THE ANTIEMETIC EFFICACY OF CYCLIZINE (MAREZINE) AND TRIFLUPROMAZINE (VESPRIN)

J. Weldon Bellville, M.D., Irwin D. J. Bross, Ph.D., William S. Howland, M.D.

One of the most frequent complaints a practicing anesthesiologist encounters upon his postoperative rounds is that of nausea and vomiting. In order to gain more insight into this problem, we set up a controlled study in January 1958 to evaluate antiemetic compounds, both in respect to their effect on incidence and on severity of postoperative nausea and vomiting. This report summarizes our findings with the first two compounds evaluated in this study, cyclizine (Marezine) and triflupromazine (Vesprin).

Method

The double blind method and scoring of nausea and vomiting has been described in detail in the preceding paper.[1] In this study the patients received one of five medications, either a placebo, or 50 or 100 mg. of cyclizine, or 15 or 30 mg. of triflupromazine. Later triflupromazine was studied at the 7.5 and 15 mg. dose level with the 50 or 100 mg. of cyclizine and the placebo. At the same time a control group of patients was studied. Patients in the control group met all criteria applied to those who received the study medication except that permission of their attending surgeon for prophylactic medication was not asked. This group of patients will be referred to as the control group throughout this presentation. This report is concerned with observations from 2,214 patients, of whom 748 were controls, 331 received placebo, 274 received 100 mg. of cyclizine, 263 received 50 mg. of cyclizine, 203 received 7.5 mg. of triflupromazine, 266 received 15 mg. of triflupromazine and 129 received 30 mg. of triflupromazine.

Received from the Department of Anesthesiology, Memorial Center for Cancer and Allied Diseases, and the Section of Experimental Anesthesia, Division of Experimental Surgery, Sloan-Kettering Institute, New York City, New York, and accepted for publication June 2, 1959. Dr. Bellville is Assistant Attending Anesthesiologist, Memorial Hospital, and Assistant, Sloan-Kettering Institute; Dr. Bross is Head, Research Design and Analysis Service, Sloan-Kettering Institute, and Dr. Howland is Chairman, Department of Anesthesiology, Memorial Center, and Head, Section of Experimental Anesthesia, Sloan-Kettering Institute.

Results

No significant difference was found between the incidence of nausea and vomiting in the control group (19.4 per cent) as compared with the placebo group (18.1 per cent). The combined incidence of nausea and vomiting for these groups was 19 per cent. Both cyclizine and trifluprazine reduced the incidence of nausea and vomiting. Cyclizine at the 50 mg. dose level reduced the incidence of nausea and vomiting to 11.0 per cent whereas the higher dose of 100 mg. of cyclizine reduced

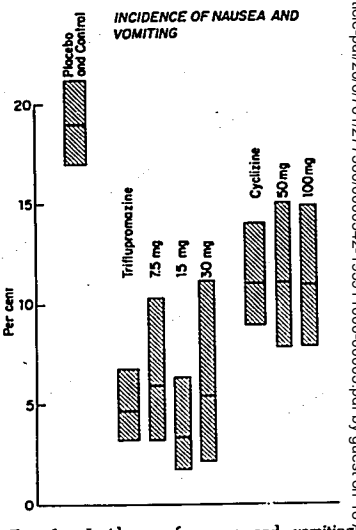

Fig. 1. Incidence of nausea and vomiting among the various drug groups plotted as percentage of patients in each group. Mean values indicated by heavy line in each bar and 95 per cent confidence limits indicated by length of cross hatched bar.

incidence of nausea and vomiting to 10.9 per cent. The difference between the incidence of nausea and vomiting following 50 compared with 100 mg. of cyclizine was not significant. Trifluprómazine was significantly better than cyclizine as an antiemetic. The 7.5 mg. dose of trifluprómazine reduced the incidence of nausea and vomiting to 5.9 per cent and the 15 mg. dose level reduced it to 3.4 per cent while the 30 mg. dose level reduced it to 5.4 per cent. The effects of these agents on the incidence of nausea and vomiting are shown graphically in figure 1.

The percentage of patients vomiting at any observation period can also be analyzed. In control and placebo patients a peak of 2.8 per cent vomiting was reached at one hour (fig. 2). When all the patients receiving cyclizine are considered it appears that the whole time incidence curve is displaced downward about 0.6 per cent after the first half hour. Trifluprómazine was more effective reducing the incidence of vomiting to 0.5 per cent. The percentage of awake patients reporting nausea at any one observation can also be analyzed (fig. 3). In the combined placebo and control group, it increased almost linearly to two hours. Cyclizine was effective in reducing it significantly but trifluprómazine was even more effective.

