THE EFFECTIVENESS OF ANTI-EMETIC AGENTS: A COMPARISON OF THE ANTI-EMETIC ACTIVITY OF TRIFLUOPROMAZINE (VESPRIN®), PERPHENAZINE (TRILAFON®), AND TRIFLUOPERAZINE (STELAZINE®) WITH THAT OF DIMENHYDRINATE (GRAVOL®) IN POSTANAESTHETIC VOMITING*

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THE EFFECTIVENESS of individual anti-emetic drugs in reducing the incidence of postoperative vomiting in patients who would otherwise receive no anti-emetic is readily established. This has led to a proliferation of anti-emetic agents, making the choice of one agent for any patient extremely difficult. Belleville¹ has pointed out the difficulties of making comparisons between well-controlled studies of different investigators, and recommends further controlled comparative studies. However, unless consideration is given to the large numbers of interacting factors affecting the incidence of postoperative vomiting, it may be impossible to grade the effectiveness of the test agents, and recommendations on the choice of agent may have to be based upon the absence of undesirable side-effects.²

In this study, in addition to recording the incidence of side-effects, an attempt has been made to reduce the number of variables by selecting certain operations, using standard anaesthetic techniques, and a standard pre-anaesthetic medication, in the hope that clearer distinctions might appear regarding the anti-emetic activity of the agents used.

The anti-emetic activity of dimenhydrinate (Gravol®) has been well documented³⁻⁶ and this agent was the one most frequently used in this hospital to control postoperative nausea and vomiting. It was included in the survey as a "control" agent against which to measure the activity of the three newer drugs.

Investigation of trifluoperazine (Stelazine®) showed prolonged protection against apomorphine-induced vomiting,⁷ good results in nausea and vomiting of pregnancy,⁸ and in the suppression of seasickness.⁹ Perphenazine (Trilafon®) was 16.6 to 47.8 times more effective than chlorpromazine in preventing apomorphine-induced vomiting,¹⁰ and substantially reduces postoperative vomiting.^{11,12,13} Significant reduction in postoperative vomiting has been demonstrated by a number of workers using trifluopromazine (Vesprin®).^{2,14,15,16}

METHOD

Selection of Patients

In order to provide an effective challenge for the test agents, ten operations expected to be associated with a high incidence of nausea and vomiting were

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selected. The selection was based on the site of operation, and on the expected age and sex distribution of patients undergoing the operation, factors known to influence the incidence of vomiting.^{17,18} All patients included in the survey received a standard narcotic premedication (meperidine 50–100 mg. with atropine 0.4–0.6 mg. roughly according to body weight), which has been reported to increase the incidence of postoperative vomiting.¹

Data were collected from 2491 patients, of whom 345 were excluded, 269 because they received a premedication other than meperidine and atropine, and 76 because of inadequate data. The age and sex distribution, distribution among operations, and incidence of nausea and vomiting of those patients excluded were similar to those of the patients retained.

With the exception of those patients whose condition was unsatisfactory pre-operatively (physical status 3 or 4) or postoperatively (marked hypotension or underventilation), all patients scheduled to undergo one of the selected operations were included in the survey.

The distribution of the remaining 2146 patients according to sex and operation is presented in Figure 1 and shows the preponderance of female patients arising from the method of selection, especially in the intra-abdominal and perineal groups.

FIGURE 1. Patient distribution by operation type.

Allocation of Drugs

The test agents were placed in separate multi-dose vials, the concentration of the solution being adjusted as shown in Table I, to allow an effective anti-emetic dose when given at the rate of 0.01 ml. per lb. of body weight (0.02 ml./kg.).

A master list of trial numbers containing four anaesthetic types (nitrous oxide/oxygen, halothane, cyclopropane, ether) for each of the ten operations was used to select the appropriate drug. As each patient arrived in the recovery room, he was identified as to operation and anaesthetic given, and allocated the next available trial number under that heading. Against each trial number was a code letter identifying the vial to be given. The code letters were arranged in sequence,

with a space at every fifth trial number, where no anti-emetic was given. From the appropriate vial 0.01 ml. per pound of body weight was withdrawn and injected intramuscularly. Thus the selection of anti-emetic agent was not biased by the selection of the administering nurse, or by the observer. Tables II and III, showing the distribution of patients by operation, anaesthetic, and anti-emetic, reflects the incidence of the four anaesthetic techniques used, and indicates an even distribution of anti-emetic drugs.

