ATARAXIC DRUGS IN PREANESTHETIC MEDICATION
BLIND STUDIES IN 1,852 PATIENTS

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THE SYNTHESIS of the ataraxic or tranquilizing drugs has made available a new series of compounds with potential usefulness in preanesthetic medication. Preliminary reports with the earliest drug in this series indicated that hypotension was frequently associated with its use and that this hypotension was refractory to most vasopressors.[1, 2, 3] While the tranquilizers and their chemically-related antihistamines are used in premedication, the paucity of controlled studies has created doubt over the role, if any, these compounds should occupy in preoperative preparation of the surgical patient.

The current study was undertaken to evaluate several representative compounds employing blind techniques in controlled studies. Seven phenothiazines and one diphenylmethane derivative were chosen. The phenothiazine group contained representative members of the propylamine and isopropylamine side chain series, and members of the piperazine and piperidine containing side chains. The phenothiazine compounds studied are listed in table 1.

METHOD

The patient population of a large municipal hospital served as subjects for the study. Their ages ranged from 12 to 95 years; sex distribution was approximately equal. Data were tabulated on special sheets which were checked daily by the research fellow. Adequate information was obtained on 1,852 patients. All study drugs were supplied to the patients' floors in similar containers which bore the inscription *thiazine* plus a code number. In some instances the drugs and placebo material were assigned two numbers to confuse attempts at identification; when different dose ranges were employed for a single drug, capital letters were used in addition to the code number (see fluphenazine *A* and *B* in table 2). The key to this code was held by one of us against the possibility of untoward reactions. All preanesthetic medication during the study was supervised by one research fellow who was unaware of the material being investigated. Initially, attempts were made to use the study drugs in random fashion. Approximately one third of the study was completed this way. Because of nursing problems, however, we switched to running one unknown for a time followed by another, etc., finally beginning the cycle over although not necessarily in the same rotation as in previous runs.

Study material was ordered on a volumetric basis (example: "Thiazine 30," 1.5 cc., I.M.). The material was so prepared that a patient of similar risk and age group would receive the same volume of study material preoperatively regardless of the compound being studied at the time. The placebo material used during the course of these investigations was the vehicle for two phenothiazines and did not contain active material.

All drugs were administered intramuscularly two hours prior to operation. The floor nurses observed the patients for changes in vital signs and behavior; pertinent information was charted on the individual's check-off sheet, or if necessary, the research fellow was called to verify observations. One hour before operation, the patients received meperidine (12.5–50 mg.) and atropine (0.4–0.2 mg.) intramuscularly. The use of scopolamine preoperatively was avoided. The schedule of premedication for the entire study is summarized in table 2.

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TABLE 1

PHENOTHIAZINE COMPOUNDS STUDIED

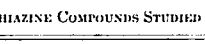
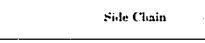
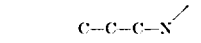
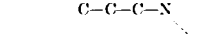
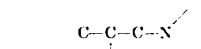
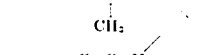
Generic Name	Trade Name	Side Chain	Substitution Second Position
Trifluprom azine	Vesprin		CF_3
Chlorpromazine	Thorazine		Cl
Trimeprazine	Temaril		H
Promethazine	Phenergan		H
Pipamazine	Mornidine		Cl
Perphenazine	Trilafon		Cl
Fluphenazine	Prolixin		CF_3

TABLE 2

SCHEDULE OF PREMEDICATION

Drug	Dose (mg.)	Time Preoperative (hours)
Placebo*	(0.5–2.0 ml.)	2
Pipamazine	2.5–10	2
Meperidine†	25–100	1
Trimeprazine	12.5–50	2
Hydroxyzine	12.5–50	2
Promethazine	12.5–50	2
Perphenazine	2.5–10	2
Chlorpromazine	12.5–50	2
Trifluprom azine	10–40	2
Fluphenazine (*B*)	0.6–2.5	2
Fluphenazine (*A*)	1.25–5.0	2

All drugs were given intramuscularly.

* The placebo material used in this study was the vehicle (only) for perphenazine and for pipamazine.

