The Use of Fentanyl, Meperidine or Alphaprodine for Neuroleptanesthesia

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The suitability of fentanyl, meperidine or alphaprodine for the production of neuroleptanesthesia in conjunction with droperidol and nitrous oxide–oxygen was investigated in a double-blind study of 527 surgical patients. Because of the greater stability of the circulatory and respiratory systems associated with their use, fentanyl and meperidine were found to be preferable to alphaprodine for the production of neuroleptanesthesia. Except for a lower incidence of apnea and more rapid recovery of consciousness, fentanyl does not seem to offer any significant advantages over meperidine as a component of neuroleptanesthesia. (Key words: Neuroleptanesthesia; Droperidol; Fentanyl; Meperidine; Alphaprodine.)

A BUTYROPHENONE DERIVATIVE, droperidol (Inapsine), in combination with a potent, short-acting narcotic analgesic, fentanyl citrate (Sublimaze) and nitrous oxide–oxygen, has been widely used for the production of neuroleptanesthesia both in the United States and abroad. After obtaining some experience with this technique,[1] we were interested in determining whether droperidol and/or fentanyl are essential for the production of neuroleptanesthesia, or whether they could be replaced by other ataractic drugs, or narcotics, without sacrificing any of the advantages attributed to the technique. Preliminary studies (unpublished data) with combinations of 0.15 mg/kg droperidol, 0.6 mg/kg chlorpromazine (Thorazine), 0.3 mg/kg trifluprom azine (Vesprin) and 1.0 mg/kg hydroxyzine (Vistaril) and fentanyl revealed that droperidol is preferable for the production of neuroleptanesthesia. Comparison of combinations of droperidol with 0.003 mg/kg fentanyl, 3 mg/kg meperidine hydrochloride (Demerol), and 1.2 mg/kg alphaprodine hydrochloride (Nisentil) in relatively small groups of patients, however, failed to show a clear-cut superiority of any of the three short-acting narcotics over the others. Consequently, a double-blind study was undertaken in a larger number of patients with combinations of these three narcotics and droperidol.

Material and Methods

Subjects of the investigation were 527 consecutive surgical patients more than 16 years of age who required general anesthesia. Patients scheduled for cardiac surgery or craniotomy and moribund subjects were excluded from the study.

The droperidol solution contained 2.5 mg /ml. Three narcotics were supplied in identical-looking 20-ml ampules containing 30 μg /ml fentanyl, 30 mg/ml meperidine, or 12 mg /ml alphaprodine.§ These concentrations were selected on the basis of the relative analgesic potencies of the narcotics. The analgesic potency of fentanyl relative to meperidine (1,000 to 1) was estimated from comparison of the "settling" doses of the two compounds in preliminary studies. The settling dose of narcotic was arbitrarily defined as the mg/kg dose required by more than 90 per cent of patients to enable them to tolerate incision of the skin after administration of a single 0.15

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§ Droperidol and the coded ampules containing the three narcotics were kindly supplied by the McNeil Laboratories of Fort Washington, Pa.

mg/kg dose of droperidol and inhalation of nitrous oxide–oxygen for ten to 12 minutes. The analgesic potency of alphaprodine relative to meperidine (2.5 to 1) was based on earlier studies.[2, 3]

Consecutively numbered narcotic ampules, each containing one of the three narcotics, in a randomized sequence, were delivered to the hospital pharmacy together with a sealed identification list. Identification tags were removed before the ampules were made available for the study. All narcotic ampules, with the exception of a few destroyed by breakage, were used consecutively. The identity of the narcotic was not revealed to the anesthesiologists until completion of the study, when the code was broken by the Medical Department of McNeil Laboratories.

Patients were divided into three groups. In group I, no neuromuscular blockers were used; in group II, succinylcholine chloride (Anectine) was given for intubation; in group III, succinylcholine was given for intubation and *d*-tubocurarine chloride (Tubarine) or gallamine triethiodide (Flaxedil) employed for the maintenance of surgical relaxation. After the code had been broken, each of the three groups was divided on the basis of narcotics used into fentanyl, meperidine, and alphaprodine subgroups.