Of the patients who reported nausea or vomiting, the severity of their sickness was analyzed and scored by means of the ridit transformation based on the area under the time effect curve "score." [1] The average patient in the identified population who became ill had a score of 0.5 ridit or about 3.5 units.

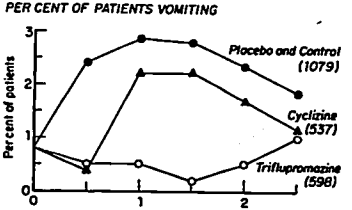

FIG. 2. Percentage of patients vomiting at any half-hour observation period.

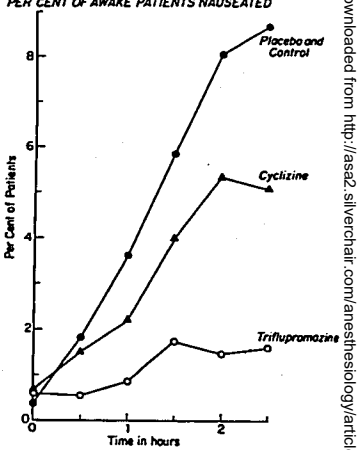

FIG. 3. Percentage of awake patients reporting nausea at any half-hour observation period.

A ridit value greater than 0.5 would mean that the patient was sicker than the average patient in the combined placebo and control group (fig. 4). The average ridit value of the group of patients who received 50 mg. or 100 mg. of cyclizine did not differ significantly from the average ridit for the combined placebo and control group whereas there appeared to be a trend in that as the dose of trifluprómazine was increased above 7.5 mg. the average ridit value declined. This indicates a decrease in severity of nausea and vomiting following 15 or 30 mg. of trifluprómazine.

The effects of the drugs on incidence and severity may also be appreciated by considering the frequency distribution of the scores (areas under the curve) in relation to the total number of patients in that group (fig. 5). In the combined placebo and control group the peak incidence (5.2 per cent) of the patients occurred at a score of 3 units. Both cyclizine and trifluprómazine effectively reduced the incidence of those with a score below 5 units. Trifluprómazine appeared to be more effective in this regard. In addition it was very effective in eliminating responses

above a severity of 6 units while cyclizine did not appear to be as effective in this area.

Side-Effects

Table 1 shows the effects of medication on the blood pressure of the patients during their first 2½ hours in the recovery room. This table indicates that 64.5 per cent of patients who received a placebo had a stable blood pressure in the recovery room. Ten per cent experienced a sudden fall of 30 or more mm. of mercury systolic blood pressure between one-half and one hour after receiving a placebo and 15 per cent had a gradual fall in blood pressure of less than 30 mm. of mercury. When the effects of 50 and 100 mg. of cyclizine are compared to the effects seen in the placebo group, there does not appear to be an appreciable hypotensive side effect due to the cyclizine. On the other hand the patients treated with trifluprom azine tended to have more hypotension. The percentage of patients with an increase in blood pressure over the first reading was lower, and the percentage of patients who showed a sudden or gradual fall in blood pressure was greater. Furthermore,

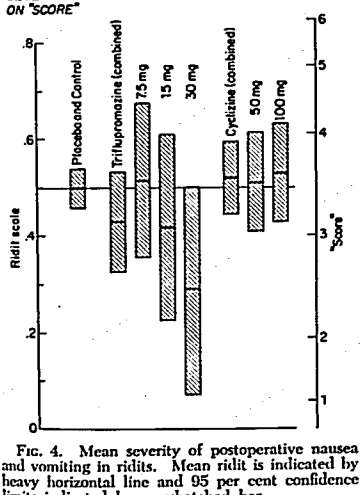

Fig. 4. Mean severity of postoperative nausea and vomiting in ridits. Mean ridit is indicated by heavy horizontal line and 95 per cent confidence limits indicated by crosshatched bar.

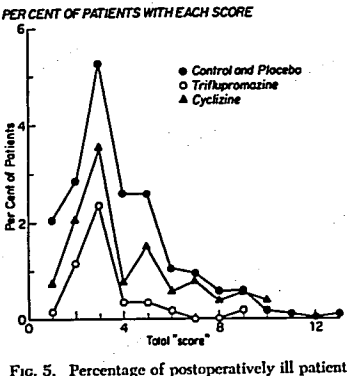

Fig. 5. Percentage of postoperatively ill patients with each score. "Score" indicated increasing severity of nausea and vomiting from 1 to 13.

there seems to be a dose effect relationship in that as the dose of trifluprom azine is increased, the percentage of patients showing a fall in blood pressure of 30 mm. or more increased and those who showed an increase in blood pressure over the first reading decreased. This slope or increase in number of patients having hypotension of greater than 30 mm. of mercury following 30 mg. trifluprom azine is statistically significant (P for $Chi^2 > 0.01$).

