A REVIEW OF OXYMORPHONE HYDROCHLORIDE (NUMORPHAN*) ANALGESIA EMPLOYED FOR GENERAL SURGERY

Including Clinical Experience With Five Hundred and Twenty-Eight Patients

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THIS paper presents a clinical evaluation of the synthetic analgesic, oxymorphone hydrochloride (Numorphan*), when used for preoperative medication, as a supplementary agent during general anesthesia, and for the relief of postoperative pain.

Chemical and Physical Properties of Numorphan

Numorphan hydrochloride is a colorless salt that has one molecule of water of crystallization. It is freely soluble in water and sparingly soluble in alcohol. The base melts in a temperature range from 248 to 249 C., and is readily soluble in acid and alkaline solutions. It is also soluble in chloroform and in acetone, and moderately soluble in ethanol and in benzene. The solution of the hydrochloride is stable at room temperatures and is not decomposed by light. It is miscible with atropine and thiopental and sodium without precipitation.

Figure 1 shows the chemical structure of Numorphan. It is an alkaloid, differ-

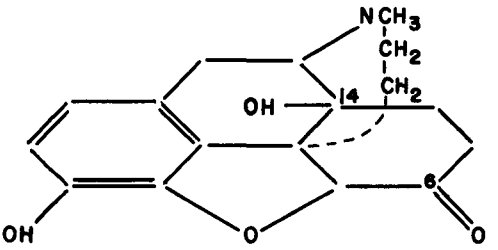

Fig. 1. Chemical structure of Numorphan (l-14-hydroxydihydromorphinone).

ing from dihydromorphinone by the addition of a hydroxyl group at the fourteenth position of the phenanthrene ring.

Numorphan hydrochloride, Endo Laboratories Inc.
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Pharmacologic Properties of Numorphan Experimentally Deduced

In an experimental study Eddy and Lee[1] established that in humans, 1.02 mg. of Numorphan is equivalent to 10 mg. of morphine. Blumberg, Carson, and Stein[2] found that in mice doses exceeding therapeutic concentrations produced bradycardia. Blumberg and Carson[3] reported that Numorphan was not so constipating as morphine administered in equivalent doses. They[2,3] reported that N-allylnormorphine hydrochloride (Nalline*) reversed the respiratory depression induced by Numorphan.

It is postulated[4] that Numorphan possesses a certain amount of the so-called "tranquilizing" effect of such compounds.

Operative Administration in Humans

Previous clinical trials utilizing Numorphan indicate it may be sucessfully administered orally, rectally, or parenterally.

Preoperative medication. Numorphan as a preoperative medication was evaluated[5-7] when administered subcutaneously, intramuscularly, or orally in 513 patients. Coblentz and Bierman[5] commented on the absence of untoward side-effects, particularly of gastrointestinal disturbance, before and during surgery. They employed doses of 1 mg. of Numorphan with 0.4 mg. of atropine. In 38 patients who received intravenous injections of from 0.3 to 1 mg. of Numorphan in combination with 100 mg. of pentobarbital sodium two hours before operation, one patient had some respiratory depression; however, there was no evidence of respiratory depression in the other 37 patients, nor in those patients who received only Numorphan and atropine.[6]

McInnes, Engler, and Saliba[7] considered Numorphan to be a potent drug, with a low incidence of side-effects and offering a wide margin of safety. Appleton[8] prefers Numorphan as premedication before spinal analgesia or fluothane anesthesia.

Use during anesthesia. The use of Numorphan during anesthesia for operations on the head and neck was reported by Seigleman and Wasmuth.[9] They were impressed by the profound analgesia induced by this drug, and the patient's early return to consciousness and regaining of the vital reflexes. They also found a synergistic effect with thiopental sodium in producing respiratory depression, and used this to advantage. They augmented the analgesic action of Numorphan by hyperventilating their patients with nitrous oxide and oxygen mixtures; i.e., by creating a "narcotic-induced controlled apnea" similar to that produced by Foldes[10] with alphaprodine hydrochloride (Nisentil†).

