EFFECT OF *N*-ALLYLNORMORPHINE AND LEVALLORPHAN ON RESPIRATION DURING AND AFTER ETHER ANESTHESIA

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THE usefulness of the so-called antinarcotic drugs, *N*-allylnormorphine (Nalline) and levallorphan (Lorfan), for overcoming the respiratory depression caused by morphine and allied drugs has been established (1, 2). *N*-allylnormorphine is chemically related to morphine; levallorphan (3 hydroxy *N*-allylmorphinan) to methyl morphinan (Dromoran). The drugs do more than act as simple antagonists, as was first believed, and evidence has been presented that they possess some degree of narcotic activity (3). Depression of the central nervous system results instead of stimulation when these drugs are used alone (4). Depression may also occur if large doses are given in attempting to antagonize narcotics (5). They not only are ineffective as antagonists for aliphatic hypnotics, barbiturates, and other non-narcotic drugs, but may even enhance an existing respiratory depression (6). The impression exists that *N*-allylnormorphine causes respiratory depression when used in conjunction with ether. Apparently this belief stems from a statement made by Eckenhoff and his associates (7) in a report on the use of the drug in obstetrics. They comment as follows: "In view of the well-known depressant effect of ether on new-born infants, the interpretation is difficult, but the suggestion is apparent that normorphine [because of its lack of ability to counteract respiratory depression in the newborn] should not be administered to mothers given ether anesthesia." Presumably more has been read into this statement than the authors intended because the belief is prevalent among certain groups of surgeons, obstetricians and occasional users of the drug that *N*-allylnormorphine should not be used with ether in any situation. Adriani and Kerr (8) reported the successful reversal of narcotic depression in a group of surgical patients anesthetized with various inhalational anesthetics, the greater portion of whom were given ether. Enhancement of respiratory depression was not observed. However, in a number of patients receiving ether, the anticipated antinarcotic response did not occur. It was assumed, in these, that the respiratory depression was due to some other cause and not to the narcotic. Enhancement of depression may possibly have been overlooked in these cases since minute volume exchange was not measured and other tests of respiratory function were not done. The greater portion of the three most commonly used gases, cyclopropane, ethylene

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or nitrous oxide, is eliminated within several minutes after discontinuing anesthesia; therefore, untoward effects with these would be unlikely. Ether, on the other hand, is eliminated slowly and remains in detectable quantities in the body for some time after its administration has been terminated. Depression with the combination, therefore, could be possible. In view of the foregoing facts and the accumulating evidence that *N*-allylnormorphine possesses weak narcotic properties, clarification of this question appeared in order. Consequently this study was undertaken.

Methods and Results

In order to have a basis for making comparisons the minute volume exchanges of 45 adult patients undergoing operations with ether were determined. The depth of anesthesia, estimated clinically by the signs of Guedel, was in lower second or upper third plane. The duration of anesthesia ranged from one and one-half to four and one-half hours. The majority of patients studied underwent abdominal operations for cholecystectomy, colectomy, or gastrectomy. Minute volume exchange was determined over a period of two to three minutes using a ventilation meter. Measurements were made as soon as the mask was removed and at ten-minute intervals, three or four times afterwards. All patients studied had been given a narcotic as premedication, usually morphine (10 mg.) or meperidine (75 mg.), together with atropine intramuscularly (0.4 mg.) or scopolamine (0.4 mg.), one and one-half hours prior to anesthesia. The administration of the narcotic was deliberate because it was the object of the study to obtain information which would be clinically applicable. The use of antinarcotics in patients anesthetized with ether who have had no narcotic is unlikely. Anesthesia was induced with nitrous oxide, ethylene, or cyclopropane and maintained with ether-oxygen in a closed system. No barbiturates or muscle relaxants were used.

In 42 of the 45 patients, the minute volume exchange immediately upon termination of anesthesia was higher, by as much as 40 per cent in many cases, than it was ten minutes later. This exaggerated respiratory response disappeared quickly and was no longer apparent after five minutes. This behavior was a typical and consistent finding in all of the control patients studied. The pattern of ventilation for this group is shown graphically in figure 1. Since this same general pattern of ventilation was consistent in all patients it was believed that it could serve as the basis for making comparisons.

