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The Interaction of Caffeine with Pentobarbital as a Nighttime Hypnotic

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The interaction of caffeine with pentobarbital taken for its hypnotic effect was studied in 42 medical and surgical patients. Each patient received the following medications orally: a lactose placebo; 250 mg caffeine; 100 mg pentobarbital; and 250 mg caffeine plus 100 mg pentobarbital. Hypnotic effects were determined by patient evaluation of sleep. Caffeine had an adverse effect on sleep, whereas pentobarbital was an effective hypnotic. Together, their effects appeared additive, and the 250 mg caffeine plus 100 mg pentobarbital combination was not distinguishable from the placebo. (Key words: Caffeine; Pentobarbital; Drug interaction; Hypnotics.)

PRESENT HOSPITAL PRACTICE often permits patients to drink beverages containing caffeine in the evening and then obtain barbiturates to enable them to sleep at night. This may be an example of a problem of considerable magnitude, for 47 per cent of college student's wives surveyed by Goldstein and Kaiser[1] thought their coffee-drinking habits caused some degree of insomnia, while 49 per cent of hospital patients studied by Shapiro *et al.*[2] received at least one of four commonly used hypnotics for treatment of insomnia. Since coffee is widely drunk and barbiturates are commonly used to treat insomnia, we decided to investigate the effects on sleep of the interaction of these two drugs when taken together in the evening. In a controlled study, utilizing a population of medical and surgical patients, we determined the effects on nighttime sleep of caffeine,§ pentobarbital,¶ and the two in combination. We have previously demonstrated the sensitivity of our method in a study of patients in a Veterans Administration Hospital.[3]

Method

PATIENT SELECTION

All patients on the medical and surgical wards of the Palo Alto Veterans Administration Hospital who were staying in the hospital for at least a week, needed nighttime hypnotics, and were not taking interfering drugs such as tranquilizers, analgesics, or other long-acting sedatives, were considered candidates. They were informed that we were interested in studying the effects that several drugs would have on sleep and that their bedtime medications would contain caffeine, pentobarbital or a combination of the two. They were further advised that if sleep was not satisfactory after four hours, they could receive a supplemental hypnotic (100 mg secobarbital or pentobarbital). Patients who consented and signed a release form were admitted to the study. The study group consisted of 41 men and a woman. Mean age was 46.4 years, mean height 173.5 cm, and mean weight 67.4 kg.

MEDICATIONS

For each participant, a "round" of all four medications—250 mg caffeine, 100 mg pentobarbital, a lactose placebo, and 250 mg caf-

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§ As the citrate.
¶ Sodium pentobarbital (Nembutal), supplied by Abbott Laboratories.

TABLE 1. Rating of Interview Questions

Question 1 (*How did you sleep last night?*)	Question 2 (*How many minutes passed before you fell asleep?*)	Question 3 (*How many hours did you sleep?*)	Question 4 (*How did your sleep compare with your usual night's sleep at home?*)
5 Very good	8 0–10	0 0–0.5	3 Better than } usual night's
4 Good	7 11–20	1 0.6–1.5	2 Same as } sleep at
3 Fair	6 21–30	2 1.6–2.5	1 Worse than } home.
2 Poor	5 31–45	3 2.6–3.5	
1 Terrible	4 46–60	4 3.6–4.5	
	3 61–120	5 4.6–5.5	
	2 121–180	6 5.6–6.5	
	1 more than 181	7 6.6–7.5	
		8 7.6–8.5	
		9 8.6 or more	

feine plus 100 mg pentobarbital—was prepared in identical capsules and administered randomly under double-blind conditions. Medications were taken orally at 9:30 PM, normal hospital bedtime, on consecutive nights. Patients were instructed not to drink coffee, tea or cola after 6:00 PM.

DATA COLLECTION

Each patient was interviewed the morning of the day following medication by a nurse–observer trained in the subjective-response interview technique. She asked the following questions: "How did you sleep last night?"; "How many minutes passed before you fell asleep?"; "How many hours did you sleep?"; "How did your sleep compare with your usual night's sleep at home?"

Answers were rated as shown in table 1.

Patients who needed a second medication because of unsatisfactory sleep were asked to consider only the first medication and the period between the first and second medications when grading their responses. Finally, the nurse recorded adverse effects that she observed and those volunteered by the patient. All observations were recorded on the patient's Sedative Data Form (fig. 1).

Data for all response variables were analyzed by computing mean responses, analyses of variance and incidence of adverse effects.

