CONTROL OF POSTOPERATIVE VOMITING WITH MAREZINE®: A DOUBLE BLIND STUDY

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THE effectiveness of parenteral injections of Marezine® (cyclizine lactate) to control postoperative vomiting has been both asserted (1-3) and denied (4). Consequently, a double blind study of Marezine seemed an acceptable method for re-evaluating the drug.

METHOD OF STUDY

Our standard method previously developed for the study of antiemetic drugs (5, 6) was adopted: the antiemetic drug or placebo was injected intramuscularly on call to surgery, again intramuscularly immediately on return from surgery, and then intramuscularly every four hours for 4 doses. In this experiment, 1 cc. of solution was injected each time. The Marezine solution contained 50 mg. of the drug per cc.

All patients who were to have an anesthetic for operation, regardless of its magnitude and who fell into one of 7 general classes of anesthetic techniques listed in table 1 received this "Marezine routine." No attempt at selection of surgical cases was made nor were there any alterations in the routine use of opiates or other drugs (for example, barbiturates or scopolamine) preoperatively and postoperatively. The dosages were changed only for children under five years of age, for whom each dose was reduced to 25 mg. of Marezine (0.5 cc. of solution). Children under one and one-half years of age and patients who were to undergo tonsillectomies were excluded from this routine. The latter were not included in this study since they are admitted to the hospital the morning of the scheduled operation and dismissed that afternoon; therefore, the preoperative visit as well as postoperative follow-up is usually impossible.

Twenty-four consecutively numbered boxes, each containing 25 rubber-stoppered vials with 6 cc. of solution in each vial, were prepared by the drug company. The vials in 12 of these boxes contained 50 mg. of Marezine per cc. of solvent while the other half contained the solvent only. Each of the vials in these boxes was labeled with the number which appeared on the label of the box. The identity of the solution

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in each box of 24 vials remained unknown to any of the hospital staff until completion of the study and tabulation of the results.

From August 1, 1955, to October 1, 1955, these solutions were administered to the patients by the established "Marezine routine," care being taken to see that when a patient was started on one number all other injections given that patient were from a vial marked with that specific number. As a precautionary measure, no hospital floor was furnished more than one box at any one time. The boxes containing the bottles of solution were distributed to the surgical floors at random, no effort being made to place specific numbers on the same floor; for example, the even numbers were not given to one floor and the odd numbers to another.

TABLE 1

INCIDENCE OF VOMITING IN DOUBLE BLIND STUDY

Type of Anesthesia	Solvent			Solvent Plus Marezine®		
	Total Number of Cases	Number of Patients Vomiting	Percentage of Vomiting	Total Number of Cases	Number of Patients Vomiting	Percentage of Vomiting
Ether N_2O	61	21	34.4	55	12	21.8
Cyclopropane	5	2	40.0	7	2	28.6
Thiopental-N_2O	56	18	32.1	52	8	15.4
Thiopental	4	1	25.0	7	0	0
Regional nerve block*						
Cervical plexus block	2	2	100.0	6	1	16.7
Intercostal-celiac plexus block	22	1	4.5	24	2	8.3
Other peripheral nerve blocks	21	3	14.3	18	2	11.1
Spinal	42	9	21.4	58	5	8.6
Epidural						
Caudal area	8	5	62.5	7	1	14.3
Lumbar area	55	15	27.3	39	8	20.6
Total	276	77	27.9	273	41	15

* Block of nerves after they have emerged from the intervertebral foramina.

All patients in this series were seen before the operation, within the first twenty-four hours after the operation, and daily thereafter. They were questioned as to whether or not they had vomited, asked to estimate the amount, and to describe the character of the vomitus, its color and viscosity. Their responses were checked against the nurses' notes and comments, as well as observed contents of the emesis basin and stains on the bed linens. Vomiting was defined as the emesis of any material which measured 50 cc. or more. The spitting up of mucous or bile was not considered vomiting in this study unless it exceeded this stipulated amount. The Chicago key-sort anesthesia card was used for tabulation.

TABLE 2

COMBINED RESULTS FOR ALL ANESTHETIC PROCEDURES

Routine	Number of Patients Vomiting	Number of Patients Not Vomiting	Total
With Marezine® and solvent	41	232	273
With solvent	77	199	276
Total	118	431	549

The (corrected) $X^2 = 12.7$; $P = .004$.

The number of the box from which the ampul was taken and the amount and the character of the vomiting was charted on the key-sort cards. The key-sort cards were not reviewed and the incidence of vomiting was not determined until the entire series had been run. After the results obtained with the specially labeled material prepared for this series were tabulated, the key to the identity of the solution in each vial was received.

RESULTS

Decoding the tabulated information revealed that: (1) of the 276 patients who received the "Marezine routine" with the solvent only, 77 vomited, or 27.9 per cent; and (2) of the 273 patients who received the "Marezine routine" with solutions containing Marezine, only 41 vomited, or 15 per cent (table 1).

