THE ACTION OF THIETHYLPERAZINE (TORECAN®), A NEW ANTI-EMETIC, COMPARED WITH PERPHENAZINE (TRILAFON®), TRIMETHOBENZAMIDE (TIGAN®), AND A PLACEBO IN THE SUPPRESSION OF POSTANAESTHETIC NAUSEA AND VOMITING

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POSTANAESTHETIC VOMITING has been shown to be influenced by a variety of factors, and it is therefore unlikely that any anti-emetic drug will be completely effective and without side-effects in all patients. In the absence of any clear-cut superiority of one drug over another, the physician must exercise a choice, selecting a drug with minimum side-effects but maximum anti-emetic effect. This choice can only be made on the basis of controlled studies of effectiveness and side-effects, since clinical impressions can be most misleading. Many agents can be shown to have an anti-emetic effect when compared with a placebo (e.g., atropine)¹ but they may not be clinically useful as anti-emetics. If a new drug can be shown to have an effect equal to or better than a drug which has proven highly effective against a strong clinical challenge, then it is likely that the new agent will be clinically useful.

Thiethylperazine (Torecan®) is a phenothiazine which possesses to a very marked degree the anti-emetic activity common to all drugs of this group, while the other group activities of lowering blood pressure, potentiation of narcotics and barbiturates, and extrapyramidal effects, are minimized.² There have been a number of reports of its anti-emetic effect compared with a placebo in man,^{3,4,5} and there is experimental evidence to suggest that its medullary action is not confined to the Chemoreceptor Trigger Zone (CTZ) but encompasses the vomiting centre as well.⁶

Perphenazine (Trilafon®) was chosen as a comparative standard, since this drug had ranked as the most effective agent of four in a previous comparative trial.⁷ At the same time the opportunity was taken to compare these two agents with trimethobenzamide (Tigan®) in high dosage, since clinically this latter drug appeared to have minimal anti-emetic activity.⁸

METHOD

A previous trial⁷ had shown that the highest incidence of emetic symptoms followed the operations of abdominal hysterectomy, vaginal hysterectomy, and cholecystectomy, and that symptoms were more than twice as common in female patients as in male. Accordingly, female patients undergoing hysterectomy and cholecystectomy were selected for this survey in order to provide a high

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challenge for the test drugs. All patients received a standard premedication of meperidine (Demerol®) and atropine, and a standard anaesthetic sequence of thiopentone induction with maintenance on nitrous-oxide-oxygen-halothane, succinylcholine being used for relaxation as required.

The test drugs were coded in batches in identical vials, and the appropriate dose of the selected drug was given by intramuscular injection to each patient included in the trial as she arrived in the recovery room. The selection of drug was dictated by reference to a random allocation sheet for each operation, and the amount of drug was made proportional to body weight, by giving 0.04 c.c. of test solution per pound of body weight. Perphenazine was diluted to 1.25 mg./c.c., trimethobenzamide to 100 mg./c.c. and thiethylperazine to 5 mg./c.c. using sterile 5 per cent dextrose water, which was also used for the placebo. The 140-pound patient, for example, thus received 7 mg. of perphenazine, 560 mg. of trimethobenzamide or 28 mg. of thiethylperazine.

All patients were observed for two hours in the recovery room, and incidents of nausea and vomiting were charted at 15-minute intervals using a score system. A complaint of nausea was scored as one, observed retching or gagging without liquid emesis was scored as two, while each episode of liquid emesis scored three. Patients were visited between 24 and 48 hours after operation, and the incidents of nausea and vomiting recorded on the patient's chart were correlated with the patient's observations, and scored in the same way. Scores made in the first 15 minutes were disregarded, since it was felt that the test agent had not begun to act during this period.

RESULTS

On conclusion of the survey, the observations, together with the identity of the test agents, were translated into a numerical code and placed on punch cards. The data was subjected to a $3 \times 3 \times 4$ factorial design analysis, which demonstrated that there was no significant difference in scores among the three chosen operative sites, that all sites had equal influence on the emetic scores at different

TABLE I

$3 \times 3 \times 4$ FACTORIAL DESIGN ANALYSIS SHOWING SIGNIFICANT DIFFERENCES BETWEEN TEST DRUGS AND TIME PERIODS, BUT NO SIGNIFICANT EFFECT OF OPERATIVE SITE ON DRUGS OR TIME

Source	df	Sum of squares	Mean square	F	p
Between Patients	331	2,980.655			
Between drugs	3	118.869	39.623	4.466	<0.005
Between operations	2	4.798	2.399	270	n.s.
Drug $\times$ operation interaction	6	17.816	2.969	335	n.s.
Residual	320	2,839.172	8.872		
Within Patients	664	2,793.333			
Between periods	2	269.774	134.887	36.056	<0.001
Drug $\times$ period interaction	6	58.661	9.777	2.613	<0.025
Operation $\times$ period interaction	4	18.520	4.630	1.238	n.s.
Drug $\times$ operation $\times$ period interaction	12	51.904	4.325	1.156	n.s.
Residual	640	2,394.474	3.741		
Total	995	5,773.988			

time periods, and that there was no interaction between the test drugs and the operative site (Table I).

