DOUBLE BLIND STUDY OF PHENOTHIAZINES USED IN PRE-ANAESTHETIC MEDICATION: A CLINICAL EVALUATION OF PROMETHAZINE (PHENERGAN®), PROMAZINE (SPARINE®), PROCLORPERAZINE (STEMETIL®), AND LEVOMEPROMAZINE (NOZINAN®)

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A CONTROLLED EVALUATION of the effect of pre-anaesthetic medication was carried out with a standard series consisting of promethazine and atropine, and a double blind series consisting of four phenothiazine derivates, and a placebo, each of which was combined with scopolamine. The four drugs that were tested were selected on the basis of previous clinical experience which seemed to indicate that these drugs were the most likely to prove valuable as premedicants from among the wide range of phenothiazine derivatives now available (1, 2).

METHOD

The drugs and the placebo were dispensed in identical vials which were identified to the participants in the study only by code letters. The oral preparations were similarly coded. The oral placebo was a capsule containing lactose and the placebo solution for injection was normal saline. The volume of estimated "equipotent" doses was noted on the labels. Premedication was ordered by the anaesthetist using the code letters which could be identified with the actual drugs only by the hospital pharmacist. The standard (promethazine and atropine) could not be identified with its unknown counterpart (promethazine and scopolamine), because a different test drug was assigned to each anaesthesia resident, and the assignments *and* codes were changed at intervals. Scopolamine was combined with each unknown to augment the difficulty in identifying the unknowns, and to assure a satisfactory anti-sialogogue effect, because all phenothiazines are not potent in this respect (3).

The study was limited to adult patients who were in physical status 1 or 2, and who were to have an elective operation. Patients in the extremes of age (under 19 and over 65 years) and those for intracranial, cardiopulmonary, and short minor operations were excluded from the study. For these reasons, the dose of each test drug was not varied unless the patient was extremely nervous or of very large size. A protocol was not initiated if premedication was given less than 30 min. or more than two hours from the induction of anaesthesia. These measures were adopted in order to achieve a more reliable basis for over-all comparison of the premedicant drugs. The protocol sheet that is shown in Figure 1 was

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PREMEDICATION STUDY

Purpose of Admission : Age : _____ Ht. : _____
Operation : Sex : _____ Wt. : _____
Date of Operation :
DRUG CODE :
Dose : Night before : Code _____ mg. orally.
Seconal
One hour pre-induction _____ mg. i.m.
Atrop. / Scop. Dose : _____ mg. With premed./time :
Route :

Assessment

1. Time H. S. of administering drug : _____
2. Time of onset of sleep : _____
3. Sleeping drug usually taken : _____
4. Pre-drug assessment : (1) Very nervous (2) Normal (3) Stable
5. Thyrotoxicity : Present Past
   Degree : mild severe

Pre-induction Questions :

1.	Are you comfortable ?	yes	no
2.	Are you worried ?	yes	no
3.	Are you tense ?	yes	no
4.	Are you unusually happy ?	yes	no
5.	Are you unusually sleepy ?	yes	no
6.	Is your stomach upset ?	yes	no
7.	Did you vomit ?	yes	no
8.	Do you feel tired ?	yes	no
9.	Do you see double ?	yes	no
10.	Any complaints ?	yes	no

(circle appropriate items)

Anaesthetist's Own Impression

Was the patient :

1.	comfortable	uncomfortable
2.	worried apprehensive	untroubled
3.	excited	relaxed
4.	happy euphoric	serene
5.	drowsy sleepy	wide awake
6.	talkative	quiet
7.	nauseated	
8.	able to raise eyelids	
9.	able to hand grip firmly	

Anaesthetist's Report

1. Vital Signs :
   a. Admission : B. P. _____ Pulse _____ Resp. _____ Oral T° F _____
   b. Pre-sedation : B. P. _____ Pulse _____ Resp. _____ Oral T° F _____
   c. Pre-induction: B.P. _____ Pulse _____ Resp. _____ Pupil Size _____
2. Tidal Volume : Pre-sedation _____ ml. Pre-induction _____ ml.
3. Time in minutes between i.m. drug and induction : _____
4. Character of induction : Smooth _____ Smooth but slow _____
   Difficult _____ Stormy _____
   Excessive secretions _____
5. Induction agent : Amount :
6. Anaesthetic technique :
7. Anaesthetist's estimation of adequacy of premedication :
   Adequate _____ Inadequate _____ Excessive _____

Post-operation Questions :

What do you remember happening just prior to your operation ?
1. I. M. injection ?
2. Trip to Operating Room ?
3. Movement to operating table ?
4. Was induction pleasant unpleasant indifferent or unknown

Post-operative report :

1. Amnesia _____
2. Urinary retention (Did the patient have to be catheterized within 10 hours of operation ?) __
3. Shivering _____ _____
4. Hypotension after induction _____
   post-operative _____
5. Nausea and vomiting post-operative _____
6. Delay in "awakening" after completion of operation _____ (from Recovery Room notes).
   (minutes)
7. REMARKS :

FIGURE 1. Protocol for premedication evaluation.

