N-ALLYL NORMORPHINE: AN ANTAGONIST TO THE OPIATES * † ‡

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ANESTHESIOLOGISTS frequently plan treatment for a patient who has received an actual or relative overdose of an opiate. Similarly, they are often called upon to advise therapy for an infant with asphyxia neonatorum. In infants and adults in whom depression is not excessive, supportive therapy and mild stimulants such as caffeine or ephedrine have proved adequate. In more heavily narcotized individuals, the results of treatment have not been altogether satisfactory. Within the past year studies have indicated that a hitherto clinically untried drug, *n*-allyl normorphine, is an effective antagonist to opiate depressions and may prove to be a valuable adjunct to the list of drugs employed in the practice of anesthesiology. The present paper can be considered a progress report of investigations of *n*-allyl normorphine continuing at the University of Pennsylvania.

The ability of *n*-allyl normorphine to reverse the respiratory depression produced in animals by large doses of morphine was first described by McCawley, Hart and Marsh (1) in 1941. Since that time, however, little interest has been manifest in the drug except for two studies in animals (2, 3) and several abstracts (4, 5, 6). One abstract has reported an investigation of the drug in opiate addicts (7).

We became interested in *n*-allyl normorphine about nine months ago and have since administered it to about 400 patients. In a previous report (8) we described this agent as an effective antagonist to narcosis produced by large doses of morphine sulfate or meperidine hydrochloride but ineffective in counteracting the depression produced by cyclopropane, ethyl ether and thiopental. In patients given 20 to 90 mg. of morphine sulfate or 200 to 600 mg. of meperidine, intravenous administration of 5 or 10 mg. of *n*-allyl normorphine doubled or tripled the respiratory rate and increased respiratory minute volume as much as

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250 per cent. These effects reached a peak within one to two minutes, then declined gradually, but both values remained above the depressed levels for the sixty minute period of observation. In addition to respiratory stimulation, normorphine caused an elevation of blood pressure when it had been depressed by the narcosis. It was noted that, in the doses used, the antagonist seemed to have little awakening effect. An unexpected action was that when given in 5 or 10 mg. doses to normal volunteer subjects, the drug produced a depression of respiration and blood pressure.

Our subsequent studies have progressed along two general lines. The first was an attempt to determine which of the opiates can be antagonized by *n*-allyl normorphine. The second involved exploration of the drug in counteracting neonatal depression produced by the administration of sedative and analgesic drugs to the mother in the final stages of labor.

METHODS

The methods of study were as follows: In the first, large doses of various opiates were administered before and during nitrous oxide-oxygen anesthesia for minor operations. Following the completion of the surgical procedure, respiratory minute volume and rate were measured by means of a small spirometer. Blood pressure was recorded by ordinary ausculatory methods. *N*-allyl normorphine § was injected rapidly intravenously in 10 to 40 mg. doses after a suitable period of observation. The effect of the drug was observed for a period varying from one to twelve hours. The details of this method are described in our previous report (8).

In the second or obstetric study, *n*-allyl normorphine in 10 mg. doses (2 cc.) or 2 cc. of physiologic saline solution was injected intravenously into almost every patient admitted for delivery at the Hospital of the University of Pennsylvania. The nature of the injected solution was unknown to anyone in the delivery room, since all ampules were identical and were labeled by numbers only. The drug was administered as the patient was placed on the delivery table, usually about ten minutes before birth of the infant. Nitrous oxide-oxygen was administered to all but 19 of the 270 patients to be reported here. In 40 per cent of the cases ethyl ether was used as a supplement to the nitrous oxide. In the 19 patients not receiving the above agents, the mode of anesthesia was caudal, spinal, local or none. Observations of the labor and delivery were recorded by the anesthetist and obstetricians on a specially prepared form. The data comprise a preliminary report of this particular phase of the work.

