Anesthesiology
47:241–247, 1977

Subjective Responses to Six Common Preoperative Medications

W. H. Forrest, Jr., M.D., C. R. Brown, F.F.A.R.A.C.S.,† B. W. Brown, Ph.D.,‡*

Three controlled, double-blind studies of six commonly used preoperative medications were carried out to evaluate their effects on patients' sleepiness, apprehension, restlessness, and confusion, and to determine the incidences of side effects. Separate studies each dealt with two barbiturates, an antihistaminic and a minor tranquilizer, and two narcotic analgesics. In the first study a treatment was pentobarbital, 50 or 150 mg, sodium secobarbital, 50 or 150 mg, or placebo. In the second, a treatment was diazepam, 5, 10, or 15 mg, hydroxyzine, 50, 100, or 150 mg, or placebo. In the third, it was morphine, 5 or 10 mg, meperidine, 50 or 100 mg, or placebo. Each patient received only one treatment; it was randomly assigned and administered intramuscularly 90 minutes before operation. Approximately 30 patients received each treatment. There were 509 subjects in the entire investigation. Subjective responses, scored on a scale of 0 to 9, were obtained 30 and 60 minutes after the injection was administered and were compared with baseline responses obtained before treatment. Independent ratings were also made by a nurse-observer, and an overall evaluation was provided by an anesthesiologist. Interview and medication times were controlled to assure standard measurements throughout all three studies. Five of the six compounds (all but diazepam) increased patients' subjective ratings of sleepiness, and the effects were dose-related. None of the six compounds had any significant effect upon postmedication apprehension as reported by the patients. The only frequently observed side effects, found with all six premedicants, were dry mouth and slurred speech. (Key words: Premedication; Hypnotics, pentobarbital; Hypnotics, secobarbital; Hypnotics, diazepam; Hypnotics, hydroxyzine; Analgesics, narcotic, morphine; Analgesics, narcotic, meperidine; Subjective effects: apprehension; sleepiness; restlessness; confusion.)

REFLECTING on his experience as an anesthesiologist and investigator of pain, Beecher remarked more than 20 years ago that "Empirical procedures firmly entrenched in the habits of good doctors seem to have a vigor and life, not to say immortality, of their own."[1] His words certainly characterize anesthesiologists' approaches to preoperative medication.

Depending upon clinical experience and favorite routine, the anesthesiologist may order a sedative, a tranquilizer, an analgesic, or a vagolytic agent for the patient awaiting a surgical operation. Most often the premedication is a combination of two or more compounds from different pharmacologic groups. Many different drugs are prescribed for patients facing essentially the same type of operation. One reason for the use of many different agents is that there is no general agreement about indications for premedication. Another is that most clinical investigations of efficacies of specific drugs have lacked both definition and persuasiveness, whether they have been based on objective measures or patients' subjective responses.

While it is generally accepted that patient apprehension is a major factor that should be controlled in the preoperative period,[2] there is no standard procedure for evaluating it. Objective measures, such as visual evoked responses,[3] catecholamine excretion,[4] blood pressure, pulse, and respiration,[5] have been utilized as surrogates for sedation and apprehension, but the results have been difficult to correlate with clinical behavior. Subjective measures have also been employed, based upon direct questioning of the patient.[1,6]

Very few studies of premedicant drugs are methodologically sound. Almost without exception they have utilized arbitrarily chosen dosages determined from common clinical practice. Frequently the compounds compared came from different pharmacologic groups and were tested at only one dose. Many times, combinations of two or more drugs were compared without knowledge of their individual effects. Little or no effort was expended to establish the sensitivity of the method—to demonstrate the ability of the method to distinguish the test compound(s) from placebo, or high and low doses of the same compound from each other—or to estimate the potency of a test compound relative to a standard drug in the same pharmacologic group.

