

POSTOPERATIVE NAUSEA AND VOMITING: THE RESPONSE TO ANTI-EMETIC DRUGS WITH SPECIAL REFERENCE TO CYCLIZINE AND PERPHENAZINE

HILDA ROBERTS, F.F.A.R.C.S.¹

OVER THE PAST TWO to three decades, advances in surgery have stimulated parallel advances in anaesthesia. In fact, it can be said that so many of the intricate surgical procedures would be impossible without the support of skilled anaesthetic techniques. An indication of the satisfactory progress of anaesthesia is the patient's expectation of a pleasant smooth induction and an uneventful recovery. There is no doubt that anaesthesia has attained its high standard by reason of scientific and clinical research carried out by anaesthetists and pharmacologists. However, in spite of refinements of preoperative sedation, anaesthetic technique, and careful supervision in the immediate postoperative period, the incidence of nausea and vomiting is still too high. As observed by Marcus and Sheehan (1), such complications only become highlighted when a recovery room is maintained and patients are seen together in the early postoperative period. Consequently the search for the satisfactory anti-emetic continues, and those which have been used with considerable success for travel sickness have been employed to reduce the occurrence of vomiting after operation. The anti-emetics in general use today tend to fall into two categories: (i) antihistamine compounds, for example, dimenhydrinate, cyclizine; (ii) tranquillizers, for example, chlorpromazine, promethazine, perphenazine, promazine.

It is of paramount importance that the many factors contributing towards postoperative vomiting should be appreciated, and attempts made to correct them before mere blind administration of palliative drugs is undertaken. Best and Taylor (2) maintain that the induction of vomiting can be due to such factors as:

- (a) A reflex action arising from impulses from the stomach or other parts of the alimentary tract, extending from the pharynx downwards (irritation from blood, mucus, and irritant anaesthetic drugs entering the stomach itself will provide the necessary stimulus for vomiting)
- (b) Central stimulation due to drugs which raise the excitability of the vomiting centre itself, for example, morphine and meperidine

Other causes of vomiting are discussed by Dent *et al.* (3). Impulses received from the cerebral centres in response to various stimuli, for example, rough handling of the patient during transfer from operating table to trolley and frequent changing of position during the early postoperative period, can be a factor in vomiting. Vestibular stimulation by morphine or anaesthetic drugs can increase the liability to vomiting. Best and Taylor consider that any interference with the blood supply to the vomiting centre either by haemorrhage or by tumour will

¹Associate Chief of Anaesthesia, Women's College Hospital, Toronto.

stimulate vomiting. Anoxia is thought to be a very important source of stimulation, and any severe degree of anoxia has the same effect as impairment of blood supply. General disorders such as mental stress, hysteria or even fatigue can be the cause of postoperative vomiting, and it is conceded that the nervous, anxious patient is more likely to experience an unhappy recovery than the placid patient.

In an attempt to evaluate some of the anti-emetic drugs in postoperative vomiting a survey was undertaken. The *modus operandi* was as follows:

Two general surgeons and two gynaecologists gave permission for their patients to receive the anti-emetic drugs under consideration, and the remainder of the surgical cases were observed as controls. The patients constituting the control group did not receive any of the anti-emetic drugs during the whole operative period including preoperative and immediate postoperative periods. Each group contained a similar cross-section of types of operations, and a similarity in anaesthetic techniques was maintained since all anaesthetists worked in each group. In all, 1,403 patients (1,389 females, 14 males) were observed in the recovery room and in the ward on subsequent days up to the fifth day. The ages of the patients observed ranged from 5 years to 85 years, with the majority in the middle range. Detailed records were kept on each patient. The main scrutiny concerning nausea and vomiting was made over the first 36 hours after operation since it was felt that many other extraneous factors cause or accentuate the gastric disturbance after that time. Some observers in this field confine themselves to the first 12 hours at most, as they think that with modern anaesthesia the effects of the drugs should be eliminated by that time.

Only a brief résumé of the drugs used in this survey is presented since all of them have been well described in the literature.

