A Dose-Effect Study of Preoperative Medication in Children

Herbert Rackow, M.D., and Ernest Salanitre, M.D.

THE report of Cohen and Beecher in 1951 on morphine and pentobarbital [1] reopened the question of the comparative sedative effects of narcotics and barbiturates when used for preanesthesia medication. Since then, there have been several conflicting reports on preoperative sedation in adults [2-4] and in children.[5-8] One important reason for these apparent differences may be the lack of data necessary to yield dose-effect relationships.

The principles of the dose-effect relationship were firmly established by Treven [9] in 1927 and extended by Clark [10] in 1933. Leake [11] has remarked that these principles form the basis of pharmacology as a quantitative science. Other principles, involved in reliability of data, have been discussed by Bellville [12] in an excellent report on the clinical evaluation of a drug effect. The present study is based upon these principles and is a report of the dose-sedative effect relationship in children of three drugs: secobarbital, meperidine, and morphine. These particular drugs were selected because: (1) their long usage in medicine makes their side-effects known and predictable, (2) they are often used as the basis for evaluating the effects of newly developed drugs, and (3) they are the most commonly used preanesthetic drugs in our clinic.

Methods and Case Material

The method of study was designed so that the data obtained could be used to establish dose-effect relationships. This permitted a comparison of drug responses over a wide clinical dose range rather than the comparison of the effect of single or average doses.

The case material consisted of 1,791 children admitted to the various surgical services of the Babies Hospital of the Columbia-Presbyterian Medical Center. The children were distributed among the services as follows: 37 per cent in general surgery including thoracic surgery; 43 per cent in otorhinolaryngology, most of whom were patients for tonsillectomies; 10 per cent in plastic surgery; and 9 per cent in the urological service. No distinction was made between ward and private patients: 45 per cent were ward and 55 per cent were private patients.

The study was limited to children between 10 and 60 pounds of body weight, who were to have elective operations and who were classified as having physical status 1 or 2 according to the classification of the American Society of Anesthesiologists.[13] Patients with pain were excluded from the study.

In order to reduce bias and minimize the effect of known and of unrecognized variables, the following measures were taken:

Double Blind Technique. Neither the patient nor the person evaluating the effect knew which drug, if any, was given.

Random Grouping of Patients. The subjects were grouped on the basis of the last two digits of their hospital unit number. This number is assigned by administrative personnel to consecutive admissions regardless of age and identifies the patient's chart, laboratory tests, roentgenograms, and other special examinations. The last digit of the hospital unit number made an initial division of the subjects into odd and even groups. The penultimate digit further subdivided the odd and even groups into ten subgroups making a total of 20 available groups. Since it had been decided to study 18 categories of premedication, the 20 groups of patients were reduced to 18 by assigning the nineteenth and twentieth groups in rotation to each of the remaining 18.

Association of Subject and Drug Category. The anesthesiologist assigned to administer the anesthetic ordered the preoperative medication according to a schedule which paired a patient

Accepted for publication July 6, 1962. The authors are in the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, and the Anesthesiology Service of the Presbyterian Hospital in the City of New York and Babies Hospital, New York, New York.

group with a medication category (table 1). Neither the personality of the patient nor the contemplated surgical procedure was considered in deciding which drug or dose level was to be used.

Evaluation of the Effects of Medication. The subjects were given the medication intramuscularly approximately one hour prior to the estimated time of induction. They were then brought on a stretcher to the anesthesia room by a nurse or nurse's aide. While on the stretcher and *before* being approached by the anesthesiologist, the child was evaluated by one or the other of the authors according to the following criteria:

Category A—crying, hysterical, or any degree of apprehension, agitation or disorientation. This included any subject not in Category B or C.

Category B—awake and calm.

Category C—asleep with no clinical evidence of respiratory depression.*

Errors. At the end of each day, there was a review of the day's record in order to check for correct weights and doses, proper association of patient group and premedication category, and proper time interval [2] between the giving of the premedication and evaluation (30–90 minutes). Any deviation from the predetermined criteria resulted in elimination of the subject from the study.

