

# *Studies on the Specificity of Narcotic Antagonists*

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Experiments with five narcotics, (morphine 0.3 mg./kg., oxymorphone 20  $\mu$ g./kg., levorphan 50  $\mu$ g./kg., meperidine 1.5 mg./kg. and fentanyl 1.5  $\mu$ g./kg.) and three narcotic antagonists (nalorphine 150  $\mu$ g./kg., naloxone 5  $\mu$ g./kg., and levallorphan 20  $\mu$ g./kg. were designed, to investigate whether or not the various antagonists exhibit a more pronounced effect against the pharmacological actions of their parent compounds, than against those of structurally less closely related narcotics. No such specificity of action was found. Naloxone appeared more effective than nalorphine or levallorphan. With all three antagonists there was a direct relation between the degree of narcotic-induced respiratory depression and the efficacy of the antagonist.

It has been reported in the dog that nalorphine hydrochloride (Nalline) does not antagonize meperidine hydrochloride (Demerol) induced respiratory depression.<sup>1</sup> Subsequently it was suggested that narcotic antagonists (antagonists) may exhibit group specificity and that their ability to counteract the respiratory depressant and other side effects of narcotic analgesics (narcotics) may be greater when they are more closely related to one another.<sup>2</sup> To test the validity of this assumption the influence of three antagonists, nalorphine, naloxone hydrochloride, and levallorphan tartrate (Lorfan) on the respiratory, circulatory and analgesic effects of their respective parent compounds, morphine sulfate, oxymorphone hydrochloride (Numorphan), levorphan tartrate (Levo-Dromoran) and on those of meperidine and fentanyl citrate were investigated. Nalorphine, naloxone and levallorphan are the N-allyl derivatives of morphine, oxymorphone and levorphan, respectively. There is no close

structural relationship between the three antagonists and meperidine or fentanyl.

## **Experimental Procedures**

This investigation was carried out on 200 patients in good physical condition who were to undergo elective surgical procedures. Thirty-one were male patients and 169 female patients; their ages ranging from 18 to 65 years. Ninety to 120 minutes before the start of the study they received 100 mg. pentobarbital sodium (Nembutal) and 0.4 mg. scopolamine hydrobromide intramuscularly. On arrival in the operating room an intravenous infusion of 5 per cent dextrose in 0.2 per cent sodium chloride was started. All drugs were administered through the rubber sleeve of the intravenous tubing.

Each patient's mouth and pharynx were topically anesthetized with 1 per cent tetracaine hydrochloride (Pontocaine) solution. Pulse rate, systolic and diastolic blood pressure and respiratory rate were recorded and a "sleep" dose of thiopental sodium (Pentothal) was administered at the rate of 25 mg./15 seconds. After the disappearance of the lid reflex an oropharyngeal airway was inserted into the pharynx. A gas mixture consisting of 4 liters of nitrous oxide and 1 liter of oxygen was then administered in a semiclosed carbon dioxide absorption system through a tight fitting face mask. A ventilation meter was incorporated into the inspiratory side of the anesthetic circuit. After four to six minutes of nitrous oxide-oxygen administration, pulse rate, blood pressure, respiratory rate and minute volume were again recorded. Tidal volume was circulated from minute volume and respiratory rate.

Assisted, or controlled ventilation was used when the subjects became apneic (did not breathe spontaneously for 30 seconds). For 30 seconds before and during each one minute observation period, however, the patients were

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allowed to breathe spontaneously. During this time flow rates of nitrous oxide and oxygen were each reduced to 500 ml. per minute. If the patients did not take a breath during the 30 seconds preceding an observation period, controlled respiration was resumed and the respiratory parameters were recorded as zero.

The 200 subjects were divided into 5 groups of 40 each. The 40 subjects of each group received, at zero time, 0.3 mg./kg. morphine, 20 µg./kg. oxymorphone, 50 µg./kg. levorphan, 1.5 mg./kg. meperidine or 1.5 µg./kg. fentanyl, respectively. Each group of 40 was further divided into four subgroups of ten each. The subjects of the first subgroup in each group received no antagonist; those of the other three subgroups received 150 µg./kg. nalorphine, 5 µg./kg. naloxone, or 20 µg./kg. levallorphan, respectively, 7 minutes after the administration of the narcotic. The doses of the five narcotics were selected, on the basis of preliminary trials, so as to produce about a 50 per cent decrease of the minute volume. Because of considerable individual differences in response, however, the decrease in minute volume ranged from 45 to 70 per cent in the various subgroups. The dosage of the three narcotic antagonists had been determined in earlier studies.<sup>1, 3-6</sup>

Respiratory and circulatory parameters were observed at 3, 6, and 11 minutes after the administration of the narcotics. Respiratory rate and minute volume were measured over a one minute period, starting 30 seconds before and ending 30 seconds after the time indicated. Within two to six minutes after the last observation period the patient's reaction to a painful stimulus (application of a towel clip to the skin or a skin incision) was observed. In addition the milligram per kilogram "sleep" dose of thiopental and the incidence of apnea in the various subgroups were also recorded.