1. Chlorpromazine is a derivative of phenothiazine and by reason of its neuroplegic action on the peripheral and central autonomic nervous system, it exhibits sedative and anti-emetic qualities, and also has the power to potentiate the activity of anaesthetic, analgesic and hypnotic drugs.

2. Promethazine, also a derivative of phenothiazine, has been shown to have antihistamine properties. It is also an anti-emetic and like chlorpromazine possesses potentiating properties.

3. Perphenazine has similar qualities and is an amino derivative of chlorphenothiazine. Animal studies indicate that perphenazine is five to ten times as potent as chlorpromazine but only half as toxic.

4. Cyclizine hydrochloride is an antihistamine and anticholinergic, and investigations indicate that it has a specific action on the parasympathetic ganglia.

MODE OF ADMINISTRATION OF DRUGS

Cyclizine hydrochloride was administered in three ways:

- (a) In the recovery room—by suppositories 100 mg. or 50 mg. intramuscularly if the operation involved the rectum or anus.
- (b) Preoperatively with atropine and meperidine or pantopon. Because of the potentiating action of the cyclizine, it was found necessary to halve the amount of narcotic given. Therefore, the preoperative sedation was meperidine 50.0 mg., atropine 0.6 mg., cyclizine 50.0 mg. intramuscularly.

(c) Preoperative sedation as in (b) and supported by the administration of meperidine-promethazine-chlorpromazine or by meperidine-perphenazine during anaesthesia.

Meperidine-promethazine-chlorpromazine sequence was used in association with anaesthesia. The formula contained: meperidine 100 mg., promethazine 50 mg., chlorpromazine 50 mg., in 20 ml. of normal saline. The amount used during anaesthetic varied from 4 to 10 ml., depending on the length and type of operation.

Meperidine-perphenazine was administered in the same way as the meperidine-promethazine-chlorpromazine combination. The amounts contained in the solution: meperidine 100 mg., perphenazine 50 mg., in 20 ml. of normal saline.

RESULTS

The material in the survey presents a variety of surgical procedures, and since the observations of some workers indicate that the site of operation has an influence on the incidence of postoperative vomiting, it was deemed necessary to compare the distribution of operations in the control group and in the treated patients. Table I presents the variety of major operations in each group. There is some degree of imbalance in the distribution between the two groups, but it is felt that it is due, mainly, to the small number of major orthopaedic operations, and consequently the groups are considered comparable.

TABLE I
THE DISTRIBUTION OF THE TYPES OF MAJOR OPERATIONS IN THE CONTROL AND TREATED GROUPS

	Operations								Total
	Breast	Head and neck	Gastro-intestinal	Cholecystectomies	Pelvic and other abdominal	Fothergill repairs vaginal hysterectomies	Hernia repairs	Major orthopaedic	
Control group									
Observed values	16.00	15.00	37.00	28.00	126.00	26.00	11.00	7.00	266.00
Expected values	21.26	10.33	28.64	35.43	125.77	27.75	13.28	3.54	266.00
χ^2	1.30	2.11	2.44	1.56	.00	.11	.39	3.38	11.29
Treated group									
Observed values	56.00	20.00	60.00	92.00	300.00	68.00	34.00	5.00	635.00
Expected values	50.74	24.67	68.36	84.57	300.23	66.25	31.72	8.46	635.00
χ^2	.55	.88	1.02	.65	.00	.05	.52	1.42	5.09
TOTAL	72.00	35.00	97.00	120.00	426.00	94.00	45.00	12.00	901.00
									16.38

$$\chi^2 = 16.38. \quad 7 \text{ df.} \quad P < 0.05.$$

During the course of the observations a variety of anaesthetic techniques was employed, and to estimate the effect, if any, of the main types of anaesthesia on the incidence of postoperative vomiting, Table II was constructed. The three anaesthetics presented were given in conjunction with thiopentone, and where