Temporal Controls. The study continued until there were approximately 100 subjects † in each of the 18 groups. Subjects for the 18 groups were accumulated at random throughout the period of study. The results of the study were not tabulated or analyzed until the entire series was collected.

The selection of a control group and the determination of the dose levels to be studied were necessarily influenced by a consideration of the safety of the patient. It would have

TABLE 1

Group No.*	Drug	Dose (mg./pound)	N†	A (in per cent of N)	B (in per cent of N)	C (in per cent of N)	P‡
1	(Control)		102	34	63	3	
2	Secobarbital	0.5	91	35	52	13	=.02
3	Secobarbital	1.0	94	22	55	22	<.001
4	Secobarbital	2.0	86	15	40	45	<.001
5	Morphine	.05	107	25	67	7	>.10
6	Morphine	.10	99	24	68	8	>.10
7	Morphine	.15	89	13	75	11	<.001
8	Meperidine	0.5	90	22	76	2	>.10
9	Meperidine	1.0	104	19	68	13	<.01
10	Meperidine	1.5	92	18	71	11	<.01
11	Secobarbital Morphine	.5 .05	104	15	68	16	<.001
12	Secobarbital Morphine	.5 .10	97	10	67	23	<.001
13	Secobarbital Morphine	1.0 .05	96	18	51	31	<.001
14	Secobarbital Morphine	1.0 .10	111	11	56	33	<.001
15	Secobarbital Meperidine	.5 .5	102	21	68	12	<.01
16	Secobarbital Meperidine	.5 1.0	97	18	73	9	<.01
17	Secobarbital Meperidine	1.0 .5	106	25	59	16	<.01
18	Secobarbital Meperidine	1.0 1.0	124	22	55	23	<.001

* All subjects in all groups were given scopolamine in the following dosage:
10–20 pounds—0.1 mg. 36–50 pounds—0.3 mg.
21–35 pounds—0.2 mg. 51–60 pounds—0.4 mg.
† N = number of subjects.
‡ P = compared to group (1) chi-square method.
A = percentage incidence of apprehensive children.
B = percentage incidence of awake and calm children.
C = percentage incidence of sleeping children.

* A fourth, *Category D*, was originally included and defined as: asleep with clinical evidence of respiratory depression such as cyanosis. None of the 1,791 subjects fell into this category.

† Trevan [9] introduced the concept of the LD_{50} of a drug. He calculated that, to determine the LD_{50} with reasonable statistical validity, large numbers of individuals be tested at two dose levels: the lower dose level should show an incidence of death of about 25 per cent (LD_{25}) and the higher dose an incidence of death of about 75 per cent (LD_{75}). Leake[11] suggested that the entire dose-response curve could be determined if three dose levels were tested using 30 individuals at each dose level, and that the dose levels tested be near the LD_5, LD_{50}, and LD_{95}. Because the effect studied in the present report was sedation, which is not as precise a measurement as death, and because the full range of response was expected to be considerably less than from 5 to 95 per cent, it was arbitrarily decided to test more than 30 individuals at each dose level.

been desirable to have an unpremedicated group of patients as controls, but the omission of a belladonna drug was thought to impose an unwarranted risk on the patient. Scopolomine was chosen as a control because it is the most commonly used drying agent in our clinic.

The dose levels of the sedative drugs chosen for the study represented what the authors considered to be: (1) the smallest dose of the particular drug which would give a measurable effect, (2) the largest dose compatible with the safety of the patient, and (3) a moderate dose lying somewhere in between. It was coincidental that the lowest dose levels for each drug fell into the range of doses recommended in several texts on pediatric anesthesia.[14, 15, 16]

