0.80	F = 9.53; P = 0.001;
		SD	0.95	0.96	0.95	0.93	df = 3 and 2,925
Times awoke (square root of number)		$\bar{X}$	1.25	1.22	1.10	1.25	F = 4.70; P = 0.01;
		SD	0.92	0.89	0.89	0.89	df = 3 and 2,927
Awoke during the night	Yes		584	582	539	331	$\chi^2 = 12.42$; P = 0.01
	No		215	219	266	110	
Had trouble getting back to sleep	None = 1		346	320	348	181	$\chi^2 = 16.76$; P = 0.02
	Some = 2		108	123	104	73	
	A lot = 3		130	139	87	77	
		$\bar{X}$	1.63	1.69	1.52	1.69	F = 5.11; P = 0.01;
		SD	0.82	0.83	0.76	0.83	df = 3 and 2,032
Required additional medication	Yes		148	98	84	87	$\chi^2 = 32.51$; P = 0.0001
	No		676	729	737	371	

Wherever the sample size is less than 2,931, the information either was not obtained or did not apply. For example, 85 patients (3% of the total sample) said they were unable to determine whether they had awakened during the night; hence the total sample for that question was 2,846 rather than 2,931. The sample for "had trouble getting back to sleep" was 2,036, because that question was asked only of the 2,036 patients who reported having awakened during the night. As seen in other tables of this report, the total sample was 2,930 (rather than 2,931) for five other sleep criteria and was 2,929 for one.

Table III. Comparison of four treatment groups on three measures of sleep duration

			Drug treatment				
	Scoring		*S*	*A*	*C*	*P*	*Statistical parameters*
Hours slept*		$\bar{X}$	7.16	6.97	7.40	6.90	F = 9.55; P = 0.0001;
		SD	1.97	1.93	1.77	2.15	df = 3 and 2,927
Sleep compared with home	Better = 3		376	336	410	193	$\chi^2 = 27.14$; P = 0.0001
	Average = 2		217	214	204	101	
	Worse = 1		231	277	207	164	
		$\bar{X}$	2.18	2.07	2.25	2.06	F = 7.79; P = 0.0001;
		SD	0.84	0.86	0.83	0.88	df = 3 and 2,926
Awoke too early?	Yes		135	142	109	85	$\chi^2 = 7.74$; P = 0.05
	No		689	684	713	373	

*Time slept after breakfast, but before morning interview, was included in the estimate of total time slept.

Table IV. Comparison of four treatment groups on two global measures of benefit

			Drug treatment				
	Scoring		*S*	*A*	*C*	*P*	*Statistical parameters*
How was your sleep last night?	Terrible = 1		53	31	29	30	$\chi^2 = 43.48$; P = 0.0001
	Poor = 2		99	115	69	66	
	Fair = 3		209	223	199	123	
	Good = 4		372	383	407	201	
	Excellent = 5		91	75	117	38	
		$\bar{X}$	3.42	3.43	3.63	3.33	F = 10.80; P = 0.0001;
		SD	1.05	0.96	0.95	1.03	df = 3 and 2,926
Overall help	Not at all = 1		121	113	72	92	$\chi^2 = 54.85$; P = 0.0001
	A little = 2		119	113	79	66	
	Some = 3		207	225	239	118	
	A lot = 4		275	280	307	139	
	Terrific = 5		102	96	125	43	
		$\bar{X}$	3.14	3.16	3.41	2.95	F = 15.66; P = 0.0001;
		SD	1.24	1.21	1.13	1.28	df = 3 and 2,927

the four treatments. Tables I to IV show that C provides the greatest sleep benefit, that P provides the least, and that benefits of the S and A treatments are intermediate.

To obtain more specific information, each of the six possible pairs of drug treatments (S − P, A − P, C − P, C − S, C − A, and S − A) was evaluated by t test and/or chi-square for each of the 12 outcome measures. C was superior to P on all 12 sleep criteria; C was superior to S on 10 criteria and was superior to A on 11. S was superior to P on six criteria and A was superior to P on four. S was superior to A for the measures "hours slept" and "sleep compared with home," while A was superior to S for "required additional medication."