RESULTS

Study I.—*N*-allyl normorphine has been administered to 2 patients who had received 80 to 100 mg. of pantopon, 3 patients who received 6

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to 8 mg. of dilaudid, 2 patients who were narcotized with 19 to 20 mg. of methadone, one patient given 60 mg. of morphine sulfate, and 2 patients narcotized with 150 and 200 mg. of seconal sodium. The antagonist was equally effective against all of these drugs (figs. 1, 2 and 3) except seconal sodium, where it was ineffective despite the largest doses of *n*-allyl normorphine used in the entire study (table 1). The character of the change was similar to that reported by us for morphine sulfate and meperidine (8).

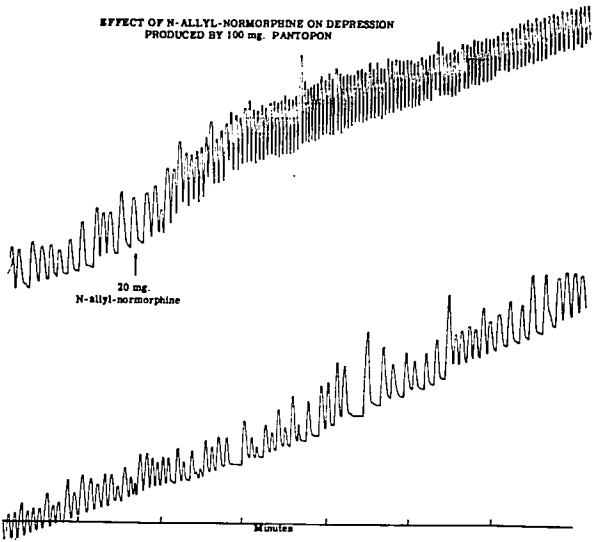

FIG. 1.

A number of observations made in this study supplement those reported previously (8). First, larger doses of *n*-allyl normorphine were more effective than the 10 mg. doses used in the first study. Second, in some patients the larger doses produced a rise in blood pressure even though the pressure had not been depressed by the narcosis. The rise was of the order of 30 to 40 mg. and was maintained above the control level for twenty to thirty minutes. In our earlier report, it was noted that a vasopressor effect was apparent only if hypotension pre-existed. Third, when an awakening action was evident, it was sometimes marked but was not sustained, for over the period of the following thirty minutes the patient would go back to sleep.

N-allyl normorphine was also administered to a patient suffering from an overdose of opiates as follows. The patient (B. C.), age 27 years, was 69 inches tall and weighed 152 pounds. For preanesthetic medication she had received 10 mg. of morphine sulfate and 0.4 mg. of scopolamine hydrobromide at 8:30 a.m. An uncomplicated hemorrhoidectomy was performed under low spinal anesthesia. Because of severe rectal pain, 8 mg. of morphine sulfate was injected intramuscularly at 12:00 noon and repeated at 12:30 p.m. Pain was relieved until 3:00 p.m. when 100 mg. of demerol was injected intramuscularly because of return of discomfort. Within ten minutes the patient became

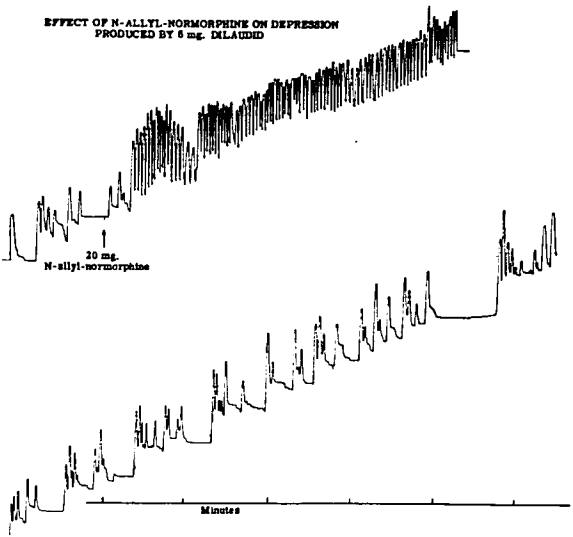

FIG. 2.

