ALPHAPRODINE HYDROCHLORIDE WITH LEVALLORPHAN TARTRATE OR RO 1-7780 POSTOPERATIVELY

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ALTHOUGH Pohl reported on the action of *N*-allylnorcodeine in 1915 (1), the specific antagonists of narcotic-analgesics received no notable attention until the synthesis of *N*-allylnormorphine in 1942 (2). The pharmacology of this drug was soon investigated by several workers (3, 4, 5), and it was introduced into clinical medicine in 1952 by Eckenhoff, Elder and King (6). More recently, other agents which oppose the action of narcotics have been synthesized and evaluated (7, 8). These newer drugs include *l*-3-hydroxy-*N*-allylmorphinan(levallorphan) tartrate,* the early use of which was published in 1952 and 1953 (9, 10), and *l*-3-hydroxy-*N*-propargyl-morphinan tartrate * (Ro 1-7780), a preliminary study of which has been made in this laboratory (11); in the present work these two agents are used in combinations with alphaprodine hydrochloride * in man.

The purpose of this research was to determine the actions of these drugs, when given simultaneously with alphaprodine, over a wide range of ratios of the antagonists to the narcotic. Such investigation was important for two reasons: (*1*) the combined use of either of these antagonists with alphaprodine might have a favorable effect on respiration without altering analgesia, and (*2*) a recent report has indicated that the ratios of narcotic and antagonist, and their doses, may be critical in determining the combined effect, which can vary from depression to stimulation (12).

METHODS

Suitable patients were selected following surgery, experiments being carried out in the usual postoperative environment of the recovery room. Ventilation, blood pressure, pulse, and general responsiveness of the patients were observed at five-minute intervals until they had been stable for three successive readings. Alphaprodine, physiological

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* Generic names without salt designations are used throughout the rest of the paper. Levallorphan is available under the name Lorfan and alphaprodine as Nisentil.

saline, Ro 1-7780, levallorphan, or a combination of alphaprodine with Ro 1-7780 or levallorphan was then injected slowly by vein. The ventilation, blood pressure, pulse, and responsiveness were recorded at 2, 5, 10, 15, 20, 25 and 30 minutes; in some cases later observations were also made at longer intervals. Any unusual manifestations which occurred during the experiments were also noted.

One hundred and seventy patients were initially chosen for the study, but 27 of these were rejected before completion of observations either because they manifested annoyance with the procedure or because consistent control values of minute ventilation could not be obtained. All the patients in the study had received spinal or local anesthesia, and 13 had been given light general anesthesia in addition. No one who had been under deep or prolonged general anesthesia was used. After the first 20 or 30 patients, age or general condition was not considered, but those individuals in poor cardiovascular status, manifested by a systolic blood pressure of less than 90 mm. of mercury or a pulse rate above 120, were not used. Age range was 12 to 81 years, average 48 years; the weight varied from 36 to 109 kg., average 69 kg. All patients had been given medication preoperatively according to the orders of an anesthetist who had no knowledge that they would be used in this study.

Blood pressure was taken by auscultation using an aneroid sphygmomanometer, and radial pulse was counted either just before or just after the observations on respiration. Inspiratory volume was measured for one minute of every five using a Bennett respiratory ventilation meter, and respiratory rate was counted simultaneously. Four to seven such sets of observations were usually required before three successive consistent values (varying by not more than 10 per cent), that were considered to be "normal" ventilation for each patient, were obtained. The drug, drug combination, or indifferent solution (physiological saline) was then injected, usually through an infusion tubing but occasionally by direct venipuncture.

Minute ventilation and respiratory rate were calculated as per cent of the "normal" value for each patient, "normal" being considered 100 per cent. Responsiveness was graded on a scale of *1* to *4*; *1* meaning aroused with difficulty; *2*, aroused with ease; *3*, no change in responsiveness after the medication; and *4*, showing signs of central nervous system stimulation. Since no practical objective method for measuring relief of pain, quantitatively, has been developed, responsiveness was regarded as a measure of analgesia; a change in responsiveness clearly reflects an altered sensibility to any disturbing stimulus.