Appleton,[8] on the other hand, purposely avoided the respiratory depressant action, when using the drug in combination with thiopental sodium, by reducing

**Nalline hydrochloride, Merck, Sharp & Dohme.*

†Nisentil hydrochloride, Roche Laboratories.

the dose of thiopental sodium to between 100 and 125 mg. He believed that the recovery time of the patient was prolonged when larger doses of thiopental sodium were used. When employing fluothane anesthesia, however, he noted that the narcotic action was useful in reducing the amount of fluothane required, and also for counteracting the tachypnea sometimes associated with fluothane anesthesia. He recommended that small increments (0.2 mg.) of the drug be administered intravenously during fluothane anesthesia.

Postoperative Analgesia

Numorphan also has been injected subcutaneously and intramuscularly for postoperative analgesia.[5] In 811 patients who received subcutaneous injections of from 0.5 to 1 mg. of Numorphan, effective analgesia was maintained for from three to six hours.[5] Other anesthesiologists[6] injected doses of from 0.5 to 1 mg. intramuscularly or subcutaneously into their patients, and found that adequate relief from pain was provided for from four to six hours. Appleton[8] employed intramuscular injections of Numorphan (from 0.5 to 1.5 mg. doses) during the recovery period, and noted that the patients were free from side-effects, especially nausea and vomiting, and also that a euphoria or a hypnosis was absent.

Methods of Our Study

Patients who received injections of Numorphan as premedication, during surgical operations, or during the recovery period, were carefully observed for the effects of the drug on cerebral activity, blood pressure, and respiratory and pulse rates. The occurrence of side-reactions such as nausea, vomiting, itching, or mental confusion were also noted and recorded. In addition, the drugs or anesthetic agents used in conjunction with Numorphan, the use of antidotes when required, the patient's physical state, and other factors such as loss of blood, were recorded and were taken into consideration in the evaluation of this drug.

Results

Premedication. Table 1 shows the results of the observations made concerning 66 patients who received premedication with Numorphan. In 18 of these patients the drug was injected intravenously; in 48 it was injected intramuscularly. Mental confusion, restlessness, and euphoria were absent, as were significant changes in blood pressure and respiratory rate. In six patients there was some itching about the nose. Nausea and vomiting were absent.

Use during anesthesia. In the patients in group A *(Table 2),* Numorphan was administered in conjunction with thiopental sodium, nitrous oxide, and oxygen, to produce a "narcotic-induced controlled apnea" as described by Foldes.[10] This group included the patients in whom this technic was used by Seigleman and Wasmuth[9] for surgical procedures involving the head and neck. The technic

Table 1.—*Use of Numorphan for premedication in 66 adults*

Drugs	Dose, mg.	Number of patients: Total	Sedation: Good	Sedation: Fair	Sedation: Poor	Blood pressure change, mm. Hg: +10	Blood pressure change, mm. Hg: =	Blood pressure change, mm. Hg: -20	Respiration rate: +16	Respiration rate: -14	Respiration rate: -10	Mental confusion	Itching	Nausea
Pentobarbital sodium Numorphan Atropine (I.M.*)	100 1.0 0.4	20	16	2	2	5	12	3	6	14	0	1	3	0
Numorphan Atropine (I.M.*)	1.5 0.6	12	3	9	0	3	8	1	12	0	0	0	1	0
Numorphan Atropine (I.M.*)	0.75 0.4	16	2	10	4	4	12	0	16	0	0	0	1	0
Numorphan Atropine (I.V.†)	0.75 0.4	18	0	10	8	6	12	0	14	4	0	0	0	0

*I.M. = Intramuscular injection approximately two hours preoperatively.

†I.V. = Intravenous injection from 5 to 10 minutes preoperatively.

Table 2.—*Use of Numorphan during anesthesia in 198 adults undergoing surgery*

Group	Anesthetic agents	Increment dose of Numorphan, mg.	Average total dose of Numorphan, mg.	Number of patients							
					B. P. change, mm. Hg			Respiratory rates			Nalline required, 5 to 10 mg.
				Total	+20	=	−20	+16	−14	−10	
A	Thiopental sodium (150-600 mg.) N_2O-O_2	0.375	1.375	62	10	50	2	7	30	25	30
B	Fluothane N_2O-O_2 Thiopental sodium induction (100-250 mg.)	0.375	0.75	53	2	36	12	70	33	0	5
C	Methoxyflurane N_2O-O_2 Thiopental sodium induction (100-200 mg.)	0.375	0.75	31	10	20	1	10	19	1	3
D	Cyclopropane Oxygen Thiopental sodium induction (100-200 mg.)	0.375	0.75	20	2	18	0	3	17	0	0
E	Spinal and	0.375	0.75	20	5	15	0	19	1	0	0
	epidural	0.375	0.75	12	5	7	0	11	1	0	0

included the reliance on respiratory depression and its potentiation by relatively large doses of thiopental sodium, together with the counteraction of such depression by the administration of Nalline. An average dose exceeding 200 mg. of thiopental sodium was administered to patients in group A.

