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COMPARISON OF MEPROBAMATE, PENTOBARBITAL, AND PLACEBO AS PREANESTHETIC MEDICATION FOR REGIONAL PROCEDURES

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DESPITE the variety of preanesthetic medications available, it would appear that no one of them is completely satisfactory.[1-5] Since all have undesirable side effects, and since there is lack of agreement as to what is desirable in preanesthetic medicants, disagreement exists as to which is the best.[1-5] It would, therefore, seem desirable to carefully examine any drug which appears to promise something more than those drugs currently in use as preanesthetic medicants.

The tranquilizer, meprobamate (Miltown, Equinal), is a recent discovery. Berger in 1951 first described its structure and anticonvulsant actions,[6] and in 1954 published an elaborate study of its pharmacological properties in various animals.[7] This drug was reported to eliminate sham rage in monkeys, and convert normally hostile monkeys to docile, gentle animals. It appeared to have muscle relaxing properties in dose ranges which did not depress ventilation in these animals. No ganglionic blockade was found, and little cortical depression was seen. The blood pressure in animals was only slightly affected.

Many of the reports on the use of meprobamate in man have included clinical impressions or uncontrolled observations. The overwhelming majority of these reports have enthusiastically praised its ataractic properties. More closely controlled studies are less dramatic, but, in general, support claims for meprobamate as a tranquilizer.[8-11] One dissension might be noted: Koteen reported that he could find no difference between the ataractic properties of a placebo and of meprobamate in tension states.[12]

So far, there has been no report of the use of meprobamate as a preanesthetic medication, although Rushia described its use the night before surgery.[13]

It would seem, from the clinical and laboratory reports, that meprobamate possesses properties useful for preanesthetic medication. As a result, we undertook the task of comparing meprobamate, pentobarbital, and placebo as preanesthetic medicants for patients to whom regional anesthetics were administered (infiltration, nerve block, epidural, or spinal anesthesia).

METHODS

Drugs. Identical bottles containing seven or eight identical capsules (identical in appearance in each bottle and between all bottles) were prepared. All capsules within any one bottle contained the same material. Each capsule was filled with either meprobamate 400 mg., or pentobarbital 40 mg., or a placebo of lactose. No one prescribing, giving, or receiving a capsule knew the specific contents,

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although the physicians and nurses knew it was one of the three materials listed above. The patient had no knowledge of what was in the capsule, except that he might be told it was a mild sedative that would help him relax.

Dosage and Schedule. Three separate oral administrations of capsules from a single container were made to each patient: the first immediately after the preoperative visit of the anesthetist in the afternoon of the day before surgery; the second, at bedtime of the day before surgery; and, the third, one hour before the anticipated time for the administration of the anesthetic. The first dose always consisted of one capsule and was used to rule out any idiosyncrasy or drug reaction. No such reaction was encountered. The second administration consisted of one or two capsules. The third consisted of one, two, three, or four capsules. The variations in dosage were determined partially by age and partially by weight (table 1). The series was also divided into two relatively equal groups of patients; the first receiving the lower dosage of drugs, the second receiving the higher dosage of drugs (table 1). Thus, the minimum preoperative medication was placebo, or pentobarbital 40 mg., or meprobamate 400 mg. The maximum preoperative medication was placebo, or pentobarbital 160 mg., or meprobamate 1600 mg.

TABLE 1

LOW DOSAGE SCHEDULE

Age	Less than 125 pounds		Greater than 125 pounds	
	h.s.	Pre-operative	h.s.	Pre-operative
16–45	2 capsules	2 capsules	2 capsules	3 capsules
45–60	1 capsule	1 capsule	2 capsules	2 capsules
Over 60	1 capsule	1 capsule	1 capsule	1 capsule

HIGH DOSAGE SCHEDULE

Age	Less than 125 pounds		Greater than 125 pounds	
	h.s.	Pre-operative	h.s.	Pre-operative
16–45	2 capsules	3 capsules	2 capsules	4 capsules
45–60	2 capsules	2 capsules	2 capsules	3 capsules
Over 60	1 capsule	1 capsule	2 capsules	2 capsules

Personnel. Observations were made mainly by first and second year residents in anesthesia. A few observations were made by the anesthesia staff, by surgical residents on the anesthesia service, and by an occasional intern on the anesthesia service. In all cases, the physician who saw the patient the afternoon before surgery also saw him before, during, and following the administration of the anesthetic.

