

SUPPLEMENTATION OF NITROUS OXIDE ANESTHESIA WITH OPIATES AND A NEW OPIATE ANTAGONIST*†‡

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THE lack of potency of nitrous oxide has given rise to the technique of using other drugs to supplement its action. In recent years, the most popular of these adjuvant drugs has been the ultra short acting barbiturate, pentothal® sodium. The wide acceptance of this combination is evidence that it is a satisfactory form of anesthesia. However, the search for other drugs indicates that it is not entirely ideal. Probably a major fault in this anesthetic technique is the fact that the barbiturates are primarily sedative or hypnotic drugs and less effective in obtundation of painful sensations. The results of using such a drug, then, may be depression of vital functions out of proportion to the amount of anesthesia obtained and production of unnecessary post-anesthetic depression.

In an attempt to avoid this situation, many anesthesiologists have added various opiates to the nonvolatile drugs used to supplement nitrous oxide. The addition of these opiates has appeared to supply useful analgesic function and reduce the amount of barbiturates needed to attain satisfactory anesthesia. However, the depressant effect on respiration, common to all opiates, has kept them from being a completely satisfactory addition. Recently there has been renewed interest in the importance of adequate ventilation and emphasis upon the role played by hypoventilation in bringing about some undesirable events during and after anesthesia (1, 2). It seems undesirable, therefore, to use drugs which almost specifically depress respiration.

N-allyl normorphine hydrochloride is effective in overcoming the respiratory depression produced by narcotic drugs. Another compound of similar properties recently has been made available for investigation. This drug is levo-3-hydroxy-N-allylmorphinan tartrate (generic name levallorphan tartrate). Its relationship to levorphan tartrate § is similar to that of N-allyl normorphine to morphine (fig. 1). This drug was investigated as an antagonist to morphine, meperidine

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§ The tartrate of the levorotatory form of 3-hydroxy-N-methylmorphinan is levo-dromorphan® tartrate (generic name levorphan tartrate).

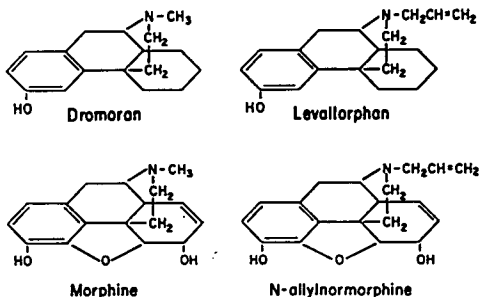


FIG. 1. Structural formulae showing chemical relationship between the two opiates, morphine and 3-hydroxy-N-methylmorphinan, and their antagonists, N-allylnormorphine and 3-hydroxy-N-allylmorphinan.

and levorphan tartrate in animals and man (3-5). It was found to antagonize depression of respiration induced by these drugs and appeared to offer some protection against depression if the opiates were administered subsequent to levallorphan tartrate. In the course of investigation of these drugs rather large doses of opiates were administered to patients who were receiving nitrous oxide anesthesia for operative procedures. It was noticed that although respiratory depression was successfully antagonized, the patients did not awaken or appear to become more lightly anesthetized. It then seemed de-

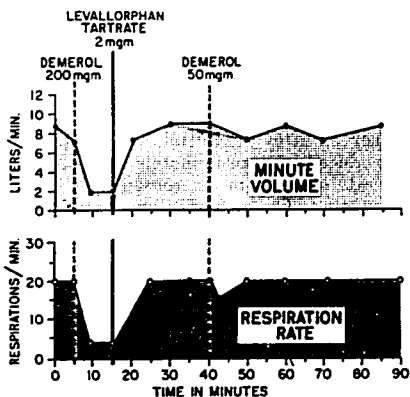


FIG. 2. Graphic representation of respiratory rate and volume of a representative case (Case 27).

sirable to investigate the use of this drug in conjunction with opiates as a supplement to nitrous oxide anesthesia. In other words, could nitrous oxide anesthesia be supplemented by opiates without the disadvantage of respiratory depression?

TECHNIQUE

Forty patients scheduled to undergo surgical procedures requiring minimal relaxation were selected. They were given premedication usually consisting of morphine and scopolamine and occasionally oral barbiturates. Nitrous oxide was administered in nonhypoxic concentrations and opiates were added intravenously in quantities sufficient to produce surgical anesthesia. When respiratory depression appeared, levallorphan tartrate was administered and an attempt made to evaluate the effect upon respiration and depth of anesthesia.