In the patients in groups B, C, and D, who received intravenous injections of Numorphan to supplement anesthesia induced by inhalation agents, the average dose of thiopental sodium did not exceed 200 mg., and the incidence of noticeable respiratory depression was much lower. However, four patients required respiratory stabilization with intravenous injections of Nalline (from 5 to 10 mg.). Hypotension attributable to Numorphan was not encountered.

In patients in groups D and E, in whom Numorphan was used to supplement spinal and epidural anesthesia, there were no noticeable side-reactions, despite the

fact that premedication for most of these patients had included pentobarbital sodium (Nembutal*).

Postoperative observations. All the patients had satisfactory blood pressures and respiratory rates on admission to the recovery room *(Table 3).* No patient whose blood pressure was being supported by a vasopressor or a blood transfusion was included in this series.

Table 3.—*Postoperative observations in 264 patients receiving Numorphan**

	Number of patients										
		Pain relief			Duration		B. P. fall, minutes	Respiratory rate		Nausea and vomiting	Mental confusion
	Total	Good	Fair	Poor	30+ min.	2+ hr.	20 mm. Hg	16	10		
	26	12	6	4	20	6	0	2	0	4	1
	60	24	16	10	52	4	2	0	3	10	0
	40	14	10	16	6	2	0	2	0	10	0
	70	24	38	6	46	14	7	6	5	0	0
	28	20	8	0	28	12	2	0	0	0	0
	16	2	12	2	16	0	5	4	0	2	0
	24	14	2	4	16	0	2	2	0	4	0
Grand total	264	110	92	42	184	38	18	16	8	30	1

*Intravenous injection, 0.5 mg. to total of 2 mg., according to patient's age, weight, and severity of pain.

Each of the eight patients in whom there was gross depression of respiratory rate was more than sixty years of age, and had received total doses of more than 1.5 mg. of Numorphan during the recovery period. Administration of 5 mg. of Nalline reversed the depression rapidly and completely in each patient.

Although the 18 patients in whom a decrease in blood pressure was encountered had each received less than 1.5 mg. of Numorphan, it was believed that the drug may have been responsible for the hypotension. No related respiratory depression was apparent clinically in any of these patients. However, alveolar ventilation was not measured, and changes in plasma carbon dioxide content could have caused some of the alterations in blood pressure.

There was a significant absence of sedative and hypnotic effects, but in some patients (11 per cent) nausea and vomiting occurred which could not easily be attributed to factors other than the administration of Numorphan. All medication was injected intravenously, and this may in part account for the incidence of side-effects in our trial.

**Nembutal sodium, Abbott Laboratories.*

Summary and Conclusions

1. Numorphan is found to be a satisfactory narcotic for premedication, as a supplement to general anesthesia, and for postoperative analgesia.

2. It is not devoid of side-effects, the most undesirable effect being the depression of pulmonary ventilation. This reaction may be avoided to a great extent by reduction of the dosage of Numorphan, and may be counteracted by the injection of Nalline.

With certain technics of general anesthesia, central depression of respiration may be used to advantage as a means of instituting controlled respiration or for counteracting tachypnea. Vasomotor depression is not apparent even when relatively large doses of Numorphan are employed.

3. The potentiation of Numorphan by barbiturates is evident, and may be an advantage or a disadvantage, depending on whether or not it is intentional or inadvertent.

4. The absence of sedative effects and suppression of coughing, and the low incidence of gastrointestinal disturbance, make Numorphan valuable for premedication and postoperative analgesia. The drug may augment the action of sedative or tranquilizing drugs administered additionally, and the dose used should be adjusted accordingly.

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