† The meperidine schedule refers to the use of this agent as control or standard premedication. One half the dose was ordered and administered as an unknown two hours preoperatively. The remainder of the meperidine dose was given as known material one hour preoperatively. Patients who received study material were also given meperidine 12.5–50 mg intramuscularly one hour preoperatively. All patients received atropine 0.2–0.4 mg one hour preoperatively.

Age and sex of the patient, drug dose, control blood pressures, anesthetic techniques, and areas of operation were recorded (tables 3, 4 and 5). Postoperatively, data were collected on the incidence and severity of nausea, retching, and vomiting. Postoperative blood pressures, reaction times following anesthesia, emergence delirium, and narcotic requirements were recorded and evaluated. The recording of recovery room data was by trained nurses; the evalution of postoperative complications was by the research fellow.

The evaluation of preoperative sedation is difficult. The method of rating sedation on the basis of the patient's response to questions was not satisfactory since individuals with a favorable score on questioning (*i.e.*, comfortable, unworried, etc.) were frequently difficult to mange during the insertion of the intravenous needle or application of the face mask. On the other hand, individuals whose responses to questioning indicated apprehension and discomfort, were often easily handled with regard to administration of intravenous

TABLE 3

AGE DISTRIBUTION
(Per Cent of Study Group)

Drug	Age in Years		Total* 10-55	Age in Years		Total* 56-95
	10-40	41-55		56-70	71-95	
Pipamazine	20	31.5	54.5	27.5	18	45.5
Placebo	27	20	47	33	20	53
Meperidine	26	20.5	46.5	31	22.5	53.5
Trimeprazine	30.5	19	49.5	23	27.5	50.5
Hydroxyzine	37	21	58.0	29	23	42.5
Promethazine	30	25	55.0	22	23	45.0
Perphenazine	17	23	40.0	19	41	60.0
Chlorpromazine	26	24	50.0	30	20	50.0
Triflupromazine	40	14	54.0	22	24	46.0
Fluphenazine (*B*)	25	14	39.0	26	35	61.0
Fluphenazine (*A*)	34	21	55.0	20	25	45.0

*Statistical comparisons of these columns revealed no difference among drug groups as regards age distribution. This is of importance in evaluating the incidence of hypotension, since this complication occurred twice as frequently in our 56-95 year old age groups.

fluids and application of face mask or subsequent induction of anesthesia.

Patients were observed as they first came to the operating theater. Their response to subsequent preparations such as application of blood pressure apparatus, placement on the operating table, and onset of intravenous therapy, was noted. Conversation between the anesthetist and patient afforded additional insight to the state of preoperative sedation. Blood pressures and pulses taken immediately as the patient was brought into the room were compared to those taken several minutes later prior to the induction of anesthesia. The

TABLE 4

DISTRIBUTION OF INTRA-ABDOMINAL AND EXTRA-ABDOMINAL SURGERY WITHIN STUDY DRUG GROUPS

Drug	Intra-abdominal Surgery	Extra-abdominal Surgery
Pipamazine	30	70
Placebo	32	68
Meperidine	31	69
Trimeprazine	32.5	67
Hydroxyzine	31	69
Promethazine	24	76
Perphenazine	25	75
Chlorpromazine	47	53
Triflupromazine	29	71
Fluphenazine (*B*)	31	69
Fluphenazine (*A*)	33	67

patients' responses to the induction of anesthesia such as the prick of the spinal needle or the placement of the mask over the face were also evaluated.

On the basis of the preceding information and the subsequent course of anesthesia, each patient was evaluated into one of several categories (table 6). The totals of the patients considered calm-awake, calm-drowsy, and calm-asleep were taken as the adequately sedated group.