Data were analyzed for statistical significance with Student's *t* test.

### Results

The "sleep" dose of thiopental in the 20 subgroups ranged from  $3.9 \pm 0.2$  to  $6.7 \pm 0.6$  mg./kg. and averaged  $5.3 \pm 0.1$  mg./kg. (mean  $\pm$  S. E.). The effects of the five narcotics administered alone or followed in seven minutes by one of the three antagonists are presented in figures 1, 2, 3, 4 and 5 and tables 1, 2 and 3. The five narcotics caused a significant decrease of respiratory rate and minute volume. Among the 40 subjects in each group receiving morphine, oxymorphone, levorphan, meperidine or

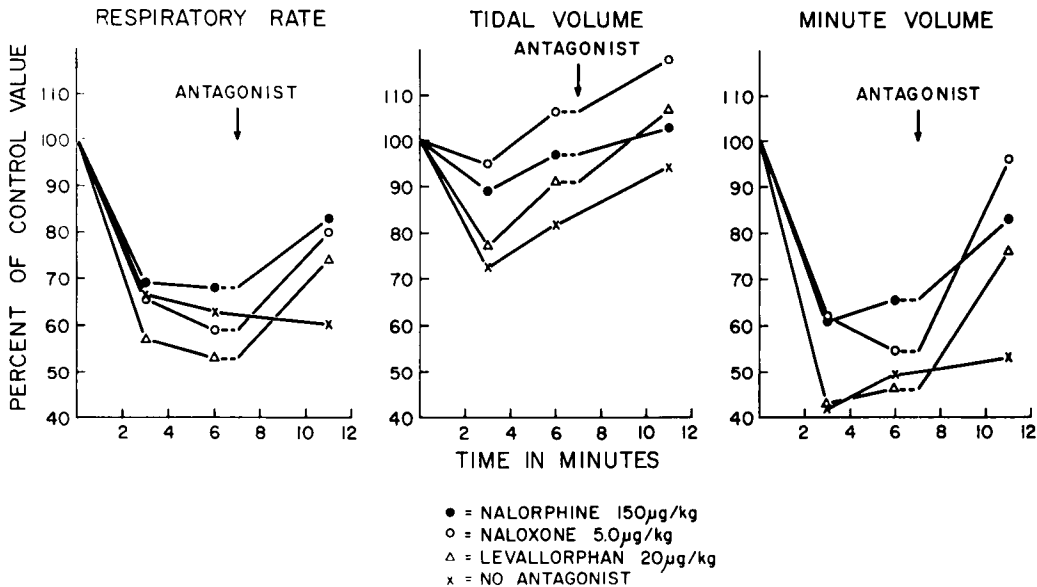


FIG. 1. The influence of narcotic antagonists on the respiratory effects of morphine (0.3 mg./kg.).