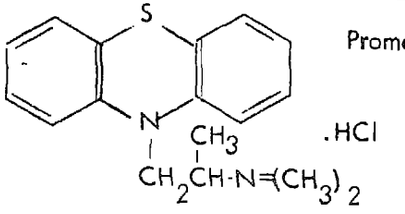
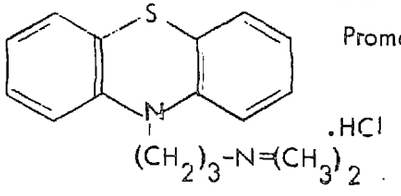
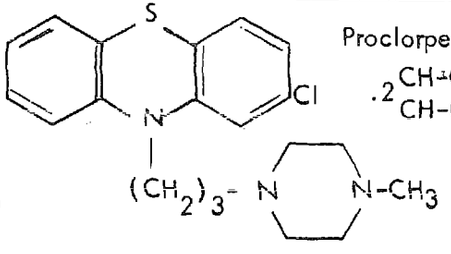
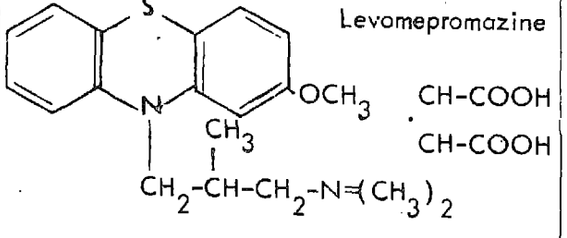
DRUGS	OFFICIAL NAME & STRUCTURAL FORMULA	ORAL MEDICATION at H.S.	INTRAMUSCULAR MEDICATION ONE HOUR BEFORE ANAESTHESIA
PHENERGAN ATROPINE	 Promethazine .HCl	50 mg. + SECONAL 100 mg.	25 mg. 0.6 mg.
PLACEBO SCOPOLAMINE		LACTOSE + SECONAL 100 mg.	NORMAL SALINE 0.4 mg.
SPARINE SCOPOLAMINE	 Promazine .HCl	50 mg. + SECONAL 100 mg.	25 mg. 0.4 mg.
STEMETIL SCOPOLAMINE	 Proclorperazine .2 CH-COOH CH-COOH	10 mg. + SECONAL 100 mg.	5 mg. 0.4 mg.
NOZINAN SCOPOLAMINE	 Levomepromazine CH-COOH . CH-COOH	25 mg. + SECONAL 100 mg.	15 mg. 0.4 mg.
PHENERGAN SCOPOLAMINE		50 mg. + SECONAL 100 mg.	25 mg. 0.4 mg.

FIGURE 2. Route and dose of drugs used for premedication.

initiated and completed on 772 patients. The dose of each drug that was ordered is listed in Figure 2.

General anaesthesia was started with a sleep dose of intravenous thiopental in every case in order to assure a quiet induction. Maintenance of anaesthesia was left to the discretion of the anaesthetists, most of whom used cyclopropane or nitrous oxide with trichlorethylene or ether. No supplements of the test drugs or related phenothiazine derivatives were given to any of these patients during anaesthesia. In the postoperative period, those patients who vomited were given perphenazine (Trilafon®) (4). The code in this study was not revealed until the data on each patient's chart and protocol were completely abstracted, tabulated, and analysed.

It was realized at the outset that it was not possible to distinguish reliably between the feelings expressed by the patient in answering the ten direct questions, and the opinions noted in the anaesthetist's own impression of the patient's mental state. Therefore, in analysing the data, the greatest weight was given to the statements made by the patient when he made complaints, because we felt that it was unfair to conclude at any time that an individual was not apprehensive when the direct answers by the patient indicated that he was tense or worried. On the other hand, the anaesthetist's impression was given more weight when the patient showed a variety of signs and symptoms that appeared sufficient to indicate that the patient was apprehensive although he might have answered that everything was satisfactory. In other words, the analysis of the data from that part of the protocol which contained the subjective and objective assertions were weighted to indicate that the patient was apprehensive whenever there was any indication of this. In addition, the anaesthetist also noted whether he considered the premedication was adequate, inadequate, or excessive, using the usual criterion for adequacy: a quiet patient who is drowsy or moderately sleepy, but can be roused easily, and has suppression of salivary secretions.