Results

Table 1 summarizes the dose schedule for the 18 groups studied and the findings. *N* represents the number of subjects in each group. The columns labeled *A*, *B*, and *C* show the percentage of *N* in each of the three categories: *A*, apprehensive children; *B*, awake and calm children, and *C*, sleeping children. The chi square method was used for statistical analysis. Each "*P*" compares the *A*, *B*, *C* distribution of the group indicated with the control, group 1. The overall effect of secobarbital (groups 2, 3, 4) added to the control medication was to reduce progressively the number of children in category *A* and to increase the number in category *C*. This *double* effect, however, was apparent only at the two higher dose levels. Although the group receiving the lowest dose of secobarbital (group 2) showed a statistically different *A*, *B*, and *C* distribution from the control ($P < .02$), this difference was due to an increase in sleeping children (*C*) and not to a decrease in unsatisfactorily sedated children (*A*). This would indicate a different threshold dose level of secobarbital for each of two functions (wakefulness and anxiety). The lowest dose was insufficient to reduce anxiety, but did increase the incidence of sleep.

Meperidine also showed separate threshold dose levels for each of the two functions (table 1, groups 8, 9, 10). However, contrary to the findings with secobarbital, the lowest dose was sufficient to reduce anxiety but had no effect on sleep.

The dose-effect relationships of the three individually tested drugs, secobarbital, morphine and meperidine, are shown in figures 1 and 2. The doses of all three drugs are represented on the abscissa in logarithmic scale. Figure 1 demonstrates the effect of each drug upon the incidence of apprehension (category *A*). The range of response is similar for all three drugs. At the maximum dose level for

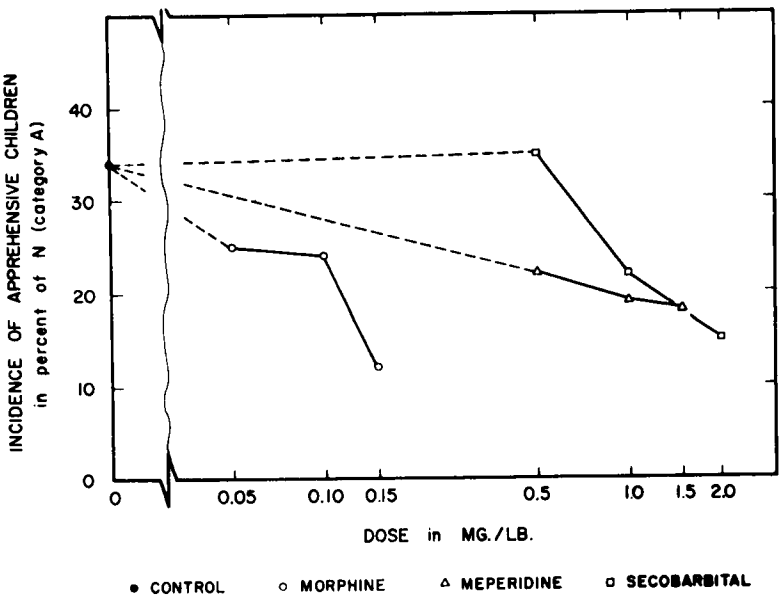

FIG. 1. Dose-effect relationship: incidence of apprehension in children premedicated with secobarbital, meperidine, or morphine.