As already mentioned, the factorial structure of the study provides a general measure of the sedative effect and a general measure of the analgesic effect, where each is the average effect obtained in the presence and absence of the other drug. Table V lists results for each of 12 measures of sleep benefit when the sedative effect is measured by (C + S − A − P)/2 and the analgesic effect is measured by (C + A − S − P)/2. Results are reported for the total sample of 2,931 subjects and for the two subgroups distinguished by whether or not pain was present when the nighttime medication was given. For each of the 12 outcome variables, two stepwise regression analyses were performed on the total sample and on each of the two subgroups. One regression in each pair tested the significance of the sedative effect after controlling for the analgesic effect; the other tested the significance of the analgesic effect after controlling for the sedative effect. The F values and associated probability levels in Table V were obtained under these constraints.

Significant beneficial effects of both drugs on sleep are evident in all three samples, but primarily because the smaller subsamples have larger error terms, benefits are more persuasive in the total sample than in either of the subsamples. In the total sample, 11 of the 12 measures show a significant sleep benefit due to the sedative, and nine show a significant sleep benefit due to the analgesic. Thirty-one of the 48 comparisons involving the two subsamples (pain and pain-free) are significant. In the pain-free sample, the benefit of the sedative tends to be greater than that of the analgesic on most outcome measures, and the opposite relationship prevails in the pain sample (see Table V). The finding that the analgesic effect was significant for five measures in the pain-free sample was unanticipated; its potential importance will be discussed later.

Tables I to IV show that the sleep benefit due to the combination treatment (C − P) is approximately equal to the sum of the two individual treatment contrasts (S − P plus A − P) for six outcome measures and is substantially larger than that sum for the remaining six. Thus the sedative effect tends to be larger in the presence of the analgesic than in its absence, and the analgesic effect tends to be larger in the presence of the sedative than in its absence. The sedative and analgesic effects are at least additive and, on some measures, might be synergistic.

For subjects who reported pain at the time the nighttime medication was given, a chi-square value of 29.68

Table V. Sleep benefit analyzed by factorial measures of the sedative and the analgesic effects: F values for the total, pain, and pain-free samples

	Total sample (n = 2,931)		*Pain sample (n = 1,617)*		*Pain-free sample (n = 1,314)*	
	Sedative	*Analgesic*	*Sedative*	*Analgesic*	*Sedative*	*Analgesic*
Helped get to sleep	17.27*	29.79*	11.31†	21.06*	6.15‡	9.05‡
Minutes to fall asleep	14.24†	23.90*	7.11‡	15.60*	7.57‡	8.40‡
Helped stay asleep	20.96*	11.30†	3.48	12.91†	24.09*	1.15
Square root of number of times awoke	4.10§	8.43‡	0.37	7.47‡	6.02‡	1.74
Awoke during night	5.83§	7.09‡	1.77	10.38†	4.51§	0.34
Trouble getting back to sleep	11.26†	3.06	3.06	2.04	11.33†	0.88
Required additional medication	1.11	32.73*	0.13	24.13*	2.41	9.76‡
Hours slept	24.53*	5.52§	6.39‡	5.92§	23.54*	0.57
Sleep compared with home	21.89*	1.97	5.50§	1.82	20.81*	0.35
Awoke too early	5.37§	3.00	4.65§	1.69	1.07	1.30
How was sleep	16.75*	18.28*	4.82§	12.23†	15.97*	6.62‡
Overall help	24.72*	28.71*	7.80‡	29.19*	19.30*	4.12§

A patient's factorial score for sedative is "1" if C or S was given and "0" if A or P was given. Similarly, the analgesic score is "1" if the trial medication was C or A and "0" if it was S or P. Each F value has one degree of freedom for drug effect. Degrees of freedom for the error terms are n − 3; see text.
Significance values: *P = 0.0001; †P = 0.001; ‡P = 0.01; §P = 0.05.