Results

Tables I, II, and III contain a summary of the pertinent data from the 772 patients on whom information was complete.

In each test drug series there were more females than males. The variation in the number of females among these did not appear to affect the observations that were analysed.

Effect on Inducing Sound Sleep (Table I)

The combination of secobarbital with promazine and with levomepromazine provided the most satisfactory conditions for sound sleep.

Effect on Psychic Preparation (Table I)

In the anaesthetist's evaluation of the premedication, the placebo and the standard groups were the only ones that did not have at least 85 per cent of the patients well prepared. If the standard (promethazine-atropine) is compared with the agents used in the blind study, it is evident that scopolamine provided a significant sedative effect. From the subjective and objective answers, levome-

TABLE I

PRE-ANAESTHETIC EVALUATION OF PREMEDICATION

Drugs	Number of patients	Females (%)	Delayed or unsatisfactory sleep (%)	Anaesthetists' evaluation of premedication			Subjective and objective evaluation of premedication		
				Adequate (%)	Inadequate (%)	Excessive (%)	Apprehensive (%)	Nauseated (%)	Drowsy-sleepy (%)
Promethazine Atropine (Standard)	129	64	8	81	19	0	42	2	48
Placebo Scopolamine	119	57	10	84	16	0	27	0	59
Promazine Scopolamine	143	59	2	95	3	2	21	2	78
Proclorperazine Scopolamine	168	71	8	88	12	0	29	3	55
Levomepromazine Scopolamine	71	62	3	92	2	6	12	0	90
Promethazine Scopolamine	142	72	6	89	10	1	30	1	60

TABLE II

EFFECT OF PRE-ANAESTHETIC MEDICATION ON VITAL SIGNS

Drugs	Before induction: Hypotension >15% (%)	Hypertension >15% (%)	Bradycardia >15% (%)	Tachycardia >15% (%)	Bradypnoea >20% (%)	Tachypnoea >20% (%)	After induction hypotension >20% (%)
Promethazine Atropine (Standard)	19	23	13	44	4	34	7
Placebo Scopolamine	42	16	42	37	7	13	9
Promazine Scopolamine	43	10	23	35	3	20	21
Proclorperazine Scopolamine	60	5	48	18	2	44	11
Levomepromazine Scopolamine	38	12	24	30	24	14	6
Promethazine Scopolamine	28	19	30	26	9	12	14

TABLE III

POSTOPERATIVE EVALUATION OF PATIENTS

Drugs	Hypotension >20% (%)	Nausea and Vomiting (%)	Delay in recovery of consciousness (mins.)	Amnesia (%)	Shivering (%)	Urinary retension 10 hours (%)
Promethazine Atropine (Standard)	12	20	28	8	7	12
Placebo scopolamine	10	21	33	8	13	4
Promazine scopolamine	17	17	55	7	11	4
Proclorperazine scopolamine	11	15	46	7	12	3
Levomepromazine scopolamine	20	9	53	24	8	3
Promethazine scopolamine	19	17	45	13	8	7

promazine caused the greatest incidence of drowsy or sleepy patients, and also appeared to suppress apprehension to the greatest degree.

Effect of Premedication on Vital Signs (Table II)

Hypertension and tachycardia occurred more often in the standard test than with any of the blind tests. Hypotension and bradycardia occurred most often with proclorperazine-scopolamine. There was no significant difference among the agents (except proclorperazine) with respect to the incidence of tachycardia. Hypotension occurred less frequently with promethazine—both in the standard and in the blind test. It was interesting to observe that the incidence of hypotension in the placebo group was higher than in both promethazine groups.

The determination of tidal volumes was abandoned early in this study because the application of the face mask of the ventilation meter in the immediate preoperative period was unpleasant to the patient, so that only respiratory rates were recorded thereafter. A slower respiratory rate was observed most often with levomepromazine. Tachypnoea was observed most often with proclorperazine.

After induction of anaesthesia, hypotension occurred most often with promazine. There were no cases of profound hypotension, but at least 20 per cent reduction in blood pressure was observed in more than 5 per cent of the patients in each group.