At the outset of the study it was intended that opiates be the only supplemental drug used. It became apparent, however, that these drugs were rather slow in producing sleep and, as a result, very large doses of the drugs were necessary for induction. To avoid this, small doses of pentothal® were used in conjunction with the opiates to induce sleep. If patients required additional supplementary drugs, as evidenced by the usual signs of light anesthesia, small doses of opiates were given intermittently throughout the procedure.

In 9 of these patients, ventilation was measured by means of a ventigrator (fig. 2) and in the remainder, respiratory rate and depth were evaluated by clinical observation. The opiates used as supplements in this study were meperidine and levorphan tartrate. The former was used in 30 cases and the latter in 10 cases. All opiates and the antagonist were given by the intravenous route in a period of time not exceeding five minutes for the initial dosage.

RESULTS

In all patients receiving this form of anesthesia, definite respiratory depression was observed after the initial dose of opiates (tables 1 and 2). Apnea was produced in approximately half of the series. In all cases, respiratory rate and volume increased after the administration of levallorphan tartrate. The response was rapid, usually being apparent in less than one minute, and respiration was maintained without return to previously depressed levels. Levallorphan tartrate appeared to offer protection against undue respiratory depression occurring with subsequent doses of opiates.

In nine of the cases in which meperidine was used, some lightening of anesthesia was noted. This was contrary to earlier observations. Lightening of anesthesia was not seen in the cases in which levorphan tartrate was used. When lightening did occur, the administration of 25 to 50 mg. doses of meperidine appeared to provide additional depth to anesthesia with only slight transient depression of respiration.

TABLE 1

EFFECT OF LEVALLORPHAN TARTRATE UPON MEPERIDINE-INDUCED DEPRESSION OF RESPIRATORY RATE IN 30 SURGICAL PATIENTS

Case	Age, Years	Operation	Initial Dose of Meperidine (mg.)	Depressed Respiratory Rate	Dose of Levallorphan Tartrate (mg.)	Respiratory Rate after Levallorphan Tartrate	Effect on Anesthetic Depth	Pentothal Supplement (mg.)	Total Dose of Meperidine (mg.)
1	79	Radical Mastectomy	100	Apnea	2	16	lighter	none	150
2	28	Carotid Angiogram	200	Apnea	2	16-18	none	275	300
3	63	Below Knee Amputation	100	Apnea	2	18	none	none	100
4	27	Otoplasty	100	Apnea	2	24	lighter	100	175
5	37	Hip Arthroplasty	150	Apnea	2	22	lighter	100	275
6	35	Hernia Repair	75	2	2	12	none	none*	75
7	24	Vein Ligation	100	Apnea	1.5	16	none	100	100
8	75	Hip Nailing	100	5	1.5	14	none	none	200
9	55	Craniotomy	225	7	2	16	none	none	265
10	64	Craniotomy	25	6	1	16	none	150	25
11	55	Carotid Angiogram	300	Apnea	6	20	none	none	475
12	66	Excision of Ear	300	2	1	12	none	none	550
13	29	Caldwell-Luc	150	6	1.5	12	none	250	150
14	17	Harelip Repair	125	5	3	10	lighter	500	200
15	68	Skin Graft	300	Apnea	2	14	none	none	400
16	54	Thyroidectomy	200	4	2	14	lighter	100	200
17	47	Radical Mastectomy	250	Apnea	2	15	?	none	250
18	53	Angiogram	200	Apnea	1	28	none	500	300
19	43	Neck Dissection	450	Apnea	2	16-18	none	none	450
20	40	Arthrodesis of Ankle	300	Apnea	2	16	none	none	400
21		Skin Graft	200	Apnea	2	16	none	350	200
22	44	Bone Graft	300	Apnea	1	14	none	300	175
23	76	Hip Nailing	100	Apnea	2	18	lighter	125	175
24	52	Fothergill	200	Apnea	2	20	lighter	none	275
25	40	Sequestrectomy	200	Apnea	1.5	16	none	200	250
26	13	Triple Arthrodesis	100	Apnea	1.5	18	lighter	325	150
27	32	Skin Graft	200	4	2	20	none	300	250
28	26	Arthroplasty	150	Apnea	2	20	none	75	200
29	71	Bone Graft	60	8	1.25	16	none	125	85
30	59	Parotidectomy	200	Apnea	1.25	18	lighter	275	225

* Patient curarized for relaxation.