The drugs and combinations and the number of patients receiving each are indicated in table 1. The dose of alphaprodine was 0.375 or 0.75 mg./kg., Ro 1-7780, 0.0375 or 0.075 mg./kg., levallorphan, 0.075 mg./kg., and saline solution, 1.5 or 2.0 cc.; these were the control medica-

tions. Combinations of Ro 1-7780 or levallorphan with alphaprodine (0.375 or 0.75 mg./kg.) were given in ratios of the antagonist to analgesic of 1:100 to 1:5 in order to determine the combined effects. (All ratios are expressed as antagonist to narcotic throughout this paper.) The various drugs and combinations were given in random order except at the beginning of the experiment, when the useful range of antagonist dosage was not known, and at the end, when each group was filled out to a certain number of patients. The very high doses of alphaprodine (1.0, 1.5 and 2.0 mg./kg.) were also added at the end of the experiment.

At the beginning of the experiment patients were told, "We are going to study your breathing for a while." If they asked questions,

TABLE 1

NUMBERS OF PATIENTS RECEIVING VARIOUS DRUGS AND DRUG COMBINATIONS

Alphaprodine (mg./kg.)	Ratio: Ro-1-7780 to Alphaprodine, or Dose Ro-1-7780	Number of Patients	Alphaprodine (mg./kg.)	Ratios: Levallorphan to Alphaprodine, or Dose Levallorphan or Saline	Number of Patients
0.375	0	9	0.375	1:50	6
	1:50	6		1:25	6
	1:25	6	0.75	1:100	6
	1:10	6		1:50	6
	1:5	6		1:37.5	6
0.75	0	9		1:25	6
	1:100	6		1:10	6
	1:50	6		1:5	6
	1:25	6	1.0	1:25	3
	1:10	6	1.5	1:25	3
			2.0	1:25	3
0	Ro-1-7780:0.0375 *or* 0.075 mg./kg.	8	0	levallorphan (0.075 mg./kg.)	6
			0	physiological saline (1.5 or 2.0 ml.)	6

they were told, "We are measuring the breathing of a lot of patients to see how it goes after operation." After a satisfactory "normal" value of minute ventilation had been obtained, the drug or combination was administered by a different person from the one making the observations. The patients had no real knowledge of the nature or purpose of the work.

After a number of experiments had been carried out, it was found that respiration returned to essentially "normal" values within less than a half hour after drug administration. Once this had been established, observations were continued for only thirty minutes after the medication had been given. Following this period, the patient was

kept under close observation in the recovery room for an additional thirty to sixty minutes, measurements being made at 15 minute intervals in some cases. No remarkable changes were seen during this postexperimental interval.

Results

The study clearly indicated that within a critical range of ratios the addition of progressively increasing proportions of the antagonists to narcotic was accompanied by an increasing protection against respiratory depression while effective "analgesia" (as manifested by altered