Subjects. Patients in the general hospital population of the State University of Iowa Hospitals, or of the United States Veterans Administration Hospital, Iowa City, Iowa, who were to undergo surgery for which a regional anesthetic was to be administered were used in the study. In general, these were older male patients upon whom procedures such as transurethral resections, amputations, herniorraphies, or hemorrhoidectomies were performed. The patients were usually indigent, although no attempt was made to exclude private patients. None were informed that a study was being undertaken. Excluded from the study were psychotic patients, patients unable to communicate, patients who were seen by one investigator on the preoperative visit, but whose anesthetic was administered by another investigator, patients for emergency procedures, and patients for whom the records were incomplete.

The patients were divided into three groups. These were: (1) the young, which included (arbitrarily) all patients under 60, (2) the old, which included all patients over 60 except for (3) the senile, which included all patients having some mild to severe mental impairment apparently due to diseases of advancing age. Obviously, there is much overlapping between these groups, some patients over 60 being younger in body and spirit than many of those under, and vice versa. But, on the whole, the division into young, old, and senile proved both natural and convenient.

Method of Evaluation. The method of evaluation may be divided into five sections:

(1) The placing of the patient in one of the three groups listed above (young, old, senile). Hereafter, these categories are collectively called "age."

(2) Each patient was evaluated on the preoperative visit as to the degree to which he demonstrated apprehension and demonstrated

cooperation, each being assigned separately into one of three categories: 1 or minimal, 2 or moderate, or, 3 or marked. Thus, the "best" score would be: apprehension, 1 or minimal; and, cooperation, 3 or marked. Before, during, and after the administration of the anesthetic on the following day, the patient was again evaluated by the same investigator as to the degree of apprehension and the degree of cooperation. These were graded in the same manner as before. However, if the investigator felt that one of the qualities (apprehension or cooperation) had changed, but that his original evaluation preoperatively would prevent this from being noted, he was instructed to regrade his original evaluation so this might occur. For example, if a patient on the afternoon of the day before surgery appeared to be quite apprehensive, he would be graded 3, or marked. If, however, on the day of surgery his apprehension increased still further, the original grade of 3 would be demoted to 2, or moderate, or even 1, or minimal, so that the grade of 3 on the day of surgery would denote his change and the degree of change. Thus, for this particular set of qualities the more important record is that of change rather than of particular degree, although the latter, too, may be of importance, especially the second (that made on the day of surgery). In the actual analysis of the data, the degree of change proved to be of no value, because relatively few changes of more than one step (i.e., minimal to moderate, or moderate to marked) occurred. It was left to the individual investigator to define apprehension and cooperation. This was also true of all other qualities to be determined in the study.

(3) On his arrival in the operating room (after the patient had received his third and final dose of capsules), but before the anesthetic was administered, the patient was asked the following questions: (A) Did you have a good night's sleep? (B) Are you comfortable? (C) Are you worried? The answers were recorded without gradation as yes or no.

(4) During the period in which the patient was in the operating room, he was evaluated as to (A) drowsiness, (B) reaction to painful stimuli (usually a needle), (C) talkativeness, and (D) emesis. As with cooperation and apprehension, these were graded on a scale of 1 to 3, i.e., (1) minimal, (2) moderate, and (3) marked. Nausea was also noted as a yes or no function.