Postoperative Condition of the Patients (Table III)

Hypotension was observed in at least 10 per cent of the patients in all groups. It occurred least often in the patients who were premedicated with the placebo. However, it is difficult to equate postoperative hypotension with the premedicants without detailed consideration of the wide variety of factors of each anaesthetic course. Nausea and vomiting occurred postoperatively in approximately 20 per cent of patients in the standard series and with the placebo. The least incidence of nausea and vomiting was in the patients who received levomepromazine, but the difference from the other groups was not great.

There are numerous factors that may cause prolonged postoperative "sleep" even though each anaesthetist strives to have his patients aroused shortly after the end of an operation. On the average, the patients slept significantly more than half an hour if they received scopolamine with any of the phenothiazine derivatives. The longest sleep was seen with promazine and levomepromazine.

The occurrence of amnesia related to the period extending from the administration of the pre-anaesthetic medication until postoperative recovery of consciousness was recorded in at least 7 per cent of the patients in each series. The greatest incidence of amnesia was recorded for the patients who received levomepromazine. This might reflect the greater number of patients who were drowsy or sleepy, but amnesia was not a characteristic of the patients who received promazine, even though most of these patients were sleepy preoperatively and slept longer postoperatively.

The occurrence of postoperative shivering and urinary retention did not show any significant variation among the groups that could be related directly to the premedicants.

Discussion

In every branch of medicine, the student is informed that the initial approach to his patients and his explanation of the physical and mental complaints may contribute as much to ultimate cure as any specific therapeutic measures. The effect of his personality and the acquired ability of the physician to reassure and to calm those who are fearful are particularly important attributes of the anaesthetist. Few of us have this ability. Most physicians will always depend mainly on the aid of drugs to subdue apprehension (5, 6, 16).

The greatest problem which faces the anaesthetist who strives to suppress emotional stress is how to evaluate the effect of drug therapy. From previous

discussions of this problem (7, 8), one aspect requires further consideration: most anaesthetists overestimate their ability to diagnose functional disorders. Often, even in ordinary life situations, we are unable to distinguish the fearful and anxious who have a "dead pan" or a "poker face" from the really composed and tranquil stranger, without the use of searching questions and "cross examination." For instance, when a stoical woman is being prepared for removal of a painless lump in her breast which might be carcinomatous, can we identify easily her emotional stress? Can we differentiate that from the physical and mental stress that might develop when she was about to have a painful ingrown toenail excised? Furthermore, do we have a certain method for differentiating the tranquillity that might be caused by morphine from that by promethazine in these two situations? Only those who have no difficulty with these questions can decide on the correct drugs to choose for use in premedication.

The valid arguments for disuse and use of narcotics (9, 10) and barbiturates (11) as premedicants in anaesthesia apply equally well to the use of ataractics (1, 12). For that matter, it appears evident to each experienced anaesthetist that he can usually provide satisfactory pre-anaesthetic sedation, without serious physiological upset to the patient, with many different drugs, even though their mode of action may vary widely (2, 13).

In designing this clinical experiment, every effort was exercised to make the evaluation as sensitive as possible (14, 15). The subjective and objective questionnaire was used to reveal physical and mental signs and symptoms, and the over-all evaluation of the premedicant effect was noted also for the wider perspective. Both placebo control and double-blind control were employed to protect against bias and psychic factors which cannot be eliminated, and to protect against spurious data. An "internal control" was employed by the use of a standard which was identical with one of the unknown drugs, to provide a competent indicator of positive effects, and to determine how much the anti-sialogogue (scopolamine) might contribute to the various aspects of premedication that were being studied.

The development of drowsiness or sleepiness may not be the only condition for allaying anxiety and fear, but it is often true that the sleepy patient is less apprehensive than the patient who is wide awake, and acutely aware of his environment. It appears, therefore, that part of the success of a pre-anaesthetic sedative in suppressing apprehension depends in some measure on its hypnotic effect. The other important attribute of such a drug is its ability to produce a period of amnesia. These attributes must be weighed against the occurrence of marked hypotension during induction of anaesthesia, and delayed post-anaesthetic recovery of consciousness.

From this study, one may be able to decide: Does it pay to add a phenothiazine to a barbiturate to reduce the incidence of unsatisfactory preoperative sleep by at least 5 per cent, and does it pay to use a phenothiazine with scopolamine to reduce pre-anaesthetic apprehension, reduce postoperative nausea and vomiting, and increase the incidence of amnesia for the operative period, without serious disturbance of the patient's vital signs (16)?