somnolent and began to perspire. Respiratory depression ensued and cyanosis was evident. During the next few minutes respiratory effort diminished to a gasp every thirty to forty seconds. The patient could not be aroused by painful stimuli. The pulse was strong and there was no apparent evidence of circulatory collapse although the blood pressure was not taken at that particular time. Artificial respiration was instituted and maintained by means of a bellows resuscitator. When the anesthesiologist arrived, respiratory efforts consisted of one or two gasps a minute, and cyanosis continued despite artificial respiration. Ten milligrams of *n*-allyl normorphine were injected intravenously

Within thirty seconds regular diaphragmatic breathing began and within another minute the respiratory rate was 24 per minute, with a satisfactory respiratory exchange. The color improved and the patient began to respond. Within several minutes the patient opened her eyes if spoken to. Her condition improved steadily after this episode.

Study II.—The preliminary results of the investigation of the use of the drug in obstetrics are summarized in tables 2, 3 and 4. We have excluded from these statistics all cases in the following categories: (1) Those in which we had reason to believe the drug had not been delivered into the infant's circulation. This included those instances in which

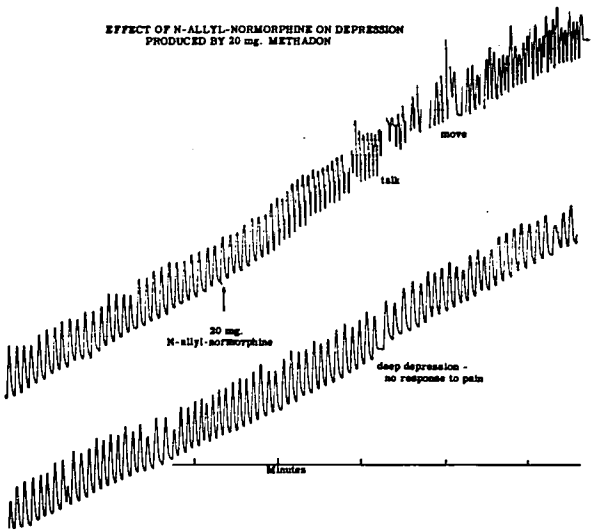

FIG. 3.

the drug was not completely injected intravenously, in which it had been injected less than four minutes or more than forty minutes before delivery. The figures of 4 and 40 are arbitrary and should not be interpreted as having been selected on the basis of evidence to indicate destruction of the drug or the time required to cross the placental barrier. (2) Those cases in which interpretation of the results was made difficult by the presence of unusual birth trauma or the delivery of twins.

The patients included in table 2 are those who were considered by the anesthesiologist to be (1) moderately depressed (no response to name or questions but response to pain stimuli), or (2) deeply depressed

TABLE 1

Effect of *N*-allyl Normorphine Administered Intravenously on Respiratory Minute Volume and Rate, Pulse Rate and Blood Pressure of Subjects Receiving Various Opiates

M.V. = minute volume in cc./minute
R.R. = respiratory rate/minute
P.R. = pulse rate/minute
B.P. = systolic and diastolic pressure in mm. Hg

Subject's age and weight are listed in first column, together with the total dose of the opiate administered and the dose or doses of *n*-allyl normorphine. Analeptic effect is graded from + = mild, to +++ = marked. J. M. is the only male.