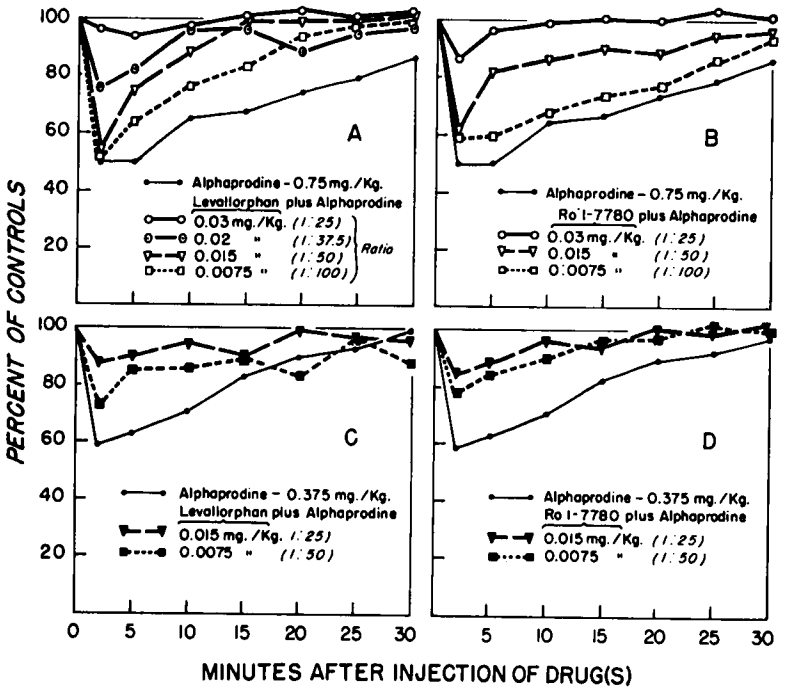

FIG. 1 (A, B, C and D). Minute inspiratory ventilation following alphaprodine alone or combined with levallorphan or Ro-1-7780.

responsiveness †) persisted. A ratio was found at which no respiratory depression was observed. Increasing the antagonist above this ratio produced no further change in respiration, but side effects increased markedly. No appreciable alterations in pulse or blood pressure were noted after any of the drugs or combinations used. The actions of the narcotic alone and of the antagonist-narcotic combinations which were considered most important are summarized in figures 1, 2 and 3 and in table 2. Pertinent statistical data appear in tables 3,

† "Analgesia" is used to refer to a state of diminished responsiveness, which indicates decreased sensibility to *all* stimuli, painful or otherwise.

4 and 5. Because of the quantity and complexity of the results, the extreme doses and ratios are not presented in the tables and figures.

The 6 subjects who received saline showed very small changes (less than 10 per cent, if any) in respiratory rate or minute ventilation from their "normal" values during the period of observation. The minor fluctuations seen were neither consistent nor statistically significant. These patients remained quiet and cooperative for the most part, but none of them fell asleep.

After alphaprodine alone, 0.375 mg./kg., the average minute ventilation fell to 60 per cent of normal (fig. 1, C and D, table 3) within two

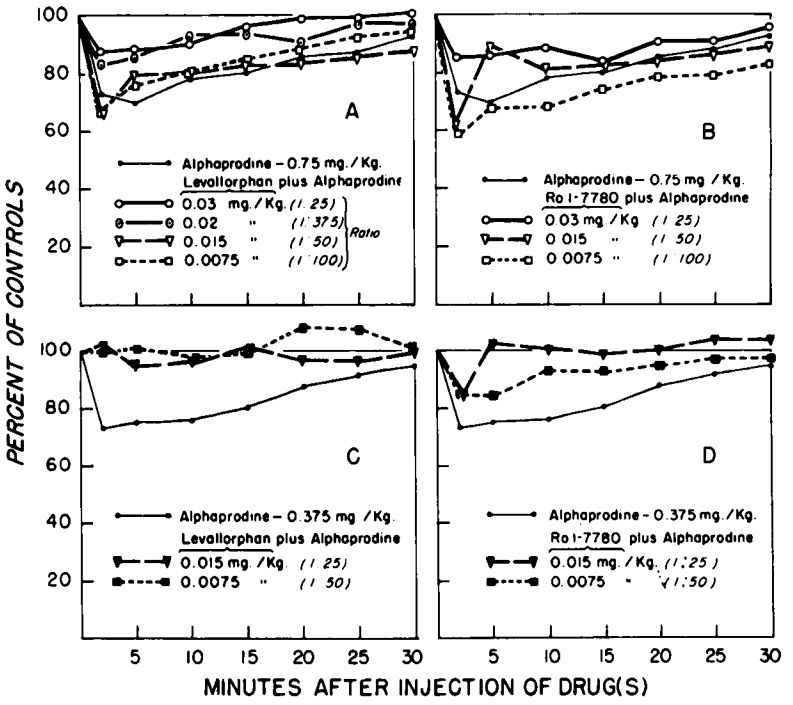

FIG. 2 (A, B, C and D). Respiratory rate following alphaprodine alone or combined with levallorphan or Ro-1-7780.

minutes but returned nearly to the normal within twenty minutes. Minute ventilation was significantly lower after this medication than after saline for the first fifteen minutes (table 4). This dose of alphaprodine produced some decrease in respiratory rate (fig. 2, C and D), which was occasionally significant, while tidal volume (fig. 3, C and D) was not significantly altered; a larger series would probably establish significance for one or both of these factors. As to responsiveness, the patients were drowsy or lightly asleep during the entire observation period (table 2).