TABLE I
DRUG CONCENTRATIONS

Drug	Concentration (mg./c.c.)
Dimenhydrinate	50
Trifluopromazine	12 5
Perphenazine	2 5
Trifluoperazine	1

TABLE II
DISTRIBUTION OF PATIENTS BY OPERATION AND ANAESTHETIC

	Number of patients receiving:			
	Nitrous oxide	Cyclo- propane	Halothane	Ether
Tonsillectomy	24	30	87	30
Breast	32	84	81	29
Cholecystectomy	32	92	84	83
Appendectomy	28	83	93	36
Abdominal hyst.	20	66	84	20
Vaginal hyst.	25	60	93	21
D. & C.	81	80	83	23
Haemorrhoidectomy	28	80	94	35
Herniorrhaphy	19	51	91	30
Varicose veins	23	35	65	11
Total (2146)	312	661	855	318

TABLE III
DISTRIBUTION OF PATIENTS BY OPERATION AND ANTI-EMETIC AGENT

Operation	No anti-emetic	Dimen- hydrinate	Tri- fluopromazine	Perphenazine	Trifluoperazine
Tonsillectomy	28	37	33	38	35
Breast	40	45	46	50	45
Cholecystectomy	61	55	65	59	51
Appendectomy	48	49	53	44	46
Abdominal hyst.	43	44	37	23	43
Vaginal hyst.	42	40	42	43	32
D. & C.	60	53	56	39	59
Haemorrhoidectomy	29	22	23	29	31
Herniorrhaphy	45	45	54	43	50
Varicose veins	36	46	40	32	37

Observations

Using a special proforma, recovery room nurses observed the patient at 15-minute intervals. In addition, every episode of retching or vomiting occurring after the first 15 minutes was recorded. A score system was used, nausea having a value of 1, retching 2, and vomiting 3. After discharge from the recovery room, nausea and emesis recorded on the patient's chart were scored in a similar manner.

In order to assess subjective responses, patients were visited between 24 and 48 hours postoperatively and questioned as to the extent of the vomiting remembered, which was graded as mild where patients reported nausea only, or one episode of vomiting, moderate where two episodes of vomiting had been experienced, and severe when there had been three or more remembered episodes of vomiting. While discrepancies did occur between the score value and the vomiting reported by the patient, these were not frequent, and occurred equally in either direction. Those patients who had had previous anaesthesia were invited to compare their experiences, and to state whether they had experienced less, more, or the same amount of vomiting with this anaesthetic.

Additional data recorded included the occurrence of hypotension during the anaesthetic and in the recovery room, the timing and number of postoperative analgesic and subsequent anti-emetic injections, and the duration of postoperative sleep, judged by the ability to respond to verbal commands.

RESULTS

The main effect of an anti-emetic agent given prophylactically may be to reduce the numbers of patients with a positive score for nausea and vomiting, while the main effect of a drug given therapeutically is to bring about cessation, or a reduction in the severity of, established nausea and vomiting. In this study of patients given a single prophylactic test injection, comparisons were made of the effects of the drugs on both the incidence and severity of nausea and vomiting.

1. Incidence

In those patients receiving the test anti-emetic only, shown in Table IV, a significant reduction in the number vomiting is seen in the period from 15 minutes to 6 hours with patients receiving phenothiazines. Perphenazine was significantly better than no anti-emetic or dimenhydrinate ($p < 0.1$) while trifluoperazine and trifluopromazine were better than dimenhydrinate ($p < 0.5$).

When all the data are considered, except for 40 patients who received a subsequent anti-emetic as a routine procedure rather than on the basis of need, and for 23 patients in whom the emesis data were incomplete, the phenothiazine derivatives emerge as significantly better than no medication in both the period 15 minutes to 6 hours and the period 15 minutes to 24 hours (Table V). This clearly separates the phenothiazines as more effective anti-emetic agents than dimenhydrinate, and indicates that the effects of a single injection carry over into the 24-hour period. The differences between the phenothiazines are not sufficiently large to distinguish between them on the basis of their effects on incidence.