The purposes of the studies described here were 1) to evaluate the sensitivities of subjective methods for determining efficacies of premedicant drugs; 2) to gain knowledge about commonly used premedicant drugs for future comparisons with new compounds; 3) to develop information about dose–response relationships as a foundation for future premedicant drug-interaction studies; 4) to develop an ongoing program for evaluating new methods of studying premedicants. Three groups of frequently used premedicants—sedatives, "minor tranquilizers," and analgesics—were studied in three separate studies. Each was a randomized double-blind study, and each compound was studied at at least two dose levels, in the clinical range of safety. Medications were adminis-

* Associate Professor of Anesthesia, Stanford University School of Medicine, Stanford, California.

† Assistant Professor of Anesthesia, Stanford University School of Medicine, Stanford, California.

‡ Professor and Head, Division of Biostatistics, Department of Family, Community and Preventive Medicine, Stanford University, Stanford, California.

Accepted for publication April 22, 1977. Supported by research funds from Pfizer Laboratories.

Address reprint requests to Dr. Forrest: Department of Anesthesiology, Stanford University School of Medicine, Stanford, California 94305.

TABLE 1. Patient Distribution by Type or Location of Operation for All Three Studies

Type or Location of Operation	Percentage of Patients (n = 509)
Spine and knee	31
Uterus and/or adnexa	25
Stomach and large intestine	10
Spleen	8
Breast	6
Diagnostic	5
Plastic	4
Prostate	3
Great vessels	3
Kidney	2
Other	3

tered intramuscularly 90 minutes prior to operation and evaluations of apprehension, sleepiness, confusion and restlessness were made.

Method

Patient Selection

All subjects were adult patients at Stanford University Hospital. They had been screened to be sure they would be able to tolerate the test medications; did not have any major organ system disease except the condition that required surgical treatment and were otherwise in good health; and would be able to communicate with the nurse-observer. Consents of the patient, surgeon, and anesthesiologist were obtained for each subject.

Five hundred and nine patients took part in the investigation—149 in the barbiturate study, 210 in the study of diazepam and hydroxyzine, and 150 in the narcotic analgesic study. Of the 509, 63 per cent were women and 37 per cent were men. The mean age of all patients was 40 years. There were no significant differences among treatment groups with regard to age, height, or weight. There was very nearly equal distribution of patients in the treatment groups. Fourteen of the groups had 30 patients each, while two had 29 patients and one had 31. The proportions of male subjects in individual groups ranged from 20 per cent (one group) to 50 per cent (two groups). Table 1 shows the percentage distribution of patients by type or location of operation.

Treatments

Each subject received a single intramuscular injection at 6 AM on the day of operation. All treatments were assigned randomly and administered in identical syringes. A special nurse, other than the nurse-observer, prepared the syringes, which were marked with the study case number only. There were 17 treatment groups. In the first study, treatment was pentobarbital, 50 or 150 mg, secobarbital, 50 or 150 mg, or placebo (lactose). In the second study, treatment was diazepam, 5, 10, or 15 mg, hydroxyzine, 50, 100, or 150 mg, or placebo. In the third study, treatment was morphine, 5 or 10 mg, meperidine, 50 or 100 mg, or placebo.

All patients received pentobarbital, 100 mg, orally, at 10 PM on the night before operation, and no other medication was administered after 6:30 PM that evening.

Data Collection and Analysis

The data were obtained by a nurse-observer trained to interview patients for their subjective responses to medication. Each patient was visited the night preceding the operation. The study was described and an informed consent was signed when the patient agreed to participate in the study. The nurse-observer described the questions to be asked in the interviews the following morning.

Just before 6 AM on the day of operation, the nurse-observer interviewed the patient, obtaining the patient's own estimate of his/her degree of sleepiness, apprehension, confusion, and restlessness. The nurse-observer also recorded the presence and extent of headache, dizziness, nausea, sweating, vomiting, dry mouth, and slurred speech. These 11 items, each scored on a scale of 0 (none) to 9 (most severe), became the baseline data for examining the effect of premedication.