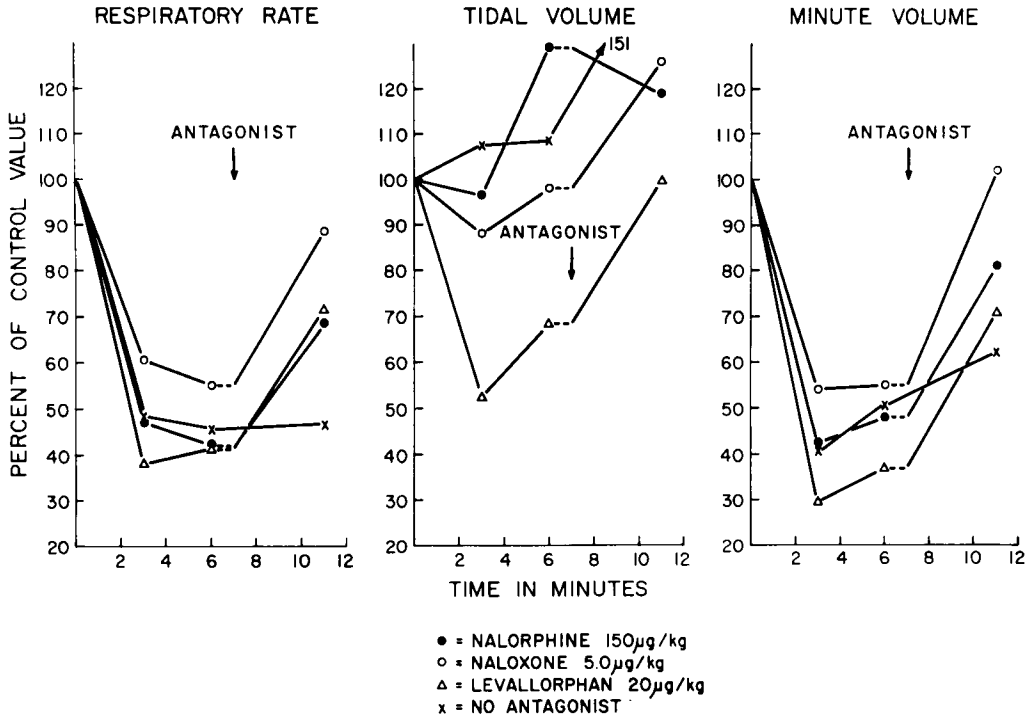


FIG. 2. The influence of narcotic antagonists on the respiratory effects of oxymorphone (20 µg./kg.).

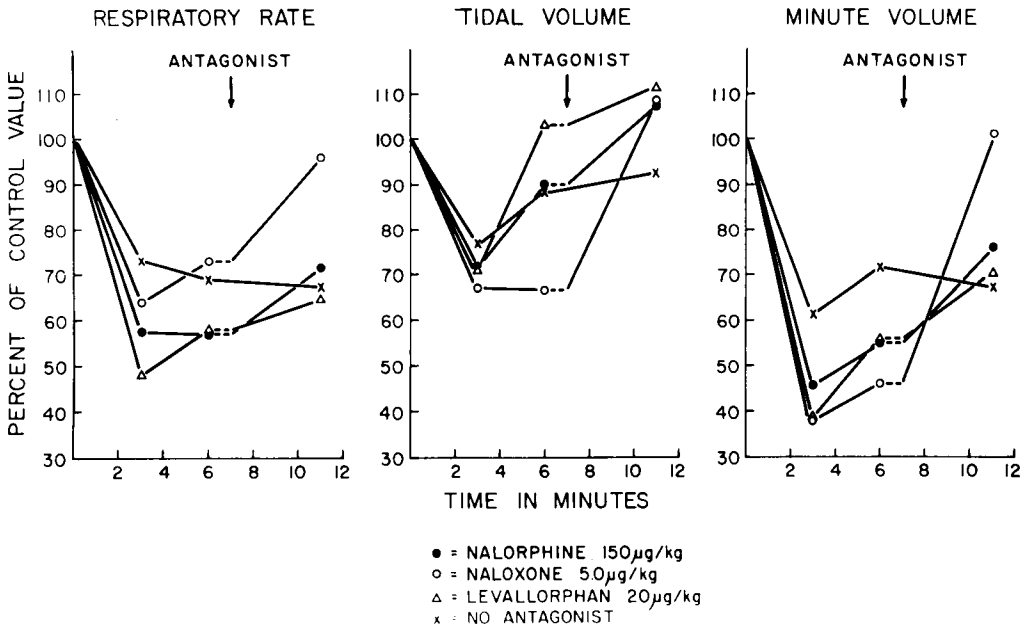


FIG. 3. The influence of narcotic antagonists on the respiratory effects of levorphan (50 µg./kg.).