was obtained when the four drug treatments were compared regarding pain relief. With three degrees of freedom, the probability value of that chi-square is P = 0.0001. Pain relief after receiving A, C, S, and P was reported by 79%, 82%, 69%, and 69% of the subjects. These results indicate that differences among treatments regarding pain relief are due almost entirely to the analgesic, a conclusion supported by recasting the 4 × 2 table as six 2 × 2 tables. The chi-square results for the 2 × 2 tables were significant for A vs. P, C vs. P, C vs. S, and A vs. S, but were not significant for S vs. P and C vs. A.

For the full sample (2,931 subjects), chi-square analysis was used to compare the four drug treatments regarding frequency of report of unpleasant anticholinergic effects (dryness of mouth or nose, severe thirst, or difficulty swallowing) as well as frequency of reports of feeling drugged, well rested, hung over, tired, alert, and energetic upon awakening. As seen in Table VI, three of those seven variables revealed significant differences among the four drug treatments: felt tired, felt well rested, and felt drugged. Further evaluation with 2 × 2 chi-square analyses showed that those significant overall results derive from the fact that the treatments containing the analgesic (A and C) are associated with reports of feeling well rested and not tired, while the treatments containing the sedative (S and C) are associated with reports of feeling drugged.

Earlier unpublished sleep studies performed on postoperative patients at the Massachusetts Eye and Ear Infirmary have shown that the type of operation performed, presence or absence of pain, extent of drowsiness when medication is administered, and several other nondrug variables can influence measures of sleep outcome. In the present study, each of three extraneous variables (operative category, pain, and expect trouble getting to sleep) was found to account for substantially more criterion variance than the drug variable itself; six others (expect trouble staying asleep, drowsiness, inquiry about back-up medication, sex, age, and type of admission) were all similar to the drug variable regarding influence on outcome measures; and three (whether a sedative was given on the night preceding the study, which of the three nurses performed the evening interview, and which one performed the morning interview) were significant but were somewhat less influential than the drug variable.

Considered one at a time, these 12 extraneous variables indicated a satisfactory balance across the four drug treatment groups. As a check for possible bias due to multivariate imbalance, 24 stepwise regression analyses were performed in which each of the 12 sleep outcome measures (see Table V) was predicted twice from a 14-variable prediction battery. In all analyses, the two factorial drug measures were tested after statistically controlling for the effects of the 12 extraneous variables just mentioned; i.e., the drug variables were entered as the 13th and 14th predictor variables in the stepwise regression. Subjects given C or S were scored "1" on the factorial sedative measure; those given A or P were scored "0." Similarly, subjects given C or A were scored "1" on the factorial analgesic measure

Table VI. Comparison of four treatment groups on seven nonsleep outcome measures

		Drug treatment						
	Scoring	*C*	*S*	*A*	*P*	χ^2	*df*	*P value*
Upon awakening this morning did you feel tired?	Yes	196	237	209	140			
	No	626	587	618	318	9.58	3	0.02
Upon awakening this morning did you feel well rested?	Yes	593	551	602	313			
	No	229	273	225	145	9.27	3	0.05
Upon awakening this morning did you feel drugged?	Yes	56	53	24	14			
	No	766	771	803	444	20.49	3	0.0001
Upon awakening this morning did you feel alert?	Yes	450	428	450	232			
	No	372	396	377	226	2.99	3	NS
Upon awakening this morning did you feel energetic?	Yes	258	244	270	136			
	No	564	580	557	322	2.22	3	NS
Upon awakening this morning did you feel any unpleasant effects such as dry mouth, dry nose, severe thirst, or difficulty swallowing?	Yes	7	3	2	4			
	No	815	821	825	454	4.23	3	NS*
Upon awakening this morning did you feel hung over?	Yes	22	28	22	13			
	No	800	796	805	445	1.04	3	NS