The effect of administering *N*-allylnormorphine was then determined. As in the case of the controls, anesthesia was of the same depth and of one and one-half hours or more duration. Ten patients were given the 5 mg.-dose, intravenously five to ten minutes prior to termination of anesthesia. The character of respiration was determined in the same manner as in the controls. There was no change in rate or depth

of respiration. The mask was removed and ventilation determined with the meter. Nine of the 10 patients showed the same respiratory pattern characterized by the initial hyperventilation and the decline to the baseline manifested by the controls. The average minute volume exchange was identical to that of the controls (fig. 1). Fifteen patients were then given 10 mg. of *N*-allylnormorphine intravenously five minutes prior to the termination of anesthesia. Again the respiratory rate and depth remained unchanged. The mask was removed and the ventilation was determined in the same manner as before. The initial exaggeration in breathing followed by a decline characteristic of the controls was again noted in 9 patients. Five did not show a significant initial hyperventilation. Instead, the first reading was the

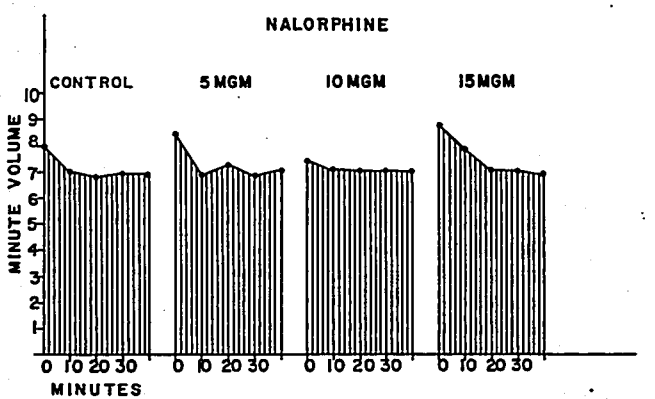

FIG. 1. Average minute volume exchange in 45 control patients compared to the average of 10 patients receiving 5 mg., 15 receiving 10 mg. and 10 receiving 15 mg. *N*-allylnormorphine (Nalline) during ether anesthesia.

same as the subsequent readings. The average minute volume exchange was similar to that of the controls and to that of patients receiving 5 mg. of *N*-allylnormorphine (fig. 1). Fifteen milligrams *N*-allylnormorphine was then given to 10 patients. Again, no change in rate or depth of respiration was apparent after injection of the drug. The mask was removed and the minute volume exchange was determined. Seven showed the identical ventilatory patterns manifested by the controls. Three did not show the initial exaggerated breathing. However, in all of the 3, the minute volume exchange was the same in the subsequent two readings. There was no remarkable variation in the average minute volume exchange between 35 patients who had received the drug and 45 who had not (fig. 1).

The response to carbon dioxide while anesthetic concentrations of ether were being administered was next studied. The ventilation meter was incorporated into the closed circle system, the soda lime absorber was then turned off and endogenous carbon dioxide was allowed to accumulate until the maximal degree of hypernea was obtained. The absorber was then turned on, and the carbon dioxide removed. When the ventilation had reverted to the control level, 15 mg. of *N*-allylnormorphine were administered intravenously. Usually a period of thirty minutes was allowed to elapse from the moment the carbon dioxide was absorbed until the drug was injected. After a period of not less than five and not more than ten minutes, the absorber was again turned off and a hypernea was once again allowed to develop to the point of maximum minute volume exchange. Seven patients undergoing surgical

THE MAXIMUM MINUTE VOLUME EXCHANGE IN LITERS WHICH DEVELOPED IN RESPONSE TO CARBON DIOXIDE, THE TIME REQUIRED TO OBTAIN THIS RESPONSE, AND THE MAXIMUM ELEVATION IN BLOOD PRESSURE DURING ETHER ANESTHESIA BEFORE AND AFTER *N*-ALLYLNORMORPHINE