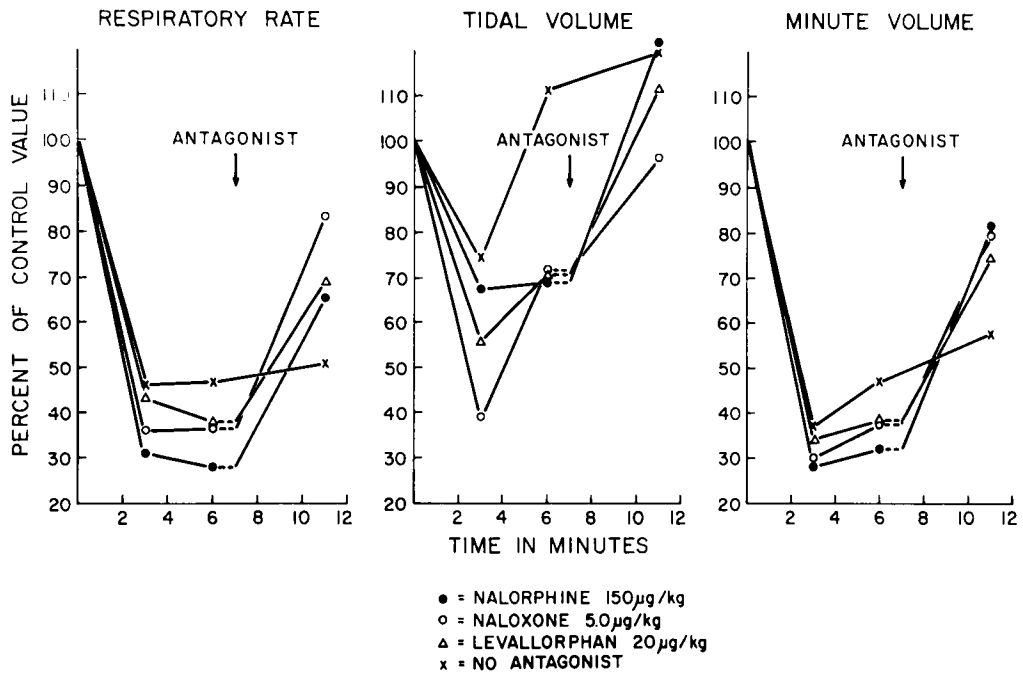


FIG. 4. The influence of narcotic antagonists on the respiratory effects of meperidine (1.5 mg./kg.).

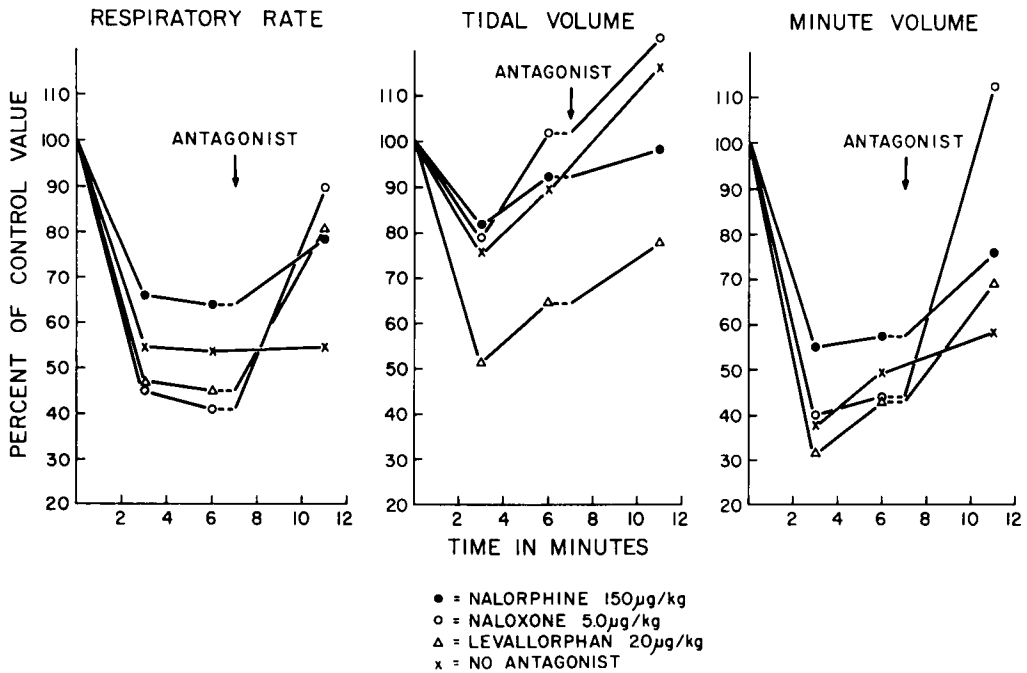


FIG. 5. The influence of narcotic antagonists on the respiratory effects of fentanyl (1.5 µg./kg.).

TABLE 1. The Effect of Antagonists on Narcotic-Induced Depression of Respiratory Rate

Narcotic	Antagonist*							
	None		Nalorphine		Naloxone		Levallorphan	
	6 Minutes†	11 Minutes†	6 Minutes	11 Minutes	6 Minutes	11 Minutes	6 Minutes	11 Minutes
Morphine	63.0 ± 6.6‡	60.2 ± 7.4	68.1 ± 4.3	83.0 ± 4.7§	59.3 ± 4.3	80.5 ± 2.3§	53.7 ± 7.4	74.1 ± 5.3§
Oxymorphone	45.3 ± 6.2	46.3 ± 4.0	42.2 ± 4.7	68.5 ± 2.2§	56.1 ± 6.6	88.3 ± 3.2§	41.7 ± 8.2	71.2 ± 5.7§
Levorphan	68.9 ± 4.9	67.1 ± 5.7	57.5 ± 7.5	71.4 ± 4.0	72.7 ± 15.3	96.1 ± 4.5	58.2 ± 4.7	64.3 ± 4.4
Meperidine	46.6 ± 4.8	50.9 ± 4.5	28.0 ± 9.8	65.6 ± 3.8§	36.7 ± 7.9	83.3 ± 3.2§	38.1 ± 8.6	69.0 ± 1.7§
Fentanyl	53.8 ± 2.7	54.9 ± 2.3	63.8 ± 5.8	78.5 ± 4.6	41.1 ± 6.8	89.9 ± 3.4§	41.9 ± 8.2	80.7 ± 4.9§

\* Administered seven minutes after the narcotic.