The data from all operations could thus be combined, and was analysed with reference to incidence and severity of emetic symptoms, and to the side effects of hypotension in the recovery room, potentiation of narcotics, and prolongation of postoperative sleep.

Incidence of Emetic Symptoms

Table II shows the increase in emetic symptoms in each group of patients with the passage of time. Thiethylperazine was given to 86 patients, of whom 33.7 per cent showed symptoms in the first two hours. No more patients vomited during the next four hours, but by twenty-four hours, 54.7 per cent had shown symptoms. Of the 79 patients receiving perphenazine, 24.1 per cent showed symptoms after two hours, and 27.8 per cent after six hours, but by twenty-four hours, 48.1 per cent had shown emetic symptoms. These figures compared favourably with the placebo group of 83 patients, where 44.6 per cent were affected in the first two hours, the figure rising to 50.6 per cent after six hours, and reaching 66.3 per cent over the twenty-four hour period. In contrast, 40.5 per cent of the 84 patients receiving trimethobenzamide had symptoms in the first two hours, and the percentage increased to 52.4 per cent after six hours and 82.1 per cent after twenty-four hours. The percentage of patients showing symptoms in these last two periods was thus greater than that seen in the placebo group.

Statistical analysis of these figures (Table III) shows perphenazine to be significantly more effective ($p < 0.05$) than the other agents at two hours, but over the six-hour period, perphenazine loses some of its effectiveness, while thiethylperazine does not, and thiethylperazine emerges as significantly more effective than placebo or trimethobenzamide over the six-hour period. Trimethobenzamide now ranks as less effective than the placebo at this period, and this difference becomes significant over the twenty-four-hour period. Both perphenazine and triethylperazine are significantly superior to both placebo and trimethobenzamide over the twenty-four-hour period, with perphenazine ranking as the most effective. The differences between perphenazine and triethylperazine are not significant on the basis of these incidence comparisons. The results are shown graphically in Figure 1.

Severity of Emetic Symptoms

The average score for emetic symptoms (including scores of zero) for all patients is shown in Table IV. With thiethylperazine, the average was 1.035 over the first two hours, rising to 1.326 over the six-hour period, and reaching 2.628 for the full twenty-four hour period. Perphenazine was slightly less effective, the scores for the three periods being 1.127, 1.747, and 3.266. Trimethobenzamide was less effective than the other drugs, with average scores of 1.381, 2.083, and 4.560 over the three time periods, but it was still more effective than placebo, which showed average scores of 2.325, 3.120, and 5.241 at these times.

TABLE II

INCIDENCE OF POSTOPERATIVE EMETIC SYMPTOMS IN PATIENTS RECEIVING THIETHYLPERAZINE, PERPHENAZINE, TRIMETHOBENZAMIDE, OR A PLACEBO

	15 min.-2 hours		15 min.-6 hours		15 min.-24 hours	
	Total number of patients	Number with symptoms	Per cent with symptoms	Number with symptoms	Per cent with symptoms	Number with symptoms
Thiethylperazine	86	29	33.7	29	33.7	47
Perphenazine	79	19	24.1	22	27.8	38
Trimethobenzamide	84	34	40.5	44	52.4	69
Placebo	83	37	44.6	42	50.6	55

TABLE III
ANALYSIS OF VARIANCE

Source of variation	Sum of squares	df	Mean square	F	p
15 min.-2 hours					
Between drugs	1.951	3	.650	2.867	<0.05
Residual	74.395	328	.227		
15 min.-6 hours					
Between drugs	3.6732	3	1.2244	5.2302	<0.005
Residual	76.7937	328	.2341		
15 min.-24 hours					
Between drugs	5.5196	3	1.8399	8.392	<0.001
Residual	71.9111	328	.2192		

STUDENT NEWMAN-KEULS' TEST

15 min.-2 hours	<u>Perphenazine</u> <u>Triethylperazine</u> <u>Trimethobenzamide</u> <u>Placebo</u>
15 min.-6 hours	<u>Perphenazine</u> <u>Triethylperazine</u> <u>Placebo</u> <u>Trimethobenzamide</u>
15 min.-24 hours	<u>Perphenazine</u> <u>Triethylperazine</u> <u>Placebo</u> <u>Trimethobenzamide</u>

The test ranks drugs in order of effectiveness, from the most effective on the left, to the least effective on the right. Drugs underscored with the same line are not significantly different. Those not underscored by the same line are significantly different at the 0.05 level.