TABLE II
THE EFFECT OF DIFFERENT ANAESTHETICS ON THE POSTOPERATIVE VOMITING:
MAJOR OPERATIONS

	Nitrous oxide	Volatile anaesthetic	Cyclopropane	Total
Absence of vomiting				
Observed values	266.00	195.00	65.00	526.00
Expected values	238.19	209.00	78.81	526.00
χ^2	3.25	.94	2.42	6.61
One episode of vomiting				
Observed values	77.00	91.00	43.00	211.00
Expected values	95.55	83.84	31.61	211.00
χ^2	3.60	.61	4.10	8.31
More than one episode of vomiting				
Observed values	65.00	72.00	27.00	164.00
Expected values	74.26	65.16	24.58	164.00
χ^2	1.15	.72	.24	2.11
TOTAL	408.00	358.00	135.00	901.00
				17.03

$\chi^2 = 17.03$. 4 df. $P < 0.01$.

necessary, relaxant drugs were used. There is a significant increase in the amount of postoperative vomiting in the patients receiving a volatile anaesthetic, and also in the cyclopropane group. In the latter patients the increase appears to be more confined to one episode of vomiting. Since it is felt that the type of anaesthetic does influence the results in this series, a study of the distribution of the types of anaesthetics used in each group of anti-emetic treatment is presented. Table III shows this distribution, and it is seen that the patients in the control group received more volatile anaesthetics and cyclopropane than those given anti-emetics. A further analysis was made of each anti-emetic group and also of the controls. In every such group the incidence of vomiting was studied in relation to the type of anaesthetic used; but it was found that none of the tables produced significant

TABLE III
THE DISTRIBUTION OF TYPES OF GENERAL ANAESTHESIA IN RELATION TO ANTI-EMETIC DRUGS:
MAJOR OPERATIONS

	Nitrous oxide	Volatile anaesthetic	Cyclopropane	Total
Controls				
Observed values	82.00	132.00	52.00	266.00
Expected values	120.45	105.69	29.86	266.00
χ^2	12.27	6.55	3.70	22.52
Meperidine and tranquillizer				
Observed values	140.00	100.00	27.00	267.00
Expected values	120.91	106.09	40.00	267.00
χ^2	3.01	.35	4.23	7.59
Combined cyclizine groups				
Observed values	186.00	126.00	56.00	368.00
Expected values	166.64	146.22	55.14	368.00
χ^2	2.25	2.80	.01	5.06
TOTAL	408.00	358.00	135.00	901.00
				35.17

$\chi^2 = 35.17$. 4 df. $P < 0.001$.

TABLE IV
AN ANALYSIS OF PATIENTS RECEIVING NITROUS OXIDE SUPPORTED BY THIOPENTONE,
WITH OR WITHOUT RELAXANT DRUG: MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Controls				
Observed values	36.00	23.00	23.00	82.00
Expected values	53.26	15.68	13.06	82.00
χ^2	5.59	3.42	7.56	16.57
Meperidine-tranquillizer sequences				
Observed values	99.00	30.00	11.00	140.00
Expected values	90.94	26.76	22.30	140.00
χ^2	.71	.39	5.73	6.83
Cyclizine				
Observed values	130.00	25.00	31.00	186.00
Expected values	120.81	35.56	29.63	186.00
χ^2	.70	3.14	.06	3.90
TOTAL	265.00	78.00	65.00	408.00
				27.30

$\chi^2 = 27.30$. 4 df. $P < 0.01$.

results. This appeared to indicate a fairly steady action on the part of the individual anti-emetics whatever anaesthetic was employed. However, an analysis of the individual anaesthetic groups (Tables IV and V) points to the significant effect of meperidine-tranquillizer administrations. The numbers in Table VI are rather too small to be effective.