Alphaprodine, 0.75 mg./kg. (fig. 1, A and B, and table 3) produced an average fall in minute ventilation to 50 per cent of the normal in the first 2 minutes. The ventilation remained significantly lower than

that after saline or after the 0.375 mg./kg. dose of the drug for twenty-five to thirty minutes (table 4). The higher dose of narcotic thus produced a more severe and prolonged depression of ventilation than the lower dose. The respiratory rate did not differ significantly from that following the low dose of alphaprodine but was significantly lower than that in the saline controls during the first ten minutes (fig. 2, A and B). Tidal volume, again variable, did not change significantly. Responsiveness was depressed to a point where most of the patients were asleep but aroused with ease (table 2), and they did not react appreciably to the experimental manipulations.

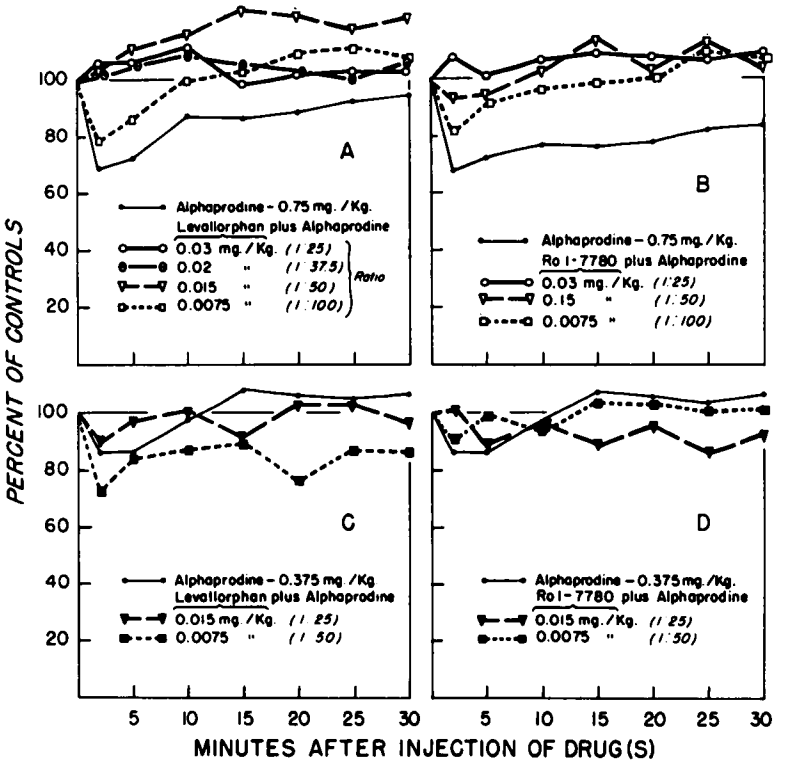

FIG. 3 (A, B, C and D). Tidal volume following alphaprodine alone or combined with levallorphan or Ro-1-7780.

As to the antagonists by themselves, neither levallorphan nor Ro 1-7780 had any effect on respiration. Although levallorphan (0.075 mg./kg.) had only a slight effect on responsiveness, Ro 1-7780 produced depression to a point where the patients were drowsy or lightly asleep (table 2).

These observations on the effects of saline solution, alphaprodine, and the antagonists afforded a basis for evaluation of the combined effect of alphaprodine and the antagonists given together.