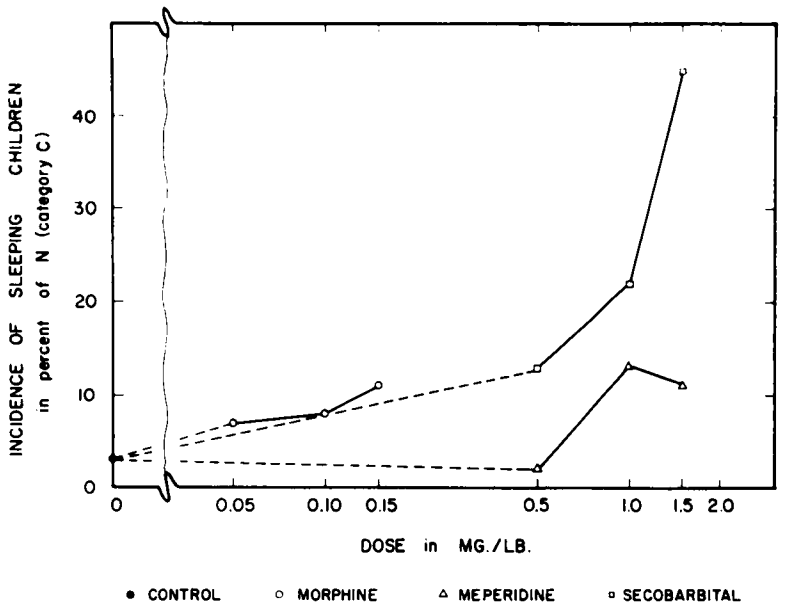

FIG. 2. Dose-effect relationship: incidence of sleep in children premedicated with secobarbital, meperidine, or morphine.

each drug, the control incidence of 34 per cent was reduced to 15, 13 and 18 per cent, respectively.

Figure 2 shows the effect of the drugs upon the incidence of sleeping children (category *C*). The findings here show that the maximum dose of secobarbital (the same dose as in figure 1) increased the control incidence from 3 to 45 per cent, while the maximum doses of morphine and meperidine increased the incidence to 11 and 13 per cent.

Figure 3 presents the dose-effect relationships of combinations of secobarbital and morphine, and of secobarbital and meperidine for category *A*. Figure 4 shows the effects for category *C*. In each figure, the dashed line represents the response to secobarbital alone, in doses indicated on the abscissa, while the solid lines show the responses to secobarbital in the same doses, combined with a fixed amount of narcotic. The break on the left of the abscissa permits the plotting of a zero dose of secobarbital which otherwise could not be shown on semilog paper. For example, in figure 3, the curve *MOR*^{1} shows that 0.05 mg./pound body weight of morphine alone resulted in a 25 per cent incidence of apprehensive children. When this fixed dose was combined with 0.5 mg./pound of secobarbital the incidence fell to 15 per cent. The same dose of morphine combined with 1.0 mg./pound of secobarbital gave an incidence of 18 per cent of apprehensive children.

The technique of randomization was checked to determine the homogeneity of the 18 groups. Using the mean and standard deviation of the weights of each of the 18 groups, the *F* test of variance confirmed this homogeneity ($P > .30$).

Discussion

Doughty [17] correctly implied that there can be no universal answer to the question of which drug or combination of drugs is best for the preoperative medication of children. For one thing, anesthesiologists differ widely in the desired goal of the preoperative medication. Freeman and Bachman [18] prefer a child to arrive in the operating room asleep, but able to open his eyes in response to a mild stimulus. Eckenhoff and Helrich [3] believe that in the adult patient, at least, the optimally sedated patient is awake, alert, yet free of apprehension.

It was not the purpose of this study either to determine which of the preoperative medication objectives was most desirable or to prove the merits of a specific drug or dosage schedule. Our sole aim was to accumulate data from which the sedative effects of three commonly used drugs could be predicted over a wide clinical dose range.