† From the administration of the narcotic.

‡ Mean, expressed as per cent of control, ± standard error.

§ Indicates statistical significance ( $P < 0.05$ ) between the values obtained before and after the administration of the antagonists.

fentanyl, apnea developed in 0, 5, 4, 11 and 3 instances, respectively. Following a brief, but consistent initial decrease, tidal volume increased rapidly with all the narcotics tested. Consequently within 6 minutes the tidal volume was close to, or above, control values. Maximum decrease of respiratory rate occurred at 6 minutes; but because of the compensatory increase in tidal volume the decrease in minute volume was greatest at 3 minutes.

The intravenous administration of each of the three antagonists at seven minutes markedly antagonized the respiratory depressant effect of the five narcotics. The effect of the three antagonists in reversing depression of the respiratory rate caused by morphine, oxymorphone and meperidine was statistically significant ( $P < 0.05$ ). Fentanyl induced depression of respiratory rate was antagonized significantly only by naloxone and levallorphan, and that caused by levorphan was not antagonized statistically significantly by any of

the three antagonists. In contrast, the effects of the three antagonists on depression of the minute volume caused by all five narcotics was statistically significant. The effect of the antagonists on tidal volume was less consistent. Occasionally this parameter, instead of being increased, was decreased after the administration of the antagonists. In general, 5  $\mu\text{g./kg.}$  naloxone had a greater antagonistic effect than 20  $\mu\text{g./kg.}$  levallorphan or 150  $\mu\text{g./kg.}$  nalorphine. The degree of recovery, following the administration of the antagonists was related to the intensity of the narcotic induced respiratory depression. The greater the initial respiratory depression the more marked was the effect of the antagonist (fig. 6 and 7). None of the three antagonists counteracted the respiratory depressant effects of their parent compound to a greater extent than those of the other four narcotics.

The circulatory effects of five narcotics administered alone or followed by one of the

TABLE 2. The Effect of Antagonists on Narcotic-Induced Depression of Tidal Volume

Narcotic	Antagonist*							
	None		Nalorphine		Naloxone		Levallorphan	
	6 Minutes†	11 Minutes†	6 Minutes	11 Minutes	6 Minutes	11 Minutes	6 Minutes	11 Minutes
Morphine	81.8 ± 5.4‡	94.1 ± 6.7	97.3 ± 5.5	102.7 ± 5.8	106.4 ± 4.5	117.7 ± 3.1	91.1 ± 5.8	107.0 ± 9.6
Oxymorphone	108.7 ± 17.7	151.7 ± 19.1	129.1 ± 17.0	118.8 ± 5.8	97.9 ± 5.8	115.8 ± 5.3	68.6 ± 11.6	99.9 ± 5.6§
Levorphan	88.1 ± 3.9	92.3 ± 2.8	89.8 ± 11.6	107.7 ± 4.6	66.5 ± 10.5	108.4 ± 9.9§	102.7 ± 10.9	116.0 ± 11.9
Meperidine	111.5 ± 12.7	119.9 ± 11.4	69.3 ± 13.5	122.6 ± 6.7§	71.7 ± 15.5	96.3 ± 6.8	71.0 ± 15.3	111.2 ± 5.1§
Fentanyl	89.8 ± 10.6	116.5 ± 6.8	92.6 ± 7.0	98.5 ± 7.1	102.3 ± 13.1	122.9 ± 5.4	64.4 ± 13.4	87.9 ± 5.9

\* Administered seven minutes after the narcotic.

† From the administration of the narcotic.

‡ Mean, expressed as per cent of control, ± Standard error.

§ Indicates statistical significance ( $P < 0.05$ ) between the values obtained before and after the administration of the antagonists.

TABLE 3. The Effect of Antagonists on Narcotic-Induced Depression of Minute Volume

Narcotic	Antagonist*							
	None		Nalorphine		Naloxone		Levallorphan	
	6 Minutes†	11 Minutes†	6 Minutes	11 Minutes	6 Minutes	11 Minutes	6 Minutes	11 Minutes
Morphine	49.5 ± 3.9‡	53.2 ± 4.7	65.5 ± 4.3	82.8 ± 3.1§	54.6 ± 6.3	95.9 ± 2.1§	45.8 ± 4.8	76.1 ± 2.8§
Oxymorphone	50.6 ± 8.8	62.1 ± 1.6	48.1 ± 5.1	81.0 ± 3.1§	55.1 ± 6.3	101.9 ± 6.6§	37.3 ± 8.5	70.8 ± 6.2§
Levorphan	71.6 ± 7.2	67.1 ± 6.2	55.8 ± 7.5	76.0 ± 3.9§	46.3 ± 7.0	101.0 ± 7.0§	55.0 ± 3.5	70.3 ± 4.6§
Meperidine	47.1 ± 4.3	57.5 ± 5.9	32.1 ± 11.9	81.6 ± 8.8§	37.5 ± 8.3	89.4 ± 5.6§	37.9 ± 8.7	74.3 ± 3.2§
Fentanyl	49.5 ± 5.7	58.4 ± 5.8	57.6 ± 5.5	76.0 ± 5.1§	44.2 ± 6.5	112.9 ± 9.6§	43.1 ± 8.0	69.1 ± 4.7§