The combined effect of Ro 1-7780 with alphaprodine in ratios of 1:100, 1:50, and 1:25 is shown in figures 1, 2, and 3 (B and D) and in

tables 2 and 3; the statistical findings concerning ventilation are detailed in tables 4 and 5. When Ro 1-7780 was administered in the ratios of 1:50 and 1:25 to alphaprodine at a dose of 0.75 mg./kg., the inspiratory ventilation was significantly greater than that following the narcotic alone; but the 1:100 combination produced no significant change in ventilation. Respiratory rate was not affected by adding the an-

TABLE 2

AVERAGE GENERAL RESPONSIVENESS* AFTER THE VARIOUS MEDICATIONS

Alphaprodine (mg./kg.)	Dose of Antagonist or Salt Solution, or Ratio Antagonist to Alphaprodine	Responsiveness* Time in Minutes After Drug Administration						
		2	5	10	15	20	25	30
0	Physiological salt solution 1.5 or 2.0 ml.	3.0	3.0	3.0	3.0	3.0	3.0	3.0
	Levallorphan							
0	Levallorphan: 0.075 mg./kg.	3.0	3.0	2.5†	2.5	2.5	2.5	2.5
0.75	0	2.0	2.0	2.0	2.0	1.5	1.5	1.5
	1:100	1.5†	1.5	1.5	1.5	1.5	1.5	1.5
	1:50	1.5	1.5	1.5	1.5	1.5	2.0	2.0
	1:37.5	2.0	2.0	2.0	2.0	2.0	2.0	2.0
	1:25	2.5	2.5	2.5	2.5	2.5	3.0	3.0
0.375	0	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	1:50	2.5	2.0	2.0	2.0	2.0	2.0	2.0
	1:25	2.5	2.0	2.0	2.0	2.0	2.0	2.5
	Ro-1-7780							
0	Ro-1-7780:0.0375 or 0.075 mg./kg.	2.5	2.0	2.0	2.0	2.0	2.5	2.5
0.75	1:100	2.0	1.5	1.5	1.5	1.5	2.0	2.0
	1:50	2.0	2.0	1.5	1.5	1.5	2.0	2.0
	1:25	2.0	2.0	2.0	2.0	2.0	2.0	2.0
0.375	1:50	2.5	2.0	2.0	2.0	2.0	2.0	2.5
	1:25	2.5	2.0	1.5	1.5	2.0	2.0	2.5

* General responsiveness evaluated by objective observation of patients:
4 = excitement. 2 = asleep and easily aroused.
3 = same as before drug administration. 1 = asleep and aroused with difficulty.
† Values of 1.5 and 2.5 were arrived at by averaging the individual results and rounding off to the nearest 0.5 unit.

tagonist, while tidal volume was increased significantly at both the 1:25 and the 1:50 ratios, compared to the effects of alphaprodine alone (0.75 mg./kg.), over a period of twenty-five to thirty minutes. General responsiveness remained in the range of *1.5* to *2.5* for all ratios of the combined medication.

The effects of combining levallorphan with alphaprodine, 0.75

mg./kg., in the ratios of 1:25, 1:37.5, 1:50, and 1:100 are shown in figures 1, 2, and 3 (A and C) and in tables 2 and 3, and their significance in tables 4 and 5. At the higher ratios of antagonist (1:25, 1:37.5) the ventilation did not differ from that following physiological saline, while it was significantly different from the narcotic alone. Respiratory