TABLE IV

INCIDENCE COMPARISONS

A comparison of the number of patients with no nausea or vomiting (zero score) in each treatment group, excluding all patients receiving one or more additional anti-emetics

Group	Total patients	Zero scores			
		15 min. to 6 hr.		15 min. to 24 hr.	
		Number of patients	%	Number of patients	%
No medication	308	230	76.2	210	69.5*
Dimenhydrinate	344	248	72.7	228	66.9
Trifluopromazine	382	305*	80.3	276	72.6
Perphenazine	344	286†	83.1	267	77.6
Trifluoperazine	335	257*	79.6	230	71.2

*Significantly different from dimenhydrinate ($p < 0.5$).

†Significantly different from dimenhydrinate and no medication ($p < 0.1$).

TABLE V

INCIDENCE COMPARISONS

A comparison of the number of patients with no nausea or vomiting (zero score) in each treatment group, including all patients requiring an additional anti-emetic

Group	Total patients	Number of zero scores	
		15 min. to 6 hr.	15 min. to 24 hr.
No medication	420	230	210
Dimenhydrinate	423	248	228
Trifluopromazine	445	305*	276*
Perphenazine	391	286*	267*
Trifluoperazine	404	257*	230*

*Significantly different from no medication.

2. Severity

To compare the effect of the test drugs on the severity of nausea and vomiting, average emesis scores were determined for each group, pooling the data from all operations and including all patients except those who received a second anti-emetic as a routine. The averages were adjusted for inequalities in sex distribution, additional anti-emetics required, and disproportionate assignments to operations by the use of a mathematical model. As shown in Figure 2, all the anti-emetics reduced the severity of nausea and vomiting, the effects persisting into the 24-hour period. All the phenothiazines except trifluoperazine were significantly better than no medication, and perphenazine was significantly better than dimenhydrinate. Once again, there was no significant difference between the three phenothiazines, showing that this comparison was not sufficiently sensitive to detect minor differences.

The next possibility investigated was that there might be one class of patients with nausea and vomiting that responded best to the action of anti-emetic drugs and that the differences in response to the test drugs in this class of patients

might be a more sensitive test of difference in effectiveness of the anti-emetic agents. It seemed likely that the greatest differences would emerge at the ends of the severity scale, either showing as a shift of the mild class to the no-vomiting class, or in a shift from the severe class to the moderate score class.

FIGURE 2. Average emesis scores.

Figure 3 shows the cumulative percentage of patients in each score category with the different test drugs, and suggests that the differences are most marked at the score levels of 1 and 2. Comparisons here would obviously yield similar results to those of incidence since these are determined by the percentage of patients with a zero score.

FIGURE 3. Emesis scores, 15 min. to 6 hr., cumulative frequency distribution.

When the severe end of the scale is considered, the careful recording of postoperative data made it possible to separate a class of patients with severe postoperative nausea and vomiting. These were patients who required a subsequent injection of an uncoded anti-emetic in the recovery room or on return

to the ward. Comparisons in this group produced very interesting results, as shown in Table VI. All the anti-emetic agents, including dimenhydrinate, were significantly better than no medication ($p < 0.1$). In addition, perphenazine was significantly better than dimenhydrinate ($p < 0.1$) and than trifluoperazine ($p < 0.5$), while trifluopromazine outshone dimenhydrinate ($p < 0.5$). These comparisons reflect the trend shown graphically in Figure 2 and make it possible

TABLE VI *
COMPARISON OF PATIENTS RECEIVING ONE ANTI-EMETIC WITH THOSE
REQUIRING ADDITIONAL ANTI-EMETICS

Group	Total patients	Anti-emetic		% patients requiring more
		One	More	
No medication	420	308	112	26 7
Dimenhydrinate	423	344	79*	18 7
Trifluopromazine	445	382	63*†	14 2
Perphenazine	391	344	47*‡	12 0
Trifluoperazine	404	335	69†	17 1

*Significantly different from no medication ($p < 0.1$).

†Significantly different from dimenhydrinate ($p < 0.5$).

‡Significantly different from dimenhydrinate ($p < 0.1$) and from trifluoperazine ($p < 0.5$).

to rank our anti-emetics in order of effectiveness. The three phenothiazines emerge as better anti-emetics than dimenhydrinate, but the difference between trifluoperazine and dimenhydrinate appears only in a reduction in incidence. Trifluopromazine reduces both the incidence and severity of nausea and vomiting as compared with dimenhydrinate, but ranks quite close to trifluoperazine, while perphenazine outshines trifluoperazine in reducing the severity of nausea and vomiting. It must be emphasized, however, that the difficulty in showing differences between the phenothiazines indicates that there is in fact little difference between their clinical effectiveness.