It should be noted here that the questions asked of the patient were always presented in the same way and in the same order. In the orientation session of the preceding evening, the patient had been told that a rating, from zero to nine, would be expected in answer to each query, and certain points on the scale had been described verbally to provide some anchoring of the scale across patients. A ten-point scale is certainly more than sufficient in studies of subjective responses such as these, and it causes no problem and does afford finer analysis than a scale with fewer points. Coarser scales may hide real differences, especially when the ends of the scales are not anchored well in orienting the patient. Of course, the randomized, double-blind nature of the studies assures that when a difference is uncovered, whether on a four- or a ten-point scale, it can be taken as real, with the stated statistical risk.

At 6 PM the nurse-observer administered the treatment. At 6:30 AM she returned to the patient's room for a second interview, asking about the same four main effects, the seven specified side effects, and any other side effects noticed by the patient. At 7 AM, after the patient had been transported to the surgical suite

but before entry into the operating room, the nurse-observer interviewed the patient again about the main and side effects.

In addition to obtaining ratings from the patient, the nurse-observer recorded independent ratings of the patient's sleepiness, apprehension, confusion, and restlessness, prior to questioning the patient. In the operating room, the anesthesiologist rated each patient for adequacy of medication and for ease of induction (satisfactory or unsatisfactory).

By admitting no more than two patients to the study each day, and by controlling the movements of patients and hospital personnel, it was possible to standardize the interviewing.

Studies were designed to facilitate comparisons among the commonly used drugs, and standard parallel-line bioassay techniques[7] were employed. When results did not show parallel lines with significant common slope for the two preparations tested in a study, the bioassay potency calculations were not done, and individual treatments were compared with placebo (one-sided t-tests). The data analyzed were changes from baseline (*i.e.*, the score at the first interview subtracted from the score at the 30-minute and 60-minute interviews, post-medication). As a check on the randomization, preliminary analyses were done to assure that the groups were not different at baseline.

Results

Sleepiness

The only response variable for which most of the drugs studied demonstrated any consistent effect was sleepiness. Five of the six drugs (all but diazepam) showed dose responsiveness, with increased sleepiness accompanying an increased dose (fig. 1). Only three of the assays for sleepiness (sedatives at 30 and 60 minutes and analgesics at 60 minutes) satisfy the criteria for validity of a parallel-line bioassay, that is, significant common slope, nonsignificant nonparallelism between individual dose–response curves, and a significant difference between placebo and the pooled mean for active treatments. These valid assays indicate that pentobarbital, 75 mg, produces approximately the same preoperative sedation as secobarbital, 150 mg, in 30 minutes and secobarbital, 100 mg, at one hour. For the analgesics, at one hour meperidine, 80 mg, produces the same preoperative sedation as 10 mg morphine. For the analgesics at one-half hour, there was a trend toward dose responsiveness, but the common slope was not significant ($P > 0.5$). However, meperidine, 100 mg, was significantly different from placebo ($P < 0.01$). Neither the one-half nor the one-hour assays of diazepam and hydroxyzine were valid