*Because of the small cell sizes in this comparison, chi-square tests were performed comparing C + S vs. A + P, and comparing C + A vs. S + P. In addition, Fisher exact tests were performed for the two contrasts just mentioned and for C − P, A − P, and S − P. None of these supplemental analyses showed a significant anticholinergic effect due either to the sedative or the analgesic.

and those given S or P were scored "0." In 12 of the 24 analyses, the effect of the sedative was tested after testing (thus after controlling) the effect of the analgesic; that order was reversed in the other 12 analyses. In the analyses in which the sedative variable was entered last (14th), the effect of the sedative was significant in predicting all of the 12 outcome measures except "required additional medication." In the analyses in which the analgesic was entered last, its effect was significant in predicting all outcome measures except "sleep compared with home," "trouble getting back to sleep," and "awoke too early." Thus, as measured by most outcome variables, even with the stringent analytic controls just described, both the sedative and the analgesic induced significant sleep benefit. The pattern of significant results was the same as that shown in the first two columns of Table V.

The size and direction of the univariate and multivariate effects of the extraneous (nondrug) variables on sleep will be considered in a later report. The point to be noted here is that several nondrug variables strongly influenced the outcome variables, but, as anticipated, randomization and the use of a very large sample prevented those powerful extraneous variables from biasing drug comparisons.

DISCUSSION

Our study supports previous findings[17,19] that doxylamine succinate enhances sleep and concurs with somewhat later reports[20,21,23,26] that sleep is benefited by antihistamine/analgesic combinations. However, as noted by the Food and Drug Administration,[11] demonstrating the efficacy of such combinations is not, by itself, unambiguously interpretable. Does the analgesic add to the sedative efficacy of the antihistamine, or is the benefit of such combinations due entirely to the effect of the antihistamine? If the analgesic does add to sleep benefit, how much does it contribute and under what circumstances? Does the analgesic facilitate sleep only among individuals who have pain at bedtime, or is its contribution to sleep more general? If both drugs facilitate sleep, what is their relative contribution, and how does the combined effect compare with the sum of the two separate effects? Such questions can best be answered with information collected in a factorial design; our literature search revealed no factorial study of the effects of an antihistamine/analgesic combination on sleep.

In the present factorial study, both components of the sedative/analgesic combination contributed significantly to sleep facilitation. In the total sample, the two components were approximately equal in their contribution to sleep benefit. The combined effect was at least as large as the sum of the two separate effects, and some sleep measures indicated the likely presence of synergism. The effects of the analgesic and sedative were influenced by the presence or absence of pain at bedtime. Among subjects with pain, the analgesic was more useful than the sedative. Among those who were free of pain, the sedative was more useful, but even

pain-free subjects obtained significant benefit from the analgesic on certain measures of sleep outcome.

Interpretation of the findings just summarized is constrained by the population studied and by the methods used. Subjects were either pain free or had mild to moderate pain levels at bedtime. The unusual and sometimes distracting circumstances of hospitalization posed potential difficulty for sleep, and 63% of the subjects stated that they thought they would have difficulty sleeping if not given a sleep aid; an additional 27% said they were unsure. Even so, this is not a population with long-standing or serious sleep problems. Only 2.1% reported either frequent or nightly use of sedatives as sleep aids at home. Most of our subjects were of the type characterized in the Consensus Conference[6] as individuals with transient insomnia; some appeared to have no insomnia of any kind. The fact that heavy sedation was not needed by most subjects in this sample is illustrated by the highly favorable placebo response obtained: 64% of subjects given placebo reported sleeping at least as long as they typically sleep at home, only 19% required additional sedative and/or analgesic dosing, and only 27% reported that the medication did not help them get to sleep. The high placebo response was due partly, no doubt, to our deliberate suggestion that the medication was likely to be effective; but that suggestion would probably have been less effective in subjects with more severe sleep problems.