Premedication

Patients received 50 to 100 mg diphenhydramine hydrochloride (Benadryl) and 0.3 to 0.4 mg scopolamine hydrobromide or 0.3 to 0.6 mg atropine sulfate intramuscularly 90 minutes prior to the start of anesthesia.

Anesthetic Management

On the patient's arrival in the operating room, pulse rate, blood pressure and respiratory rate were recorded and an intravenous infusion of 5 per cent dextrose containing 0.2 per cent NaCl was started. All drugs were injected through the rubber sleeve of the infusion set. Immediately after the start of the infusion, 0.15 mg/kg droperidol was administered and the patient's mouth and pharynx were anesthetized topically with a 1 per cent tetracaine hydrochloride (Pontocaine) spray. Six to eight minutes after injection of droperidol the initial dose of narcotic was injected. This initial dose consisted of a third of the previously determined settling dose (0.1 ml/kg body weight, *i.e.*, 0.003 mg/kg fentanyl, 3 mg /kg meperidine, 1.2 mg/kg alphaprodine) of the unknown narcotic solution. A minute after administration of the narcotic, a mixture of 6 to 8 l/min nitrogen oxide and 2 l/min oxygen was administered by face mask for three minutes. Flow rate of nitrous oxide was decreased to 3 to 4 l/min and that of oxygen to 1 l/min for an additional three minutes. If the patient did not require endotracheal intubation, the nitrous oxide–oxygen mixture was administered for another ten minutes, after which the flow of nitrous oxide was decreased to 2 l/min and that of oxygen kept at 1 l/min. An oropharyngeal airway was inserted, usually within one or two minutes after the start of the nitrous oxide–oxygen administration.

Fractional doses of narcotic consisting of a sixth to a fourth of the calculated dose were given, as required, until the patient seemed to tolerate surgical stimuli. In the majority of patients less than the empirically selected settling doses of narcotics were required to obtain analgesia. Most patients were adequately anesthetized when respiratory rates were between 12 and 16/min.

When endotracheal intubation was indicated, 0.6 mg/kg succinylcholine was administered intravenously over 30 seconds. The lungs were ventilated with a high flow of oxygen for 30 seconds and the trachea was intubated. Following intubation, nitrous oxide–oxygen was administered as described for the nonintubated patients.

Whenever muscle relaxants were indicated, 0.2 mg/kg *d*-tubocurarine or 1 mg/kg gallamine was administered three to five minutes before relaxation was required. When the pulse rate was 80 beats/min or more, *d*-tubocurarine was given; when it was less than 80 beats/min gallamine was used. Each subsequent fractional dose of the neuromuscular blocker was about a third of the initial dose.

Indications for administration of fractional doses of narcotic were voluntary movements, elevation of pulse rate or blood pressure despite adequate ventilation, and irregular breathing or breath-holding. Fractional doses of narcotic were not used to deepen anesthesia in patients with adequate analgesia. In the

TABLE 1. Categories of Patients Studied

Groups	Narcotic	Number of Patients	Age (Years)	Sex		Physical Status		Duration of Anesthesia (min)
				Per Cent Male	Per Cent Female	Per Cent I and II	Per Cent III and IV	
I. No muscle relaxant	Fentanyl	87	38.5 ± 1.7*	13.8	86.2	98.8	1.2	54.6 ± 1.8
	Meperidine	91	34.7 ± 1.4	18.6	81.4	97.8	2.2	50.3 ± 5.7
	Alphaprodine	77	35.4 ± 1.7	13.0	87.0	97.4	2.6	40.6 ± 4.4
II. Relaxant for intubation only	Fentanyl	22	51.6 ± 3.6	45.5	54.5	90.9	9.1	140.4 ± 12.8
	Meperidine	13	49.3 ± 3.7	38.4	61.6	100.0	0.0	127.0 ± 17.0
	Alphaprodine	23	55.2 ± 2.5	39.0	61.0	83.5	16.5	152.3 ± 14.9
III. Relaxant before intubation and during surgical operation	Fentanyl	68	55.2 ± 1.8	47.1	52.9	86.8	13.2	158.7 ± 9.1
	Meperidine	68	51.5 ± 1.8	47.0	53.0	79.4	20.6	147.4 ± 7.9
	Alphaprodine	78	51.7 ± 1.9	41.0	59.0	88.5	11.5	139.9 ± 6.8