\* Administered seven minutes after the narcotic.  
 † From the administration of the narcotic.  
 ‡ Mean, expressed as per cent of control, ± Standard error.  
 § Indicates statistical significance ( $P < 0.05$ ) between the values obtained before and after the administration of the antagonists.

three antagonists are presented in tables 4 and 5. Morphine, oxymorphone, levorphan and fentanyl caused a 15 to 20 per cent decrease of the pulse rate. Meperidine induced slowing of the pulse rate was 12 per cent or less. As a rule the subsequent administration of antagonist had no significant effect on the narcotic bradycardia (table 4). The five narcotics also caused a 15 to 20 per cent fall in the systolic blood pressure. All three antagonists consistently counteracted the narcotic induced hypotension. This effect was (in nine of the 15 subgroups, where antagonists were used) statistically significant (table 5). The effect of the antagonists on diastolic blood pressure paralleled those exerted on the systolic blood pressure.

Reaction of the subjects to painful stimuli,

applied 12 to 16 minutes after the administration of the narcotic, revealed that the analgesic effect of levorphan in equidepressant doses were less than that of the other narcotics (table 6). Of the three antagonists, nalorphine interfered the least with the analgesic effect of the narcotics. The analgesic effect of morphine was antagonized less and that of meperidine and fentanyl more frequently by the antagonists than that of the other two narcotics.

Discussion

The results reported herein do not confirm the assumption that the antagonists have a more specific action against the respiratory depression caused by structurally similar narcotics than against that caused by less closely related

FIG. 6. The relation between the degree of narcotic induced depression of respiratory rate and the effect of antagonists.

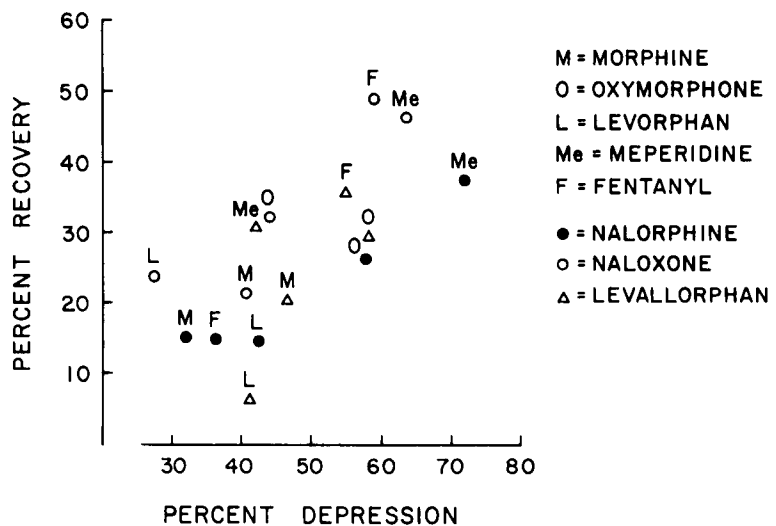


TABLE 4. The Effect of Antagonists on Narcotic-Induced Changes of Pulse Rate

Narcotic	Antagonist*							
	None		Nalorphine		Naloxone		Levallorphan	
	6 Minutes†	11 Minutes†	6 Minutes	11 Minutes	6 Minutes	11 Minutes	6 Minutes	11 Minutes
Morphine	78.9 ± 3.4‡	78.7 ± 2.9	88.5 ± 4.2	86.2 ± 3.2	83.1 ± 3.2	87.9 ± 4.7	86.7 ± 3.1	85.7 ± 2.8
Oxymorphone	83.7 ± 3.5	82.8 ± 5.8	84.1 ± 3.3	82.8 ± 3.3	86.3 ± 2.5	86.6 ± 2.1	81.3 ± 3.9	83.6 ± 4.1
Levorphan	79.3 ± 3.2	75.9 ± 3.4	84.2 ± 3.3	85.0 ± 2.7	81.6 ± 3.1	81.1 ± 4.3	91.8 ± 9.5	80.3 ± 4.5
Meperidine	88.4 ± 5.0	101.7 ± 8.8	104.3 ± 2.5	92.2 ± 4.1§	93.4 ± 3.4	95.8 ± 3.5	91.4 ± 3.0	87.8 ± 3.3
Fentanyl	78.2 ± 3.7	77.5 ± 3.6	83.9 ± 2.2	84.6 ± 2.7	77.8 ± 3.1	87.4 ± 2.7§	79.8 ± 3.7	82.0 ± 4.8

\* Administered seven minutes after the narcotic.