The effects of placebo, trifluprom azine and cyclizine on post-anesthesia sleeping time are shown in figure 6. We have charted the percentage of patients asleep at each half hourly observation. There appears to be a slight prolongation of sleeping time due to cyclizine. However, those patients treated with trifluprom azine have a longer sleeping time than those given cyclizine, which becomes most obvious after one-half hour. When the data on the patients receiving trifluprom azine are analyzed in terms of the dose, no significant difference can be detected between the 7.5, 15, and 30 mg. dose level in respect to sleeping time (fig. 7).

Discussion

The ideal antiemetic agent would be one that completely suppressed nausea and vomiting and produced no untoward side effects. Complete suppression of retching and vomit-

TABLE 1

BLOOD PRESSURE IN RECOVERY ROOM

	Placebo	Cyclizine		Triflupromazine		
		50 mg.	100 mg.	7.5 mg.	15 mg.	30 mg.
Total number patients	330	262	270	202	266	129
Percent stable	64.5	65.3	63.0	58.4	58.3	52.7
Hypotension >30 mm. Hg	16.4	11.4	15.6	15.0	20.3	32.5
(½–1 hour)	(10.6)	(6.1)	(6.3)	(5.0)	(12.8)	(24.8)
(After 1 hour)	(5.8)	(5.3)	(9.3)	(9.9)	(7.5)	(7.7)
Hypotension <30 mm. Hg	15.2	13.0	14.8	24.8	24.8	14.7
Increase over first reading	4.5	4.6	4.1	2.5	2.3	1.6

ing is probably possible. Whether complete suppression of nausea is possible or not is a moot question, for nausea is a subjective phenomenon. In any study of nausea and vomiting there will be a few patients who report nausea because they expect to be nauseated postoperatively. This can be illustrated by the reaction of one patient who said, "I know I had ether; I must be sick."

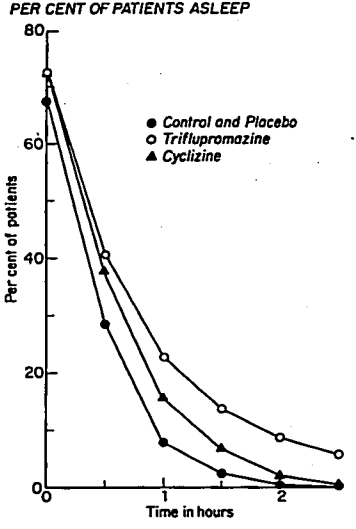

FIG. 6. Effect of placebo, triflupromazine and cyclizine on postanesthetic sleeping time. The percentage of patients asleep at each half-hour observation period is plotted for each drug.

Effective antiemetic agents probably act centrally. Because the chemoceptor trigger zone and the vomiting center are near other vital centers, it is postulated that those agents which decrease the incidence of nausea and vomiting will produce side effects such as prolongation of sleeping time, depression of respiration or hypotension.

Cyclizine did not show an appreciable prolongation of the postanesthetic sleeping time, whereas triflupromazine did. One might inquire whether the prolongation of the postanesthetic sleeping time is due to prevention of noxious stimuli from reaching higher centers and thus preventing arousal or whether this is a central pharmacologic action of triflupromazine *per se*. The latter seems more likely. Cyclizine at the 50 and 100 mg. dose level did not produce significant hypotension, whereas the higher dosage of triflupromazine, especially the 30 mg. dose, did. On the other hand, the 7.5 mg. dose of triflupromazine did not appear to produce much more hypotension than the placebo. This hypotensive effect seemed to have a dose response relationship in that its incidence increased as the doses were raised above 7.5 mg. Although hypotension of greater than 30 mm. of mercury was observed, shock or untoward effects from hypotension were not observed in any patients. No gross changes in respiratory rate or depth suggestive of respiratory depression were observed during this study.

There is no doubt that cyclizine and triflupromazine reduced the incidence of postoperative nausea and vomiting. This decrease of 50 per cent following cyclizine compares well with that reported in other studies.[3, 4] It has

been reported[5] that there is no significant difference between the incidence of nausea and vomiting following cyclizine and that following a placebo. However, we have no assurance that the method employed was sensitive enough to detect a difference. The method employed in this study is sensitive enough to detect the difference in the incidence of nausea and vomiting following placebo as compared with cyclizine. Furthermore, we were able to demonstrate a significant difference between the reduction in nausea and vomiting following cyclizine and that following triflupromazine. Triflupromazine was the more effective. We elected not to increase the dose of cyclizine above 100 mg. since doubling the dose from 50 to 100 mg. did not increase its effectiveness.