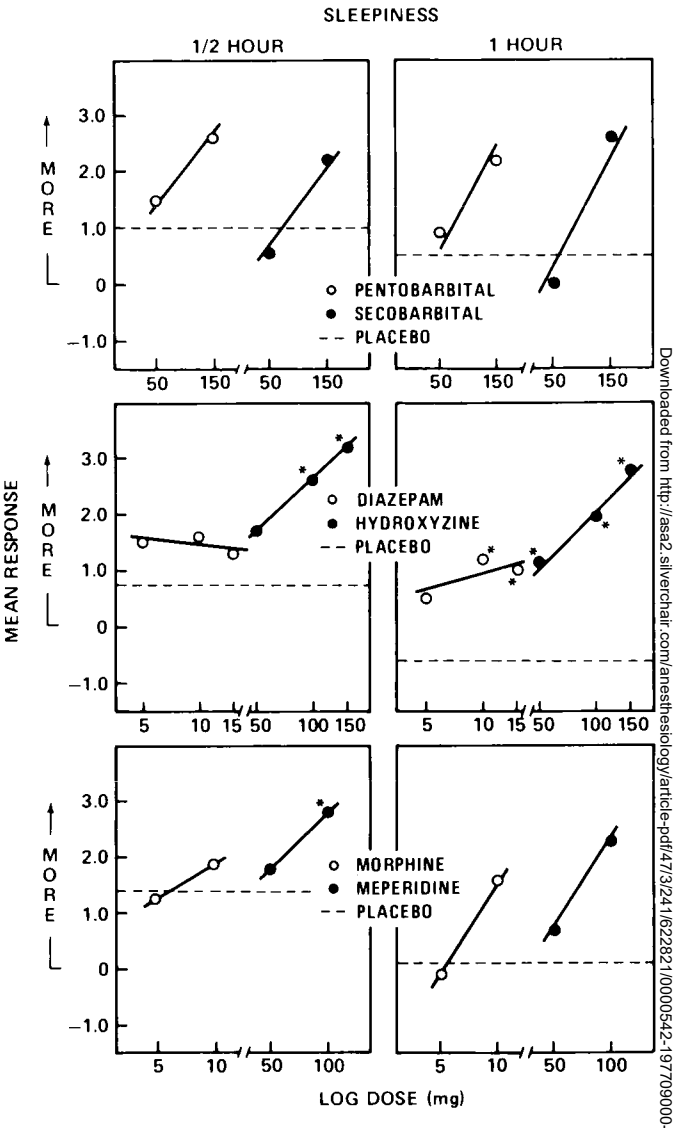

FIG. 1. Mean patient sleepiness scores at 30 and 60 minutes, plotted as differences from baseline (pretreatment). Dose–response curves are drawn parallel for the three assays that are valid, sedatives at one-half and one hour, and analgesics at one hour. For the remaining nonvalid assays the dose–response curves are drawn as the best representation of the treatment points for each drug. In these nonvalid bioassays, treatments significantly different from placebo ($P < 0.01$) are marked with asterisks. Negative scores indicate less sleepiness than pretreatment baseline.

because of the lack of dose responsiveness with diazepam. All of the hydroxyzine treatments except 50 mg at one-half hour and two of the diazepam treatments (10 and 15 mg at one hour) were significantly different from placebo ($P < 0.01$), and there was a significant slope for hydroxyzine—that is, 150 mg was significantly different from 50 mg ($P < 0.01$) at one hour.

In each study the nurse's evaluation of sleepiness paralleled those of the patients.