Table VII analyses the postoperative vomiting after major operations in the control group and the meperidine-tranquillizer series. The effect of the latter is significant. Patients receiving cyclizine are presented in three groups in Table VIII which shows the most satisfactory results are obtained when the cyclizine is supported by meperidine and tranquillizer. Comparisons of the main groups

TABLE V
THE INCIDENCE OF POSTOPERATIVE VOMITING AFTER THE USE OF VOLATILE ANAESTHETICS:
MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Controls				
Observed values	57.00	29.00	46.00	132.00
Expected values	71.90	33.55	26.55	132.00
χ^2	3.09	.62	14.25	17.96
Meperidine-tranquillizer sequences				
Observed values	69.00	29.00	2.00	100.00
Expected values	54.47	25.42	20.11	100.00
χ^2	3.88	.50	16.31	20.69
Cyclizine				
Observed values	69.00	33.00	24.00	126.00
Expected values	68.63	32.03	25.34	126.00
χ^2	.00	.03	.07	.10
TOTAL	195.00	91.00	72.00	358.00
				38.75

$\chi^2 = 38.75$. 4 df. $P < 0.001$.

TABLE VI
AN ANALYSIS OF THE EFFECT OF CYCLOPROPANE ANAESTHESIA:
MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Controls				
Observed values	22.00	18.00	12.00	52.00
Expected values	25.42	16.18	10.40	52.00
χ^2	.46	.20	.25	.91
Meperidine-tranquillizer sequences				
Observed values	19.00	8.00	.00	27.00
Expected values	13.20	8.40	5.40	27.00
χ^2	2.55	.02	5.40	7.97
Cyclizine				
Observed values	25.00	16.00	15.00	56.00
Expected values	27.38	17.42	11.20	56.00
χ^2	.21	.12	1.29	1.62
TOTAL	66.00	42.00	27.00	135.00
				10.50

$\chi^2 = 10.50$. 4 df. $P < 0.05$.

(Tables IX and X) show highly significant results in favour of the meperidine-tranquillizer treatment. Similar analyses of the 760 minor operation cases did not give any significant results, and this may have been due to the fact that very few patients received the meperidine-tranquillizer treatment.

Observations were made on 401 patients who experienced postoperative vomiting. Type of operation, anaesthetic received, and any prophylactic treatment given preoperatively or during operation were not taken into consideration. The anti-emetic given for the treatment of the vomiting was left to the discretion of the surgeon concerned. The drugs used were cyclizine and dimenhydrinate and

TABLE VII
THE RELATION BETWEEN POSTOPERATIVE VOMITING AND THE TYPE OF ANTI-EMETIC
ADMINISTERED DURING ANAESTHESIA FOR MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Control group				
Observed values	115.00	70.00	81.00	266.00
Expected values	150.70	68.40	46.90	266.00
χ^2	8.46	.04	24.80	33.30
Meperidine-promethazine-chlorpromazine during anaesthesia				
Observed values	103.00	45.00	7.00	155.00
Expected values	87.80	39.80	27.40	155.00
χ^2	2.63	.68	15.09	18.40
Meperidine-perphenazine during anaesthesia				
Observed values	84.00	22.00	6.00	112.00
Expected values	63.50	28.80	19.70	112.00
χ^2	6.69	1.61	9.62	17.92
TOTAL	302.00	137.00	94.00	533.00
				69.62

$\chi^2 = 69.62$. 4 df. $P < 0.001$.

TABLE VIII
THE INCIDENCE OF POSTOPERATIVE VOMITING IN THE CYCLIZINE SERIES:
MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Cyclizine given in recovery room				
Observed values	31.00	18.00	22.00	71.00
Expected values	43.22	14.28	13.50	71.00
χ^2	3.46	.97	5.35	9.78
Cyclizine given preoperatively				
Observed values	72.00	37.00	37.00	146.00
Expected values	88.87	29.36	27.77	166.00
χ^2	3.20	1.99	3.07	8.26
Cyclizine given preoperatively, supported by meperidine-tranquillizer sequences				
Observed values	121.00	19.00	11.00	151.00
Expected values	91.91	30.26	28.73	151.00
χ^2	9.21	4.25	10.94	24.40
TOTAL	224.00	74.00	70.00	368.00
				42.44

$\chi^2 = 42.44$. 4 df. $P < 0.001$.

observations were made after the administration of a maximum of two doses at 4-hour intervals within 36 hours after operation. A number of patients received no treatment for vomiting within the same period of time, and have been recorded as controls. Table XI compares the observations made on the three groups. Cyclizine presents the most satisfactory results and there is a significant reduction in vomiting following its administration. Dimenhydrinate produces little effect, if any at all, on the incidence of vomiting.