† From the administration of the narcotic.

‡ Mean, expressed as per cent of control, ± standard error.

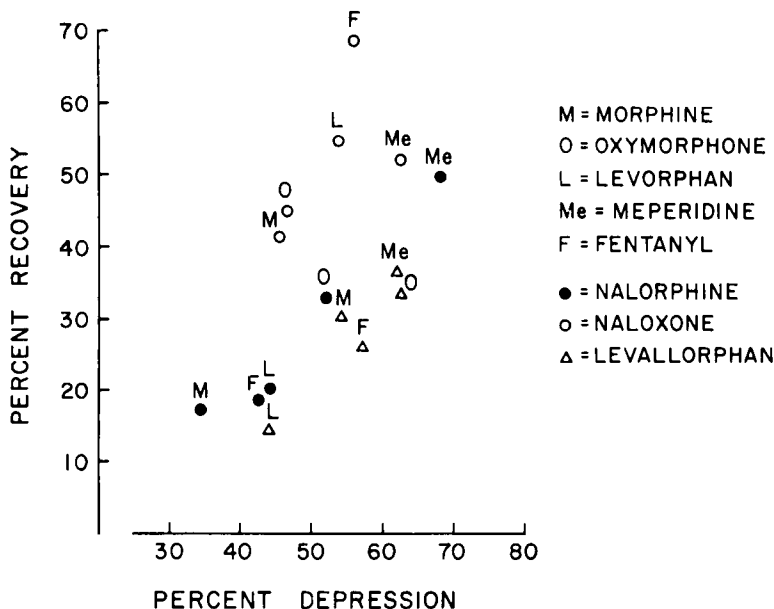
§ Indicates statistical significance ( $P < 0.05$ ) between the values obtained before and after the administration of the antagonists.

FIG. 7. The relation between the degree of narcotic induced depression of minute volume and the effect of the antagonists.

TABLE 5. The Effect of Antagonists on Narcotic-Induced Changes of Systolic Blood Pressure

Narcotic	Antagonist*							
	None		Nalorphine		Naloxone		Levallorphan	
	6 Minutes†	11 Minutes†	6 Minutes	11 Minutes	6 Minutes	11 Minutes	6 Minutes	11 Minutes
Morphine	86.9 ± 2.3‡	86.2 ± 2.8	90.7 ± 5.1	103.4 ± 4.1	88.3 ± 2.0	96.6 ± 2.5§	83.9 ± 1.3	95.2 ± 3.1§
Oxymorphone	80.6 ± 3.8	78.1 ± 3.8	86.5 ± 1.3	100.4 ± 2.4§	93.2 ± 2.0	98.6 ± 2.3	81.5 ± 3.9	95.6 ± 4.5§
Levorphan	83.4 ± 1.9	81.5 ± 2.6	83.3 ± 3.4	96.3 ± 4.0§	85.7 ± 3.7	93.8 ± 4.1	85.2 ± 3.4	90.3 ± 3.2
Meperidine	88.8 ± 3.3	91.2 ± 4.5	95.5 ± 2.3	112.5 ± 4.5§	96.1 ± 3.0	107.0 ± 4.2§	87.2 ± 5.9	80.3 ± 4.1
Fentanyl	78.7 ± 3.1	82.0 ± 3.2	87.7 ± 2.9	97.2 ± 3.4§	80.8 ± 2.1	92.2 ± 2.4§	83.2 ± 2.0	89.7 ± 2.6

\* Administered seven minutes after the narcotic.

† From the administration of the narcotic.

‡ Mean, expressed as per cent of control, ± standard error.

§ Indicates statistical significance ( $P < 0.05$ ) between the values obtained before and after the administration of the antagonists.

compounds. The several antagonists were not more effective against the respiratory depression induced by their parent compound, than against that caused by the other four narcotics. To the contrary, morphine was antagonized to a greater extent by naloxone or levallorphan than by its own N-allyl derivative, nalorphine. Similarly, the antagonistic effect of levallorphan on levorphan induced respiratory depression was the least marked. Furthermore, the three antagonists counteracted the respiratory depressant effects of the structurally least similar compounds, meperidine and fentanyl, to the same extent as that of their parent compounds, or that of the other two, structurally more similar narcotics.