When a patient in this survey vomited, he almost invariably vomited an amount far in excess of the 50 cc. volume, that is, 200 to 500 cc. There was no correlation between the character of the vomitus and the amount vomited.

TABLE 3

ANALYSIS OF RESULTS BY SEPARATE ANESTHETIC PROCEDURE, X^2 VALUE AND ITS PROBABILITY

Anesthesia Procedure	X^2 (uncorrected)	P
Ether-N_2O	2.26	.13
Cyclopropane	.171	.68
Pentothal N_2O	4.14	.04
Pentothal	1.92	.16
Regional nerve block		
Cervical block	4.44	.036
Intercostal deep splanchnic	.270	.60
Other peripheral nerve blocks	.087	.76
Spinal	3.32	.07
Epidural		
Caudal area	3.62	.06
Lumbar area	0.564	.45
	Total $X^2 = 20.79$	$P = .02$

These results were analyzed for their significance by B. M. Bennett, Ph.D., of the Statistical Laboratory, Department of Public Health, University of Washington, Seattle, Washington. He reported:

"The statistical analysis of the data of the Marezine study consisted in a comparison of the percentage vomiting for patients in the Marezine treated group with those for patients who did not receive Marezine. The method of the 'Chi-square' test was used (7), and the comparisons were made both for the combined results of all anesthesia procedures (table 2) and also for their results by the separate procedures (table 3).

"A highly significant difference is to be noted in comparing the percent vomiting ($\times$ 15.0) in the combined Marezine group with the percent ($\times$ 27.9) of the combined 'solvent' group (table 2).

"A significant difference in the percent of patients was rated in about 5 of the procedures (cervical block, spinal, thiopental-N_2O, epidural-caudal, and possibly ether-N_2O), and these procedures included 347 patients (table 3). Independent confirmation by this analysis of the significant reduction in the percentage vomiting due to Marezine is to be noted in the significance ($P = .02$) of the Chi-square ($= 20.79$) obtained by adding the values for the separate procedures (table 3)."

Discussion

Perhaps it could be argued that the ideal method for this study would have been to give the solutions only to patients receiving ether as the primary agent, since the incidence of vomiting is believed to be high following its administration. Also, it might have been better if all the patients in the study had the anesthetic administered by one anesthesiologist and following the operation and been returned to only one ward, where specially instructed nurses could have been in charge. However, we believe that if a drug is to be of value in postoperative vomiting it must control the incidence of postoperative emesis regardless of the anesthetic method or agent used or the ability of the personnel involved. There are so many variables that may result in vomiting that such a narrow study might not have been significant.

In table 1, it will be noted that the primary anesthetic agent (inhalation and intravenous) or the nerve block procedure is the one under which the anesthetic procedure was classified. By primary agent we mean the agent used to obtain and maintain relaxation during the surgical procedure. Not uncommonly, we induce anesthesia with thiopental sodium when we intend to use ether or cyclopropane as the primary anesthetic agent. A dose of 0.25 Gm. is seldom exceeded. If a procedure lasts over one hour, the thiopental probably has been detoxified by the end of the surgical procedure so that it seldom has an influence on the postoperative period. With thiopental, induction is smooth and much of the anoxia of induction, which may influence vomiting in the postoperative period, is avoided. However, since thiopental

was used as an induction agent in both the control series and the Marezine series with equal frequency, its effect should not influence the results.

The regional nerve block and spinal procedures were executed with tetracaine-epinephrine solutions. The epidural (peridural) blocks were performed with a lidocaine solution to which 2 mg. of tetracaine had been added per cc. of lidocaine along with epinephrine. Under no circumstances was more than 0.25 cc. of epinephrine added to any of the solutions, regardless of the volume of the local anesthetic solution to be injected.

No tissue necrosis has occurred following the parenteral administration of Marezine. Burning, the prevalence of which forced us to discontinue the injection of Marezine when it was first tried in 1953, caused only an occasional complaint during this study. Perhaps this is explained by the care which was taken in this series to avoid the inadvertent placement of the solution subcutaneously, since it had been suggested that too superficial a placement of this drug might have been responsible for the burning.

Since Marezine belongs to the class of antihistaminic drugs, side reactions might be expected to occur in some patients. To date, we have seen no reactions other than an occasional case of drowsiness. Because of this effect, reduction or omission of the routine dose of preanesthetic and postoperative medication might be considered when Marezine is to be injected so that a synergistic action between drugs used for sedation and Marezine will not occur. However, while this study was conducted, we did not vary the usual premedication dose of morphine, scopolamine, or barbiturate or interfere with postoperative sedation, and no serious over-medication occurred.

Summary

Marezine (cyclizine lactate) significantly reduced the incidence of postoperative vomiting during this double blind study. This would seem to substantiate previous reports which had asserted the effectiveness of Marezine but which had not employed the double blind technique of evaluating the drug.

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