THE USE OF DROMORAN HYDROBROMIDE (3-HYDROXY-N-METHYLMORPHINAN HYDROBROMIDE) FOR PREOPERATIVE MEDICATION *

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THIS report concerns the use of 3-hydroxy-N-methylmorphinan hydrobromide (dromoran hydrobromide),† a new analgesic drug, in the preoperative medication of 1500 patients.

Dromoran hydrobromide is a synthetic phenanthrene ring compound with the following structural formula:

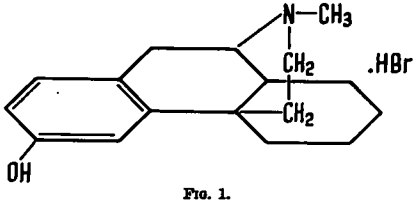

FIG. 1.

The drug is in the form of colorless crystals and melts at 193 to 195 C. The crystals are moderately soluble in water and alcohol but insoluble in ether. The material used in this study was supplied in 1 cc. ampules containing 5 mg. of the drug.

Pharmacologic data ‡ from experiments performed on mice and rats have shown many interesting comparative values for dromoran hydrobromide, morphine sulfate and amidone. The median lethal dose (LD_{50}) of each drug given subcutaneously demonstrated that on a weight for weight basis dromoran hydrobromide is less toxic than amidone but much more toxic than morphine sulfate. The intensity and duration of analgesic potency of dromoran hydrobromide, as measured by the hot spot reaction time method of Ercoli and Lewis, appeared to be greater than that provided by an equal amount of morphine sulfate or amidone. Tolerance to analgesia, provided by dromo-

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† Supplied by Dr. M. J. Schiffrin of Hoffmann-La Roche, Inc., Nutley, New Jersey.

‡ These pharmacologic data were supplied by the manufacturer.

ran hydrobromide or morphine sulfate, developed at about the same rate in the rat. Dromoran hydrobromide depressed the rate of respiration to about the same degree as an equal amount of morphine sulfate in the anesthetized rabbit when both of these drugs were given intravenously. The therapeutic index or ratio between the median lethal dose (LD_{50}) and the moderately active analgesic dose (MAD) expresses the safety factor of a drug. Such a determination showed the margin of safety of dromoran hydrobromide to be comparable to that of morphine sulfate and to be approximately twice that of amidone.

These pharmacologic properties of potency, long duration of action, wide margin of safety and minimal respiratory depression prompted the Department of Anesthesiology to use the drug for preoperative medication. Dromoran hydrobromide was substituted for morphine sulfate in the premedication of adults and children. The drug was given subcutaneously on the ward, with atropine sulfate or scopolamine hydrobromide sixty to ninety minutes before the induction of anesthesia. Patients scheduled for emergency surgical procedures received

TABLE 1

COMPARATIVE VALUES OF DROMORAN HYDROBROMIDE, MORPHINE SULFATE AND AMIDONE

Drug	LD_{50} Value (subcut.) mg./kg.		MAD mg./kg.		Therapeutic Index LD_{50}/MAD	
	Mice	Rats	Mice	Rats	Mice	Rats
Dromoran Hydrobromide	108	125	0.75	0.75	144	167
Morphine Sulfate	360	600	3	3	120	200
Amidone	48	45	0.75	0.75	64	60

the premedication by the intravenous route. The respiratory rate was recorded by the nurse before administration of the drug. The degree of depression, respiratory rate, mental state and any adverse side effects were checked on all patients prior to the induction of anesthesia. The patients were observed closely throughout anesthesia and postoperatively on the ward.

Nine hundred and eighty-six adults and 514 children are included in this report. Nine hundred and eleven of the patients were females and 589 were males. The average age of the adults was 46 years, with a range of 16 to 89 years. The average weight was 140 pounds, with a range of 80 to 300 pounds. A finer breakdown was indicated in the pediatric group. In the group up to 2.5 years of age, the average age was 2.3 years, with a range of 3 months to 2.5 years. The average weight was 28 pounds with a range of 12 to 50 pounds. Children from 2.5 to 5 years of age averaged 4.5 years. The average weight was 39 pounds with a range of 23 to 92 pounds. Patients between 5 and 10 years of age averaged 8 years. The average weight was 61 pounds with a range 30 to 120 pounds. Children from 10 to 16 years of age averaged 13

years. This group of patients averaged 98 pounds with a range of 37 to 172 pounds.