TABLE 3

MEANS AND STANDARD ERRORS OF OBSERVATIONS ON INSPIRATORY MINUTE VENTILATION

Alphaprodine (mg./kg.)	Dose of Antagonist or Salt Solution, or Ratio Antagonist to Alphaprodine	Means and Standard Errors Time in Minutes After Drug Administration						
		2	5	10	15	20	25	30
0	Physiological salt solution 1.5 or 2.0 ml.	98±2	97±3	101±3	96±4	98±3	95±5	94±5
	Levallorphan							
0	Levallorphan: 0.075 mg./kg.	90±9	94±3	98±6	98±4	97±2	102±2	98±2
0.75	0	50±6	50±3	65±4	67±3	74±4	79±5	86±4
	1:100	52±3	64±3	76±5	83±7	93±5	96±4	99±4
	1:50	53±4	75±6	88±6	99±2	98±2	97±3	99±3
	1:37.5	76±10	82±7	96±6	96±8	88±4	94±3	97±2
	1:25	96±5	94±4	97±2	100±2	102±1	100±1	100±1
0.375	0	59±4	63±6	71±8	83±8	90±6	93±6	99±2
	1:50	73±11	86±9	86±9	88±8	84±8	95±6	88±7
	1:25	89±5	92±4	94±4	88±4	98±6	96±3	97±4
	Ro-1-7780							
0	Ro-1-7780:0.0375 or 0.075 mg./kg.	98±4	97±2	100±2	100±4	98±3	101±3	99±1
0.75	1:100	59±4	60±4	68±4	74±4	77±4	86±5	93±4
	1:50	57±8	82±4	86±5	90±5	88±6	94±4	95±3
	1:25	92±4	92±4	98±4	95±4	100±3	99±3	105±5
0.375	1:50	78±4	85±4	91±4	96±2	98±1	102±1	98±1
	1:25	85±2	89±3	96±5	95±5	100±4	99±4	102±4

rate was not much affected by combining the narcotic and antagonist (fig. 2, A and C). Although tidal volume increased significantly with the 1:50 ratio, the over-all effect of the added levallorphan on respiratory rate and tidal volume was not consistent. Following the various combinations of alphaprodine with levallorphan the patients remained drowsy; but responsiveness was in the range of *2* to *2.5* for the 1:25 and higher ratios, while for the narcotic alone or with lower antagonist ratios, responsiveness averaged between *1.5* and *2.0*.

Combinations of levallorphan and alphaprodine in ratios of 1:5, 1:10, and 1:25 were equally effective in preventing respiratory de-

TABLE 4

STATISTICAL COMPARISON* OF THE EFFECTS OF ALPHAPRODINE AND SALINE TO THE EFFECTS OF ALPHAPRODINE-ANTAGONIST COMBINATIONS ON INSPIRATORY MINUTE VENTILATION

Dose (mg./kg.)	Ratio Antagonist to Alphaprodine	Probability of Difference, or Significance Time in Minutes After Drug Administration						
		2	5	10	15	20	25	30
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.75 mg./kg.						
0.375	0	N.S.†	<0.01	N.S.	<0.01	<0.01	<0.01	<0.01
0.75	1:100	N.S.	<0.01	N.S.	<0.05	<0.05	<0.02	<0.02
	1:50	N.S.	<0.01	<0.01	<0.01	<0.01	<0.02	<0.05
	1:37.5	<0.05	<0.01	<0.01	<0.01	<0.05	<0.05	N.S.
	1:25	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.05
Alphaprodine with Ro-1-7780								
0.75	1:100	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	1:50	N.S.	<0.01	<0.01	<0.01	<0.05	<0.05	N.S.I
	1:25	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.02
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.375 mg./kg.						
0.375	1:50	N.S.	<0.05	N.S.	N.S.	N.S.	N.S.	N.S.
	1:25	<0.01	<0.01	<0.02	N.S.	N.S.	N.S.	N.S.
Alphaprodine with Ro-1-7780								
0.375	1:50	<0.01	<0.01	<0.05	N.S.	N.S.	N.S.	N.S.
	1:25	<0.01	<0.01	<0.02	N.S.	N.S.	N.S.	N.S.
Alphaprodine with Levallorphan		Compared to: Saline Solution 1.5 or 2 cc.						
0.75	0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N.S.
	1:100	<0.01	<0.01	<0.01	N.S.	N.S.	N.S.	N.S.
	1:50	<0.01	<0.01	N.S.	N.S.	N.S.	N.S.	N.S.
	1:37.5	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	1:25	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
0.375	0	<0.01	<0.01	<0.01	<0.02	N.S.	N.S.	N.S.
	1:50	<0.02	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	1:25	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Alphaprodine with Ro-1-7780								
0.75	1:100	<0.01	<0.01	<0.01	<0.01	<0.01	N.S.	N.S.
	1:50	<0.01	<0.01	<0.01	N.S.	N.S.	N.S.	N.S.
	1:25	<0.02	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
0.375	1:50	<0.01	<0.02	<0.02	N.S.	N.S.	N.S.	N.S.
	1:25	<0.01	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

* By "*t*" test of Student. † N.S. = not significant.

pression; but the 1:10 and 1:5 medications were followed by a high incidence of side effects, usually dizziness, nausea, or a sensation of falling, or both. The two higher ratios were less effective than 1:25 in producing analgesia; they did not uniformly diminish responsiveness.

