# THE ANTISIALOGOGUE EFFECT OF TRIMETHOBENZAMIDE HCL (TIGAN®), TRIMEPRAZINE TARTRATE (PANECTYL®), DIPHENHYDRAMINE HCL (BENADRYL®), DIMENHYDRINATE (GRAVOL®, DRAMAMINE®), AND CYCLIZINE LACTATE (MARZINE®, MARAZINE®)*

ALLEN B. DOBKIN,† and V. GUY CRISWICK‡

IT IS DIFFICULT to tell clinically whether an ancillary drug, which is useful in association with anaesthesia, has useful physiological effects other than those of its primary action unless they are studied specifically. The antisialogogue effects of the following drugs which are used primarily as antihistaminics and anti-emetics are reported here.

*Trimethobenzamide HCL* (*Tigan®*) is a substituted benzamide which contains the active substance 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)-benzylamine HCL. It is a white, odourless, crystalline powder which is water soluble (more than 50 per cent at 25° C), and has a bitter taste. It has been used primarily as an anti-emetic.[1] Its anti-emetic effect appears to act at the chemoreceptor trigger zone, as with the phenothiazine derivatives, although its chemical structure resembles the dimethyl aminoethoxy antihistamines, such as diphenhydramine. It is not as effective in preventing vomiting caused by strong reflex visceral impulses. It does not cause any hypnotic sedation or behavioural depression as is observed with chlorpromazine. Tigan does not have the antihistaminic or antiadrenaline effects of the phenothiazines or structurally related compounds.[2]

*Trimeprazine tartrate* (*Panectyl®*) is a phenothiazine derivative whose antihistaminic and anti-emetic properties exceed those of promethazine. It has only a weak antiadrenaline effect, but its spasmolytic effect exceeds that of chlorpromazine. The hypnotic sedative action is of the same order as promethazine. It has been used in the treatment of a variety of allergic disorders to relieve itching, and as a premedicant for children.[3,4,5]

*Diphenhydramine HCL* (*Benadryl®*) is a benzhydryl derivative which has potent antihistaminic and antispasmodic properties. The other main action of this drug is a marked hypnotic-sedative effect which lasts several hours. An atropine-like action which inhibits sweating and dries secretions is often observed, and is useful in the control of the symptoms of Parkinson's disease.[6]

*Dimenhydrinate* (*Gravol®*, *Dramamine®*) is a benzhydryl derivative which exhibits some antihistamine properties, but is employed chiefly in the prevention and treatment of motion sickness, irradiation sickness, and post-anaesthetic

*From the Department of Anaesthesia, University Hospital, University of Saskatchewan, Saskatoon, Sask.

†Present address: Department of Anesthesia, University Hospital, Syracuse, New York.

‡Student Research Assistant from the University of Saskatchewan College of Medicine.

nausea and vomiting. It has been used with only fair results in the treatment of nausea and vomiting of pregnancy. The mechanism of the antiemetic action of this drug has not been elucidated. Drowsiness is the principal side effect.[7]

*Cyclizine lactate* (*Marzine®*, *Marazine®*) is N-benzhydryl-N-methyl piperazine. This substance exerts both antihistaminic and anticholinergic actions. The antihistaminic action is equal to that of diphenhydramine. Its anticholinergic activity (as measured by its ability to block the blood pressure reducing effect of vagal stimulation) is about 5 per cent of the potency of atropine. Its spasmolytic effect on the gut, however, is less than one per cent when compared to atropine. Its hypnotic sedative effect is less than that of diphenhydramine.[8]

## Method

Serial tests were done on eight healthy adult male subjects (ages 20–30 years) using a technique that was reported previously.[9,10,11,12] Each subject had at least twelve tests. Duplicate tests were done with carbaminoyl-choline chloride and adrenaline mixture (control) and the five drugs described above.

The intravenous dose of each drug was selected within the therapeutic range of their optimum antihistaminic or antiemetic effect.

In the control test, saliva was collected for 10 min. before any drug was administered, and then for 30 min. after the intravenous injection of the mixture. In the remaining tests, each drug was injected intravenously at the beginning of the experiment, and saliva was collected for 10 min. Then the mixture was injected, and saliva was collected for a further 30 min. The same parotid gland as was initially selected in each subject was used throughout the series of tests, and volumes of saliva were recorded at 10 minute intervals.