(5) At the end of the procedure, the investigator indicated yes or no, whether or not he felt the premedication had been adequate. In addition to the five subjective measurements made above, the blood pressure taken immediately before the administration of the anesthetic was compared with that taken from the case history.

Although some qualities in some of the data sheets were not recorded, the patient was included in the study unless at any point the quality apprehension or the quality cooperation were not evaluated. Several questions were eliminated from the study as the work progressed because they contributed nothing as instruments for obtaining information. They were the preanesthetic questions to the patient "Are you unusually happy?"; and "Are you unusually sleepy?"; the quality "restlessness," and the quality "episodes of sweating," the postoperative questions: "Do you remember the anesthetic procedure?"; "Was this procedure unpleasant?"; "Do you remember the operative procedure?"; "Was this procedure unpleasant?"

A total of 666 subjects were deemed suitable for analysis. The mean age and ranges for the age groups as well as the numbers of patients in the various categories are detailed in table 2. The number of patients in the various categories who had a fall in blood pressure of at least 25 per cent were examined and no evidence of significant differences among groups was found.

Statistical Method. Each quality was tabulated into the eighteen categories determined by two dose levels, three treatments, and three "ages." Heterogeneity chi squares were calculated by the methods outline in Mather.[14] Each quality was examined for evidence of significant heterogeneity in the eighteen categories together, and then the totals for dose level, treatments, and age groups were tested. With the exception of nausea, the dose levels did not differ and, therefore, with all other qualities, the dose levels were pooled. Usually the effects of treatments were examined separately within the age groups. Other details of the analysis are described in the text.

TABLE 2

NUMBER OF PATIENTS AND AGES WITHIN THE VARIOUS GROUPS

Treatment	Young		Old		Senile	
	N	A	N	A	N	A
Low Dosage Group						
Placebo	32	40.2 (17–59)	43	70.6 (56–83)	24	75.5 (68–91)
Meprobamate	33	43.4 (18–59)	51	74.2 (63–90)	37	75.1 (48–96)
Pentobarbital	34	41.1 (17–60)	42	72.1 (61–96)	38	76.8 (61–96)
High Dosage Group						
Placebo	37	43.1 (16–59)	40	70.4 (58–82)	27	76.3 (60–89)
Meprobamate	36	42.4 (20–60)	43	70.2 (55–87)	46	76.3 (63–86)
Pentobarbital	27	43.4 (17–58)	46	71.3 (60–87)	32	77.0 (62–89)

N = Number of patients.
A = Mean age (and range).

RESULTS

Responses to Questions. See table 3.

(1) Did you have a good night's sleep? In this category, a highly significant difference appeared between those receiving placebo and those receiving meprobamate or pentobarbital ($p < 0.001$). Of those receiving placebo 56.4 per cent felt they had had a good night's sleep, while 81.8 per cent thought so after receiving meprobamate, and 79.3 per cent after receiving pentobarbital. This agrees with the work of Lasagna.[15] No significant differences were found between meprobamate or pentobarbital in any group.

(2) Are you comfortable? No significant differences were found.

(3) Are you worried? A significant difference ($p < 0.01$) was found among the young, old, and senile groups. Within the young group alone, a comparison of placebo versus meprobamate and pentobarbital showed a significant difference ($p < 0.05$), the same comparison in the old and senile groups showed no significant difference. Thus, within the young group, 36.8 per cent of those receiving placebo felt they were worried, but 21.7 per cent felt so after receiving meprobamate, and 25.0 per cent after pentobarbital.

Degree of Apprehension; Change in Apprehension. Table 4 gives the summary of the change in apprehension that occurred following the administration of the drugs. The degree of change is not given, merely the direction. It is to this table (table 4) that the following statistical description applies.