FIGURE 1. Percentage of patients having no emetic symptoms at two, six, and twenty-four hours after administration of perphenazine, thiethylperazine, trimethobenzamide, or a placebo.

TABLE IV

AVERAGE POSTOPERATIVE SYMPTOM SCORES OVER THREE TIME PERIODS IN PATIENTS RECEIVING THIETHYLPERAZINE, PERPHENAZINE, TRIMETHOBENZAMIDE, OR A PLACEBO

Drug	Total number of patients	Average symptom score		
		15 min.-2 hrs.	15 min.-6 hrs.	15 min.-24 hrs.
Thiethylperazine	86	1.035	1.326	2.628
Perphenazine	79	1.127	1.747	3.266
Trimethobenzamide	84	1.381	2.083	4.560
Placebo	83	2.325	3.120	5.241

TABLE V

ANALYSIS OF VARIANCE

Source	Sum of squares	df	Mean square	F	p
15 min.-2 hours					
Between drugs	86.980	3	28.993	3.914	<0.01
Residual	2429.656	328	7.407		
15 min.-6 hours					
Between drugs	147.5099	3	49.1700	3.6023	<0.05
Residual	4477.0323	328	13.6495		
15 min.-24 hours					
Between drugs	356.5701	3	118.8567	4.5409	<0.005
Residual	8585.3938	328	26.1750		

STUDENT NEWMAN-KEULS' TEST

15 min.-2 hours	<u>Thiethylperazine Perphenazine Trimethobenzamide Placebo</u>
15 min.-6 hours	<u>Thiethylperazine Perphenazine Trimethobenzamide Placebo</u>
15 min.-24 hours	<u>Thiethylperazine Perphenazine Trimethobenzamide Placebo</u>

See legend following Table III.

Table V shows that statistically, thiethylperazine ranks as most effective in reducing emetic symptoms, and together with perphenazine is significantly more effective than placebo. Trimethobenzamide does not show any significant difference from placebo at the two-, six-, or twenty-four-hour periods. While it is difficult to demonstrate any significant difference between the test drugs at the two- and six-hour periods, thiethylperazine is significantly superior to trimethobenzamide at the twenty-four-hour period, while perphenazine is not. The results are shown graphically in Figure 2.

Ridit Analysis

Using the criteria of Belleville *et al.*⁹ the symptoms observed in the first two hours were ranked in order of increasing severity, and subjected to Ridit analysis, using the placebo group as the identified distribution. This form of analysis allows the comparison of dissimilar categories and serves to compare incidence and severity combined. The results shown graphically in Figure 3

FIGURE 2. Average score of emetic symptoms at two, six, and twenty-four hours after administration of perphenazine, thiethylperazine, trimethobenzamide, or a placebo.

FIGURE 3. Ridit analysis of the incidence and severity of emetic symptoms over the first two hours following injection of perphenazine thiethylperazine and trimethobenzamide, using a placebo group as the identified distribution. Bars indicate mean Ridit for group, blocks indicate the 95% confidence limits. Where these confidence limits do not overlap, the differences are significant at the .05 level.

do not differ greatly from the incidence comparisons at the two-hour period already presented. Only perphenazine is statistically superior to a placebo at this time, while trimethobenzamide lies closer to the placebo and thiethylperazine lies closer to perphenazine in effectiveness.

Side-Effects

The blood pressure was recorded at 15-minute intervals in the recovery room, and the lowest observed systolic blood pressure was expressed as a percentage fall, compared to the pressure recorded immediately before induction of anaesthesia. The 15-minute interval in which the patient awoke, as determined by her ability to respond to her name, was recorded as the waking time. The time of the first analgesic injection required by a patient was recorded, as was the number of injections that each received in the 24-hour period. The need for a further injection of an anti-emetic drug was also recorded.

Hypotension. The effects of the drugs on postoperative blood pressure are shown graphically in Figure 4. Perphenazine was associated with significantly

FIGURE 4. Postoperative hypotension following perphenazine, thiethylperazine, trimethobenzamide, and a placebo.

more hypotension ($p < 0.05$) than the other active agents, which did not differ significantly from placebo.