RESULTS

Preoperative Sedation. A significantly greater number of patients were adequately

TABLE 5

DISTRIBUTION OF ANESTHETIC TECHNIQUES (PER CENT OF STUDY GROUP)

Drug	Inhalation			Conduction				Intravenous
	Cyclopropane	Nitrous	Halothane	Spinal	Block	Epidural	Local	CI-400*
Pipamazine	38	20	7	33	2	—	—	—
Placebo	38	26	—	28	4	2	—	1
Meperidine	50	22	4	21	0.5	2.5	—	—
Trimeprazine	45.5	25.5	1.5	22	—	2	—	3.5
Hydroxyzine	53	15	—	28	—	3	1	—
Promethazine	39	31	—	25	0.75	0.75	—	3.5
Perphenazine	30	30	—	33	—	—	4	3
Chlorpromazine	33	13	—	39	2	1	1	11
Triflupromazine	33	31	—	21	—	2	—	13
Fluphenazine (*B*)	33	29	1	33	—	3	—	1
Fluphenazine (*A*)	45	18	5	30	—	—	—	2
Average	40	23.5		28.5				

* CI-400 (Cyclohexamine) is a sensory blocking agent (Lear, Suntay, Pallin and Chiron: ANESTHESIOLOGY 20: 330, 1959).

TABLE 6

EVALUATION OF PREANESTHETIC SEDATION
(Control Meperidine Series)

Psychic State	Physical State		
	Patients Awake	Patients Drowsy	Patients Asleep
Calm	85	17	0
Apprehensive	60	2	
Disoriented	2	0	

Sample of sedation distribution: control drug = meperidine (25–100 mg. I.M. preoperatively). Adequately sedated = 102/165 = 61.8 (62 per cent).

sedated by trimeprazine, perphenazine, and chlorpromazine ($P < .05$). The comparative sedation data on all the study material is shown in table 7. In order to minimize errors introduced by the "calm-awake" classification, a separate analysis was made in which only the "calm-drowsy" and the "calm-asleep" statistics were used. Trimeprazine, perphenazine, and chlorpromazine were again noted to be statistically different compared to control (table 8).

Blood Pressure Effects. Previous experiences with phenothiazine derivatives have revealed an increased incidence of hypotension associated with the use of these compounds; this complication was particularly frequent in the immediate postoperative period.[4] The study groups were analyzed to ascertain that there was a similar distribution of control blood pressures of 140/90 or greater (table 9) because of the increased incidence of hypotension in patients with elevated control pressures (neurogenic and arteriosclerotic). The fall in blood pressure of 40 mm. of mercury or greater for each individual (as compared to baseline) was considered as hypotension for purposes of this study. Pipamazine, triflupromazine, and chlorpromazine were associated with the highest incidences of postoperative hypotension (figure 1). Trimeprazine and perphenazine hypotension compares similarly with standard meperidine medication, yet the sedation afforded by these compounds is statistically better than meperidine alone.

Postoperative Nausea and Vomiting. Observations were made in the recovery room prior to the use of any postoperative medication such as narcotics. A statistically significant reduction in the incidence of this complication was noted in all series in which a study drug was employed (table 10). To further evaluate the study material it was necessary to determine whether any relationship existed within the study groups between the use of cyclopropane and postoperative nausea and vomiting; it was also necessary to determine whether any relationship was present between intra-abdominal surgery and postoperative nausea and vomiting. The data were plotted and revealed no relationship between the various factors. The correlation coefficient (r) for each plot was as follows: cyclopropane/nausea and vomiting, $r = .5$ (ns);

TABLE 7

EVALUATION OF PREOPERATIVE SEDATION

Drug	Number Patients	Calm Awake (per cent)	Calm Drowsy (per cent)	Calm Asleep (per cent)	Adequately Sedated (per cent)
Chlorpromazine	208	50	15	13	78
Trimeprazine	215	41	33.5	2.5	77
Perphenazine	103	34	40	1	75
Pipamazine	102	51	21.5	—	72.5
Triflupromazine	210	37	26	6	69
Promethazine	271	50	13.5	2	65.5
Fluphenazine (*A*)	104	50	13.5	1	64.5
Hydroxyzine	262	54	9.5	—	63.5
Meperidine	165	51.5	10.5	—	62
Fluphenazine (*B*)	104	48	11.5	1	60.5
Placebo	100	39	1	0	40