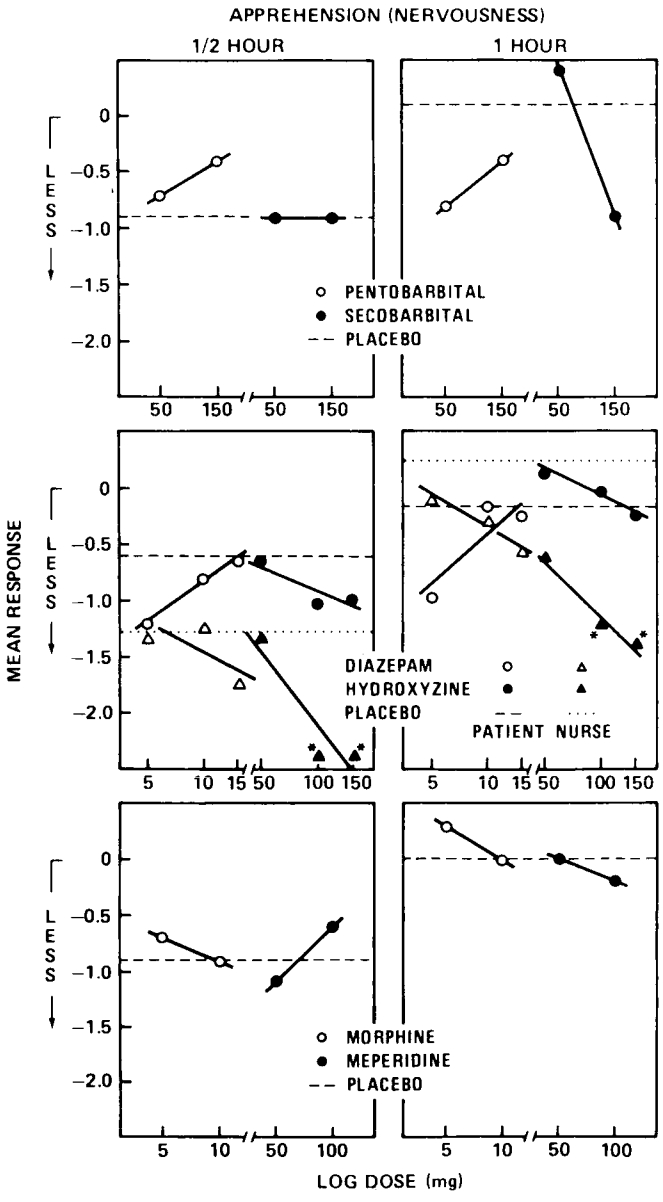

FIG. 2. Mean patient and nurse scores at 30 and 60 minutes, plotted as differences from baseline (pretreatment) for apprehension (nervousness). Nurses' ratings are shown because they are strikingly different from patient scores. All assays are nonvalid. Treatments significantly different from placebo ($P < 0.01$) are marked with asterisks. Negative scores indicate less apprehension than pretreatment baseline.

APPREHENSION

There was no valid assay for this variable, and the striking finding was that none of the drugs at any dose had a significant effect ($P < 0.01$) upon apprehension (fig. 2) relative to placebo as reported by the patient.

In each study patients who received a placebo had higher apprehension scores in the operating suite than half an hour earlier in their rooms. More apprehension in the later interview was also reported by most of the groups receiving non-placebo drugs.

The nurse's ratings for apprehension resembled the patients' responses for two of the three studies. In the study of hydroxyzine and diazepam, however, her ratings for both observation times showed decreased apprehension with increasing doses of diazepam and hydroxyzine, but neither of the slopes was statistically significant. There were significant effects ($P < 0.01$) with all hydroxyzine treatments relative to placebo for both observation times, except for the 50-mg dose at one-half and one hour.

CONFUSION AND RESTLESSNESS

No significant effect ($P < 0.01$) could be demonstrated for any drug evaluated with regard to these variables.

ANESTHESIOLOGISTS' RATINGS

Table 2 summarizes anesthesiologists' ratings of all 17 treatments for ease of induction and the adequacy of medication. Little effort was made to standardize these ratings or insure completeness. It was felt that the randomization and blindfold nature of the studies would minimize bias in the comparisons across treatment groups and, beyond that, it would be useful to have the clinical judgments of the anesthesiologists relatively undisturbed by any effort to change, define, or standardize. In the opinion of the anesthesiologists, placebo was a reasonably satisfactory premedicant.

SIDE EFFECTS

The two most frequent side effects at one hour in all three studies were dry mouth and slurred speech (table 3). The incidences of dry mouth ranged from 26 to 87 per cent among the 17 treatment groups, showed a trend toward dose reponsiveness for all drugs except pentobarbital, and were significantly different from placebo ($P < 0.01$) for all analgesic treatments except morphine, 5 mg. Slurred speech was reported 10 to 57 per cent of the time among the treatments and was significantly different from placebo ($P < 0.01$) for meperidine, 100 mg. There was a suggestion of dose responsiveness for hydroxyzine and meperidine.