TABLE 1

Case Number	Dose of *N*-allylnormorphine (mg.)	Minute Volume Exchange Before *N*-allylnormorphine (liters)	Minute Volume Exchange After *N*-allylnormorphine (liters)	Time for Effect Before Drug (minutes)	Time for Effect After Drug (minutes)	Maximum Blood Pressure Before Drug After Carbon Dioxide (mm. Hg)	Maximum Blood Pressure After Drug After Carbon Dioxide (mm. Hg)
1	15	19.6	19.9	10	10	140/110	150/98
2	15	28.0	25.5	6	6	140/100	Same
3	15	20.8	18.2	10	10	140/80	Same
4	15	11.0	9.2	8	13	150/100	160/100
5	15	9.0	9.2	5	4	170/120	160/98
6	15	21.5	20.0	10	10	168/90	160/90
7	15	19.6	22.1	8	13	168/90	

procedures under ether anesthesia were studied in this manner. There was no change in ventilation following the administration of the drug. All the patients responded to carbon dioxide both before and after the drug was given and manifested a notable degree of hyperventilation and an elevation in blood pressure (table 1). The increase in ventilation in 4 patients, however, was slightly less than in the control. In the remaining 3 it was slightly more than the control. When the absorber was turned on and the carbon dioxide removed, after the drug had been given, the minute volume exchange returned to the control values in all 7 patients. At the conclusion of the operation the minute volume exchange showed the same pattern as the controls and the other patients who had received *N*-allylnormorphine (fig. 1). In view of the fact that the maximal ventilation caused by the carbon dioxide, the time for achieving it, and its duration after the absorber was turned on were

alike both before and after the drug was given, it was presumed the carbon dioxide tensions were nearly alike. In order to verify this, carbon dioxide tensions were determined in the inspired gases at the height of the hyperventilation before and after 15 mg. of the drug had been given in 6 patients. The inhaled carbon dioxide concentration in these was 10.2 mm. of mercury before and 9.9 mm. of mercury after *N*-allylnormorphine, 10.8 and 9.9, 10.0 and 10.7, 16.2 and 15.4, 7.7 and 8.1. The times for achieving the maximal response and the maximum value obtained were nearly identical before and after in all six cases.

The responses of levallorphan used in conjunction with ether were similar to those of *N*-allylnormorphine. It is our impression, from clinical use, that both drugs behave similarly as far as antagonizing respiratory depression from narcotics is concerned. We have observed

THE MAXIMUM MINUTE VOLUME EXCHANGE IN LITERS WHICH DEVELOPED IN RESPONSE TO CARBON DIOXIDE, THE TIME REQUIRED TO OBTAIN THE RESPONSE AND THE MAXIMUM ELEVATION IN BLOOD PRESSURE DURING ETHER ANESTHESIA BEFORE AND AFTER LEVALLORPHAN

TABLE 2

Case Number	Minute Volume Exchange Before Levallorphan (liters)	Dose of Levallorphan (mg.)	Minute Volume Exchange After Levallorphan (liters)	Time for Effect Before Drug (minutes)	Time for Effect After Drug (minutes)	Maximum Blood Pressure Before Drug After Carbon Dioxide	Maximum Blood Pressure After Drug After Carbon Dioxide
1	24.3	1.5	25.1	8	8	170/100	190/100
2	26.0	1.5	31.5	12	12	144/95	155/90
3	14.1	2	13.3	9	4	110/70	110/70
4	16.8	1	14.0	7	5	—	110/70
5	25	1.5	23.3	14	10	180/140	190/130
6	5.3	1.0	9.1	4	7	115/90	110/90
7	10.6	1.0	13.0	4	4	150/90	140/90
8	19.4	1.5	17.6	7	7	—	—
9	6.1	1.0	13.3	7	4	—	150/90
10	26.6	1.0	21.5	11	11	—	—

that the reversal of the depression in patients who have inadvertently been given excess morphine may be obtained with as little as 1 mg. of levallorphan. In other words, levallorphan appears to be more potent on a weight for weight basis than *N*-allylnormorphine, perhaps five to ten times as great, in accomplishing narcotic reversal.

