CONTROL OF POSTOPERATIVE NAUSEA AND VOMITING:
A COMPARATIVE STUDY OF DIPHENIDOL (VONTROL®) AND
DIMENHYDRINATE (GRAVOL®)*

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NAUSEA AND VOMITING, unpleasant under any circumstances, are particularly disagreeable to the postoperative patient. Despite the progress of medical science, postoperative nausea and vomiting remain constant problems for the surgeon and anaesthetist. The aetiological factors are complex. Symptoms may be due in part to the surgery and in part to the anaesthetic medication, and their severity may vary considerably between individuals. Peripheral stimuli arising from the abdominal viscera or from regurgitation of bile due to antiperistalsis may be responsible. Central factors may also be involved, for vomiting may occur following medication only, without surgical intervention. Like swallowing and coughing, vomiting is a typical example of the manner in which integrated visceral reflexes in the medulla are composed of co-ordinated somatic and visceral elements. The activities of all the structures involved are controlled and co-ordinated at the moment vomiting occurs by the vomiting centre, located in the lateral reticular formation of the medulla at the level of the olivary nuclei. The vomiting centre is in intimate contact with other vital centres, especially the respiratory and vasomotor centres, the salivary nuclei, and the vestibular nuclei. Borison and Wang¹ have demonstrated the existence of an accessory medullary area which responds to chemical stimuli and serves to mediate vestibular stimuli, described as the chemoreceptor trigger zone.²

It can be said without intent to malign that perhaps the greatest single factor in the development of postoperative nausea and vomiting is the use of anaesthetics and concomitant drugs which are prone to cause such symptoms. For instance, premedication with certain drugs such as morphine and its derivatives may provoke nausea and vomiting. Among older anaesthetic agents,³ cyclopropane and ether are particularly prone to cause emesis, whereas recent statistics have shown only about a 10 per cent incidence of vomiting when the newer agents, halothane and methoxyflurane, are used. Certain medications used concomitantly with anaesthesia, for example oxytocics and anticholinesterase drugs, can play a decisive role in the production of symptoms.

Other factors such as age, sex, obesity, and site and duration of operation may be equally responsible.³ Women and children are more often subject to postoperative nausea and vomiting, as are those who present with a history of such symptoms. Certain states such as uraemia, acidosis, and electrolyte imbalance increase the likelihood of nausea and vomiting, as do emergency situations.^{4,5} Consideration of all of these factors makes obvious the need for clinical research on antiemetics.

The ideal antiemetic has yet to be found. However, the main criteria which

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must be met by candidates for consideration in this regard may be stated. Any medication effectively depressing or inhibiting the bulbar centres should do away with all, or at least a major part of, the associated discomfort. A good antiemetic should be effective without attendant serious side-effects. Obviously, substantial risk is unwarranted in eliminating an inconvenience of only secondary importance.

We were attracted to diphenidol because of its novel features; although not a phenothiazine derivative, it is reported to be as potent; it is unrelated to the antihistamines, the barbiturates, or other known antivertigo or antiemetic agents. Dimenhydrinate was selected for comparison because it is well known and was the antiemetic used routinely on our service. A placebo was considered unnecessary, the effects of dimenhydrinate being sufficiently established to warrant its use as the sole standard of comparison. Cholecystectomy, hysterectomy, colpoperineorrhaphy, and uterine fixation were chosen to challenge the antiemetic agents since, according to Purkis and Ishii,^{6,7} these operations are followed by the highest incidence of symptoms. The chemical structures and principal pharmacological activities of the two drugs are shown in Figure 1.

FIGURE 1. Chemical structures of the diphenidol (left) and dimenhydrinate (right) molecules. Respective pharmacological activities are given below.