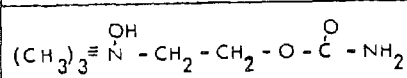
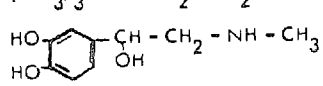
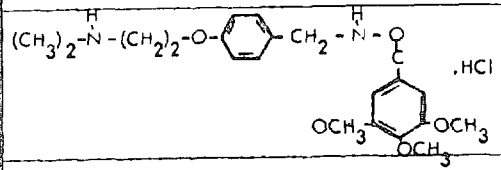
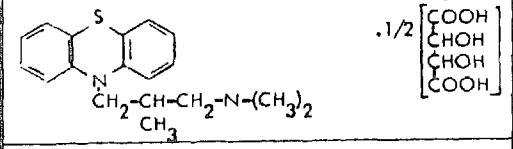
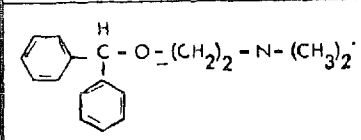
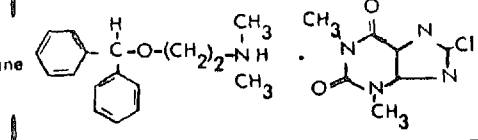
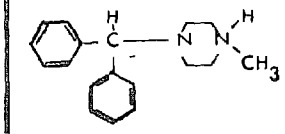
## Results

A summary of the data is shown in Figure 1. The mean volume of saliva collected during the 10 min. immediately following the injection of the carbaminoylcholine-adrenaline mixture was taken as 100 per cent. All other measured volumes were then tabulated on this percentage basis. Standard deviations were calculated from the mean volumes of salivary secretion collected, and also expressed as a percentage.

Trimethobenzamide exhibited little consistent effect on salivary secretion, and had no evident side effects.

Trimeprazine, diphenhydramine, and dimenhydrinate caused suppression of salivary secretion during the initial 10-min. period and were more than 50 per cent effective in preventing the secretion of saliva in response to the carbaminoylcholine-adrenaline mixture. Trimeprazine and diphenhydramine consistently caused marked drowsiness in every subject. Only slight or moderate drowsiness was caused by dimenhydrinate.

Cyclizine did not suppress salivary secretion during the initial 10 minutes after administration, but it was very effective in suppressing salivation after administration of the stimulant mixture. Drowsiness was observed more often

| DRUGS | OFFICIAL & CHEMICAL NAME | STRUCTURAL FORMULA | I.V. dose mg. | SECRETION OF SALIVA % OF CONTROL TEST RESPONSE WITH CARBACHOL-ADRENALINE. | | | PERCENT REDUCTION of SALIVARY SECRETION |
|---|---|---|---|---|---|---|---|
| | | | | 10 min. BEFORE | 10 min. AFTER | 20 min. AFTER | 30 min. AFTER | |
| CARBACHOL | Carbaminoylcholine |  | 0.12 | 2 | 100* | 15 | 9 | - |
| ADRENALIN (Control) | Epinephrine |  | 0.06 | ± 2 | ± 81 | ± 18 | ± 7 | - |
| TIGAN | Trimethobenzamide HCl (Roche) N - (p - (2 - dimethylaminoethoxy) benzyl) - 3, 4, 5 - trimethoxybenzamide HCl |  | 200 | 2 ± 1 | 78 ± 85 | 5 ± 5 | 5 ± 8 | Not Significant. |
| PANECTYL TEMARIL | Trimeprazine tartrate (Poulenc) 10 - (3 - dimethylamino - 2 - methylpropyl) - phenothiazine tartrate |  | 5 | 1 ± 1 | 47 ± 35 | 7 ± 8 | 5 ± 11 | 53 |
| BENADRYL | Diphenhydramine HCl (Parke Davis) 2 (benzohydryloxy) - N, N - dimethylethylamine HCl |  | 50 | 1 ± 1 | 43 ± 54 | 4 ± 5 | 2 ± 3 | 57 |
| GRAVOL DRAMAMINE | Dimenhydrinate (Homer, Searle) 2 - (benzohydryloxy) - N, N - dimethylethylamine 8 - chlorotheophyllinate |  | 50 — | 1 ± 1 | 41 ± 48 | 4 ± 4 | 2 ± 2 | 59 |
| MARZINE MAREZINE | Cyclizine lactate (Burroughs Wellcome) diphenylmethyl - 4 - 1 - methylpiperazine lactate |  | 50 | 2 ± 1 | 29 ± 28 | 2 ± 2 | 2 ± 2 | 71 |

* ALL salivary volumes were computed on the basis of this volume = 100.

FIGURE 1

than with dimenhydrinate, but was not as marked as with trimeprazine or diphenhydramine.

## Discussion

Trimethobenzamide is suitable only for use as an anti-emetic, as it has no apparent other effects which might be useful as an adjunct to clinical anaesthesia.

Trimeprazine, diphenhydramine, dimenhydrinate, and cyclizine are useful for premedication because they not only have anti-emetic, antihistaminic, and hypnotic sedative properties, but are also effective in partially inhibiting salivary secretions. Since their antisialogogue activity is significantly less than the belladonna derivatives, it is advisable to include one of the latter when one of the above drugs is used for a pre-anaesthetic medicant.