Considering all these, one is seldom justified in using a placebo for preoperative sedation. Proclorperazine may not be worthy of further trial because its hypnotic;

amnesic, anti-emetic, and tranquillizing actions were not good at a dose level that frequently caused hypotension. Promazine appeared to have a good hypnotic activity, but it was a weak anti-emetic and amnesic, hypotension occurred too frequently after induction of anaesthesia, and post-anaesthetic sleep was much prolonged. Levomepromazine was an excellent hypnotic and had a good anti-emetic and amnesic activity, but prolonged post-anaesthetic sleep was common. The discriminate use of levomepromazine is worthy of further trial at slightly reduced dosage from that tested here. An increase in the dosage of promethazine (combined with scopolamine) might improve its activity without depressing vital signs, but in this study its over-all performance was not as good as levomepromazine and promazine.

Summary and Conclusions

Pre-anaesthetic medication with promethazine, promazine, proclorperazine, and levomepromazine was studied under controlled clinical conditions employing the double blind method with a placebo, and a known standard. The test drugs were combined with secobarbital and administered by mouth the night before an elective operation to determine their effectiveness for inducing undisturbed sleep. Approximately one hour before induction of anaesthesia, each patient received an intramuscular injection of the same test drug, combined with scopolamine in the blind study or promethazine with atropine in the standard study. Data were collected on a special protocol. This contained information recorded from the initial visit, before induction of anaesthesia, in the post-anaesthetic recovery room, and 24 hours postoperatively. On completion of the study, these data were tabulated and analysed *before revealing the code.* Analysis of the data showed whether the administered drugs disturbed the vital signs, allayed apprehension, induced light sleep or caused amnesia. The data from each series of drug tests were compared. In this study, levomepromazine was the most effective premedicant without causing any more undesirable effects than were seen among the others.

It appears as if the "price" we pay for tranquillity should depend partly on the pharmaceutical industry and on the skill exercised by the anaesthetists who use their drugs, just as it does for our primary anaesthetics. The greatest value from individual drugs—whether they are narcotics, barbiturates, phenothiazines, or other ataractics—will depend ultimately on the ability of the individual anaesthetist to prepare the patient by his own personal approach, and by his considered and experienced selection from a wide range of drugs. The greatest emphasis should be placed on the individual selection of a drug in relation to the age, size, temperament and physical state of the patient.

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RÉSUMÉ

Dans des conditions cliniques contrôlées et en employant la méthode du "double inconnu" avec un placebo et un standard connu, nous avons étudié la médication préanesthésique avec de la prométhazine, de la promazine, de la proclorperazine et de la levomepromazine. Nous avons associé le médicament à étudier à du secobarbital que nous donnions, par la bouche, la veille d'une opération élective, pour bien préciser leur pouvoir d'induction calme du sommeil. Environ une heure avant l'induction de l'anesthésie, chacun des malades recevait une injection intra-musculaire du même médicament à étudier avec de la scopolamine pour l'étude avec l'inconnu ou avec de la promethazine et de l'atropine pour l'étude standard. Les données ont été colligées sur un protocole spécial. Ce protocole contenait les renseignements obtenus dès la première visite, avant l'induction de l'anesthésie, dans la salle de réveil après l'anesthésie et, enfin 24 heures après l'opération. A la fin de l'étude, les données ont été mises en tableaux et analysées avant de révéler la légende. L'analyse des résultats devait montrer si les médicaments donnés modifiaient les signes vitaux, faisaient disparaître l'appréhension, provoquaient un léger sommeil ou entraînaient de l'amnésie. Nous avons comparé les données de chaque série de médicaments. Après cette étude, nous sommes d'avis que la levomepromazine a été la médication la plus efficace sans pour cela entraîner plus d'effets indésirables qu'aucun des autres médicaments.

Il nous semble que le tribut à payer pour assurer notre paix dans ce domaine doit aller en partie à l'industrie pharmaceutique et en partie à la capacité des anesthésistes qui emploient ces médicaments, comme il en est d'ailleurs pour les anesthésiques de base. La plus grande vertu de tout médicament—qu'il s'agisse de narcotiques, de barbituriques, de phenothiazines ou d'autres ataraxiques—va dépendre en définitive de l'habileté de l'anesthésiste, comme individu, qui prépare le malade, par son contact personnel et par le choix judicieux et bien informé d'un médicament entre plusieurs. Il faut insister beaucoup sur le choix particulier de chacun des médicaments selon l'âge, le poids, le tempérament et l'état physique du malade.

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