When it became apparent that the 1:25 ratio of levallorphan to alphaprodine in combined administration did not produce the respiratory depression seen with the narcotic alone, the total dose of narcotic was increased to 1, 1.5, and 2.0 mg./kg., combined with levallorphan at

TABLE 5

STATISTICAL COMPARISON* OF INSPIRATORY MINUTE VENTILATION AFTER VARIOUS COMBINATIONS OF ALPHAPRODINE WITH ANTAGONISTS

Dose (mg./kg.)	Ratio Antagonist to Alphaprodine	Probability of Difference, or Significance Time in Minutes after Drug Administration						
		2	5	10	15	20	25	30
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.75 mg./kg. and levallorphan 1:100						
0.75	1:50	N.S.†	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	1:37.5	<0.05	<0.05	<0.05	N.S.	N.S.	N.S.	N.S.
	1:25	<0.01	<0.01	<0.01	<0.01	<0.01	N.S.	N.S.
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.75 mg./kg. and levallorphan 1:50						
0.75	1:37.5	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	1:25	<0.01	<0.02	N.S.	N.S.	N.S.	N.S.	N.S.
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.75 mg./kg. and levallorphan 1:37.5						
0.75	1:25	N.S.	N.S.	N.S.	N.S.	<0.02	N.S.	N.S.
Alphaprodine with Levallorphan		Compared to: Alphaprodine 0.375 mg./kg. and levallorphan 1:50						
0.375	1:25	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Alphaprodine with Ro-1-7780		Compared to: Alphaprodine 0.75 mg./kg. and Ro-1-7780 1:100						
0.75	1:50	N.S.†	<0.01	<0.01	<0.01	N.S.	N.S.	N.S.
	1:25	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Alphaprodine with Ro-1-7780		Compared to: Alphaprodine 0.75 mg./kg. and Ro-1-7780 1:50						
0.75	1:25	<0.01	<0.05	<0.05	N.S.	<0.05	N.S.	<0.05
Alphaprodine with Ro-1-7780		Compared to: Alphaprodine 0.375 mg./kg. and Ro-1-7780 1:50						
0.375	1:25	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

* By "t" test of Student. † N.S. = not significant.

this ratio. No narcotic controls were done because it was believed that 1.5 or 2 mg./kg. was above the safe clinical dose for alphaprodine alone, while it would be safe if levallorphan were added at 1:25. These doses of alphaprodine with antagonist were not depressant to respiration in any of the 9 patients; but there was a high incidence of side effects such as nausea, weird dreams, restlessness, and confusion, as frequently seen with excessive doses of narcotics.

Discussion

The value of antagonists in combatting the toxic depressant effects of narcotic overdosage (13, 14, 15) and in revealing addiction (16) is well established. These applications represent a rather limited use for the antagonists.

Efforts to combine an antagonist with a narcotic to produce analgesia without undesirable side effects have not previously been wholly successful for two reasons: (*1*) the fact that differences in the amount either of the narcotic or of the antagonist may result in variations of over-all effect from stimulation to synergistic depression (12) has not been appreciated, and (*2*) adequate control studies of the effects of narcotic alone, antagonist alone, and of some indifferent injection have not been included in the results of previous workers. The combined action of levallorphan with alphaprodine at ratios of 1:100, 1:50, and 1:25 has been reported by Swerdlow, Foldes, and Siker (17), while the combined action of levallorphan and levorphan (levodromoran) at a ratio of 1:10 was studied by Cullen and Santos (18). Both groups commented favorably on the analgesic and respiratory actions of this combined medication.