SIDE-EFFECTS

No matter how effective an anti-emetic agent may be, it may have side-effects which may make it less useful or even dangerous in certain patients. The phenothiazines commonly produce drowsiness (which may be prolonged), hypotension, and potentiation of anaesthetic and narcotic drugs. Any investigation of the effectiveness of anti-emetic agents must include an assessment of the price to be paid in unwanted side-effects. Comparisons were made of the incidence of hypotension in the recovery room, prolongation of postoperative sleep, and the reduction in postoperative narcotics occurring with the test agents and with no medication.

1. Hypotension

Hypotension was recorded as the difference between the lowest recorded systolic pressure in the recovery room and the resting systolic pressure, expressed

as a percentage of the latter. The incidence of this side-effect is shown in Table VII. The allocation of patients to the "no-medication" group was biased in some instances by the nursing staff, who occasionally refrained from giving an anti-emetic to a patient showing hypotension, and allocated them out of sequence to the "no-medication" group. Hence a greater than normal incidence of hypotension is probably represented in this group, and the control group here should

TABLE VII
AVERAGE PERCENTAGE FALL IN SYSTOLIC PRESSURE IN RECOVERY ROOM

Anti-emetic	No change	1-29% fall	30-40% fall	41%+ fall	No. of patients
No anti-emetic	72 4	16 4	7 2	4 0	305
Dimenhydrinate	77 9	16 9	4 2	1 0	331
Trifluopromazine	63 6	21 4	12 7	2 3	378
Perphenazine	69 8	18 0	11 0	1 2	344
Trifluoperazine	72 3	20 3	5 6	1 9	321

probably be the dimenhydrinate group. It is seen that all the phenothiazines are associated with an increased incidence of hypotension, the changes being least marked with trifluoperazine and most marked with trifluopromazine. With patients showing a 30 to 40 per cent fall in blood pressure, the changes approach statistical significance with perphenazine and trifluopromazine.

2. Duration of Postoperative Sleep

The 15-minute period during which the patient became able to respond to verbal commands was recorded as the "waking time." The majority of patients awoke in the first 15 minutes, and nearly all the remainder during the succeeding 45 minutes, but a small proportion slept beyond the first hour. The percentages of patients in each category are shown in Table VIII. It must be remembered that

TABLE VIII
DURATION OF POSTOPERATIVE SLEEP

Anti-emetic	Number of patients	% waking in		
		0-15 min.	16-60 min	60+ min
No anti-emetic	308	30 8	61 4	7 8
Dimenhydrinate	344	38 4	52 3	9 3
Trifluopromazine	382	43 4	44 8	11 8
Perphenazine	344	37 8	53 8	8 4
Trifluoperazine	335	47 5	46 9	5 6

the anti-emetic drug was given on arrival in the recovery room, and would not greatly influence the numbers of patients waking in the first 15 minutes. Drug effects are most apparent in the patients who slept longer than one hour, and approached statistical significance with trifluopromazine. With perphenazine, a characteristic state of prolonged drowsiness occurred, in which the patient responded but had to be retained in the recovery room for much longer periods than with trifluopromazine and trifluoperazine.

3. Potentiation of Narcotics

Although the concept of potentiation of narcotics by phenothiazines has recently been challenged by workers estimating pain thresholds, it is noted that in the clinical situation of this study, when the patient's need is determined by the observation of a nurse, fewer narcotic injections are given to patients who have received phenothiazine derivatives, as shown in Table IX. Because the patient is

TABLE IX

Anti-emetic	Number of patients	% not receiving narcotics in first 12 hours	% not receiving narcotics in first 24 hours
No anti-emetic	310	47.4 ₁	30.7
Dimenhydrinate	343	51.2 ₂	32.5
Trifluopromazine	375	63.2 [†]	40.8 ^{*††}
Perphenazine	343	58.4 ^{*†}	33.6
Trifluoperazine	345	58.4 ^{*†}	38.9 _§

*Significantly different from no anti-emetic ($p < 0.1$).

†Significantly different from dimenhydrinate ($p < 0.5$).