Perhaps the most surprising finding was that nausea occurred no more frequently with the analgesics, where it is usually a common side effect, than with placebo. On the other hand, sweatiness, another effect often ascribed to analgesics, was most prominent with the analgesics and significantly different from placebo ($P < 0.01$) for meperidine, 100 mg. No patient reported vomiting. For all side effects the half-hour data

TABLE 2. Ratings by Anesthesiologists for Adequacy of Medication and Ease of Induction

	Sedative Study					Minor Tranquilizer Study							Analgesic Study				
	Pentobarbital		Secobarbital		Placebo	Diazepam			Hydroxyzine			Placebo	Morphine		Meperidine		Placebo
	50 mg (n = 30)*	150 mg (n = 29)	50 mg (n = 29)	150 mg (n = 30)	(n = 31)	5 mg (n = 30)	10 mg (n = 30)	15 mg (n = 30)	50 mg (n = 30)	100 mg (n = 30)	150 mg (n = 30)	(n = 30)	5 mg (n = 30)	10 mg (n = 30)	50 mg (n = 30)	100 mg (n = 30)	(n = 30)
Ease of induction																	
Satisfactory	93†	79	83	67	87	73	80	93	90	83	80	80	83	90	80	83	87
Unsatisfactory	3	0	0	13	3	6	3	3	0	3	3	6	6	0	0	3	10
No rating	4	21	17	20	10	21	17	4	10	14	17	14	11	10	20	14	3
Adequacy of medication																	
Satisfactory	67	48	45	60	45	63	43	53	60	63	57	37	48	60	40	63	63
Unsatisfactory	17	28	48	27	29	17	33	27	33	13	23	40	37	33	57	27	30
No rating	16	24	7	17	26	20	24	20	7	24	20	23	15	7	3	10	7

* Number of patients.

† The percentage of patients in each treatment group who received the rating.

TABLE 3. Incidence of Side Effects* One Hour after Medication

	Sedative Study					Minor Tranquilizer Study							Analgesic Study				
	Pentobarbital		Secobarbital		Placebo	Diazepam			Hydroxyzine			Placebo	Morphine		Meperidine		Placebo
	50 mg (n = 30)†	150 mg (n = 29)	50 mg (n = 29)	150 mg (n = 30)	(n = 31)	5 mg (n = 30)	10 mg (n = 30)	15 mg (n = 30)	50 mg (n = 30)	10 mg (n = 30)	150 mg (n = 30)	(n = 30)	5 mg (n = 30)	10 mg (n = 30)	50 mg (n = 30)	100 mg (n = 30)	(n = 30)
Dry mouth	30‡	28	34	47	26	30	37	37	50	37	47	27	77	83§	83§	87§	50
Slurred speech	20	38	21	43	23	10	30	20	27	30	37	23	33	33	33	57§	17
Headache	13	7	7	10	13	10	7	3	13	0	7	0	7	17	0	7	13
Dizzy	10	10	3	13	6	3	13	13	3	3	13	3	13	17	17	23	13
Nauseated	7	7	7	10	10	3	0	7	3	0	3	10	3	10	20	3	17
Sweaty	13	7	10	7	3	0	20	7	0	17	3	17	23	27	7	33§	7
Hungry	0	3	3	7	0	0	3	7	0	0	0	3	10	10	0	0	7
Relaxed	0	3	0	7	3	10	7	20	3	7	17	3	10	30§	30§	20	7
Euphoric	3	0	0	10	0	0	13	10	0	3	3	7	0	0	0	10	0
Cold	7	0	0	0	3	10	0	0	7	13	3	0	0	7	0	0	3
Visual disturbance	7	10	3	7	0	0	0	0	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* Side effects were tallied when severity was greater than baseline (pretreatment).

† Number of patients.

‡ The percentage of patients in each treatment group who reported the effect.

§ Significantly different from placebo control group for that study ($P < 0.01$), by chi-squared test.

showed the same general trends, but with lower incidence rates.

Only ten of the 509 patients (2 per cent) complained of severe pain at the site of injection. Four of these had received hydroxyzine, 100 mg; two each received pentobarbital, 150 mg, or diazepam, 15 mg; one each was given hydroxyzine, 150 mg, and morphine, 10 mg. Twenty-four per cent of the subjects had slight pain at the injection sight, and 74 per cent reported no pain at all.

Discussion

The findings regarding drug-induced sleepiness are consistent with what is known about these compounds. Sedation is the primary effect of the barbiturates. It is also a major side effect of the narcotic analgesics and hydroxyzine, an antihistamine. In contrast, sedation is not a principal effect of diazepam except at higher doses[8] or during chronic administration, where this is a recognized side effect.