Although the placebo was helpful, the active treatments—especially the combination—were even more beneficial. Among those who received 25 mg doxylamine with 1 gm acetaminophen, 75% reported sleeping at least as long as they typically slept at home, only 10% required additional sedative and/or analgesic, and only 14% reported that the medication did not help them get to sleep. Thus the percent requiring additional medication after P and C was 19% and 10%, and the percent reporting no help in getting to sleep after P and C was 27% and 14%. Despite the low failure rate with P, the failure rate with C was approximately half that of P on those two measures. Both the modest potency of the active drugs studied and the high placebo effect make more difficult the demonstration of statistically significant benefits of the active drugs; in the present study, however, that problem was offset by the use of a large sample.

Another problem that could have caused interpretational difficulties relates to the powerful effect on sleep outcome of extraneous variables such as sex, age, pain, expectations of sleep difficulty, drowsiness, and type of operation. Fortunately, randomization and the large sample prevented those extraneous variables from biasing our drug comparisons. However, the extensive influence of those variables on sleep indicates that they should be measured routinely in studies such as this and checked for maldistribution on drug treatments. This is especially important if the sample size is small. The influence of many extraneous variables is eliminated in crossover studies in which each subject is his or her own control, but some extraneous variables, such as expectations of sleep difficulty and drowsiness, are as problematic in crossover studies as in studies in which each subject is studied only once.

Because the overall benefit of a sleep aid depends in part on how the patient feels on the morning after medication, it should be mentioned again that acetaminophen was associated with feeling well rested and not tired, and that doxylamine was associated with feeling drugged. The latter agrees with the report of Sjoqvist and Lasagna[19]; the former might simply reflect the improved sleep provided by acetaminophen. Anticholinergic effects were reported slightly more often by those who received doxylamine than by those who did not, but the effect was too small to be significant.

One particularly interesting result is the sleep benefit when acetaminophen was given to subjects who had no pain. It is important to remember that all subjects were postoperative patients. Such individuals are likely to experience pain periodically during their postoperative recovery (i.e., they are temporarily pain prone). Even if such a patient is pain free when the nighttime medication is given, he or she might benefit prophylactically from an analgesic that helps forestall sleep-disrupting nighttime pain. Although the interpretation just suggested is conjectural, the finding itself is an empiric fact. To the best of our knowledge, this is the first published report of a quantitative demonstration that a mild analgesic can, by itself, facilitate the sleep of individuals who are pain free when the analgesic is taken. This suggests the possible usefulness of investigating the sleep benefit of acetaminophen given at bedtime to individuals other than postoperative patients who are pain free at bedtime but whose illness or injury is apt to induce recurrent pain.