	Control				After injection								
					1–2 min.				3–5 min.				Analeptic Effect
	R.R.	M.V.	P.R.	B.P.	R.R.	M.V.	P.R.	B.P.	R.R.	M.V.	P.R.	B.P.	
A. Pantopon													
K. R. 44–112 lbs. 80 mg. pantopon 10 mg. normorph.	8	4010	88	114/70	12	5310	—	—	17	7140	—	120/74	0
A. W. 49–129 lbs. 100 mg. pantopon 20 mg. normorph.	8	1380	72	106/70	20	4830	—	—	19	3820	—	150/96	+
B. Dilaudid													
L. T. 51–140 lbs. 6 mg. dilaudid	8	2730	64	94/60	15	6030	—	—	15	5125	48	110/70	+
20 mg. normorph. and in 40 min. another 15 mg.	14	4220	76	120/78	17	5810	80	140/70					++
J. M. 16–107 lbs. 8 mg. dilaudid 20 mg. normorph.	12	4100	—	150/90	25	9000	—	—	25	7500	104	160/104	++
E. S. 33–135 lbs. 6 mg. dilaudid 20 mg. normorph.	6	1140	—	106/54	19	4900	—	—	23	4180	—	144/94	+
C. Methadon													
J. C. 54–161 lbs. 10 mg. methadon 15 mg. normorph.	20	6070	88	140/90	17	6840	—	—	20	7240	—	—	++
R. B. 35–115 lbs. 20 mg. methadon 20 mg. normorph.	9	1770	72	115/80	13	2570	—	—	18	3320	80	124/86	++
D. Morphine													
E. W. 53–139 lbs. 60 mg. morphine 20 mg. normorph.	apnea 105 sec.		76	144/90	15	9050	84	154/94	would not tolerate mask				++
E. Secobarbital Sodium													
D. J. 22–115 lbs. 150 mg. secobarb. 30 mg. normorph.	9	3330	56	100/60	10	4000	—	—	11	3520	60	105/70	0
E. S. 44–138 lbs. 200 mg. secobarb. 40 mg. normorph.	15	4340	—	—	15	3900	—	—	14	3640	—	—	0

(no response to pain). In these two groups the average sedative and analgesic medication consisted of 0.2 to 0.3 Gm. of secobarbital sodium, 200 mg. of meperidine and 0.7 mg. of scopolamine hydrobromide administered over an average of five hours before delivery. As can be seen from table 2, the time required for the infant to take his first gasp and to establish respiration was approximately twice as great in the control group. Statistically, these differences are highly significant.

In table 3 are listed those patients classified as being mildly depressed, that is, the patient would go to sleep if left undisturbed, but

TABLE 2

MODERATELY OR DEEPLY DEPRESSED

	N-allyl Normorphine	Control	t Value
Number of patients	33	30	
Time to gasp (sec.)	19.2±18.5	34.9± 33.7	2.28*
Time to establish cry (sec.)	51.2±55.4	104.4±102.7	2.57*

TABLE 3

MILDLY DEPRESSED

	N-allyl Normorphine	Control	t Value
Number of patients	56	48	
Time to gasp (sec.)	23.7±20.7	36.7±45.8	1.89
Time to establish cry (sec.)	72.3±79.7	90.1±94.3	1.02

TABLE 4

NOT DEPRESSED

	N-allyl Normorphine	Control	t Value
Number of patients	43	45	
Time to gasp (sec.)	32.4±30.7	27.5± 32.9	0.66
Time to establish cry (sec.)	72.2±70.1	86.1±151.6	0.48

* Indicates high statistical significance.

would awaken during uterine contractions. The average sedation consisted of 0.2 Gm. of secobarbital sodium in 50 per cent of this group of patients and no barbiturate in the remainder, 150 mg. of meperidine and 0.6 mg. of scopolamine hydrobromide administered during an average of four hours before delivery. The averages of the times required for the infant to gasp and to establish respiration are higher in the control groups but are not as statistically significant as in the more depressed group.

Table 4 contains the data from those patients considered to be not depressed and who were alert mentally. In this group the average

medication was 0.2 Gm. of secobarbital sodium in 20 per cent and no barbiturate in the remainder, 100 mg. of meperidine and 0.4 mg. of scopolamine hydrobromide administered in an average of two hours and forty minutes before delivery. The differences between the two groups were not statistically significant.

On several occasions *n*-allyl normorphine was injected directly into the umbilical vein of a depressed newborn infant. The dose used was 0.1 mg. in 2 cc. of solution. The indications for such therapy were failure of an infant to breathe, cyanosis or poor muscle tone. On each occasion the result was most satisfactory, with establishment of respiration within one minute and improvement in color and muscle tone.