TABLE 8

CHI-SQUARE COMPARISONS OF THE "DIFFERENT" DRUGS WITH REMAINDER OF STUDY DRUGS

	Perphenazine	Trimeprazine	Trifluopromazine	Chlorpromazine
	P values*	*P* values*	*P* values*	*P* values*
Trimeprazine	N.S.	—	—	—
Trifluopromazine	.01	N.S.	—	—
Chlorpromazine	.001	N.S.	N.S.	—
Pipamazine	.001	.02	N.S.	N.S.
Promethazine	.001	.001	.001	.01
Fluphenazine (*B*)	.001	.001	.01	.02
Fluphenazine (*A*)	.001	.001	.001	.01
Meperidine	.001	.001	.001	.001
Hydroxyzine	.001	.001	.001	.001
Placebo	.001	.001	.001	.001

* $P < .05$ is statistically significant.
N.S. = No significant difference.
Table is based on the distribution of calm-drowsy and calm-asleep patients within each study group.

intra-abdominal surgery/nausea and vomiting, $r = .2$(ns).

The possibility that the reduction in preoperative narcotic influenced the incidence of postoperative nausea and vomiting was also investigated. Two separate studies were done. In the first, fluphenazine was combined with standard doses of meperidine (25–100 mg.) and with reduced doses of meperidine (12.5–50 mg.) preoperatively. In the second study, the antiemetic trimethobenzamide was given preoperatively in conjunction with standard and reduced doses of meperidine. The results of these subsidiary series indicate the reduction in preoperative narcotic dose plays a role in the reduction of postoperative nausea and vomiting (fig. 2).

Postoperative Narcotic Requirements. The time interval from admission to the recovery room until pain relief was requested, was noted for each patient. There was a statistically significant reduction in narcotic re-

TABLE 9

DISTRIBUTION OF BASELINE BLOOD PRESSURES >140/90 MM. OF MERCURY

Number of Patients	Drug	Per Cent
100	Placebo	32
102	Pipamazine	22.5
165	Meperidine	31.5
215	Trimeprazine	31
262	Hydroxyzine	35
271	Promethazine	34.5
103	Perphenazine	36
208	Chlorpromazine	40.5
210	Trifluopromazine	36
104	Fluphenazine (*B*)	33
104	Fluphenazine (*A*)	33.5

The incidence of hypotension is greater in patients with control blood pressures of 140/90 and over.[2] Accordingly, the distribution of patients with control pressures of 140/90 or greater was noted for each drug group to be certain that this ancillary factor was similar throughout the study groups.

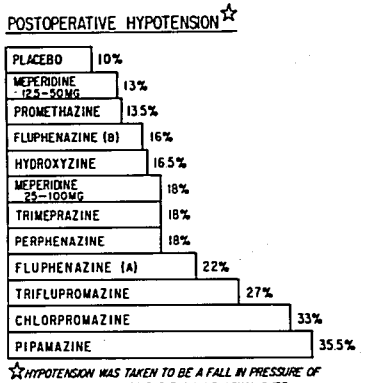


FIG. 1. The placebo was used in a series of patients who received pentobarbital 100 mg. preoperatively in place of reduced doses of meperidine (12.5–50 mg.). The series in which placebo was combined with narcotic is reported in the block "meperidine 12.5–50 mg." In every instance the actual placebo was the same material (vehicle only for two phenothiazines).

TABLE 10

POSTOPERATIVE NAUSEA AND VOMITING (Recovery Room Period)

Drug	Number of Patients	Percentage Incidence	V_2	Meperidine
Meperidine (25–100 mg.)	165	18	χ^2	*P* value
Pipamazine	102	11	1.87	N.S.
Placebo*	100	9	2.10	N.S.
Chlorpromazine	208	11	3.17	N.S.
Hydroxyzine	262	10	5.01	<.05
Promethazine	271	10	5.11	<.05
Trimeprazine	215	9	5.85	<.02
Trifluopromazine	210	8	7.61	<.01
Fluphenazine (*A*)	104	5	8.43	<.01
Fluphenazine (*B*)	104	5	8.43	<.01
Perphenazine	103	4	10.01	<.01

P values of .05 or less are considered statistically significant, although a *P* value of .05 is borderline.
* Since the placebo material is inactive, the values reported here actually represent half-doses of meperidine (12.5–50 mg.) preoperatively.