DIPHENIDOL	DIMENHYDRINATE
α - α -diphenyl-1-piperidinebutanol	2-(benzhydryloxy)-N, N-dimethylethylamine 8-chlorotheophyllinate
antivertigo, especially in vertigo of peripheral origin	mild sedative
antiemetic; inhibitory effect on chemoreceptor trigger zone	antiemetic
weak parasympatholytic activity	spasmolytic
no antihistaminic activity	antihistaminic

METHODS

Adult males or females undergoing cholecystectomy, and females undergoing abdominal or vaginal hysterectomy, colpoperineorrhaphy, or uterine fixation were chosen for study. Patients with pre-existing neuropathology were excluded, as were those for whom hypotension might be dangerous. Those admitted were assigned to the study drugs according to a randomized procedure, but the experiment was not conducted under double-blind conditions.

The anaesthesia procedure was as follows. Premedication administered h.s. the night before the operation consisted of one or more of the following, according to the needs of the patient: diazepam 5 or 10 mg., promethazine 25 mg., secobarbital 50 or 100 mg., methypylon 300 mg., diphenhydramine 25 mg. One

hour preoperatively, atropine 0.4 mg. was given, together with meperidine 75 or 100 mg. or anileridine 25 mg. Intravenous thiopentone and succinylcholine chloride were employed for induction in all cases, and for maintenance, halothane, nitrous oxide, and oxygen were used, together with succinylcholine in infusion. The same two anaesthetists administered the anaesthesia in all cases.

An initial prophylactic dose of diphenidol (0.2 mg. per pound of body weight) or dimenhydrinate (0.5 mg. per lb.) was given intravenously during the operation, approximately thirty minutes before its anticipated completion. About 15 minutes after the patient awakened (time of awakening averaged about 15 minutes after discontinuance of anaesthesia) an intravenous infusion was begun, consisting of 40 mg. diphenidol or 100 mg. dimenhydrinate, in 500 c.c. of 10 per cent glucose-in-water solution. Thereafter, beginning when the intravenous solution was exhausted, or earlier if warranted by the appearance of symptoms (but never sooner than one hour after initiation of the intravenous infusion), intramuscular doses were given every six hours during the remainder of the first 24 postoperative hours. Like the initial intravenous dose, the intramuscular dose was, for diphenidol, 0.2 mg./lb., and for dimenhydrinate, 0.5 mg./lb. Gastric suction was applied at eight-hour intervals as required throughout.

Symptoms, vital signs (blood pressure, pulse and respiration), and drug side-effects were monitored and recorded at the time the patient awakened and at 30-minute intervals for some hours thereafter, always by the same nursing personnel. When the patient had left the recovery room and it was evident that vital signs had stabilized at a normal level, the interval between evaluations was increased to one hour, then to 1½ hours during the night, and only symptoms and side-effects were noted. These later readings were taken in the various wards by other nursing personnel trained to do so.

The arbitrary scale used in rating the severity of nausea and vomiting symptoms was as follows:

0	no nausea	}	since previous evaluation
1	nausea		
2	retching		
3	vomited once		
4	vomited more than once		

Each patient was observed in this manner for 24 hours, after which the anaesthetist recorded a global evaluation of that patient's over-all response to the study medication, according to the following criteria:

excellent	no nausea or vomiting	}	over the entire evaluation period
good	no vomiting, two or fewer instances of nausea		
fair	more than two instances of nausea and/or one of vomiting		
poor	vomited more than once (siphon necessary)		

The case report form used in the study appears as Figure 2.

RESULTS

Initially, 74 patients were admitted. One, through an oversight, received no intramuscular doses, and so was not included in the analyses. Of the 73 remaining, 36 were treated with diphenidol and 37 with dimenhydrinate. Table I shows the composition of the two patient groups with respect to several factors, including sex, age, weight, and nature and duration of operation. The two groups were found to be comparable.

Over-all ratings of results appear in Table II. The difference in proportion of satisfactory (excellent or good) results—86 per cent with diphenidol vs. 54 per cent with dimenhydrinate—is highly significant ($p < .01$). Although the number of cases in any one operation category was too few to demonstrate significant differences, the trend obviously favours diphenidol.