* Standard error.

rare instance where the patient with good analgesia showed signs of awakening, 25 to 50 mg diphenhydramine were injected intravenously.

At termination of anesthesia, the lungs were ventilated with 100 per cent oxygen for three to four minutes. Five minutes after the end of nitrous oxide administration the state of consciousness was tested by observing whether the patient was capable of answering questions, obeying commands, and responding to stimulation. When he was unable to answer questions, the time at which he was able to do so was recorded.

If, because of the length of the operation or for other reasons, the amount of narcotic contained in the 20-ml ampules supplied was not sufficient, analgesia was maintained with fentanyl for the remainder of anesthesia. This happened in six cases. In two of these, operation lasted for more than six hours, and in four there were histories of chronic alcoholism. These cases were not included in analysis of the data.

Whenever reversal of the residual effect of the neuromuscular blocker was indicated, depending on the patient's pulse rate, 0.4 to 0.6 mg atropine sulfate, followed immediately by 1.0 to 1.5 mg neostigmine methylsulfate (Prostigmine), was administered. When this dose of neostigmine improved respiration but not satisfactorily, additional 0.5-mg doses of neostigmine were administered three to five minutes apart as long as each dose was followed by further improvement. If bradycardia developed in the course of reversal, additional 0.1- to 0.2-mg doses of atropine were given.

OBSERVATIONS DURING ANESTHESIA

Pulse rate, blood pressure (by auscultation) and respiratory rate were recorded four to five minutes after administration of droperidol, three minutes after the injection of the initial dose (1 μg/kg fentanyl), 1 mg/kg meperidine, or 0.4 mg/kg alphaprodine) of narcotic, five minutes after intubation, and at 10 minute intervals throughout anesthesia and immediately after extubation. The time of incision of the skin (measured from the administration of the first dose of narcotics), or that of the first painful stimulus, and the patient's reaction was noted. Apnea (defined as no spontaneous breathing for 20 seconds or more), except that caused by succinylcholine, and ventilatory difficulty owing to expiratory spasm of the respiratory muscles (diagnosed from the increased inflation pressure of the lungs in the absence of neuromuscular blockers) were also recorded.

POSTANESTHETIC FOLLOW-UP

Every patient was visited by his anesthetist 16 to 24 hours after operation. The following questions were asked: a) How do you feel? b) Do you remember anything about your operation? c) If the answer is yes, what do

TABLE 2. Changes in Pulse Rate

	Narcotic	Pulse Rate (Beats/min)			
		Control	After Droperidol	After Narcotic‡	At End of Anesthesia
Group I	Fentanyl	87.9 ± 2.0*	93.5 ± 2.1	84.1 ± 2.0	81.5 ± 1.8†
	Meperidine	91.3 ± 1.9	92.6 ± 2.3	92.7 ± 1.8	90.1 ± 1.6
	Alphaprodine	87.0 ± 1.8	93.2 ± 2.2†	80.7 ± 1.7†	80.9 ± 2.0†
Group II	Fentanyl	87.3 ± 3.2	87.3 ± 4.0	83.0 ± 4.2	76.5 ± 3.5†
	Meperidine	81.2 ± 5.3	88.6 ± 3.0	82.5 ± 4.0	83.6 ± 4.5
	Alphaprodine	80.0 ± 3.3	95.9 ± 3.3	79.1 ± 4.7†	89.0 ± 4.9
Group III	Fentanyl	87.0 ± 2.2	90.9 ± 2.1	83.3 ± 1.6	86.5 ± 1.7
	Meperidine	88.7 ± 2.1	91.2 ± 1.9	86.1 ± 2.1	85.4 ± 1.7
	Alphaprodine	88.1 ± 1.6	95.7 ± 1.5†	83.4 ± 1.6†	86.4 ± 1.7

* Standard error.
† Statistically significant ($P < 0.05$) change from control.
‡ Three minutes after administration of the initial dose.

you remember? d) Did you feel nauseated? e) Did you vomit? f) Do you have anything unusual to report?