The effects of levallorphan upon the response to carbon dioxide were studied in 10 surgical patients given ether using the same procedure described in the foregoing paragraphs. One was given 2 mg., 4 were given 1.5 mg. and five 1 mg. of the drug intravenously. As was the case in the procedure using *N*-allylnormorphine, five to ten minutes were allowed to elapse before the response to carbon dioxide was tested. Seven of 10 patients manifested an increased response to carbon dioxide slightly more than 1 per cent over the control, 2 a decrease of 1

per cent (table 2). In one case in which there was no response to carbon dioxide in the control, the ventilation increased 146 per cent when carbon dioxide was added after the thirty-minute ventilation.

Discussion

It was the primary intent of this study to determine in as direct a manner as possible whether or not respiratory depression of clinical significance develops when ether and *N*-allylnormorphine or levallorphan are used together.

The study was undertaken with the realization that the respiratory response immediately following anesthesia is subject to such uncontrollable variables, as rapidity of emergence, the degree of pain, ether blood level, and other factors, that the data obtained might not be amenable to analysis because of these variables, and thus some other approach to the study might become necessary. However, it was surprising to note the general degree of sameness in respiratory response in each of the individuals in the control series and between various groups of patients receiving the drug. As the study proceeded and the findings appeared to be negative, it was believed that extensive blood gas analysis and other complicated research procedures would yield little data of clinical significance.

The data indicate that doses of 5 to 15 mg. *N*-allylnormorphine used in conjunction with ether in patients given a narcotic premedicant cause no remarkable change in ventilatory pattern as manifested by minute volume exchange, respiratory rate or depth. Respirations of patients who have had or are being given ether continue to be stimulated by carbon dioxide when doses up to 15 mg. are administered intravenously.

The effects of doses larger than 15 mg. *N*-allylnormorphine were not studied because quantities exceeding 10 mg. are usually unnecessary for antagonizing narcotics. We have noted, when using *N*-allylnormorphine as an antagonist, that the respiratory depression caused by narcotics in adults was partially reversed by doses of 5 mg. and that 10 mg. invariably caused a well-defined response. In our experience, when no stimulation appeared after 10 mg. had been administered, larger doses were found to be without effect. Some response is invariably noted when quantities ranging between 5 and 10 mg. are administered if the depression is due to a narcotic. Thus the 15 mg. dose is seldom required and should not be exceeded when no response is obtained with smaller fractions.

Summary

An impression exists among certain clinicians that *N*-allylnormorphine used simultaneously with ether may cause respiratory depression. The minute volume exchanges in a series of surgical patients who were given 5 to 15 mg. *N*-allylnormorphine or 1 to 2 mg. levallorphan during and after ether anesthesia were no different than in 45 control patients

anesthetized with ether who received no drug. Likewise, the response to endogenous carbon dioxide in surgical patients during ether anesthesia was not appreciably altered by either *N*-allylnormorphine or levallorphan administered intravenously in therapeutic doses. In other words, neither drug causes a notable degree of stimulation or depression of respiration when used in patients who have been given a narcotic as premedication and anesthetized with ether.

Merck Sharp & Dohme supplied the *N*-allylnormorphine (Nalline) and Hoffmann-LaRoche, Inc., the levallorphan (Lorfan) used in this study.

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ELEVENTH NEW YORK POSTGRADUATE ASSEMBLY

The Eleventh Postgraduate Assembly of the New York State Society of Anesthesiologists will be held in the Hotel New Yorker, New York City, December 10–14, 1957.

The House of Delegates will meet on December 10.

Scientific Sessions and Round Table Luncheons are scheduled for December 11 and 13.

Hospital Clinics have been arranged in various Hospitals in the New York metropolitan Area for December 12.

The Residents' program will be presented on December 14.