In the present study, control observations of the actions of Ro 1-7780, levallorphan, physiological salt solution, and alphaprodine have been made over comparable observation periods to those used in the tests of combined action; this has permitted the development of definite conclusions, using the statistics of small numbers. The significance of the differences between the controls and the tests has been demonstrated for inspiratory ventilation. Furthermore, the actual doses of narcotic and the ratios of antagonist to it have been varied from an amount presenting minimal narcosis and no perceptible antagonistic action to one where side effects of the combined medication have been prominent. The dose of alphaprodine itself, combined with antagonist, has been increased into the toxic range without notable depression of vital functions in a small number of cases, using the intravenous route which presents the greatest hazard.

Where analgesia was needed, the patients have gone lightly to sleep after the combined medication, indicating a satisfactory effect; a study of analgesic effects of the combined medication is, therefore, being initiated. In a number of patients outside the statistical study, where analgesia was a problem during or after abdominal surgery, administration, intramuscularly, of combined medication (levallorphan and

alphaprodine at 1:30) has produced excellent effects, as shown by cessation of restlessness, quieting of respiration with an actual increase in ventilation, and the induction of a light sleep. While the effects of the opiate alone or of the combined medication on respiratory rate and tidal volume proved to be variable, their actions on the inspiratory minute ventilation were consistent and significant. It is probable that a larger series would permit definite conclusions with respect to rate and tidal volume.

The effects of injecting salt solution, Ro 1-7780, or levallorphan were negative, except that Ro 1-7780, and levallorphan to a lesser extent, produced a slight depression in responsiveness. The combined medications at ratios of 1:100 and 1:50 produced a significant depression of ventilation below that seen in the controls during the first ten minutes of observation. By contrast the ventilation was not significantly depressed at any time following the 1:37.5 and 1:25 combinations. Alphaprodine alone, at both doses, produced a significant depression of ventilation and responsiveness below the values which were seen after Ro 1-7780 alone, levallorphan alone, or the salt solution. Again, the depression of ventilation with the 1:100 and 1:50 ratios of combined medication during the first ten minutes after injection did not differ significantly from that following the narcotic itself, while the 1:37.5 and higher ratios were followed by higher ventilation (than after alphaprodine alone) throughout the period of observations. Thus the combined medication, when compared to the salt solution on the one hand and to alphaprodine alone on the other, produced consistent results.

Findings with respect to general responsiveness indicate that Ro 1-7780 may be a more favorable drug for use with alphaprodine than is levallorphan. While respiration was affected approximately equally when either of the drugs was added to the narcotic, responsiveness (a qualitative measurement not susceptible to statistical evaluation) was lower after the 1:25 combinations containing Ro 1-7780 than after those containing levallorphan.

The effectiveness of combining either Ro 1-7780 or levallorphan with alphaprodine in preventing narcotic respiratory depression is apparent. It further appears that the combined medications afford adequate analgesia. Evaluation of other opiate and antagonist combinations and more exact measurements of their physiological effects are currently under way in this laboratory.

Summary

Alphaprodine at doses of 0.375 to 2.0 mg./kg. has been combined with the narcotic antagonists, levallorphan or Ro 1-7780, for postoperative medication. Ratios of the later drugs to the former have varied from 1:100 to 1:5.

At ratios of 1:100 and 1:50, the added antagonists did not significantly alter the respiratory depression of the narcotic during the first

ten minutes after administration. At ratios of 1:37.5 or higher, both agents were equally effective in preventing respiratory depression by the narcotic. The analgesic effect of the combined medication at ratios of 1:25 to 1:100 still appeared adequate by the criterion of diminished responsiveness. The ratios of antagonist to narcotic of 1:25 and 1:37.5 appeared most favorable, producing diminished responsiveness to all stimuli. With admixture of levallorphan at a ratio of 1:25, alphaprodine, 2 mg./kg., an ordinarily unsafe dose, produced no significant respiratory depression. Combined medications containing Ro 1-7780 at the more favorable ratios allowed a greater depression in responsiveness than those containing levallorphan.

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