For the patients in whom ventilation was measured, minute volumes are indicated in table 3. Tidal volumes were maintained above 400 cc. in all but 2 cases in which the value fell to 330 cc. for a brief period. In none of the patients was any consistent change in circulation noted

TABLE 2

EFFECT OF LEVALLORPHAN TARTRATE UPON LEVORPHAN TARTRATE-INDUCED DEPRESSION OF RESPIRATORY RATE IN 10 SURGICAL PATIENTS

Case	Age, Years	Operation	Dose of Levorphan Tartrate (mg.)	Depressed Respiratory Rate	Dose of Levallorphan Tartrate (mg.)	Respiratory Rate after Levallorphan Tartrate
31*	44	Herniorrhaphy	14	Apnea	1	16
32	69	Orchiectomy	5	11	.5	18
33	25	Tubal Ligation	9	4	.9	12
34	57	Dilatation and Curettage, Biopsy	10	14	1	18
35	65	Colon Resection	5	9	.5	14
36	71	Inguinal Node Dissection	5	8	.5	18
37	57	Fothergill	6	10	.6	20
38	36	Cystocele Repair	5	12	.5	18
39	68	Cystocele Repair	8	6	.6	12
40	70	Radical Mastectomy	6	5	.6	16

* This case is identical with patient C. K. listed in table 1 (Hamilton and Cullen). *Anesthesiology* 14: p. 551 (Nov.) 1953.

even with the largest doses of opiates. A few patients exhibited increase in generalized muscle tone after administration of the opiates. This immediately disappeared after the injection of levallorphan tartrate.

TABLE 3

EFFECT OF LEVALLORPHAN TARTRATE UPON LEVORPHAN TARTRATE AND MEPERIDINE-INDUCED DEPRESSION OF RESPIRATORY VOLUME IN 9 SURGICAL PATIENTS

Case*	Opiate Used and Dose	Depressed Minute Volume (cc.)	Dose of Levallorphan Tartrate (mg.)	Respiratory Minute Volume after Levallorphan Tartrate (cc.)
32	Levo Dromoran® Tartrate 5 mg.	4400	0.5	7400
33	Levo Dromoran® Tartrate 9 mg.	2600	0.9	7500
34	Levo Dromoran® Tartrate 10 mg.	5950	1.0	11700
25	Demerol 200 mg.	Apnea	1.5	9000
26	Demerol 100 mg.	Apnea	1.5	8600
27	Demerol 200 mg.	2000	2.0	9500
28	Demerol 150 mg.	Apnea	2.0	8200
5	Demerol 150 mg.	Apnea	2.0	7800
16	Demerol 200 mg.	1900	2.0	8200

* Number designations correspond to case numbers in tables 1 and 2.

The combination of nitrous oxide, opiate and antagonist provided adequate anesthesia for a wide variety of surgical procedures. In the absence of a muscle relaxant this technique did not provide sufficient muscular relaxation for intra-abdominal operations.

It was noted that although respiratory depression was antagonized the patients who received large amounts of opiates were frequently quite sleepy after operation and some continued to sleep for several hours after return to their rooms. No untoward effects of levallorphan tartrate have been noted in this series.

DISCUSSION

The evaluation of a drug sequence such as this in terms of definite specific results is very difficult. The inability to measure objectively and accurately the analgesic or anesthetic activity, or both, of a drug forces reliance upon clinical impression. Therefore, the value of this technique will be determined only after more extensive exploration by many more investigators. This report is not intended to advocate this combination of drugs as being superior to any currently used anesthetic agents or techniques. It does seem certain that this drug is an effective antagonist to opiate-induced respiratory depression. It also appears that some effect of the opiates used in this study may remain unantagonized, which provides useful supplementation of nitrous oxide anesthesia. This observation is consistent with those previously made. The fact that some awakening or lightening of anesthesia was noted in 9 cases suggests that the degree of antagonism of the effects of the opiates used is a function of relative dosage ratios. However, no definite ratio of opiate to antagonist has been found which antagonizes respiratory depression and does not antagonize other effects of the opiates.

One of the more interesting observations in this investigation was the increased muscle tone that appeared not infrequently after administration of opiates. This increased tone often was sufficient to interfere significantly with ventilation and suitable operating conditions. It was promptly and completely relieved after administration of the antagonist. It is possible that this effect could be attributable to correction of deficiencies in ventilation coincident to opiate-induced respiratory depression. The relief was so immediate, however, that it seems unlikely that hypoventilation could account entirely for the rigidity.

Lightening of anesthesia after the administration of the antagonist was noted in 9 patients receiving meperidine, but not in patients receiving levorphan tartrate. This difference may be attributable to dose relationships. It also may be the result of a fundamental difference in the pharmacologic activity of the two opiates employed.

SUMMARY

The investigation of narcotic drugs in clinical situations is exceedingly interesting and confusing. It is emphasized that the material presented herewith permits no definite conclusions. The observations reported, however, warrant extended study of the combination of drugs. It may be that safer and more satisfactory anesthesia will be the result. It may be also that more precise information on the action of narcotic drugs will be obtained.

ACKNOWLEDGEMENT

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