EFFECT OF LEVALLORPHAN TARTRATE UPON OPIATE INDUCED RESPIRATORY DEPRESSION * †

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N-ALLYLNORMORPHINE has been reported to be an effective antagonist to the respiratory depression induced by morphine, demerol®, dl dromoran® (racemic 3-hydroxy-N-methylmorphinan hydrobromide), methadone, codeine, dilaudid, and pantopon in animals and man (1, 2, 3, 4). More recently another drug has been investigated in laboratory animals (5, 6). This drug is 3-hydroxy-N-allylmorphinan and chemically bears a relationship to dl dromoran similar to that of N-allylnormorphine to morphine. This new drug was found to be an effective antagonist to respiratory depression and analgesia induced by dl dromoran hydrobromide, levo dromoran tartrate (levo 3-hydroxy-N-methylmorphinan tartrate), codeine, and nisentil® hydrochloride. Salts of both the racemic form and the optical isomers of 3-hydroxy-N-allylmorphinan were investigated and it was determined that all the antagonistic activity was possessed by the levo rotatory isomer, the tartrate of which, designated as levallorphan tartrate, was used in this study.

The purpose of this study was to extend the investigation of the effects of levallorphan tartrate by observing the influence upon respiratory depression caused by overdose of opiates on man. Opiates have been used as a supplement to nitrous oxide anesthesia and have always produced, as an undesirable effect, a significant degree of respiratory depression. Therefore, it was considered desirable to note whether nitrous oxide anesthesia could be induced or maintained with opiates or similar drugs if the respiratory depression was eliminated by an antagonist.

To investigate these problems, 19 patients scheduled to undergo surgical procedures that required minimal relaxation were used. These were divided into two groups. The first group, consisting of 14 patients, was anesthetized with nitrous oxide-oxygen in nonhypoxic concentration supplemented by deliberate overdoses of one of three opiates—levo dromoran tartrate, demerol and morphine. These three drugs were given intravenously in sufficient dosage to produce definite

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† Levallorphan is the generic name of 3-hydroxy-N-allylmorphinan and was originally designated as Ro 1-7700.

respiratory depression as well as to provide adequate supplement to the nitrous oxide. Anesthesia having been established and the operative procedure begun, the antagonist was administered intravenously, the effects upon respiration were noted and an attempt was made to determine clinically any effect on the level of anesthesia. In the other group of 5 patients, the antagonist was given first, followed by the analgesic drugs given in appropriate doses and during a short enough interval of time to expect respiratory depression. Nitrous oxide-oxygen was then administered and effects upon respiration were noted and operations performed. In all cases the opiates used were administered during a time interval not exceeding twenty minutes. In some patients respiratory minute volume was measured by means of a ventigrator (7), and in others respiratory patterns were recorded with an electrically recording pneumotachograph. In all patients in whom it was thought that respiration was inadequate, support by manual intermittent positive pressure breathing was provided to minimize the effects of hypoventilation.

The results in treating or preventing respiratory depression are shown in tables 1, 2, 3 and 4. Two typical pneumotachograph tracings are shown in figures 1 and 2. In all patients and with all three analgesic

TABLE 1

EFFECT OF LEVALLORPHAN TARTRATE UPON LEVO DROMORAN® TARTRATE INDUCED RESPIRATORY DEPRESSION

Patient	Age	Levo Dromoran Tartrate, mg.	Levallorphan Tartrate		Respiratory Rate (respirations per minute)			Respiratory Volume (liters per minute)		
			Dose, mg.	Time after Last Analgetic, minutes	Control	Depressed	After Levallorphan Tartrate	Control	Depressed	After Levallorphan Tartrate
N. G.	53	6	5	30	28	8	32			
C. B.	49	10	2.5	15	20	6 to 8	18			
H. R.	68	4	2.5	15	16	apnea	18			
C. K.	44	14	1	5	16	apnea	16			
N. R.	23	8	5	60	20	5 to 7	18			
F. P.	30	10	1	20	20	12	18	7	2.5	6.5

TABLE 2

EFFECT OF LEVALLORPHAN TARTRATE UPON MORPHINE INDUCED RESPIRATORY DEPRESSION

Patient	Age	Morphine, mg.	Levallorphan Tartrate		Respiratory Rate (respirations per minute)			Respiratory Volume (liters per minute)		
			Dose, mg.	Time after Morphine minutes	Control	Depressed	After Levallorphan Tartrate	Control	Depressed	After Levallorphan Tartrate
V. F.	21	40	1	7	20	6	18	10.5	4	11
H. B.	60	45	2	60	19	12 to 14	26			
A. B.	37	65	1	20	16	8	15			
M. V.	34	60	1	20	20	5	15	9	2.5	11

TABLE 3

EFFECT OF LEVALLORPHAN TARTRATE UPON DEMEROL INDUCED RESPIRATORY DEPRESSION

Patient	Age	Demerol, mg.	Levallorphan Tartrate		Respiratory Rate (respirations per minute)			Respiratory Volume (liters per minute)		
			Dose, mg.	Time after Last Demerol, minutes	Control	Depressed	After Levallorphan Tartrate	Control	Depressed	After Levallorphan Tartrate
R. C.	55	200	2.5	20	16	apnea	16			
T. L.	38	350	2.5	10	18	6	16			
H. N.	39	175	2.5	20	20	12	22			
J. F.	37	200	1.25	10	18*	0–2	20	7*	0	11

* Values obtained after 10 mgs. of Morphine, intravenously.