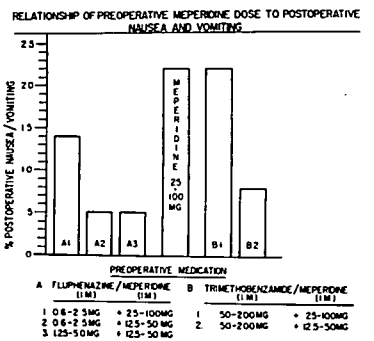


FIG. 2. The incidence of postoperative nausea and vomiting with control meperidine was 22 per cent. Combined use of fluphenazine (0.6-2.5 mg.) reduced this complication to 14 per cent. The reduction in meperidine dose when combined with fluphenazine (0.6-2.5 mg.) was associated with 5 per cent incidence of the postoperative nausea and vomiting. Doubling the dose of fluphenazine (1.25-5.0 mg.) did not further reduce this complication. In a similar series with the less potent antiemetic trimethobenzamide, the reduction in postoperative nausea and vomiting was primarily related to the dose of preoperative meperidine.

quirements in patients premedicated with chlorpromazine and with perphenazine as compared to standard preoperative meperidine. There was no narcotic reduction with the other study drugs when compared to standard premedication.

Postanesthetic Reaction Time. The average postanesthetic reaction time for standard premedication and cyclopropane was approximately 45 to 60 minutes. Promethazine, hydroxyzine, and fluphenazine supplementation affected these data minimally. The remaining drugs extended the reaction time to a range of 90 minutes with perphenazine and trimeprazine and 120 minutes with chlorpromazine, triflupromazine, and pipamazine in the dose ranges we employed.

Complications. Two patients in this series of 1,852 developed extrapyramidal symptoms. The first was a 67 year old man who had a transurethral resection under spinal anesthesia. Preoperative medication was fluphenazine 1.25 mg. intramuscularly and meperidine/atropine as described earlier in this paper. The preoperative state of the patient was calm-awake. The operative procedure required little more than one hour. Within the first recovery room hour the patient developed the oculo-gyric syndrome (rolling of the eyes, protrusion of the tongue with difficulty in speaking, salivation). There was also increased muscle tone in the upper extremities. The symptoms gradually diminished in the recovery room over a period of eight hours.

The second case was a 56 year old woman who had received 3.75 mg. fluphenazine as part of premedication. The procedure was amputation of the right forearm following brachial artery thrombosis, under cyclopropane anesthesia. Preoperatively, the patient was awake-apprehensive. Five hours from the time of drug administration, and while fully reacted in the recovery room, the patient developed generalized tremors throughout the right side of the body, but especially about the right face and neck. The coincidental use of phenazocine for pain relief ameliorated the patient's symptoms which disappeared completely within two hours.

The lack of preoperative symptoms in either patient was probably related to the use of preanesthetic narcotic which masked or prevented the appearance of central nervous system irritability.

There were no other complications except for occasional complaints of pain following the injection of phenothiazine derivatives. On further inspection we found that nearly an equal number of patients complained following meperidine/atropine injections; the majority of complaints came from women.

DISCUSSION

The experimental use of preoperative morphine by Claude Bernard in 1864, resulted in two important conclusions: premedicated subjects were less apprehensive and consequently anesthesia more easily induced; secondly, anesthesia could be maintained satisfactorily with less anesthetic agent. The basic aims of premedication have remained relatively unchanged over the years. The addition of the belladonna derivatives has assisted in controlling secretions and vagal activity.

The use of preoperative narcotic in the pain-free patient, however, has remained controversial.[5] One study stated that there was no reduction in blood ether or blood cyclopropane levels in patients premedicated with morphine.[6] These patients were in the second plane of surgical anesthesia. Other objections to narcotic premedication were the side-effects; respiratory, circulatory, and psychic. Eckenhoff and Helrich[7] demonstrated the undesirable side effects produced by narcotic premedication and concluded that adequate sedation with minimal complications might be achieved with secobarbital premedication.