Because complete absence of vomiting was one of the criteria for rating over-all results as "excellent" or "good," one would expect a clear difference between drugs in incidence of vomiting over the observation period. In fact, the 37 dimenhydrinate-treated patients suffered a total of 26 vomiting episodes, while only five such episodes occurred among the 36 patients receiving diphenidol. (Ratings of 4+ on case report forms were each counted as two vomiting episodes, though more may have occurred in some instances.)

The total nausea and vomiting symptom scores (using the symptom rating scale described previously) recorded over the 24-hour period were: in the diphenidol group, 44; in the dimenhydrinate group, 141. The distribution by sex and operation is seen in Table III. *T*-test on the over-all totals reveals a highly significant difference ($p < .01$) favouring diphenidol. It should be noted, however, that those patients in either group who developed symptoms did so, on the average, only after a considerable time. In very few instances did symptoms appear less than three hours after awakening. This may perhaps be because the dose in the intravenous drip provided additional protection before the effect of the initial intravenous dose had worn off.

The only side-effect observed in either drug group was drowsiness. Thirty of the 37 patients in the dimenhydrinate group were drowsy during at least one evaluation after awakening, while in the diphenidol group, 11 of 36 were drowsy. Here again, chi-square testing shows the difference in diphenidol's favour to be highly significant ($p < .01$). There was no evidence of any relationship between presence or absence of drowsiness and duration of operation. Average duration of sleep plus drowsiness after discontinuance of anaesthesia was 2.0 hours for the dimenhydrinate patients, 0.5 hours for those receiving diphenidol. No undue fluctuations in blood pressure, pulse, or respiratory rate were observed with either drug.

SUMMARY

Two antiemetic agents, diphenidol and dimenhydrinate, were compared as to their ability to control symptoms of nausea and vomiting during the first 24 post-operative hours in patients having undergone cholecystectomy, abdominal or vaginal hysterectomy, colpoperineorrhaphy, or uterine fixation. The experiment

TABLE I
COMPOSITION OF THE TWO GROUPS OF PATIENTS

	Diphenidol			Dimenhydrinate			over- all
	males	females	total	males	females	total	
No. of patients	7	29	36	8	29	37	73
Age (yrs.)	41.3	47.6	46.4	43.8	48.9	47.8	47.1
average							
range	37-70	26-78	26-78	20-69	26-75	20-75	20-78
Average weight (lb.)			140.2			139.3	139.8
Duration of operation (min.)							
average	114	112	112	97	110	107	110
range	65-170	55-200	55-200	50-130	60-340	60-340	50-340
Patients with N & V symptoms prior to anaesthesia			2			—	2
Nature of operation							
cholecystectomy	7	19	26	8	17	25	51
hysterectomy	—	7	7	—	6	6	13
colpoperineorrhaphy & uterine fixation	—	3	3	—	6	6	9

TABLE II
GLOBAL RATINGS BY TYPE OF OPERATION

	Diphenidol					Dimenhydrinate					
	Ex.	Good	Fair	Poor	Total	Ex.	Good	Fair	Poor	Total	
Cholecystectomy											
males	7	-	-	-	7	5	1	1	1	8	
females	9	6	4	-	19	5	5	6	1	17	
total	16	6	4	-	26	10	6	7	2	25	
	(85%)					(64%)					(100%)
Hysterectomy											
abdominal	1	2	-	-	3	-	1	2	3	6	
vaginal	3	-	-	1	4	-	-	-	-	-	
total	4	2	-	1	7	-	1	2	3	6	
Colpoperineorrhaphy											
& uterine fixation	3	-	-	-	3	3	-	-	3	6	
Grand total	23	8	4	1	36	13	7	9	8	37	
	(86%)					(54%)					(100%)

TABLE III
TOTAL N & V SYMPTOM SCORES RECORDED OVER A 24-HOUR PERIOD

	Diphenidol						Dimenhydrinate					
	Chol. (male)	Chol. (female)	Hyst. abd.	Hyst. vag.	Other	Total	Chol. (male)	Chol. (female)	Hyst. abd.	Hyst. vag.	Other	Total
Total patients	7	19	3	4	3	36	8	17	6	—	6	37
Symptom scores	0	31	4	9	0	44	13	47	48	—	33	141

was carried out under controlled but not double-blind conditions. Results in the diphenidol-treated group were superior to a statistically significant degree with regard to incidence of vomiting, presence of symptoms of nausea and vomiting (rated according to an arbitrary scale), and over-all patient response, as well as incidence of drowsiness.