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References

1. Beaubien J, Kristof FE, Lehmann HE, Ban TA: A comparison of the hypnotic properties of mandrax and its two constituents. Cur Ther Res **10:**231-232, 1968.
2. Bjerver K, Goldberg L: Central effects of antihistamine compounds and their use in motion sickness. Acta Physiol Scand **25:**10-11, 1951.
3. Boissier J, Simon P, Rault B: Action de quelques antihistamininques sur le test de la bataille electrique chez la souris. Ann Pharm Fr **26:**277-285, 1968.
4. Bordeleau JM, Saint-Hilaire J, Juretic F, Tetreault L: Association hypnotique-antihistaminique: Evaluation comparative des propriétés hypnotiques du mandrax, de la methaqualone, du secobarbital, de la diphenhydramine et du placebo chez le malade mental psychiatrique. Therapie **23:**1037-1048, 1968.
5. Chapiro S, Slone D, Lewis GP, Jick H: Clinical effects of hypnotics. II. An epidemiologic study. JAMA **209:**2016-2020, 1969.
6. Consensus Conference: Drugs and insomnia—The use of medications to promote sleep. JAMA **251:**2410-2414, 1984.
7. Douglas WW: Histamine and antihistamines. 5-Hydroxytryptamine and antagonists. *In* Goodman LS, Gilman A, editors: The pharmacological basis of therapeutics, ed 4. New York, 1970, The MacMillan Co., pp 621-662.
8. Feinberg SM, Berstein TB: Histamine antagonists; *N*-(α-pyridyl)-*N*-(α-thenyl)-*N'*,*N'*-dimethylethylenediamine, a new antihistaminic compound; experimental and clinical experiences. J Lab Clin Med **32:**1370-1373, 1947.
9. Feinblatt TM, Ferguson EA Jr: Sedative and somnifacient effects of methapyrilene-niacinate: Comparison with methapyrilene hydrochloride in 53 cases. J Am Geriatr Soc **11:**908-913, 1963.
10. Fisher RA: The design of experiments. Edinburgh, Scotland, 1935, Oliver and Boyd.
11. Food and Drug Administration: Over-the-counter drugs—Proposal to establish monographs for OTC nighttime sleep-aid, daytime sedative, and stimulant products. Fed Reg **40, 236:**57292-57317, 1975.
12. Friedlander WJ: The use of Benadryl for sleep EEG's. Electroencephalogr Clin Neurophysiol **13:**285-286, 1961.
13. Friedlaender AS, Friedlaender S: Antihistaminic antianaphylactic and antiallergic activity of *N*-(α-pyridyl)-*N*-(α-thenyl)-*N'*,*N'*-dimethylethylenediamine hydrochloride. J Med Sci **215:**530-533, 1948.
14. Jick H, Slone D, Shapiro S, Lewis GP: Clinical effects of hypnotics. I. A controlled trial. JAMA **209:**2013-2015, 1969.
15. Kierland RR, Potter RT: Evaluation of thenylene hydrochloride (*N*,*N*-dimethyl-*N'*-(alpha-pyridyl)-*N'*-(alpha-thenyl) ethylenediamine hydrochloride. Am J Med Sci **216:**20-23, 1948.
16. National Academy of Sciences-National Research Council: Drug efficacy study: Benadryl kapseals. Bethesda, 1971, National Academy of Sciences.
17. Noell WK, Chinn HI, Haberer CE: Electroencephalographic evaluation of the sedative effects of antihistaminic drugs. U.S. Air Force Report No. 55-35. Washington, D.C., U.S. Government Printing Office, 1955, pp 1-20.
18. Richels K, Morris RJ, Newman H, Rosenfeld H, Schiller H, Weinstock R: Diphenhydramine in insomniac family practice patients: A double-blind study. J Clin Pharmacol **23:**235-242, 1983.
19. Sjoqvist F, Lasagna L: The hypnotic efficacy of doxylamine. CLIN PHARMACOL THER **8:**48-54, 1967.
20. Smith GM, Coletta CG, McBride S, McPeek B: Use of subjective responses to evaluate efficacy of mild analgesic-sedative combinations. CLIN PHARMACOL THER **15:**118-129, 1974.
21. Stern FH: Sleep-inducing properties of a nonbarbiturate analgesic/sedative preparation in elderly patients. Clin Med **79:**31-33, 1972.
22. Straus B, Eisenberg J, Gennis J: Hypnotic effects of an antihistamine—Methapyrilene hydrochloride. Ann Intern Med **42:**574-582, 1955.
23. Sunshine A: A comparative study of Excedrin PM and placebo. J Clin Pharmacol **14:**166-171, 1974.
24. Sunshine A, Zighelboim I, Laska E: Hypnotic activity of diphenhydramine, methapyrilene, and placebo. J Clin Pharmacol **18:**425-431, 1978.
25. Teutsch G, Mahler DL, Brown CR, Forrest WH, James KE, Brown BW: Hypnotic efficacy of diphenhydramine, methapyrilene, and pentobarbital. CLIN PHARMACOL THER **17:**195-201, 1975.
26. Wolff BB: Evaluation of hypnotics in outpatients with insomnia using a questionnaire and a self-rating technique. CLIN PHARMACOL THER **15:**130-140, 1974.