The amount of dromoran hydrobromide required for adequate premedication was individualized for each patient. The age, weight, presence or absence of pain, metabolic state, state of hydration and nutrition and general mental and physical status were evaluated before determining the dose. Initially the dose of dromoran hydrobromide was determined by giving one-third to one-fourth of the dose of morphine sulfate which the patient would have required. It was soon observed that this dosage was generally unsatisfactory. This was particularly true in the younger age group. Children usually required and tolerated a relatively larger amount of dromoran hydrobromide than anticipated. The average adult dose of dromoran hydrobromide was 3.6 mg. with a range of 1 to 6 mg. Children from 0 to 2.5 years of age received an average of 1.3 mg. of the drug, with a range of 1 to 2 mg. Patients from 2.5 to 5 years of age averaged 1.7 mg. of dromoran hydrobromide, with a range of 1 to 3 mg. Children between

TABLE 2

Type	No.	Age in Years		Weight in Pounds		Dosage in mg.	
		Range	Av.	Range	Av.	Range	Av.
Adult	986	17–89	46	80–300	140	1–6	3.6
Pediatric	514	3/12–16	8.5	12–172	67	1–5	2.5
0–2.5	70	3/12–2.5	2.3	12–50	28	1–2	1.3
2.5–5	132	2.5–5	4.5	23–92	39	1–3	1.7
5–10	148	5–10	8	30–120	61	1.5–4	2.3
10–16	164	10–16	13	37–172	98	2–5	3.1

5 and 10 years of age averaged 2.3 mg. of the drug and the dose ranged from 1.5 to 4 mg. The average dose of dromoran hydrobromide for individuals between 10 and 16 years of age was 3.1 mg., with a range of 2 to 5 mg.

Dromoran hydrobromide was satisfactory as a premedicating drug in 1402 patients. These patients were mentally at ease and without pain or anxiety before the induction of anesthesia. They appeared drowsy but responded readily to all questions and commands. Euphoria was not evident. Patients who received the drug did not complain of any unusual sensations or nausea and vomiting. Periods of hallucinations and disorientation were not observed. There were no complications attributable to the premedication in this group, either during the induction and maintenance of anesthesia or in the postoperative period.

Ninety-eight patients were classified as having unsatisfactory premedication. Forty-six of these patients were under 16 years of age. Adequate analgesia and relief of anxiety were not obtained in 75 of

these patients. Ten of these individuals did not receive an adequate amount of dromoran hydrobromide. Failure to give the drug at the optimal time accounted for unsatisfactory results in 52 of these patients. Inadequate analgesia in these 62 patients was the result of error in dosage of the drug or failure to give the drug at the optimal time. Failure to obtain optimal analgesia in 13 patients was attributed directly to dromoran hydrobromide.

Twenty patients were classified as markedly depressed before the induction of anesthesia. A barbiturate, as well as dromoran hydrobromide, had been given to 4 of these patients. It was thought that the barbiturate played an important role in the depression. Eight patients received an excessive amount of dromoran hydrobromide. The depression noted in the other 8 patients was attributed to an unexpected pharmacologic action of the drug alone.

TABLE 3

ANALYSIS OF UNSATISFACTORY RESULTS

A. Inadequate analgesia		75
1. Given too early	40	
2. Given too late	12	
3. Given in inadequate amounts	10	
4. Failure to secure expected result	13	
B. Excessive depression		20
1. Given with barbiturate	4	
2. Given in excessive amounts	8	
3. Failure to secure expected result	8	
C. Respiratory depression during induction		2
D. Nausea following administration		1
Total		98

Two patients classified as having unsatisfactory premedication could not be grouped in either of the above classifications. Neither of these individuals had received an overdosage of dromoran hydrobromide. Each patient, however, became apneic ninety to 120 seconds after receiving cyclopropane for anesthesia. Ether was immediately substituted for cyclopropane, but each patient had shallow respirations throughout the operation.

Nausea without emesis followed the administration of dromoran hydrobromide in one patient.

DISCUSSION

The clinical evaluation of dromoran hydrobromide as a premedicating drug merits a brief discussion in view of these findings.

All types of patients tolerated this drug quite well. It was particularly adaptable in the young or elderly patient. Respiratory depression was minimal even though the patients were drowsy and sleepy. Most of the patients were in full possession of their reflexes upon ar-

riving in the operating room and were capable of responding to vocal instructions. Nausea and vomiting were not noted either preoperatively or postoperatively following the administration of dromoran hydrobromide except in the one patient referred to previously.

No untoward effects were noted in any of the patients receiving the drug intravenously. The drug was diluted with distilled water to a total of 5 cc. The intravenous injection was performed slowly over a period of two to three minutes.

Most of the unsatisfactory results obtained with dromoran hydrobromide were the result of errors in dosage or the time of administration. This is not surprising in view of the fact that to the best of our knowledge this is the first report on the use of dromoran hydrobromide for preoperative medication. We now insist on giving the drug sixty to ninety minutes prior to induction of anesthesia if the subcutaneous route is used. Fifteen to twenty minutes should be allowed for the optimal action of the drug if it is given intravenously.

The amount of dromoran hydrobromide must be individualized for each patient. We have recommended the following dosage table as a guide to the administration of the drug in the University Hospitals:

TABLE 4

Age in Years	Agent in Milligrams		
	Dromoran Hydrobromide	Scopolamine Hydrobromide	Atropine Sulfate
1.5–2.5	1–1.5		0.06–0.2
2.5–5	1.5–2		0.15–0.2
5–10	2–3	0.15–0.2	
10–16	3–4	0.3–0.4	
17–60	3–5	0.4	
60–75	1.5–2	0.3	
75–Over			0.15–0.2

SUMMARY

Clinical experience with dromoran hydrobromide, a new analgesic drug, in preoperative medication is summarized. The results with 1500 administrations are gratifying. Further clinical trial is justified.