Since a significant difference was found ($p < 0.001$), if the young, old, and senile were compared, each age group was evaluated separately. YOUNG: Significance ($p < 0.01$) occurred when placebo, meprobamate, and pentobarbital were compared. Separate comparisons of placebo versus meprobamate ($p < 0.02$), and placebo versus pentobarbital ($p < 0.01$) also gave significant differences. No difference was found between meprobamate and pentobarbital. The differences that occurred were caused by the increase in apprehension ($p < 0.01$) in the placebo group

TABLE 3

RESPONSES TO QUESTIONS*

Question		Placebo	Meprobamate	Pentobarbital
		Per Cent Yes	Per Cent Yes	Per Cent Yes
Did you have a good night's sleep?	Young	51.6	84.6	76.7
	Old	57.3	82.6	81.6
	Senile	60.4	78.9	78.3
Are you comfortable?	Young	88.3	95.7	91.7
	Old	90.4	91.3	89.7
	Senile	89.7	88.8	85.6
Are you worried?	Young	36.8	21.7	25.0
	Old	21.7	13.3	12.7
	Senile	24.2	23.2	18.8

* The questions were asked following the last administration of capsules but before the inception of the anesthetic procedure. High and low dosage groups are combined.

TABLE 4

CHANGES IN APPREHENSION AND COOPERATION

Type of Change	Placebo						Meprobamate						Pentobarbital					
	Young		Old		Senile		Young		Old		Senile		Young		Old		Senile	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Apprehension																		
Increase	32	46	17	21	8	13	16	23	22	23	11	15	14	23	8	9	15	21
Decrease	8	12	12	14	7	12	15	22	14	15	15	21	18	29	10	11	17	24
No Change	29	42	54	65	44	75	38	55	58	62	47	64	29	48	70	80	38	55
Cooperation																		
Increase	6	9	16	19	11	19	13	21	11	12	10	14	16	23	8	8	10	14
Decrease	20	29	10	12	7	12	12	20	10	11	13	19	7	10	10	11	13	18
No Change	43	62	57	69	41	69	36	59	67	77	47	67	46	67	77	81	49	68

The figures represent the number (#) or percentage (%) within any group and do not represent the degree of change.

and were not due to decreases in apprehension resulting from the other treatments.

OLD: An examination of the placebo, meprobamate, pentobarbital groups showed that a significant difference existed ($p < 0.01$). No difference was found between placebo and meprobamate, but if placebo and pentobarbital, or meprobamate and pentobarbital were compared, in each case a similar ($p < 0.05$) difference was found, those who received pentobarbital showing less increase in apprehension than those in the other groups.

SENILE: An examination of placebo, meprobamate, and pentobarbital gave no statistically significant difference.

Degree of Cooperation; Change in Cooperation. Table 4 gives the summary of the changes in cooperation that occurred. The degree of change is not given, merely the direction. Although a comparison of young, old, and senile groups revealed no statistically significant differences, the treatments were compared within age groups. There was a significant difference among the treatments ($p < 0.05$) in the young, but no difference was found in either of the remaining age groups. In the young, when comparison was made between placebo and meprobamate plus pentobarbital, the difference was found to be significant ($p < 0.01$). No significant difference was found between pentobarbital and meprobamate. With the drugs more patients became more cooperative and fewer became less cooperative than with placebo.

Appraisal of Various Qualities (drowsiness, reaction to painful stimuli, talkativeness, emesis). The above qualities were scored on a 1 (minimal), 2 (moderate), and 3 (marked) basis. Because the third group (marked) contained relatively few representatives in all cases, the groups 2 and 3 were combined and then compared to group (table 5).

TABLE 5

TABULATION OF THE INDIVIDUAL QUALITIES OF DROWSINESS AND TALKATIVENESS*

	Drowsiness				Talkativeness			
	Minimal		Moderate or Marked		Minimal		Moderate or Marked	
	#	%	#	%	#	%	#	%
Placebo								
Young	64	93	5	7	36	55	30	45
Old	72	87	11	13	57	70	24	30
Senile	47	82	10	18	36	61	23	39
Meprobamate								
Young	50	72	19	28	29	42	40	58
Old	70	71	29	29	57	62	35	38
Senile	58	81	14	19	38	52	35	48
Pentobarbital								
Young	33	56	26	44	31	53	28	47
Old	63	72	25	28	47	56	37	44
Senile	42	60	28	40	41	59	29	41

* The figures represent the number (#) or percentage (%) of individuals within each group.