Results

The findings are summarized in tables 1 to 9. Table 1 indicates that within each group the patients in the three subgroups were similar in regard to number, age, sex, anesthetic risk and duration of anesthesia.

Droperidol (table 2) caused a moderate increase in pulse rate. Of the three narcotics, meperidine had little or no effect on pulse. Both fentanyl and alphaprodine decreased pulse rate, but only the alphaprodine-induced slowing of the pulse rate was significant. At the end of anesthesia pulse rate was about the same as the control rate after meperidine, and somewhat lower after fentanyl or alphaprodine in most subgroups.

Droperidol had no significant effect on systolic (table 3) or diastolic (table 4) blood pressure. The effects of the three narcotics on these variables were similar to their effects

TABLE 3. Changes in Systolic Blood Pressure

	Narcotic	Blood Pressure (mm Hg)			
		Control	After Droperidol	After Narcotic	At End of Anesthesia
Group I	Fentanyl	114.9 ± 4.7*	112.6 ± 3.0	113.3 ± 2.8	121.2 ± 3.0
	Meperidine	121.2 ± 2.1	120.3 ± 2.2	118.9 ± 2.5	121.9 ± 2.4
	Alphaprodine	116.4 ± 2.3	115.1 ± 2.8	106.3 ± 2.2†	113.8 ± 2.2
Group II	Fentanyl	135.3 ± 5.8	135.1 ± 5.1	131.1 ± 8.2	133.2 ± 10.0
	Meperidine	125.9 ± 5.1	125.4 ± 5.7	117.2 ± 6.2	126.2 ± 5.8
	Alphaprodine	141.5 ± 4.4	139.2 ± 5.0	119.7 ± 7.3†	131.6 ± 4.5
Group III	Fentanyl	142.4 ± 3.1	138.8 ± 2.7	133.1 ± 3.1	146.7 ± 4.3
	Meperidine	136.4 ± 2.5	133.9 ± 2.5	129.7 ± 2.5	131.4 ± 2.8
	Alphaprodine	134.9 ± 3.0	131.3 ± 3.4	119.1 ± 3.1†	136.1 ± 2.7

* Standard error.
† Statistically significant ($P < 0.05$) change from control.

TABLE 4. Changes in Distolic Blood Pressure

	Narcotic	Blood Pressure (mm Hg)			
		Control	After Droperidol	After Narcotic	At End of Anesthesia
Group I	Fentanyl	71.0 ± 1.1*	70.5 ± 1.6	67.2 ± 1.5	72.2 ± 1.6
	Meperidine	71.4 ± 1.7	71.4 ± 1.5	70.4 ± 1.8	75.9 ± 1.7
	Alphaprodine	68.3 ± 1.5	67.5 ± 1.4	62.2 ± 2.1†	68.2 ± 1.5
Group II	Fentanyl	88.1 ± 5.0	79.2 ± 3.7	78.1 ± 3.5	80.5 ± 2.6
	Meperidine	74.2 ± 3.1	73.8 ± 3.0	71.1 ± 3.1	78.9 ± 3.1
	Alphaprodine	81.5 ± 1.8	79.3 ± 2.6	68.0 ± 3.7†	77.1 ± 4.3
Group III	Fentanyl	78.0 ± 2.3	75.3 ± 1.9	75.9 ± 1.9	88.0 ± 2.0†
	Meperidine	78.2 ± 1.9	78.2 ± 1.6	77.0 ± 1.3	80.8 ± 1.7
	Alphaprodine	79.2 ± 1.8	77.2 ± 2.0	69.5 ± 1.7†	82.9 ± 1.8

* Standard error.
† Statistically significant ($P < 0.05$) change from control.

on the pulse rate. Only alphaprodine caused significant (10 to 15 per cent) decreases in systolic and diastolic blood pressures. The hypotensive effects of the two other narcotics were less marked and not significant. At the end of anesthesia, blood pressures were at or near control levels.