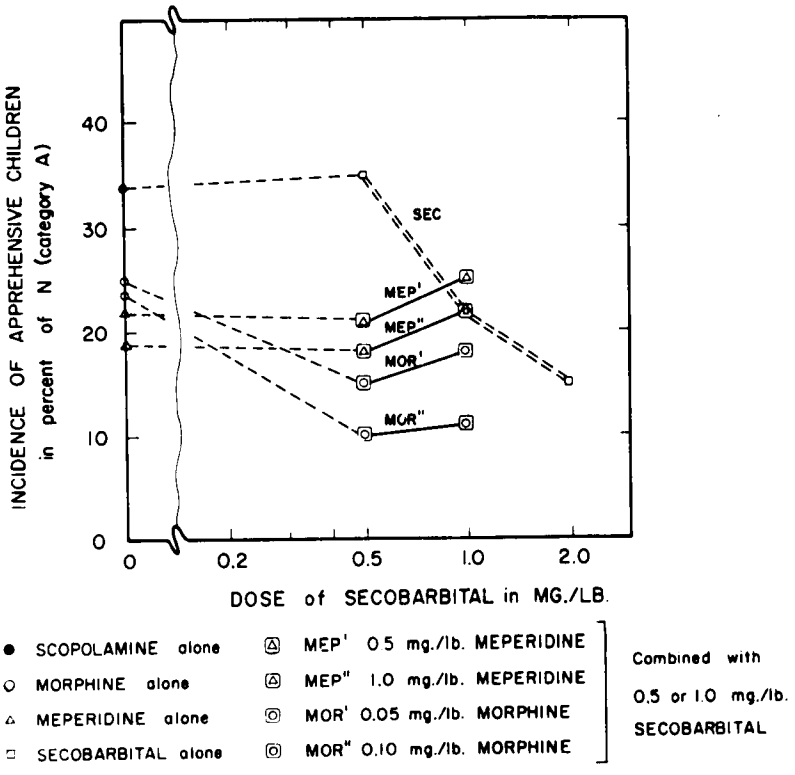

FIG. 3. Dose-effect relationship: incidence of apprehension in children premedicated with secobarbital-morphine and secobarbital-meperidine combinations. The dashed line indicates dose-response for secobarbital alone.

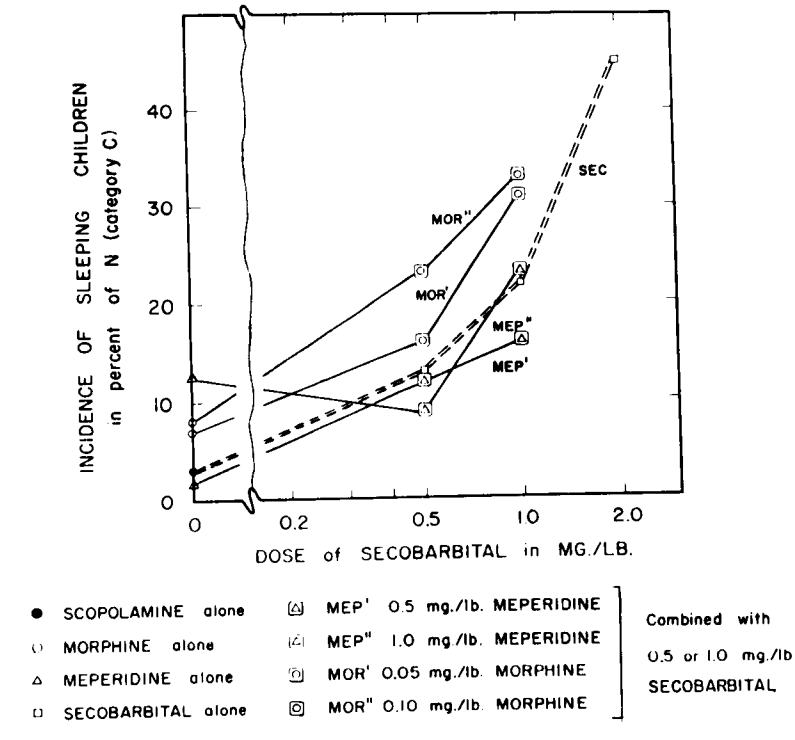

FIG. 4. Dose-effect relationship: incidence of sleep in children premedicated with secobarbital-morphine and secobarbital-meperidine combinations. The dashed line indicates dose-response for secobarbital alone.

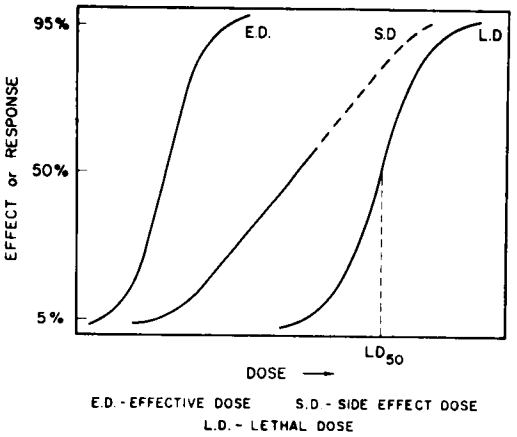

FIG. 5. Theoretical dose-response relationship for incidence of a therapeutic effect, a toxic side-effect, and death.