TABLE 6

TABULATIONS OF THOSE COMPLAINING OR NOT COMPLAINING OF NAUSEA

	Placebo		Meprobamate		Pentobarbital	
	Yes	No	Yes	No	Yes	No
Low Dosage Group						
Young	8	20	4	25	6	26
Old	8	31	11	38	4	36
Senile	3	20	7	27	4	32
TOTALS	19	71	22	90	14	94
High Dosage Group						
Young	6	28	5	30	4	22
Old	4	23	4	34	4	40
Senile	2	32	3	31	2	27
TOTALS	12	83	12	95	10	89

DROWSINESS: The age groups did not differ; however, a significant difference was found between placebo, meprobamate, and pentobarbital ($p < 0.001$). A significant difference ($p < 0.02$) was also found between meprobamate and pentobarbital, the latter drug being associated with greater drowsiness, both drugs giving greater drowsiness than placebo.

REACTION TO PAINFUL STIMULI: No statistically significant differences were found at any point under this quality.

TALKATIVENESS: If the young, old, and senile were compared, a difference ($p < 0.05$) was seen. This was most apparent between the young and old ($p < 0.01$), no difference being found between the young and senile. No difference was found in a comparison of placebo, meprobamate and pentobarbital within the young or the old or the senile.

EMESIS: No statistical analysis was done because of the low incidence.

NAUSEA: The raw data for this group appear in table 6. A significant difference was found when the high and low dosage groups were compared ($p < 0.02$). In no other comparison of groups did this occur. The effect of increasing the dose of placebo could not be distinguished from the effect achieved by the increased dosage of the other drugs.

Adequacy. Table 7 presents the responses from the anesthetists to the question, "Was the premedication adequate?" Although no differences were found between old and senile, a significant difference ($p < 0.05$) was found if the old and senile were combined and compared with the young. A comparison of placebo and meprobamate within the young showed that meprobamate was adjudged adequate significantly ($p < 0.001$) more often. Similarly, pentobarbital was more frequently adjudged adequate than placebo ($p < 0.01$) in the young, but no significant difference was found between meprobamate and pentobarbital. No difference was found if the treatments were compared within the old plus senile.

Cross Comparisons. Many of the qualities which are evaluated are vague and variable in individual definition. One of the most vague, yet most important, as far as the anesthetist is concerned, is the definition of adequacy. Was the premedication adequate? An attempt was made, therefore, to relate the quality of adequacy to other qualities determined in the study. The following is the result:

(1) Relationship between adequacy and the degree of apprehension as determined on the

TABLE 7

DATA, COMBINING HIGH AND LOW DOSAGE GROUPS, OBTAINED FROM THE ANESTHETIST IN ANSWER TO THE QUESTION: "WAS THE PREMEDICATION ADEQUATE?"

	Young			Old			Senile		
	Number Yes	Number No	% Yes	Number Yes	Number No	% Yes	Number Yes	Number No	% Yes
Placebo	22	31	41.6	48	18	72.8	31	16	66.0
Meprobamate	46	16	74.2	50	20	71.5	39	16	70.9
Pentobarbital	33	13	71.8	53	14	79.2	36	17	68.0
Totals	101	60	62.8	151	52	74.4	106	49	68.5

day of operation: A significant variation ($p < 0.001$) occurred in the degree of adequacy among the three levels of apprehension, in that adequacy varied inversely with apprehension. It is interesting to note that in categories 1 or 3 (minimal and marked apprehension), the three treatments are indistinguishable (minimal apprehension—87.5 per cent adequate, marked apprehension—20.8 per cent adequate), but in category 2 (moderate apprehension) placebo is less frequently adjudged adequate ($p < 0.05$) (placebo 47 per cent, meprobamate 68 per cent, pentobarbital 70 per cent.