TABLE IX
RESULTS OF THE MEPERIDINE-TRANQUILLIZER SEQUENCES AND
CYCLIZINE ADMINISTRATIONS: MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Controls				
Observed values	115.00	70.00	81.00	266.00
Expected values	155.00	62.29	48.42	266.00
χ^2	10.45	.95	21.92	33.32
Combined meperidine-tranquillizer sequences				
Observed values	187.00	67.00	13.00	267.00
Expected values	155.87	62.53	48.60	267.00
χ^2	6.22	.32	26.08	32.62
Combined cyclizine administrations				
Observed values	224.00	74.00	70.00	368.00
Expected values	214.84	86.18	66.98	368.00
χ^2	.39	1.72	.14	2.25
TOTAL	526.00	211.00	164.00	901.00
				68.19

$\chi^2 = 68.19$. 4 df. $P < 0.001$.

TABLE X
RESULTS WITH PATIENTS RECEIVING BOTH CYCLIZINE AND THE MEPERIDINE-TRANQUILLIZER SEQUENCE ELIMINATED FROM THE CYCLIZINE GROUP: MAJOR OPERATIONS

	Absence of vomiting	One episode of vomiting	More than one episode	Total
Controls				
Observed values	115.00	70.00	81.00	266.00
Expected values	143.64	68.10	54.26	266.00
χ^2	5.71	.05	13.18	18.94
Combined meperidine-tranquillizer sequences				
Observed values	187.00	67.00	13.00	267.00
Expected values	144.18	68.35	54.47	267.00
χ^2	12.72	.03	31.57	44.32
Cyclizine				
(a) preoperatively;				
(b) in the recovery room				
Observed values	103.00	55.00	59.00	217.00
Expected values	117.18	55.55	44.27	217.00
χ^2	1.72	.00	4.90	6.62
TOTAL	405.00	192.00	153.00	750.00
				69.88

$\chi^2 = 69.88.$ 4 df. $P < 0.001.$

DISCUSSION

The structural formulae of the phenothiazine derivatives show a close relationship, but this likeness is not always borne out in their pharmacological actions. They do possess, however, certain common properties, and the anti-emetic action is common to most of them. The two sequences employed in this investigation, that is, meperidine-promethazine-chlorpromazine and meperidine-perphenazine, do present a very definite improvement in the incidence of postoperative vomiting. The improvement may be due to two things: (a) the central action of the tranquillizers preventing vomiting; (b) the potentiation of anaesthetic agents, thus reducing the amount of potential nauseants used, as shown in Table III.

TABLE XI
RESPONSE TO THREE METHODS OF APPROACH TO POSTOPERATIVE VOMITING

	Cessation of vomiting	Continued vomiting	Total
Cyclizine postoperatively			
Observed values	137.00	62.00	199.00
Expected values	120.59	78.41	199.00
χ^2	2.23	3.43	5.66
Dimenhydrinate postoperatively			
Observed values	46.00	42.00	88.00
Expected values	53.33	34.67	88.00
χ^2	1.01	1.55	2.56
No treatment given			
Observed values	60.00	54.00	114.00
Expected values	69.08	44.92	114.00
χ^2	1.19	1.84	3.03
TOTAL	243.00	158.00	401.00
			11.25

$\chi^2 = 11.25.$ 3 df. $P < 0.01.$

The meperidine-perphenazine combination superseded the meperidine-promethazine-chlorpromazine sequence in this survey since it was found that the former provided a very smooth recovery period, and that its administration during anaesthesia did not produce the hypotension created by meperidine-promethazine-chlorpromazine. So far, perphenazine has not been found guilty of causing liver damage or agranulocytosis, but reported Parkinson-like reactions to oral perphenazine have indicated its ability to cause extra-pyramidal dysfunction. Robbie (4) describes two patients exhibiting such dysfunction after multiple doses of intramuscular injections of perphenazine. The tranquillizers present a fascinating and complex study to anaesthetists, and in using them for a specific purpose one must be fully aware of their other properties. According to Hiebel *et al.* (5) both chlorpromazine and promethazine have the unique property of depressing the arousal mechanism of the reticular activating system without affecting the cortical regions, and since areas in the reticular system are responsible for the control of muscle tone, vasomotor tone (Back (6)), respiratory activity, and the act of vomiting (Borison *et al.* (7)), the results of such depression need careful consideration.