TABLE 4

PROTECTIVE EFFECT OF LEVALLORPHAN TARTRATE AGAINST OPIATE INDUCED RESPIRATORY DEPRESSION

Patient	Age	Analgetic Type	Analgetic Drug Dose, mg.	Levallorphan Tartrate Dose mg.	Respiratory Rate (respirations per minute)		
					Control	After Levallorphan Tartrate	After Analgetic
J. S.	71	Levo Dromoran ® tartrate	18	2.5	22	18–20	16–18
F. S.	38	Levo Dromoran ® tartrate	8	5	20	18	18
J. K.	63	Demerol ®	400	5	18	14	14
W. K.	66	Demerol ®	300	5	22	20	20
J. S.	65	Morphine	60	5	14	13	13

drugs, the antagonist proved to be effective. The effect was apparent within one minute, and was of such magnitude as to leave no question in the observer's mind that the depression was antagonized quite effectively. After an initial peak response, there was some decrease in effect, but in patients observed for as long as four hours, there was nothing approaching the previously depressed levels. Despite the rather large doses of opiates used in a short period, there were no instances of circulatory depression seen and the effect of levallorphan tartrate upon such depression cannot be evaluated. The time interval between administration of the opiate and of the antagonist seemed to make no difference in its effect. Once respiration had returned to initial levels, additional levallorphan tartrate had no effect upon it. In the group in which levallorphan tartrate was given first, relatively large doses of opiates did not produce the expected respiratory depression and it was also noted in the first group that once respiratory depression had been antagonized additional doses of opiate as needed to supplement the anesthesia did not depress respiration.

Although no quantitative measurements can be made, it appeared quite definitely that the combination of any one of these narcotics and

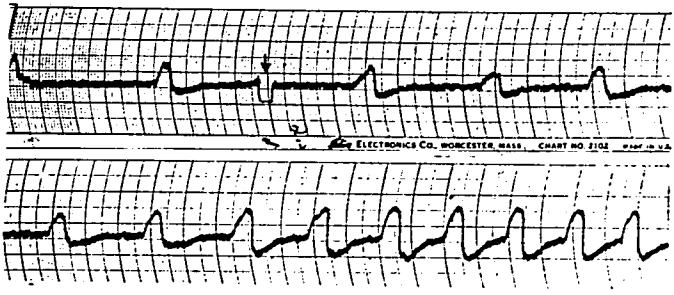

FIG. 1. Continuous pneumotachograph tracing showing increase in rate and depth of respiration following intravenous injection of levallorphan tartrate. The patient had previously been given 4 mg. of levo dromoran® tartrate. Arrow indicates administration of levallorphan tartrate.

levallorphan tartrate did provide a supplement to nitrous oxide anesthesia without the disadvantage of respiratory depression. In no patient was the abolition of respiratory depression accompanied by decrease in depth of narcosis. On the contrary, on some occasions a pronounced degree of rigidity and increased muscle tone were noted with nitrous oxide and opiate alone which disappeared immediately upon administration of the antagonist. It was also noted on two occasions that in patients who had had respiratory depression abolished some sixty minutes previously, anesthesia would "become light" and the patient would move or otherwise respond to the surgical stimulus. When they were given additional doses of opiate, the anesthesia deepened and respiration was not affected. This fact suggests that there is

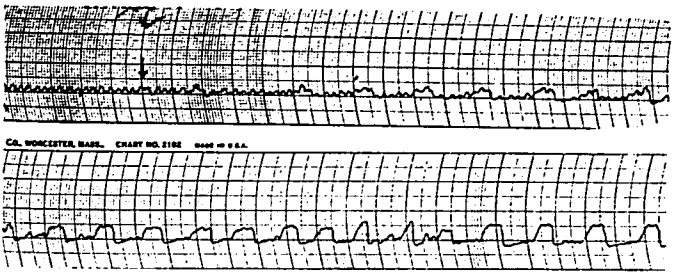

FIG. 2. Continuous pneumotachograph tracing showing recovery from apnea induced by 8 mg. of levo dromoran® tartrate after injection (at arrow) of 2.5 mg. levallorphan tartrate.

some effect of the opiate drugs which is not antagonized by this drug and which acts in some manner to supplement nitrous oxide in maintaining anesthesia. Studies investigating this problem are now underway at this institution.

When given alone and prior to the analgesic drug, levallorphan tartrate appeared to be slightly sedative in its action. It did not stimulate respiration nor in any way act as a stimulant. In this small series no undesirable effects of the drug were noted.

SUMMARY

The levo isomer of 3-hydroxy-N-allylmorphinan tartrate (levallorphan tartrate) is an effective antagonist to the respiratory depression produced by levo dromoran tartrate, morphine and demerol. When administered prior to these drugs, it protects against respiratory depression.

The findings suggest that although respiratory depression is abolished, some action of the opiate drugs used persists which enables them to serve as an effective supplement to nitrous oxide anesthesia. Additional observations are in progress relating to this matter.

ACKNOWLEDGMENT

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