Postoperative sleep. There were no significant differences among the test drugs in the duration of postoperative sleep, although 10.1 per cent of the patients receiving perphenazine slept longer than one hour, as compared to 2.3 per cent of patients receiving triethylperazine and 3.6 per cent of patients receiving trimethobenzamide. The observations are shown graphically in Figure 5.

Postoperative narcotics. Patients receiving perphenazine required fewer narcotic injections postoperatively, averaging 2.063 injections as compared to the number required with thiethylperazine (2.616), trimethobenzamide (2.667), and the placebo (2.651). This difference was significant ($p < 0.001$), as was the difference in the time of giving the first postoperative injection. The differences between the other drugs and the placebo were not significant.

Additional anti-emetic. Additional anti-emetics were required in 109 out of 332 patients at some time during the 24-hour period of observation. The average symptom scores of those receiving additional anti-emetics ranged from 6.2 for those receiving thiethylperazine and trimethobenzamide initially, to 8.2 for

FIGURE 5. Duration of postoperative sleep following perphenazine, thiethylperazine, trimethobenzamide and a placebo.

those treated with perphenazine, and 8.6 for those in the placebo group. This is substantially higher than the average symptom score range of 2.6–5.2 for all patients at the same 24-hour period.

The number of patients in each drug group who required additional anti-emetics is shown in Table VI. In the chi-square analysis, perphenazine and trimethobenzamide contributed most to chi square, perphenazine contributing less than the expected number, and trimethobenzamide more than expected. These differences are significant ($p < 0.01$), indicating that significantly fewer perphenazine patients required additional anti-emetics, whereas significantly more trimethobenzamide patients required them.

TABLE VI

NUMBER OF PATIENTS REQUIRING AN ADDITIONAL ANTI-EMETIC IN THE 2- TO 24-HOUR PERIOD POSTOPERATIVELY

Drug	Total patients	No additional anti-emetic	Additional anti-emetic	Patients needing more (%)
Thiethylperazine	86	66	20	23.3
Perphenazine	79	62	17	21.5
Trimethobenzamide	84	47	37	44.0
Placebo	83	48	35	42.0
Totals	332	223	109	32.7

DISCUSSION

The comparisons of incidence and severity of postoperative emetic symptoms indicate a close similarity in clinical effectiveness between thiethylperazine and perphenazine. Perphenazine secures a greater reduction in the incidence of nausea and vomiting, while triethylperazine is superior to perphenazine in reducing the severity of symptoms experienced. Perphenazine appears to be more effective in the first two hours after administration, after which its action steadily declines, though it is still evident over the whole twenty-four-hour period. Thiethylperazine appears to exert a steady effect over the first six hours after administration, but becomes much less effective during the later part of the twenty-four-hour period. A subsequent anti-emetic injection was necessary after discharge from the recovery room in almost a third of all patients, but the placebo and trimethobenzamide patients required additional anti-emetics almost twice as often as those in the thiethylperazine and perphenazine groups.

Although no extrapyramidal effects were seen with the limited dose schedules of perphenazine used, such effects have been noted with quite low dosages repeated three or four times daily, and with single doses as low as 10 mg.¹⁶ It is apparent that any attempt to sustain the anti-emetic activity of perphenazine by repeating the doses used in this survey three or four times in the first twenty-four hours would result in extrapyramidal symptoms occurring in some patients.

Thiethylperazine has been shown to possess little or no ability to produce extrapyramidal symptoms,² and could therefore be given at six hourly intervals to maintain maximum effect.

Trimethobenzamide appears to possess very limited anti-emetic activity and

it is difficult to distinguish it from the placebo, except over the 24-hour incidence scores, where it is significantly worse than a placebo. Such anti-emetic activity as is shown by this drug appears to be followed by a rebound phase in which there is increased incidence of emetic symptoms.

Consideration of the side-effects shown by the two most active agents is helpful in comparing their clinical effectiveness. The increased incidence of prolonged postoperative sleep noted with perphenazine has been reported in a previous study.⁷ The criteria used to determine whether the patient was responding or not may not be sufficiently sensitive to detect the patient who responds when roused by voice, but immediately lapses into sleep when left alone. Clinically, many patients receiving perphenazine seemed to follow this pattern, and yet did not fall into the slow waking group in the survey. It is likely that this relapsing sleep is one factor which contributes to the much lower requirement for postoperative narcotics in the perphenazine group, since it has been shown that there is little potentiation of analgesia by this drug.¹¹

Hypotension in the immediate postoperative period is always a cause of anxiety, since the hypotension due to drug action has to be differentiated from that due to hypovolaemia or cardiac causes, among others. The increased frequency of hypotension seen in the perphenazine group tends to limit its usefulness in the elderly and hypertensive patient; thiethylperazine is not associated with a significant increase in hypotension.