(2) Relationship between adequacy and the degree of cooperation: Again, the degree of adequacy varied significantly among the three levels of cooperation ($p < 0.001$), in that adequacy varied directly with cooperation. In the minimal and moderate categories, the three treatments were indistinguishable (minimal cooperation—50 per cent adequate, moderate cooperation—66 per cent adequate), but in the third category (marked cooperation), meprobamate was significantly more adequate than placebo ($p < 0.001$) or pentobarbital ($p < 0.01$) (placebo 72 per cent, meprobamate 95 per cent, pentobarbital 79 per cent). There was no significant difference found between placebo and pentobarbital.

(3) Relationship between the direction of change of apprehension and adequacy: The degree of adequacy varied significantly ($p < 0.001$) with the type of change in apprehension, in that those who showed an increase in apprehension were deemed less adequate. Within the category of no change, a significant difference ($p < 0.01$) occurred between placebo (74 per cent adequate) and meprobamate (89 per cent adequate), but not between any other grouping (placebo versus pentobarbital [83 per cent adequate], and meprobamate versus pentobarbital). No differences among the treatments were noted in the increased (30 per cent adequate) or decreased (84 per cent adequate) apprehension groups.

(4) Relationship between the direction of change of cooperation and adequacy: The degree of adequacy varied significantly ($p < 0.001$) with the type of change in cooperation, in that a decrease in cooperation was less adequate. Within the category of no change, placebo (67 per cent adequate) versus meprobamate (80 per cent adequate) gave a significant difference ($p < 0.05$), and placebo versus pentobarbital (82 per cent adequate) gave a significant different ($p < 0.01$), in that in each case placebo was less adequate. No difference was found here between meprobamate and pentobarbital. No differences among the treatments were noted in the increased (80 per cent adequate) or decreased (36 per cent adequate) cooperation groups.

(5) Relationship between drowsiness and adequacy: In this comparison, groups 2 and 3 (moderate to marked drowsiness) have been combined because of the smallness of numbers in the last group. There was a significant difference ($p < 0.02$) between the degree of adequacy in the minimally drowsy and the moderately or markedly drowsy (78 per cent adequate), in that the more drowsy patients were adjudged more adequate. Within the minimally drowsy group, meprobamate (71 per cent adequate) and pentobarbital (72 per cent adequate) were more likely to be adjudged adequate ($p < 0.05$ in each case) than placebo (59 per cent adequate). There was no difference between treatments in the category moderate or marked drowsiness.

It seemed possible that the qualities apprehension and cooperation might be judged on the basis of the drowsiness of the patient. Accordingly, the change in apprehension and the change in cooperation were compared with drowsiness.

(1) Apprehension: The patients in drowsiness category 1 more frequently increased in apprehension while those in categories 2 and 3 more frequently decreased in apprehension ($p < 0.02$). The treatments were not significantly different in drowsiness categories 2 and 3 with regard to changes in apprehension. In drowsiness category 1 fewer patients had an increase in apprehension with pentobarbital than with placebo ($p < 0.01$). However, placebo was not different from meprobamate, nor meprobamate from pentobarbital.

(2) Cooperation: The frequency of patients having change in cooperation did not vary among the drowsiness categories. Neither

did the treatments differ with respect to change within the drowsiness categories.