Triflupromazine decreased the incidence of nausea and vomiting to an average value of about 5 per cent. Increasing the dose above 7.5 mg. did not further decrease the incidence of nausea and vomiting. Here again it appears that we are on the flat portion of the dose response curve in respect to the effect of this agent on *incidence* of nausea and vomiting. However, there is a significant trend in the decrease in *severity* of nausea and vomiting as the dose of triflupromazine is increased above 7.5 mg.

The incidence of nausea and vomiting recorded in this study is lower than generally reported. Actually the incidence of vomiting is about one-half that of nausea and vomiting combined or about 10 per cent. This is due to multiple factors. We believe that the combination of smooth induction of anesthesia, maintenance of normal blood pressure, maintenance of light levels of anesthesia and careful attention to proper ventilation of the patient contributes to the low incidence of nausea and vomiting in our subjects. Narcotic analgesics are usually not administered during the first two hours in the recovery room and if given in the early postoperative period, small doses are prescribed. In addition, it should be remembered that we have studied these patients for only two and a half hours. However, our data indicate that the peak incidence of vomiting occurred during this time and that the percentage of awake patients reporting nausea levels off at two hours. Initially, we

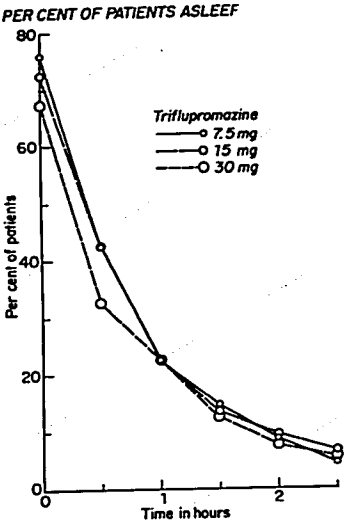

FIG. 7. Effect of different dose levels of trifluprom azine on postanesthetic sleeping time. The percentage of patients asleep at each half-hour observation period is plotted for each dose.

followed some of the patients twenty-four hours and found that there were very few additional patients reporting nausea or vomiting after they left the recovery room. In those who reported nausea or vomiting after their stay in the recovery room it was usually found to be related to the administration of a narcotic.

Cyclizine will decrease the incidence of nausea and vomiting without prolonging significantly the postanesthetic sleeping time, whereas trifluprom azine reduces the incidence of nausea and vomiting to a greater degree while producing some prolongation of the postanesthetic sleeping time. Perhaps differences in binding account for the observed clinical difference. However, this increase in protection due to trifluprom azine could be related to its sedative side effects. Knapp and Beecher have shown that pentobarbital at the 150 mg. dose level effectively reduced the incidence of post-anesthetic nausea and vomit-

ing.[6] Perhaps cyclizine plus a barbiturate would reduce the incidence of nausea and vomiting to the same degree as that achieved with the triflupromazine. The basic question is whether patients sleep longer because there is a lack of noxious stimuli to arouse them or whether they are well because they are sedated. Further work with potent antiemetic compounds devoid of sedative side effects may help clarify this question.

From this study relative potency of these two agents cannot be determined, since there was no significant slope with either agent on the dose effect curve for incidence. There likewise was no significant slope on the dose effect curve for severity with cyclizine, whereas for triflupromazine there was a significant slope. Perhaps in further studies drugs will be found that produce a similar slope with the sensitivity (ridit) scale and relative potency can then be calculated.

Summary

A double blind study has been made of the effectiveness of cyclizine and triflupromazine in the treatment of postoperative nausea and vomiting in 2,214 patients. It was found that the incidence of nausea and vomiting in the combined placebo and control groups was 19 per cent, whereas following treatment with 50 and 100 mg. of cyclizine it was approximately 11 per cent. Triflupromazine reduced the incidence of nausea and vomiting significantly more than cyclizine to approximately 5 per cent. There was no change in severity of postoperative nausea and vomiting following treatment with 50 and 100 mg. of cyclizine nor with 7.5 mg. of trifluprom azine. As the dose of trifluprom azine was increased to 15 or 30 mg. the severity of postoperative nausea and vomiting appeared to decrease. However, as the dose of trifluprom azine was increased to 15 and 30 mg. the incidence of side effects likewise increased, so that there was a statistically significant increase in hypotensive side effects in addition to the prolongation of postanesthetic sleeping time seen at the 7.5 mg. level.

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