††Significantly different from perphenazine ($p < 0.5$).

§Significantly different from no anti-emetic ($p < 0.5$).

more tranquil and complains less, narcotics do not, therefore, seem to be indicated. All the phenothiazine anti-emetics tested reduced the need for postoperative narcotics in the first 12 hours, but some carry-over of this effect into the 24-hour period is seen with trifluoperazine and trifluopromazine, with the latter emerging as a better potentiator than perphenazine.

CONCLUSIONS

Each of the comparisons presented adds some information concerning the effectiveness of the anti-emetic agents tested, but no one comparison gives all the required information. It is noteworthy that what is significant in one comparison does not quite reach significance in others, and vice versa, demonstrating that even in a trial designed to limit variables there are many unknown factors at work. Nevertheless, the comparisons all reflect the same general trend as far as emesis is concerned, and it has been established that all the phenothiazines are superior to dimenhydrinate or no medication. These drugs have a prolonged anti-emetic effect, carrying over into the 24-hour period, and have their most pronounced effect in reducing the severity of vomiting in susceptible patients when given prophylactically before the patient awakens.

Although the differences between the phenothiazines are not large, perphenazine has the greatest effect, and trifluoperazine the least effect in reducing both the incidence and the severity of nausea and vomiting.

When we consider side-effects, however, hypotension occurs most frequently with trifluopromazine, somewhat less frequently with perphenazine, and scarcely at all with trifluoperazine. A similar pattern is seen with prolongation of post-operative sleep, although narcotic potentiation is minimal with perphenazine,

better potentiation being seen over a longer period with trifluopromazine and trifluoperazine.

The choice between these three anti-emetics tested will, therefore, depend on the requirements of the clinical situation. Where minimal hypotension and rapid wakening is important the drug of choice would be trifluoperazine. Where it is essential that a minimum of postoperative narcotics be required, trifluopromazine would be the best choice. If there are no specific contraindications, then perphenazine is the drug with the greatest anti-emetic effect.

The decision to use an anti-emetic drug depends upon the susceptibility of the patient, and the nature of the operation he is to undergo. The routine use of anti-emetic agents is to be discouraged, since their use incurs certain penalties in their side-effects. However, these agents have their greatest effect when given prophylactically before nausea and vomiting are fully established.

SUMMARY

The results of a double-blind study of four anti-emetic drugs are presented, and compared with a group receiving no medication. Included in this series were 2146 patients, selected as to physical status, postoperative condition, premedication, operation and anaesthetic. All the anti-emetic agents produced a significant reduction in the incidence of nausea and vomiting as compared with the group of patients receiving no medication. Trifluopromazine (Vesprin®), perphenazine (Trilafon®), and trifluoperazine (Stelazine®) were significantly better than dimenhydrinate (Gravol®) in reducing the incidence of nausea and vomiting. Of the three phenothiazine derivatives, perphenazine was the most effective in reducing the severity of the symptoms.

An increased incidence of hypotension and prolongation of postoperative sleep noted with trifluopromazine and perphenazine was not seen with trifluoperazine.

A reduction in the need for postoperative narcotic injections was noted with all three phenothiazine derivatives, being most marked in the case of trifluopromazine and trifluoperazine.

RÉSUMÉ

Nous vous présentons une étude à double contrôle de quatre produits antiémétiques, par comparaison avec un groupe de sujets ne recevant aucune médication. Cette série comprend 2146 malades choisis en considérant l'état physique, les conditions postopératoires, la prémédication, l'opération et l'agent anesthésique. Tous ces agents ont causé une diminution importante du taux de nausées et de vomissements par rapport au groupe qui n'avait reçu aucune médication. La trifluopromazine (Vesprin®), la perphénazine (Trilafon®) et la trifluopérazine (Stelazine®) se sont avérées sensiblement supérieures au dimenhydrinate (Gravol®). Des trois dérivés de la phénothiazine, la perphénazine fut la plus efficace pour diminuer la gravité des nausées et des vomissements.

On a noté un pourcentage d'hypotension et de prolongement du sommeil postopératoire avec la trifluopromazine et avec la perphénazine, mais non avec la trifluopérazine.

On a observé une diminution dans les doses requises de sédatifs postopératoires avec les trois dérivés de la phénothrazine; ceci était surtout marqué avec la trifluopromazine et avec la trifluopérazine.

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