In a study of sedative effects of preoperative medication in adults, Eckenhoff and Helrich [3] distinguished five mental conditions: (1) alert, (2) drowsy, (3) asleep, (4) carefree, and (5) apprehensive. We believe these conditions represent degrees of two different physiological functions: (1) wakefulness (alert, drowsy or asleep), and (2) anxiety (carefree or apprehensive). Since each may have different central representations, one may speculate that a particular drug may have different effects on each function. This seems to be supported by the findings of Eckenhoff and Helrich, who showed that secobarbital had a significant effect in adults in producing calmness as compared with the control, while narcotics did not have a significant effect in this respect. On the other hand, narcotics were superior to secobarbital in producing sleep, although both were effective. In their study 1 mg. of morphine was equated to 15 mg. of secobarbital and the *average* effects of 5, 7.5 or 10 mg. of morphine per patient were compared to the *average* effects of 75, 115 or 150 mg. of secobarbital per patient. The actual dose given depended upon the judgment of the anesthesiologist.

Cohen and Beecher,[1] however, did not find a significant difference between the effects of morphine and those of pentobarbital. They equated 1 mg. of morphine to 6 mg. of pentobarbital and then compared the effects of 15 mg. of morphine 70 kg. weight of patient to 90 mg. of pentobarbital/70 kg. weight of patient.

The findings of these two studies are not necessarily contradictory since neither absolute nor relative dose levels in the two studies were the same. It is possible that dose differences account for the apparently conflicting findings even more than the fact that one group compared pentobarbital and the other compared secobarbital with narcotics.

In a comparison of drugs, this dependence on dose is eliminated if the dose-response relationship is known. For example, the curve LD in figure 5 represents the lethal dose range for a theoretical drug. The LD_{50} can be obtained from this curve. Similarly, ED represents the effective or therapeutic dose-response curve and SD the dose-effect curve for a particular unwanted side effect. Each side effect could be represented by additional curves. If either the side-effect curve or the lethal dose curve overlap the therapeutic dose range, the drug may be seriously limited in its clinical usefulness, and it may not be possible to use the full range of response.

When two drugs have the same therapeutic range of response, the choice of drug depends only upon relative toxicity. This in turn is determined by the degree of separation between therapeutic dose-response curve and toxic dose-response curves (including the LD curve). On the other hand, if the two drugs have different therapeutic ranges of response, the choice will depend upon the range of response as well as toxicity.

The curves in figure 5 owe their sigmoidal shape to the fact that different subjects require different doses of a drug for a specific effect. If each subject required the same dose for a given effect, *i.e.*, if there were no variation in dose, then the curve would become a vertical straight line at that dose. One can predict from a flat dose-effect curve or from an atypical curve (*i.e.*, not sigmoidal) that there will be a wide variation in dose for any specific response.

The dose-effect relationships in figures 1 and 2 indicate that the barbiturates and narcotics affect anxiety and sleep differently. Figure 1 reveals that in the dose ranges studied, all three agents showed the same range of response for apprehension. On the other hand, figure 2 shows that the *lowest* dose of secobarbital and the *highest* doses of the narcotics

increased the incidence of sleep to about the same degree. The full range of effect of secobarbital was almost four times that of either narcotic.

It is also of significance that in both figures 1 and 2, the secobarbital curves seem to follow the first half of a typical, normal sigmoid dose-effect curve. Both narcotics, however, show skewness (morphine, figure 1, and meperidine, figure 2) and flatness (morphine, figure 2, and merperidine, figure 1). This indicates a large range of variation in the dose of narcotic needed for a specific effect and a small range of variation for secobarbital. It may partly explain the differences in the findings of many investigators on the effects of narcotics in preoperative medication.