In order to assess the relationship between apprehension and cooperation, the change in apprehension was tabulated against the change in cooperation (increase, decrease, no change for each quality). Relatively rarely did apprehension and cooperation both increase or decrease in an individual patient. If the patients in which apprehension increase—cooperation decrease, apprehension decrease—cooperation increase, and apprehension no change—cooperation no change are considered to represent correlation between these two qualities, and the remaining patients to represent no correlation; no difference is found between treatments, ages, or dose level. Further, correlation between the two qualities was found 60.5 per cent of the time, with a 95 per cent confidence interval of 64–66 per cent. These figures would suggest that the qualities apprehension and cooperation represent separately measurable phenomena under the conditions of this study. However, it may be argued that those patients for whom no change was recorded represent only the lack of discrimination of the method of evaluation and should, therefore, be excluded from consideration. If this is done, there are 86 patients recorded in which apprehension and cooperation moved inversely, and 22 in which these qualities changed in the same direction. Thus, 80 per cent show correlation with 95 per cent confidence intervals of 71–87 per cent.

Discussion

The dose in each capsule of meprobamate (400 mg.) and pentobarbital (40 mg.) was based on an attempt to achieve comparable degrees of drowsiness. This was not achieved, and perhaps the dose of pentobarbital should have been 25–30 mg. per capsule. The indeterminate nature of dose equivalence in this study, therefore, may bias any conclusions relating to the differences between meprobamate and pentobarbital.

The original dose schedule was the one termed "low" dose, and a doubling of this dose was deemed inadvisable in the young patients. Most of the patients in this study were in the weight category of greater than 125 pounds. The dose change for the young was, therefore, relatively small; for the old and senile, a doubling of dose was, in effect, achieved. The lack of effect of dose increase is not surprising in the young. In the old and senile, this lack reinforces the impression of general lack of drug effect with respect to the qualities studied.

In general, meprobamate or pentobarbital prevented an increase in apprehension as viewed by either patient or anesthetist; this effect being most marked in the younger patients, and absent or undiscernible in the senile group. The old group may represent an intermediate between the other two. Interestingly, here the effect of meprobamate and placebo could not be distinguished. Pentobarbital was significantly more effective than either in preventing an increase in apprehension in the old.

Cooperation was affected by meprobamate and pentobarbital in a significant manner only in the young, where a decrease in cooperation was prevented.

Sleep was significantly and favorably affected by the prior administration of either meprobamate or pentobarbital, as compared to placebo.

Both meprobamate and pentobarbital caused an increase in drowsiness, the latter drug also causing a significantly greater degree than the former. No difference in the reaction to painful stimuli could be detected between the treatments. This was interesting in the light of the supposition that the ataractics affect the emotional attitude toward pain. Talkativeness, emesis, and nausea were apparently unaffected by the drugs, although, in the case of nausea, increased dose was followed by decreased incidence; the effect of increasing the dose of placebo, however, being indistinguishable from the effect achieved by the increased dosage of the other drugs.

Both meprobamate and pentobarbital were adjudged more adequate as premedicants than placebo in the young, but no such distinction could be made in the combined senile-old group. No difference was found between meprobamate and pentobarbital.

Over all, the effect of meprobamate and pentobarbital is considered to be a favorable one and is most apparent in the young group. No distinct advantage is seen in the use of one of the drugs as opposed to the other.

The lack of discrimination between active drugs and placebo in the old and senile does

not allow the inference that no treatment is equal in effect to treatment since no control group is present (i.e., no patients received zero capsules). This study does not eliminate the effect of placebo which may or may not be quite significant.

Quite apart from the effect of the drugs themselves, the age of the patient had considerable bearing on the emotional status of the patient and his response to an anxiety producing situation. The younger patients were more anxious preoperatively and tended to become much more so if medication (meprobamate or pentobarbital) was omitted (placebo given). In these patients, cooperation moved inversely with apprehension; those patients who became more apprehensive, tending to become less cooperative. In the old and senile, apprehension was much lower preoperatively than in the young, and, with or without active medication, did not rise appreciably as the operative time approached. Cooperation was similarly unaffected. Cooperation in the senile group was, as expected, the poorest of all groups. Thus, it would appear that from all viewpoints, the young most effectively discriminated between active drug and placebo.