It was notable that there was no stimulation of the mothers with the amounts of *n*-allyl normorphine used. Actually it was the consensus of the anesthesiologists that the depression of the patients was somewhat deeper than usually noted following completion of the delivery and repair of the episiotomy. This, however, was never of great concern and was not thought to be a deterrent to the use of the drug. There were no instances of undesirable effects or side reactions of the drug either in the mothers or infants. There were no antenatal or neonatal deaths in this series.

COMMENT

From the data presented it is apparent that *n*-allyl normorphine is an effective antagonist to depression produced by morphine, meperidine, pantopon, dilaudid and methadone. Although we have not as yet attempted to antagonize the depression that can be produced by metapon, we intend to do so in the near future. We have now had occasion to use the drug clinically four times in the treatment of opiate overdosage, with a satisfactory result each time. Frazer, Wikler, Eisenman and Isbell (9) have prepared a report for publication in which they describe the successful treatment of 2 patients with severe methadone poisoning. It will take time, however, to evaluate the real place the drug is to take as a therapeutic agent in the treatment of narcotic poisoning.

Our data do not yet enable us to state the optimal dose of this agent. We have seen no untoward reactions from any dose so far employed. It is probable that large doses can be used without danger in the presence of severe depression, thus following the experience common to all analeptic drugs.

Our data also indicate that *n*-allyl normorphine is a specific antagonist to depression produced by the opiates and is not effective against depression produced by other depressants of the central nervous system. In the doses we have employed it has been useless in depressions produced by cyclopropane, ethyl ether, thiopental and secobarbital sodium.

The figures presented in tables 2, 3 and 4 prove that the drug is valuable for the obstetrician and others concerned with the prevention

and treatment of neonatal asphyxia and depression. The ultimate role of the drug will depend upon the accumulation and careful analysis of a series of cases many times larger than the one here reported; this we are doing. These data will have to be analyzed from many additional aspects and not from the single viewpoint mentioned in this report. We are aware that the division of the cases on the basis of maternal depression may be improper and misleading, since it may not necessarily indicate the status of the infant.

It should be emphasized that *n*-allyl normorphine cannot be considered a panacea for all neonatal respiratory and circulatory difficulties. As mentioned previously, the drug is not an effective antagonist to barbiturates, and all of these moderately and deeply depressed obstetric patients had received barbiturates. Also, depression basically due to trauma of delivery, nuchal cord with resultant asphyxia, premature placental separation, intra-uterine pulmonary infection, or other similar conditions obviously cannot be affected by the drug. One of the infants born of a mother who had received *n*-allyl normorphine failed to breathe for five minutes after delivery. Not enough data are available as yet to analyze why this occurred. However, such instances are less common than in the control group, as is indicated by the statistics.

There are however, many intriguing aspects of the obstetric use of the drug which will bear investigating. A few are: (1) Can *n*-allyl normorphine be given simultaneously with meperidine to prevent fetal depression? (2) Will this drug enable medication to be given intravenously to mothers who are in rapidly progressing labor on admission? (3) Will a large series prove the antagonist satisfactory when administered into the cord vein of depressed infants?

SUMMARY

N-allyl normorphine has been shown to be an effective antagonist to depression produced in man by morphine, meperidine, pantopon, dilaudid and methadone.

In 255 obstetrical patients, *n*-allyl normorphine significantly shortened the interval between the delivery of the chin and the infant's first gasp or establishment of respiration when the child was born of a mother in a moderate or deep state of depression caused by analgesics and sedatives.

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THE AMERICAN BOARD OF ANESTHESIOLOGY

Written examinations of the American Board of Anesthesiology will be held in various locations, July 18, 1952. The oral examinations will be held in Swampscott, Massachusetts, September 28-October 1, 1952.

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Written examinations for candidates for Fellow of The American College of Anesthesiologists will be held in various locations on October 18, 1952. Candidates wishing to take the examination must file their applications in the office of the College not later than July 18, 1952. These applications should be sent to: The American College of Anesthesiologists, 137 West 11th Street, New York 11, New York.