CONCLUSIONS

Thiethylperazine produces a marked reduction in the incidence and severity of postoperative vomiting. Its action, which appears to last about six hours, is indistinguishable from that of perphenazine, a powerful anti-emetic drug. It does not potentiate narcotics or prolong postanaesthetic sleep, and, unlike perphenazine, does not produce a significant increase in the incidence of postoperative hypotension. Thiethylperazine is significantly superior to a placebo and to trimethobenzamide as an anti-emetic. Trimethobenzamide, even in high dosage, has little anti-emetic activity, and its use appears to be followed by a rebound increase in the incidence of emetic symptoms.

SUMMARY

A comparative trial of thiethylperazine (Torecan®), perphenazine (Trilafon®) and trimethobenzamide (Tigan®) has been carried out in a selected population of female patients anaesthetised with a standard anaesthetic technique for three operations associated with a high risk of postoperative nausea and vomiting. Compared with a placebo, both thiethylperazine and perphenazine were effective in reducing the incidence and severity of emetic symptoms, whereas trimethobenzamide showed a tendency to increase these symptoms after an initial mild anti-emetic action. Postoperative hypotension occurred more frequently after perphenazine, but this drug reduced the need for postoperative analgesic drugs. It is suggested that increased drowsiness in patients receiving perphenazine may contribute to this apparent potentiation of narcotics. Thiethylperazine did not produce significantly more hypotension than the placebo, and did not potentiate

narcotics or prolong postoperative sleep. No extrapyramidal signs were seen in any patients in this trial.

RÉSUMÉ

Chez un groupe choisi de malades, nous avons fait une étude à double inconnu de trois médicaments et du placebo. Toutes les malades étaient des femmes qui avaient reçu, comme prémédication, de la mépéridine et de l'atropine; l'anesthésie consistait en une dose ordinaire de thiopentone et du protoxyde-oxygène-halothane; elles ont subi une des trois opérations. Nous avons choisi ces trois opérations (cholécystectomie, hystérectomie abdominale et hystérectomie vaginale comme un défi aux médications anti-émétiques puisque, au cours d'une étude antérieure, elles ont été suivies du taux le plus élevé de symptômes émétiques.

Les médicaments codifiés ont été administrés au hasard, selon le poids corporel, à l'arrivée à la salle de réveil; durant leur séjour à la salle de réveil et à leur retour dans les salles, les malades ont été étiquetés selon les symptômes émétiques de nausées (1), d'efforts (2) et de vomissements (3).

Nous avons analysé les résultats selon la fréquence et la gravité des symptômes, à chacune des trois périodes suivantes: le second quart d'heure après 2 hres, le 2^{ème} quart d'heure après 6 heures et le 2^{ème} quart d'heure après 24 heures. Dans chaque cas, nous n'avons pas tenu compte du premier quart d'heure parce que nous avons l'impression que le médicament n'avait pas eu une action complète durant ce délai après une injection intramusculaire.

La perphénazine a été le médicament le plus efficace pour diminuer la fréquence des symptômes, alors que la thiéthylpérazine a été plus efficace pour diminuer la gravité des symptômes. Ces deux médicaments se sont avérés supérieurs au placebo à plusieurs points de vue. Le triméthobenzamide a été difficilement différencié du placebo, excepté à la période de 24 heures, où il est devenu pire que le placebo, c'est-à-dire qu'il a semblé augmenter la fréquence des vomissements. Dans la salle de réveil, la perphénazine a produit beaucoup plus d'hypotension que la thiéthylpérazine mais les malades recevant de la perphénazine ont reçu beaucoup moins d'injections de narcotiques.

Nous en venons à la conclusion que la thiéthylpérazine est un anti-émétique dont l'efficacité est égale à celle de la perphénazine. Là où il devient important d'éviter toute hypotension postopératoire, la thiéthylpérazine possède des avantages marqués sur la perphénazine; là où il est important d'éviter ou de diminuer l'usage des narcotiques au cours des suites opératoires, la perphénazine est supérieure. L'activité anti-émétique du triméthobenzamide n'est pas beaucoup plus grande que celle du placebo et ce médicament peut accroître les symptômes émétiques durant la première journée postopératoire.

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