The effect resulting from the combination of secobarbital with morphine was different from that of secobarbital with meperidine. Figure 3 shows that 0.5 mg./pound of secobarbital added to either 0.05 or 0.10 mg./pound of morphine (groups 11, 12) reduces the incidence of apprehensive children (category *A*) more than did either drug alone (groups 2, 5, 6). The combination of 1 mg./pound of secobarbital with the same doses of morphine (groups 13, 14) did not produce an additional response; nevertheless, the incidence of apprehension was lower than that resulting from the individual drugs (groups 3, 5, 6). Figure 4 shows that the same combinations had an increased effect on the incidence of sleeping children (category *C*) at all levels tested. There seems to be no question that the secobarbital-morphine combinations produced greater effects in both categories *A* and *C* than those produced by either drug alone.

The combinations of secobarbital and meperidine (groups 15, 16, 17, 18) did not show any increased response over that of the drug giving the higher response when tested alone. In these combinations, the possibility of a negative effect can not be ruled out. A negative effect may also explain the plateau in the dose-effect curves for the secobarbital-morphine combinations in category *A* (groups 13, 14). Beecher [20] has suggested that in the average subject narcotics produce dysphoria rather than euphoria. One may speculate that the negative effect was an expression of this undesirable response. It may also partly explain the skewness and the flatness of the dose-effect curves of both narcotics tested singly in figures 1 and 2.

The response of combinations of drugs, therefore, is not necessarily the sum of the responses of the individual drugs. Since scopolamine was combined with each drug or group of drugs, it too may have contributed to the response of the combination. Nevertheless, when these sedative drugs are used clinically, they are combined with a belladonna drug, and their responses should be studied under these clinical situations. It is possible that had atropine been used instead of scopolamine, or had a different dose of scopolamine been used, the findings might have been different. Marx and Orkin [2] have already suggested that in the adult, scopolamine and meperidine seemed to show a synergistic effect compared to atropine and meperidine. It should be noted that both Cohen and Beecher [1] and Eckenhoff and Helrich [3] used atropine in their studies.

The maximum responses shown in figures 1 and 2 were achieved with the use of high doses of all three drugs. One may expect unwanted side effects to occur at these dose levels, which, therefore, should be reserved for the unusual clinical situation. When used, close nursing supervision will be required. The role of side effects can not be completely evaluated since sufficient dose-effect data on the side effects of each drug tested are not available. However, reliable evidence suggests that narcotics give rise to more undesirable side effects than do the barbiturates.[19]

Harrison and Mayton [21] recommend the use of scopolamine alone for preoperative medication. The results of our data confirm their findings that only about one-third of children so medicated will be unsatisfactorily sedated. The three drugs studied in this report did not provide satisfactory sedation in all children. Even at the highest doses tested, as many as 10 per cent were still apprehensive and more than 50 per cent not asleep. Using medium doses, 20–25 per cent were apprehensive and about 75 per cent were not asleep.

The decision to use preoperative sedatives other than scopolamine and the selection of the dose must be a judgment based upon clinical experience. Such a decision considers the importance of sedation in a particular child, the probability of failure of pro-

ducing sedation, and also the probability of producing undesirable side effects.

If the decision to use preoperative sedatives other than scopolamine alone has been accepted, our data suggest that success will be achieved with increasing frequency as the following schedule is followed:

Group 3: Secobarbital 1.0 mg./pound.
Group 11: Secobarbital 0.5 mg./pound with morphine 0.05 mg./pound.
Group 14: Secobarbital 1.0 mg./pound with morphine 0.10 mg./pound.

Although no data is presented, groups more heavily medicated than this appeared clinically to have an excessive incidence of prolonged sleep and slower induction time. We are presently collecting data to support or refute this impression.