Droperidol caused a moderate, but not significant, decrease in respiratory rate (table 5). In contrast, the three narcotics caused significant 20 to 30 per cent decreases within three minutes after administration. Respiratory rates were slower than control rates at the end of anesthesia, but slowing was not always significant.

The incidences of apnea and ventilatory difficulties (table 5) were highest in the alphaprodine subgroups and about equal in the fentanyl and meperidine subgroups.

The settling μg/kg doses of the three narcotics (table 6) were relatively constant in the three groups: 1.92 to 2.53 for fentanyl; 1,720 to 2,170 for meperidine; and 561 to 739 for alphaprodine. In contrast, as observed

TABLE 5. Respiratory Changes

	Narcotic	Respiratory Rate (Beats/min)				Incidence of Apnea (Per Cent)	Incidence of Ventilatory Difficulty (Per Cent)
		Control	After Droperidol	After Narcotic	At End of Anesthesia		
Group I	Fentanyl	21.8 ± 0.4*	19.6 ± 0.4†	17.9 ± 0.5†	18.8 ± 0.5†	0.0	4.6
	Meperidine	21.7 ± 0.4	20.6 ± 0.4	16.5 ± 0.5†	17.4 ± 0.5†	2.2	5.5
	Alphaprodine	21.4 ± 0.4	20.2 ± 0.5	14.6 ± 0.7†	15.0 ± 0.5†	19.5‡	10.0
Group II	Fentanyl	20.7 ± 1.4	19.0 ± 1.2	15.1 ± 1.2†	16.6 ± 1.2†	0.0	9.1
	Meperidine	21.9 ± 1.4	21.3 ± 2.2	15.5 ± 1.3†	21.3 ± 2.4	15.4	7.7
	Alphaprodine	19.6 ± 1.2	20.0 ± 0.8	13.1 ± 1.1†	15.0 ± 0.9†	34.8‡	26.1
Group III	Fentanyl	20.2 ± 0.6	19.8 ± 0.5	15.7 ± 0.7†	18.7 ± 1.1	2.8	13.2
	Meperidine	20.3 ± 0.5	19.4 ± 0.4	14.1 ± 0.6†	19.6 ± 0.7	4.4	8.8
	Alphaprodine	20.1 ± 0.5	20.2 ± 0.6	14.4 ± 0.8†	18.4 ± 0.9†	19.3‡	14.1

* Standard error.
† Statistically significant ($P < 0.05$) change from control.
‡ Statistically significant ($P < 0.05$) difference from groups I and II.

TABLE 6. Dose Requirements and Degree of Analgesia

	Narcotic	Average Settling Dose of Narcotic (μg/kg)	Average Total Dose of Narcotic (μg/kg/min)	Reaction to Skin Incision (Per Cent)
Group I	Fentanyl	1.92 ± 0.06*	0.07 ± 0.005	10.3
	Meperidine	1720.0 ± 70.0	69.2 ± 3.7	8.3
	Alphaprodine	561.0 ± 21.0	26.5 ± 1.9	6.5
Group II	Fentanyl	2.53 ± 0.22	0.037 ± 0.013	4.5
	Meperidine	1880.0 ± 140.0	27.2 ± 3.1	7.7
	Alphaprodine	739.0 ± 45.0	9.04 ± 1.0	13.0
Group III	Fentanyl	2.28 ± 0.10	0.033 ± 0.002	2.1
	Meperidine	2170.0 ± 90.0	28.2 ± 1.5	10.0
	Alphaprodine	707.0 ± 23.0	10.0 ± 0.4	5.1

* Standard error.

before,[2, 3] the μg/kg/min doses of the three narcotics were greater during anesthesias of short duration (group I) than in anesthesias of longer duration (groups II, III). The incidences of reaction to skin incision, representing error in judgment with regard to depth of anesthesia, did not follow any set pattern, and varied from 4.5 to 12.1 per cent in the various subgroups.