Results

Of the 42 patients who volunteered for the study, eight did not complete a round of medications. Of these eight, four had been placed on interfering drugs, two were discharged, one was eliminated for medical reasons, and one asked to be dropped from the study after receiving caffeine.

Supplemental hypnotic during the night was requested 22 times by 14 patients. There were 12 requests after caffeine, six after caffeine–pentobarbital, three after placebo, and one after pentobarbital (the only patient who requested supplemental medication on all four nights). Clearly, caffeine affected sleep adversely.

MEAN RESPONSES

Mean responses to all questions by the 34 subjects who completed the study are shown in table 2. The responses are scaled answers to the four questions. Results were quite similar for all questions. After receiving caffeine, patients reported the poorest night's sleep, the longest time to achieve sleep, the shortest period of sleep, and poorest comparative sleep. Responses relating to the caffeine-plus-pentobarbital combination and to the placebo were similar and scored higher than responses to caffeine. Pentobarbital resulted in the highest-scoring responses to all questions, indicating the most satisfactory sleep.

TESTS OF SIGNIFICANCE

Analysis showed that patient variation was significant ($P < 0.01$) for all response variables. Individual differences in previous caffeine use, prior barbiturate use and habitual insomnia, also disturbance from ward noise may have contributed to this finding, but significant patient variation in our population of patients in a Veterans Administration Hospital is not unusual.[3] The time-order effect (*i.e.*, the day on which each medication was re-

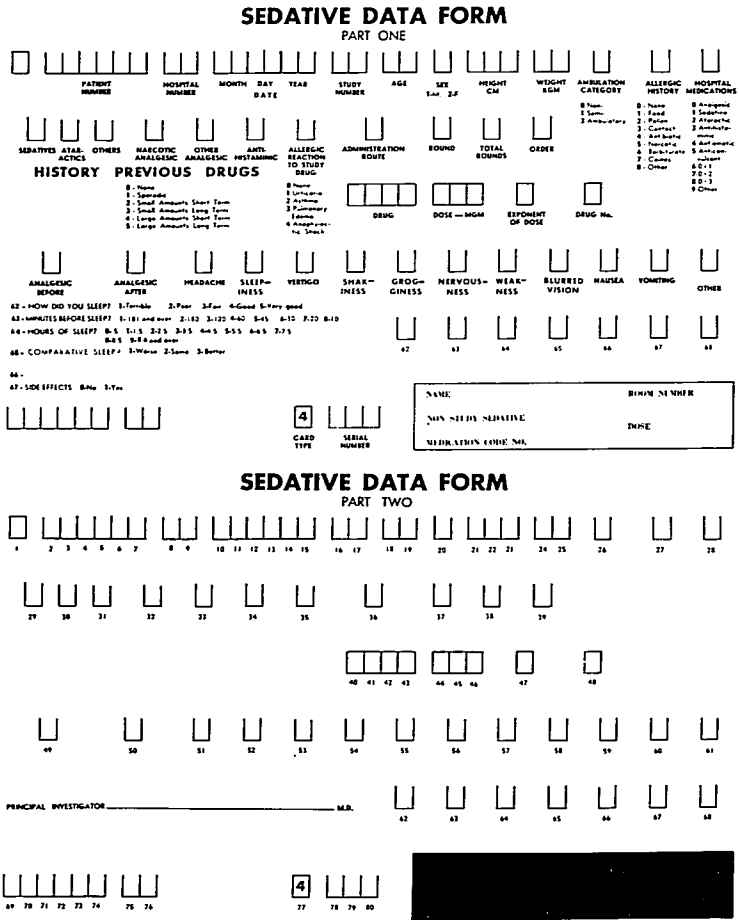

FIG. 1. Form carried by the nurse-observer to the bedside for direct recording of data. (Part two, a duplicate of part one, is sent directly to the keypunch operator without the need for data transcription.)

ceived—first, second, etc.) was significant for Question 1 only ($P < 0.03$). The medication-order effect (*i.e.*, the effect of one drug on the next to be given) was significant for Question 1 ($P < 0.01$), Question 3 ($P < 0.025$) and Question 4 ($P < 0.03$). Treatment effect was significant for all response variables ($P < 0.01$).