It had been reported earlier, that 5  $\mu\text{g./kg.}$  naloxone produced no respiratory depression<sup>6</sup> when administered to subjects, who had not previously received a narcotic. In contrast, 150  $\mu\text{g./kg.}$  nalorphine or 20  $\mu\text{g./kg.}$  levallorphan both caused significant respiratory depression.<sup>6</sup> It is of interest that despite the lack of any significant respiratory effect of its own, naloxone antagonized the respiratory depressant effects of the five narcotics more effectively than the other two antagonists tested.

The antagonists had little or no effect on the slowing of the pulse rate caused by the narcotics. They counteracted, however, the narcotic induced hypotension. These findings are in agreement with those of others<sup>8,9</sup> who observed that the effect of antagonists is less consistent against circulatory than against respiratory changes caused by narcotics.

As reported earlier by others<sup>10,11</sup> the analgesic effect, as measured by the reactivity to painful stimulation, was counteracted by all three narcotic antagonists. The effect of naloxone and levallorphan, however, was more pronounced in this respect than that of nalorphine.

### Summary

The respiratory depressant effects of morphine, oxymorphone, levorphan, meperidine and fentanyl were consistently antagonized by nalorphine, naloxone or levallorphan. Naloxone 5  $\mu\text{g./kg.}$ , was a more effective antagonist of narcotic induced respiratory depression than 150  $\mu\text{g./kg.}$  nalorphine or 20  $\mu\text{g./kg.}$  levallorphan. The three antagonists tested ex-

TABLE 6. Number of Subjects Reacting to Painful Stimuli After Narcotics Administered Alone or Followed by an Antagonist\*

Narcotic	Antagonist			
	None	Nalorphine	Naloxone	Levallorphan
Morphine	0†	1	0	0
Oxymorphone	1	0	2	6
Levorphan	4	3	4	5
Meperidine	0	1	9	5
Fentanyl	1	4	4	5

\* Stimulus applied 12 to 16 minutes after the administration of the narcotic.

† Each subgroup consisted of ten subjects.

hibited no specificity for any one narcotic. They were no more effective against respiratory depression caused by their parent compounds than against that produced by the other four narcotics. The efficacy of the antagonist seemed to parallel the degree of narcotic induced respiratory depression. The antagonists had little or no effect on the narcotic induced slowing of the pulse rate but antagonized the hypotensive effect of these compounds. The analgesic effect of the narcotics was also counteracted by the antagonists. Of the three antagonists tested nalorphine interfered the least with the analgesic effect of the narcotics. The analgesic effect of morphine was antagonized less than that of the other four narcotics.

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**THYROTOXICOSIS** Operation for thyrotoxicosis in 2,500 patients was carried out under local anesthesia with premedication consisting of mild neuroplegia by means of meprobamate with promethazine, combined with hypnotics and parasympatholytics. In patients with a lowered neurovascular reactivity, especially in older people, neuroplegics should not be given, and the dose of meprobamate should be reduced. There were only ten cases of postoperative thyrotoxic crisis among 435 patients operated on; eight of them had received no premedication, and in two cases premedication had consisted of meprobamate alone. (*Skripnichenko, D. F., and others: Experiences with Anaesthesia in Operations for Thyroxototoxicosis (Russian), Klinicheskaya Khirurgiya* **5**: 59, 1964.)

**LACTATE PRODUCTION** Ten resting and unpremedicated subjects were anesthetized with oxygen-halothane. Little change occurred in absolute concentration of lactate and pyruvate, and no excess lactate was present. This suggests that halothane may be administered without the occurrence of anaerobic metabolism. In contrast, excess lactate has been recorded during cyclopropane and ether anesthesia, which was considered to be due to release of catecholamines rather than a direct effect of the anesthetic itself. Since halothane anesthesia has been shown to result in little or no change in catechols, this may account for the difference in observed excess lactate values resulting from administration of anesthetic agents. (*Lowenstein, E., and others: Excess Lactate Production During Halothane Anesthesia in Man, J.A.M.A.* **190**: 1110 (Dec. 28) 1964.)

**ENDOBONCHIAL ANESTHESIA** Anesthesia was administered through a Gebauer (10 per cent) or Kubryakov (90 per cent) tube. Contraindications are: active tuberculosis of the tracheobronchial tree and marked stenosis of the trachea and main bronchi. Advantages are: protection of the lung from aspiration, creation of optimal conditions for gas metabolism using a nonclosed breathing system, and considerable improvement of technical conditions during surgery on the lungs and pleura. (*Savonicheva, I. P., and Vaisberg, L. A.: Experience in the Use of Anaesthetics with Separate Intubation of the Main Bronchi During Surgery for Pulmonary Tuberculosis (Russian), Khirurgiya* **3**: 98, 1964.)