The preoperative cyclizine administrations do not present any significant relief in the incidence of postoperative vomiting. As far as this survey is concerned, it is thought that in some of the cases receiving cyclizine preoperatively, a delay in starting the operation and a prolonged operating time could have impaired the action of the anti-emetic drug in the recovery period. Under such circumstances a second intramuscular injection of cyclizine at the termination of the operation, or in the recovery room, might have prolonged its effectiveness. Observations by Chinn *et al.* (8) on certain antihistamine drugs lead them to think that prophylaxis does not depend on the antihistamine action of these drugs, but on the cholinergic effect. This would explain the effectiveness of drugs with a central atropine-like action, for example, scopolamine. Marcus and Sheehan (9) maintain that cyclizine given prophylactically is more effective than later administration once vomiting has occurred; however, in this series the effect of cyclizine is significant when used postoperatively for the treatment of vomiting. There were not any untoward side-effects observed in the patients treated with cyclizine.

SUMMARY

A study of 1,403 patients has been conducted in relation to the efficiency of certain anti-emetic drugs used before and during operation. The drugs included in the survey were cyclizine and the meperidine-perphenazine, meperidine-promethazine-chlorpromazine sequences. A control group was established in which the patients did not receive any anti-emetic drugs before or during anaesthesia. The distribution of types of major operations and of anaesthetics given in the treated and control groups were compared.

The groups, established apart from the controls, were: (a) meperidine-promethazine-chlorpromazine during operation; (b) meperidine-perphenazine also during operation; (c) cyclizine suppositories 100 mg. in the recovery room; (d) cyclizine 50 mg. intramuscularly with the preoperative sedation; (e) cyclizine

50 mg. preoperatively supported by one of the aforementioned meperidine sequences during anaesthesia. The results indicate that cyclizine does not improve the postoperative vomiting to any significant degree, whereas the meperidine tranquillizer sequences show a significant decrease in the incidence of vomiting. A study of the postoperative treatment of 401 patients who vomited within 36 hours of operation indicated that intramuscular administrations of cyclizine produced significant improvement.

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RÉSUMÉ

Nous avons fait une étude chez 1,403 malades sur l'efficacité de certains médicaments employés comme anti-émétiques avant et durant les opérations. Les médicaments étudiés étaient la cyclizine et la mépéridine-perphenazine, mépéridine-prométhazine-chlorpromazine dans l'ordre. Nous avons un groupe de témoins où les malades n'ont reçu aucun médicament anti-émétique ni avant, ni durant l'anesthésie. Nous avons comparé, chez les deux groupes, le partage des types d'opérations majeures et des anesthésiques donnés.

Le partage des groupes, en-dehors des témoins, étaient comme suit: (a) mépéridine-prométhazine-chlorpromazine durant l'opération; (b) mépéridine-perphenazine également durant l'opération; (c) cyclizine 100 mg. en suppositoires à la salle de réveil; (d) cyclizine 50 mg. I.M. avec la sédation préopératoire; (e) cyclizine 50 mg. avant l'opération suivie, au cours de l'anesthésie, d'une des associations à la mépéridine mentionnées antérieurement. Les résultats nous démontrent que la cyclizine n'améliore pas de façon appréciable les vomissements post-opératoires, tandis que l'association mépéridine-tranquillisant a donné une diminution notable de la fréquence des vomissements. Une étude de 401 malades qui ont vomi durant les 36 heures suivant l'opération nous a prouvé que la cyclizine, en injections intramusculaires, a apporté une amélioration notable.

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