Although we would expect greater sedation at one hour than at 30 minutes, based on pharmacokinetic data, our results do not support this expectation. Patients who received medications other than placebo were about equally sedated at the 30- and 60-minute interviews. This probably reflects the more wakeful environment of the second interview, which was conducted just outside the operating room, while the first was carried out in the quiet of the patient's room. The responses of patients given placebo support this interpretation, for they reported less sedation at the second interview than at the first in all three studies.

The results for apprehension conflict with many anesthesiologists' clinical impressions and with the findings in the literature that these drugs are effective for the reduction of preoperative apprehension. One could explain these differences by assuming that our method of measuring apprehension is not sensitive. One might ask, though, whether a medication given to allay apprehension, yet not producing significant effects detectable by the patient in a carefully controlled study, can be achieving any clinical effect, even if a more sensitive method were to reveal a difference. Furthermore, our data suggest that the method for measuring the patients' apprehension has some sensitivity, since patients who received placebo were significantly ($P < 0.05$) more nervous or apprehensive according to their own appraisals at the time of their second postmedication interview—as the operation itself became imminent. Ofcourse, one cannot rule out the possibility that both the patient and the nurse expected greater apprehension at the second interview and that the results were influenced by this expectation.

Further support for our negative results comes from the work of Conner *et al.*[9] which strongly suggests (although indirectly) that blood levels of barbiturates higher than those used in our study reduce preoperative apprehension. These investigators administered pentobarbital, 50 and 100 mg, and lorazepam, 2 and 4 mg, *intravenously* and established a significant ($P < 0.05$) common slope for the subjective response of apprehension 30 minutes after injection, using much the same method employed by us. Much larger intramuscular doses than those administered in our study would presumably be necessary to obtain similar blood levels of pentobarbital at 30 minutes.

The inability of all these drugs to allay apprehension (when given intramuscularly in the doses used) is least surprising for the barbiturates, since they are presumably prescribed for their soporific effects.[10] Also, narcotic analgesics are not purported to be anxiolytic, although they may have euphoric effects in pain-free subjects.[11] But of course one of the principal claims for hydroxyzine and diazepam is that as premedicants they have a calming or anxiolytic effect.

At the time we first analyzed our results we were at a loss to explain the consistent failure of diazepam to reduce apprehension, because of the many claims made for this effect. Subsequently, Hillestad *et al.*[12] reported that when diazepam is administered intramuscularly it is not rapidly absorbed. Accordingly, one would expect little change from placebo in the drug's effect upon apprehension within one hour.

It is puzzling to us that both the nurse-observer and the anesthesiologists so often rated diazepam and hydroxyzine as having positive effects when the patients did not rate them that way. This did not happen with the other drugs. In figure 2, for example, the patients' responses suggested that they were feeling more apprehensive with diazepam, but the nurse-observers' scores tended to indicate the patients appeared less apprehensive as the dose increased. And with hydroxyzine, the nurse-observer's scores reached significance, indicating less apprehension, while the patient scores were not significantly different from placebo. The anesthesiologists' ratings for the effect of premedication showed the greatest differences from placebo with diazepam and hydroxyzine, again suggesting they "recognized" the patient was receiving an active drug (table 2).

Can it be that these drugs produce a certain effect that can be detected by experienced observers, even though the patient himself is experiencing a different subjective reaction at the time? If so, this might explain the disparities between our results and the findings of those previous investigators who depended almost exclusively on observer evaluations rather than patient responses. And if this effect were viewed as a positive response to the drug, that might also explain

the extreme popularity of these drugs with physicians who prescribe them so widely.

Other differences in methodology, besides the use of patient ratings rather than observer scores, might also contribute to the marked contrast between our findings and those of previous investigators. For example, Forrest *et al.*[13] and Epstein and Lasagna[14] have shown that drowsiness, sleepiness, and other sedative effects can be measured the morning after the administration of many nighttime hypnotics. Failure to control for such a variable could have a marked impact on the results of an experimental study dealing with preoperative medication.