Treatment effect was further analyzed to determine the effects of caffeine, pentobar-

TABLE 2. Mean Responses to Four Questions, 34 Completers

Question	Caffeine, 250 mg	Pentobarbital, 100 mg	Placebo	Caffeine, 250 mg, plus Pentobarbital, 100 mg
1) How did you sleep last night?	2.12 ± 0.26*	3.91 ± 0.19	3.32 ± 0.24	3.06 ± 0.29
2) How many minutes passed before you fell asleep?	3.21 ± 0.31	5.91 ± 0.26	4.74 ± 0.28	4.41 ± 0.30
3) How many hours did you sleep?	3.06 ± 0.49	6.24 ± 0.27	5.47 ± 0.28	4.65 ± 0.49
4) How did your sleep compare with your usual night's sleep at home?	1.32 ± 0.12	2.06 ± 0.15	1.74 ± 0.12	1.74 ± 0.13

* Standard error.

bital and the combination. For all four response variables the effects of caffeine and those of pentobarbital were significant ($P < 0.05$). However, the caffeine–pentobarbital interaction effect was not significant for any response variable. Therefore, on the scales used for measurement of hypnotic effects in this study, there are no data to suggest that effects of caffeine and pentobarbital when taken together in the doses studied are more than additive.

ADVERSE EFFECTS

The incidence of adverse effects is shown in table 3. Sleepiness, hangover and grogginess were reported frequently after all medications. Nervousness was reported primarily after caffeine.

Discussion

The clinical pharmacologic effects of caffeine and pentobarbital when used separately at bedtime have been reported many times,[1, 3–10] and data from this study for caffeine alone and pentobarbital alone are in accord with these reports. Caffeine ingested at bedtime caused delayed onset of sleep, shorter duration of sleep, and less satisfying sleep. Pentobarbital caused rapid onset of sleep, longer duration of sleep, and more satisfying sleep. However, our most important finding is that when these drugs are taken together at the doses studied they seem to counteract each other's effects, and the combined result is approximately the same as that of a placebo.

Caffeine can stimulate the cerebral cortex, which usually results in impaired sleep.[4]

TABLE 3. Incidence of Adverse Effects, 34 Completers

	Caffeine, 250 mg	Pentobarbital, 100 mg	Placebo	Caffeine, 250 mg, plus pentobarbital, 100 mg	Total Incidence
Number of Administrations	34	34	34	34	136
Adverse effects					
Headache	1	0	2	1	4
Sleepiness	5	5	7	4	21
Vertigo	0	1	1	1	3
Shakiness	1	0	0	1	2
Grogginess	3	5	3	2	13
Nervousness	7	0	1	1	9
Blurred vision	3	0	1	1	5
Nausea	0	0	1	0	1
Hangover	1	5	6	4	16
Dry mouth	0	0	0	1	1

When used chronically, caffeine may also contribute indirectly to the reversal of the hypnotic effects of pentobarbital. Data recently reported by Mitoma *et al.*[11] suggest that caffeine induces the hepatic microsomal system, thereby increasing the drug-metabolizing activity of the liver. Since approximately 90 per cent of pentobarbital is metabolized by hepatic transformation, its fate in the body may be markedly altered in chronic drinkers of beverages containing caffeine.

Medication order, *i.e.*, the order in which the patients received medications, was significant ($P < 0.05$) for Questions 1, 3 and 4. Several factors may have contributed to this finding, particularly the need for a good night's sleep following a restless night due to ingestion of caffeine. Anticipatory effects could also have played a role if patients expected a hypnotic (better night's sleep), having received caffeine (poor night's sleep) the night before.

There are important clinical implications in these data when one considers the possible high incidence of coffee usage concomitant with the administration of nighttime hypnotics. Many patients receive some form of hypnotic during their hospital stay, and a large proportion of these probably drink coffee at mealtime or later in the evening. Minimum standards of clinical practice would require that we be aware of prior ingestion of beverages containing caffeine and increase the dosage of barbiturate accordingly. Since use of any drug is not without hazard, particularly with increasing doses, it might be better medical practice to restrict use of caffeinated beverages before bedtime, or allow coffee substitutes only. Similarly, the intake of caffeine should be controlled when preoperative sedation is given.

There is an important methodological implication in the results of this study. Our method, used to quantify positive effects on sleep of hypnotic drugs, also appears to be sensitive for drugs which have negative effects on sleep. This statement is supported by the fact that the effect of caffeine (interference with sleep) was significant. However, to establish the method as sensitive for evaluating caffeine and other drugs which have negative effects on sleep, it would be necessary to design a study that would show a significant dose response, as well as a significant difference from the effect of a placebo.

This study was done within the framework of the Veterans Administration Cooperative Analgesic Study, in which the principal investigators are: Drs. E. G. Beer, B. J. Ciliberti, R. Defalque, W. H. Forrest, Jr., J. Katz, D. L. Mahler, P. F. Shroff and G. Teutsch. G. Feise and J. Hayden collected the data.

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