Aside from drowsiness there were no side-effects in either drug group, nor did any undue variations occur in blood pressure, pulse, or respiratory rate.

RÉSUMÉ

Plusieurs facteurs, outre les procédures chirurgicales, peuvent influencer l'occurrence ainsi que la sévérité des nausées et vomissements post-opératoires. Ceux-ci peuvent être attribuables à des stimuli d'origine centrale ou périphérique via l'intermédiaire soit du centre des vomissements soit du centre chémorécepteur (trigger zone). Par ailleurs, certains agents anesthésiques peuvent déclencher per se des nausées et vomissements. La pré-médication ainsi que les drogues employées conjointement avec l'anesthésie (e.g. morphine et ses dérivés, les oxytociques, les anti-cholinestérasiques) peuvent provoquer ces symptômes. Il en va de même d'une pléiade d'autres facteurs tels: l'âge, le sexe, l'obésité, le site et la durée de l'opération. D'où l'importance en recherche clinique de trouver de nouveaux agents anti-émétiques.

Dans la présente étude, les auteurs ont entrepris d'établir une comparaison entre un anti-émétique connu, le dimenhydrinate, avec un nouvel agent, le diphénidol. Ce dernier n'a aucun rapport avec les autres anti-émétiques et on lui attribue un potentiel comparable à celui des phénothiazines. Soixante-et-quatorze patients adultes, mâles et femelles, opérés pour cholécystectomie, hystérectomie (abdominale ou vaginale), colopérinéorraphie ou fixation utérine, ont reçu l'un ou l'autre des deux médicaments selon une distribution faite au hasard mais non à double-insu. Des 73 patients inclus dans cette étude, 36 d'entre eux furent traités par le diphénidol et 37 par le dimenhydrinate. La pré-médication, l'induction et l'anesthésie elle-même furent uniformisées.

La première dose de l'un ou l'autre des médicaments étudiés (diphénidol 0.2 mg. par lb. ou dimenhydrinate 0.5 mg. par lb.) fut administrée en perfusion i.v. 30 minutes avant la fin présumée de l'opération. Quinze minutes après son réveil, le patient recevait en perfusion i.v. 40 mg. de diphénidol ou 100 mg. de dimenhydrinate. Par la suite, ou même avant si les symptômes le réclamaient, des doses i.m. étaient administrées aux six heures: diphénidol 0.2 mg. par lb. ou dimenhydrinate 0.5 mg. par lb. Au besoin, une succion gastrique fut appliquée aux huit heures. L'évaluation des symptômes (selon un barème arbitraire pré-établi), des signes vitaux et des effets secondaires, fut faite au réveil du malade et aux 30 minutes dans la salle de réveil. Ensuite, les symptômes et les effets secondaires seulement furent notés aux heures au cours de la journée et aux 1½ heures pendant la nuit. La période d'évaluation a duré quatre heures, après quoi, une évaluation globale de la performance médicamenteuse fut faite.

Le diphénidol a surpassé le dimenhydrinate en ce qui a trait aux points suivants: (1) une plus grande proportion des résultats satisfaisants (bons et

excellents)—86 à 50 pour cent ($p < .01$), (2) moins d'épisodes de vomissements—cinq dans le groupe de diphénidol, 31 dans le groupe dimenhydrinate, (3) un total plus faible sur l'échelle d'évaluation des symptômes—44 vs. 141 ($p < .01$). La somnolence fut le seul effet secondaire que nous ayons observé, se manifestant dans 30 des 37 patients traités au dimenhydrinate et dans 11 des 36 patients traités au diphénidol ($p < .01$). Il n'y eut pas de fluctuations indésirables des signes vitaux chez aucun de ces patients.

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