We found that anesthesiologists rated all treatments, including placebo, as very satisfactory for ease of induction. This probably reflects the fact that modern-day anesthesiology has available so many potent induction agents that premedication actually exerts very little influence over induction itself.

We did not attempt to allocate treatments in order to control for differences among patients' emotional states, for variations in subjects' emotional lability, or for differences among anesthesiologists in the impact they have on patients' emotional states. The scores we analyzed were adjusted for patient condition prior to medication, however, and we hoped this would at least partially control for each patient's anxiety level and the anesthesiologist's influence on that anxiety.

We would recommend that all future studies of premedicants utilize methodology that determines the patients' own responses to treatment. We question whether studies that depend exclusively on the evaluation of an outside observer without measuring patients' subjective reactions can produce reliable and useful conclusions.

In addition to sedation, we chose to measure the variables apprehension, confusion, and restlessness because they are patient reactions to the immediate prospect of surgery that the anesthesiologist seeks to control by giving premedication. We found little in our investigation to suggest that any of the six widely used premedicants when administered alone had more than minimal clinical effect on these variables. Recognizing that many anesthesiologists use a polypharmaceutical approach when premedicating, we acknowledge that in combination these drugs may have a beneficial premedication effect. Further carefully controlled studies, however, will be required to confirm or deny the efficacies of combinations of these treatments.

The authors thank the patients, anesthesiologists, and surgeons who, through their participation, made this study possible. They also acknowledge Barbara Arnoldussen, R.N., the nurse-observer on this project, for her excellent work, and Dr. J. W. Bellville for his invaluable contribution during the planning of the study.

References

1. Beecher HK: Measurement of subjective responses: Quantitative effects of drugs. New York, Oxford University Press, 1959
2. Norris W: The quantitative assessment of premedication. Br J Anaesth 41:778–784, 1969
3. Corssen G, Domino EF: Visually evoked responses in man: A method for measuring cerebral effects of preanesthetic medication. ANESTHESIOLOGY 25:330–341, 1964
4. Martinez LR, Euler C von, Norlander OP: The sedative effect of premedication as measured by catecholamine excretion. Br J Anaesth 38:780–786, 1966
5. Nisbet HIA, Norris W: Objective measurement of sedation II: a simple scoring system. Br J Anaesth 35:618–622, 1963
6. Cohen EN, Beecher HK: Narcotics in preanesthetic medication: A controlled study. JAMA 147:1664–1668, 1951
7. Finney DJ: Parallel line assay. Statistical Method in Biological Assay. New York, Hafner Publishing Co., 1964 pp 99–136
8. Byck R: Drugs and the treatment of psychiatric disorder, The Pharmacological Basis of Therapeutics. Fifth edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1975, pp 190–191
9. Conner JT, Parson N, Katz RL, et al: Evaluation of lorazepam and pentobarbital as surgical premedicants. Clin Pharmacol Ther 19:24–29 1976
10. Stewart CH: Hypnotics and sedatives, the barbiturates, The Pharmacological Basis of Therapeutics. Fifth edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1975, pp 106–107
11. Jaffe JH, Martin WR: Narcotic analgesics and antagonists, The Pharmacological Basis of Therapeutics. Fifth edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1975, pp 247–250
12. Hillestad L, Hansen T, Melsom H, et al: Diazepam metabolism in normal man: I. Serum concentrations and clinical effects after intravenous, intramuscular and oral administration. Clin Pharmacol Ther 16:479–484, 1974
13. Forrest WH Jr, Bellville JW, Brown BW Jr: Methodologic considerations of the evaluation of hypnotics in man: A biologic assay of pentobarbital and secobarbital. J Clin Pharmacol 11:357–366, 1971
14. Epstein LC, Lasagna L: A comparison of the effects of orally administered barbiturate salts and barbiturate acids on human psychomotor performance. J Pharmacol Exp Ther 164:433–441, 1968