The ratios of the settling and the μg/kg/min doses of the three narcotics (table 7) indicate that on a weight basis, fentanyl is about 750 to 950 times more potent than meperidine and about 250 to 350 times more potent than alphaprodine. Alphaprodine was found to be about 3 to 3.8 times more potent than meperidine.

Evaluation of the states of consciousness of the subjects five minutes after discontinuation of nitrous oxide–oxygen revealed that patients who received fentanyl had higher levels of awareness of their surroundings than those receiving meperidine or alphaprodine (table 8). After fentanyl, 65.8, 77.3, and 72.2 per cent of the patients in groups I, II and III, respectively, were able to answer questions, and only 2.5, 0, and 5.8 per cent in groups I, II and III were nonreactive. Awareness of surroundings was somewhat better in those patients who received alphaprodine than in those given meperidine. The average time required for all patients to answer questions was also lowest after the use of fentanyl, in all three groups.

There were no major differences (table 9) among the various subgroups in the percentages of patients requiring narcotics in the first 24 hours postoperatively. The number of analgesic doses required in the first 24-hour periods and the incidences of nausea and vomiting were also similar in the three subgroups of groups I, II and III.

No signs of extrapyramidal excitation or unusual psychotomimetic effects were observed

TABLE 7. Ratios of the Mean Settling and Maintenance Doses of Meperidine and Alphaprodine to Those of Fentanyl

	Ratios of Settling Doses*			Ratios of Maintenance Doses†		
	Group I	Group II	Group III	Group I	Group II	Group III
Meperidine/fentanyl	896.0	743.1	951.7	974.6	735.1	854.4
Alphaprodine/fentanyl	292.2	292.4	310.1	373.2	244.3	303.0

* μg/kg before skin incision.
† μg/kg/min during anesthesia.

TABLE 8. State of Consciousness Five Minutes After Discontinuation of N_2O

	Narcotic	Patient Answers Questions (Per Cent)	Patient Obeys Commands (Per Cent)	Patient Responds to Stimulation (Per Cent)	No Response (Per Cent)	Average Time to Answering Questions (min)*
Group I	Fentanyl	65.8	14.1	17.6	2.5	7.9 ± 0.8
	Meperidine	44.0	29.7	15.3	11.0	13.9 ± 2.3
	Alphaprodine	42.8	29.9	14.3	13.0	16.7 ± 4.8
Group II	Fentanyl	77.3	18.2	4.5	0.0	7.9 ± 2.5
	Meperidine	38.4	23.1	30.8	7.7	31.4 ± 14.5
	Alphaprodine	43.5	21.8	26.1	8.6	12.9 ± 4.3
Group III	Fentanyl	72.2	14.7	7.3	5.8	10.4 ± 2.7
	Meperidine	56.0	19.1	16.2	8.7	13.3 ± 2.7
	Alphaprodine	68.0	16.6	7.7	7.7	12.3 ± 1.8

* After discontinuation of nitrous oxide–oxygen.

postoperatively. Few patients remembered (although some resented) application of the face mask. The majority of patients were well satisfied with the anesthesia and volunteered the observation that they were less nauseated than after other anesthesias.

Comments

In agreement with earlier experience,[4] droperidol had little or no effect on the circulatory and respiratory variables observed. Following the initial doses of narcotics, only alphaprodine caused significant mean decreases in pulse rate and systolic and diastolic blood pressures. At one time or another during operation, mean pulse rates and systolic and diastolic blood pressures were variously significantly higher and lower than control values in almost all subgroups. At the termination of anesthesia, however, mean values were not significantly different from control values in most subgroups. There were significant decreases in mean respiratory rate after administration of the narcotics in all subgroups. Mean respiratory rates were below control values in all subgroups at the end of operation; however, differences in the meperidine subgroup of group II and in the fentanyl and meperidine subgroups of group III were not significant.