Many of the qualities determined were significantly interrelated. Thus, apprehension, or change in apprehension, was inversely related to the adjudged adequacy of the premedication. Cooperation, or change in cooperation, was directly related to adequacy. Drowsiness was also directly related to adequacy, and inversely related to change in apprehension. Change in cooperation was not significantly related to drowsiness. Apprehension and cooperation were correlated in an inverse fashion.

Summary

A double blind comparison of placebo, meprobamate, and pentobarbital as preanesthetic medicants for regional procedures is presented. The study attempted to determine the effect of each of these treatments on patients' apprehension, cooperation, drowsiness, reaction to painful stimuli, talkativeness, nausea, and emesis. The anesthetist's evaluation of the adequacy of each premedicant was also determined. Either meprobamate or pentobarbital were more effective (as defined in the study) than placebo as premedicants in young patients, but this difference tended to become less in the older age group, and to disappear in the senile group. No significant difference could be found between meprobamate and pentobarbital (in the doses used), with a few unimportant exceptions.

The meprobamate (Miltown) for this study was supplied by Wallace Laboratories.

References

1. Cullen, S. C.: Anesthesia, ed. 5. Chicago, Year Book Publishers, 1957.
2. Dripps, R. D., Eckenhoff, J. E., and Vandam, L. D.: Introduction to Anesthesia. Philadelphia, W. B. Saunders Company, 1957.
3. Lee, J. A.: A Synopsis of Anesthesia, ed. 3. Baltimore, Williams & Wilkins Company, 1955.
4. Evans, Frankis T.: Modern Practice in Anesthesia, ed. 2. New York, Paul B. Hoeber, Inc., 1954.
5. Eckenhoff, J. E., and Helrich, M.: Study of Narcotics and Sedatives for Use in Preanesthetic Medication, J. A. M. A. **167**: 415 (May 24) 1958.
6. Berger, F. M.: Anticonvulsant Activity of Carbamate Esters of Certain 2,2-Disubstituted-1, 3-Propanediols, J. Pharmacol. & Exper. Therap. **104**: 229 (Feb.) 1952.
7. Berger, F. M.: Pharmacological Properties of 2-Methyl-2-m-Propyl-1, 3-Propanediol Dicarbamate (Miltown), New Interneuronal Blocking Agent, J. Pharmacol. & Exper. Therap. **112**: 413 (Dec.) 1954.
8. Greenberg, L. A., Lester, D., Dora, A. J., Greenhaus, R., and Rosenfeld, J.: An Evaluation of Meprobamate in Treatment of Alcoholism, Ann. New York Acad. Sc. **67**: 816 (May 9) 1957.
9. Heller, G. C., Walton, D., and Black, D. A.: Meprobamate in Treatment of Tension States, J. Ment. Sc. **103**: 581 (July) 1957.
10. Hollister, L. E., Stannard, A. N., and Drake, C. F.: Treatment of Anxious Patients with Drugs, Dis. Nerv. System **17**: 289 (Sept.) 1956.
11. Marquis, D. G., *et al.*: Experimental Studies of Behavioral Effects of Meprobamate on Normal Subjects, Ann. New York Acad. Sc. **67**: 701 (May 9) 1957.
12. Koteen, H.: Use of "Double-Blind" Study Investigating the Clinical Merits of New Tranquilizing Agent., Ann. Int. Med. **47**: 978 (Nov.) 1957.
13. Rushia, E. L.: Preliminary Report on Use of Meprobamate for Preanesthetic Sedation, J. M. A. Georgia **46**: 93 (March) 1957.
14. Mather, K.: Statistical Analysis in Biology. New York, Interscience Publishers, Inc., 1947.
15. Lasagna, L.: Study of Hypnotic Drugs in Patients with Chronic Diseases, J. Chronic Dis. **3**: 122 (Feb.) 1956.