Summary

Data are presented on the dose-effect relationships of secobarbital, morphine, and meperidine. The effects studied were: *A*, incidence of apprehensive children; *B*, incidence of awake and calm children; and *C*, incidence of sleeping children. In the dose range studied for each drug, all three drugs showed a similar response in reducing the incidence of apprehensive children. On the other hand, secobarbital was almost four times as effective as either morphine or meperidine in increasing the incidence of sleeping children. None of the three drugs had any significant effect in increasing the incidence of awake and calm children.

Combinations of secobarbital and morphine showed an increased response over either drug alone in both reducing the incidence of apprehensive children and increasing the incidence of sleeping children. This was not true for combinations of secobarbital and meperidine.

Some problems that have made difficult a comparison of the results of others in the field of preoperative medication have been discussed.

Supported in part by the Health Research Council of the City of New York.

References

1. Cohen, E. N., and Beecher, H. K.: Narcotics in preanesthetic medication, J.A.M.A. **147**: 1664, 1951.
2. Marx, G., and Orkin, L.: Comparison of Demerol, Nembutal, or Benadryl and atropine or scopolamine for premedication, New York J. Med. **59**: 78, 1959.
3. Eckenhoff, J. E., and Helrich, M.: Study of narcotics and sedatives for use in preanesthetic medication, J.A.M.A. **167**: 415, 1958.
4. Adriani, J.: Premedication—an old idea and new drugs, J.A.M.A. **171**: 1086, 1959.
5. Sadove, M. S., and Frye, T. J.: Preoperative sedation and production of quiescent state in children, J.A.M.A. **164**: 1729, 1957.
6. Lundy, J. S.: Amnesia-analgesia for management of children too young to cooperate, J.A.M.A. **166** :453, 1958.
7. Smith, R. M., and Jeffries, M.: Evaluation of sedative agents for preoperative use in children, Anesth. Analg. **38**: 166, 1959.
8. Ament, R., and Mischka, C.: Considerations in the changing management of pediatric anesthesia, New York J. Med. **59**: 3589, 1959.
9. Trevan, J. W.: Statistical Methods for Estimation of Biological Variations in Toxicity Determinations, Proc. Roy. Soc. (Biol.) **101**: 483, 1927.
10. Clark, A. J.: The Mode of Action of Drugs Upon Cells. London, Edward Arnold & Co., 1933.
11. Leake, C. D.: The scientific status of pharmacology, Science **134**: 2069, 1961.
12. Bellville, J. W., Bross, I. D. J., and Howland, W. S.: A method for the clinical evaluation of antiemetic agents, ANESTHESIOLOGY **20**: 753, 1959.
13. Saklad, M.: Grading of patients for surgical procedures, ANESTHESIOLOGY **2**: 281, 1941.
14. Stevens, C. R.: Elements of Pediatric Anesthesia. Springfield, Illinois, Charles C Thomas, Publisher, 1954.
15. Leigh, M. D., and Belton, M. K.: Pediatric Anesthesiology, ed. 2. New York, Macmillan Co., 1960.
16. Smith, R. M.: Anesthesia for Infants and Children. St. Louis, C. V. Mosby & Co., 1959.
17. Doughty, A. G.: Evaluation of premedication in children, Proc. Roy. Soc. Med. **52**: 823, 1959.
18. Freeman, A., and Bachman, L.: Pediatric anesthesia: an evaluation of preoperative medication, Anesth. Analg. **38**: 429, 1959.
19. Eckenhoff, J. E., Helrich, M., Hedge, M. J. D., and Jones, R. E.: Respiratory hazards of opiates and other narcotic analgesics, Surg., Gynec., Obstet. **101**: 701, 1955.
20. Lasagna, L., von Felsinger, J. M., and Beecher, H. K.: Drug induced mood changes in man, J.A.M.A. **157**: 1006, 1955.
21. Harrison, G. G., and Mayton, P.: Pre-anesthetic medication for children—a simplified technique, South Africa Med. J. **31**: 56, 1957.