The incidence of apnea after the initial dose of narcotic was significantly higher with alphaprodine than with fentanyl or meperidine.

TABLE 9. Postoperative Narcotic Requirements and Incidence of Nausea and Emesis

	Narcotic	Narcotic Required During First 24 Hours Postoperatively (Per Cent)	Average Number of Narcotic Doses in First 24 Hours Postoperatively	Time of Administration of First Dose of Narcotic (Hours from end of anesthesia)	Nausea (Per Cent)	Vomiting (Per Cent)
Group I	Fentanyl	27.6	2.0 ± 0.2	8.2 ± 1.6	9.3	4.6
	Meperidine	18.9	2.5 ± 0.3	6.2 ± 0.7	12.6	4.6
	Alphaprodine	13.0	1.6 ± 0.2	9.1 ± 1.3	4.0	1.4
Group II	Fentanyl	36.3	2.5 ± 0.2	4.9 ± 1.0	14.3	4.5
	Meperidine	53.8	2.0 ± 0.4	7.6 ± 1.2	15.4	15.4
	Alphaprodine	52.2	1.8 ± 0.2	7.9 ± 1.8	26.1	17.2
Group III	Fentanyl	85.4	2.5 ± 0.2	7.6 ± 0.8	19.7	12.1
	Meperidine	78.0	2.5 ± 0.2	7.0 ± 0.7	19.4	14.9
	Alphaprodine	78.3	2.3 ± 0.2	7.9 ± 0.4	28.0	10.4

Ventilatory difficulties also occurred more frequently with alphaprodine, but the differences were not significant. Although the incidence of these complications may seem relatively high, it should be remembered that every patient, without regard to age or physical condition, received a fixed initial mg/kg dose of one of the narcotics. Subsequent experience with more than 1,000 patients indicates that if the initial dose of narcotic is individualized according to age, physical condition and the presence of complicating pathophysiological factors, the incidence of apnea and/or ventilatory difficulties is significantly less.

The ratios of the settling and maintenance doses of meperidine and alphaprodine to fentanyl (see table 7) were not significantly different. This indicates that durations of the analgesic effects of the different narcotics are about the same. If this were not so, then the ratio of the maintenance doses, which in addition to analgesic potency also reflects duration of analgesia, should be significantly lower for the longer-acting drug than the ratio of the settling doses, which depends only upon analgesic potency.

In view of the seemingly similar durations of analgesic effects of the three narcotics, it is of interest that, judging from the state of consciousness at the termination of anesthesia (see table 8), the intensity and/or duration of the hypnotic effect of fentanyl was less than that of the other two narcotics. These findings suggest the possibility of a dissociation between duration of analgesia and the hypnotic effects of the three narcotics.

In conclusion, fentanyl and meperidine were found more suitable for the production of neuroleptanesthesia in conjunction with droperidol than alphaprodine. Except for the lower incidence of apnea and the more rapid recovery of consciousness at the termination of anesthesia, fentanyl does not seem to have any significant advantages over meperidine as a component of neuroleptanesthesia.

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Muscle

NEUROMUSCULAR TRANSMISSION The facilitation of the end-plate potential amplitude during low-frequency repetitive stimulation, and recovery of the already-facilitated end-plate potential after the termination of repetitive stimulation, were investigated by recording the intracellular end-plate potentials in magnesium-blocked nerve–muscle preparations of the Japanese frog. With brief repetitive stimulation, the amplitude of the end-plate potential increased almost linearly with time, and the rate of increase in the amplitude of the end-plate potential was an exponential function of the stimulation frequency. (*Maeno, T.: Analysis of Mobilization and Demobilization Processes in Neuromuscular Transmission in the Frog, J. Neurophysiol. 32: 793 (Sept.) 1969.*)