The sedation achieved by means of preoperative narcotics in the pain-free patient is not a primary drug action, but rather a side effect usually found when large doses are employed. The synthesis of the ataraxic or tranquilizing drugs, however, has made available a new approach to the problem of preanesthetic medication. Unlike the narcotics, this class of compounds exerts its specific action on those areas of the central nervous system which govern the subjective and objective response to stress.[8] The combined use of an ataraxic with a narcotic preoperatively permits a reduced dose of narcotic to be employed. Narcotic-induced side effects are minimized; at the same time analgesia and sedation are enhanced by this combination.[1, 4, 9, 10] Taylor, Faulconer, and associates[11] demonstrated potentiation of ether anesthesia by several drugs which included meperidine and chlorpromazine. These investigators employed the electroencephalogram to monitor surgical anesthesia, and measured blood ether concentrations. In our experience, patients who received tranquilizer-supplemented premedication were more easily anesthetized and managed than lightly premedicated patients (placebo series). The postoperative course was also more favorable.

The results of the current study indicate that tranquilizer-supplemented premedication is feasible without the severe hypotension formerly associated with this type of medication. A statistically significant increase in preoperative sedation was noted when trimeprazine or perphenazine were employed as adjuvants to preanesthetic medication.

The low incidence of postoperative nausea and vomiting encountered in the current study is primarily related to the reduction in dose of preoperative meperidine. The subsidiary blind studies in which the antiemetic fluphenazine was combined with standard doses of meperidine (25–100 mg.) indicated a 33 per cent reduction in postoperative nausea and vomiting. When the same dose range of fluphenazine (0.6–2.5 mg.) was again employed, but the dose range of meperidine reduced (12.5–50 mg.), there was a 73 per cent reduction in postoperative nausea and vomiting. A two-fold increase in fluphenazine dose (1.25–5.0 mg.) combined with reduced meperidine did not further diminish the incidence of this postoperative complication.

A similar series employed the antiemetic trimethobenzamide (50–200 mg.) preoperatively with meperidine. When standard doses of meperidine were combined with trimethobenzamide, the incidence of postoperative nausea and vomiting was the same as a control meperidine series. Reduction in meperidine dose by 50 per cent was associated with a 64 per cent reduction in postoperative nausea and vomiting. It is interesting to note that in both series above, the reduction by one half of meperidine dose produced a corresponding decrease in nausea and vomiting (40–60 per cent).

Summary

Seven phenothiazine derivatives and one diphenylmethane were studied as adjuvants to preanesthetic medication in 1,852 patients. Blind techniques and placebo material were employed in controlled studies.

Perphenazine and trimeprazine supplemented premedication produced statistically superior preoperative sedation when compared to standard preoperative doses of meperidine.

Hypotension with these drugs was the same as that noted with the meperidine controls.

There was a reduction in postoperative nausea and vomiting associated with tranquilizer-supplemented premedication. The favorable incidence of this complication appears related to the reduction in pre-

operative narcotic dose made possible by the use of tranquilizers in premedication.

Extrapyramidal symptoms occurred postoperatively in two patients who were premedicted with fluphenazine.

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TRANQUILIZER COMPLICATIONS

Adverse behavioral effects noted in the early use of tranquilizing drugs have become less prominent as a result of a reduction in massive doses that were previously used. Extrapyramidal effects are still seen with the presently used therapeutic doses. Three syndromes have been distinguished—classic Parkinson syndrome, akathiasia (uncontrollable restlessness), and a dystonic syndrome. Generally, children and young adults are affected and the signs appear early in the treatment within the first two days. Parenteral administration of the drugs are especially prone to produce the toxic effects. The clinical course may be shortened by parenteral antiparkinsonian drugs, caffeine or barbiturates. The phenothiazine derivatives occasionally affect the autonomic nervous system by virtue of their cholinergic action. Allergic reactions are seldom seen with this class of drugs. Patients on phenothiazine derivatives gained weight and some feminizing effects were noted. Perivenous administration of promazine or intramuscular placement of chlorpromazine near arteries has caused gangrene of extremities distally. (*Hollister, L. E.: Current Concepts in Therapy. Complications of Psychotherapeutic Drugs, New Engl. J. Med. 264: 291 (Feb. 9) 1961.*)