## Summary and Conclusions

The effect of intravenous trimethobenzamide, trimeprazine, diphenhydramine, dimenhydrinate, and cyclizine on salivary secretion was studied in eight healthy male adult subjects. A mixture of carbaminoylcholine chloride was used to stimulate secretions. The dose selected for each drug was that used for an optimum therapeutic activity of its most desirable effect.

Cyclizine was the most effective antisialogogue of this group, and it also caused moderate drowsiness. Trimeprazine, diphenhydramine, and dimenhydrinate exceeded 50 per cent effectiveness as antisialogogues, and caused varying degrees of drowsiness.

Trimethobenzamide was not effective as an antisialogogue, and did not cause any other objective effects.

## Résumé

Nous avons pratiqué, en duplicata, des tests en série sur huit adultes mâles en santé avec un mélange de chlorure de carbaminoylcholine et d'adrénaline (comme contrôle) puis avec de la trimethobenzamide, de la triméprazine, de la diphenhydramine, du dimenhydrinate et de la cyclizine pour évaluer leur pouvoir antisialagogue. Au cours du test de contrôle, la salive était prélevée du canal de la parotide durant 10 minutes avant l'administration de tout médicament et, ensuite, durant 30 minutes après l'injection du mélange. Au cours des autres tests, les médicaments étaient administrés par voie intraveineuse au début de l'expérience et la salive était ramassée durant 10 minutes. Alors, nous injections le mélange et, de nouveau, nous prélevions la salive durant 30 minutes. Nous avons employé, chez tous les sujets, la même glande parotide que nous avions choisie au début au cours de tous les tests et nous avons tenu compte des volumes à toutes les 10 minutes.

La cyclizine, parmi les médicaments mentionnés ci-haut, s'est avérée le plus efficace antisialagogue et elle a aussi causé des vertiges. La triméthobenzamide a peu ou pas de pouvoir antisialagogue. La trimeprazine, la diphenhydramine et le dimenhydrinate ont dépassé un pouvoir de 50% comme antisialogogues et ils ont causé divers degrés de vertiges.

## REFERENCES


1. WOLFSON, B., & FOLDES, F. F. Controlled Study of Tigan in Nausea and Vomiting Associated with Anaesthesia and Surgery. Presented at Colloquium on Tigan, New York (May, 1959).
2. SCHALLEK, W.; HEISE, G. A.; KEITH, E. F.; & BADGON, R. E. Antiemetic Activity of 4-(2-dimethylaminoethoxy)-N-(3,4,5,-trimethoxybenzoyl) benzylamine Hydrochloride. J. Pharmacol. & Exper. Therap. *126*: 270 (1959).
3. COURVOISIER, S.; DUCROT, R.; FOURNEL, J.; & JOULOU, L. General Pharmacological Properties of a New Phenothiazine Derivative with Powerful Neuroplegic and Faint Autonomic Nervous Activity, 10-(3-dimethylamino-2-Methyl propyl)-phenothiazine Hydrochloride. Arch. int. pharmacodyn *115*: 90 (1958).
4. COPE, R. W., & GLOVER, W. T. Trimeprazine Tartrate for Premedication of Children. Lancet *i*: 858 (1959).
5. GILLETT, G. B., & KEIL, A. M. Trimeprazine Tartrate in Pediatric Premedication. Anaesthesia *15*: 158 (1960).
6. WARRINGTON, W. R.; PASQUESI, T. J.; KULASAVAGE, R. J.; & MCCAWLEY, E. L. Benadryl Hydrochloride Given Intravenously to Control Postoperative Nausea and Vomiting. Surgery *34*: 837 (1953).
7. MOORE, D. C.; ANDERSON, L.; WHEELER, G.; & SCHEIDT, J. The Use of Parenteral Dramamine to Control Postoperative Vomiting. Anesthesiology *13*: 354 (1952).
8. MARCUS, P. S., & SHEEHAN, J. C. Treatment of Postoperative Vomiting. Anesthesiology *16*: 423 (1955).
9. WYANT, G. M., & DOBKIN, A. B. Antisialogogue Drugs in Man: Comparison of Atropine, Scopolamine (l'hyoscine) and l'hyoscyamine (bellafoline). Anaesthesia *12*: 203 (1957).
10. DOBKIN, A. B., WYANT, G. M., & AASHEIM, G. M. Antisialogogue Drugs in Man: Comparison of Some Anticholinergic and Sedative-Antihistaminic Drugs. Anaesthesia *13*: 63 (1958).
11. DOBKIN, A. B., & PURKIN, N. The Antisialogogue Effect of Phenothiazine Derivatives Comparison of Pecazine, Perphenzaine, Fluphenazine, Thiopropazate, Pipamazine and Triflupromazine. Brit. J. Anaesth. *32*: 57 (1960).
12. DOBKIN, A. B., & PALKO, D. The Antisialogogue Effect of Phenothiazine Derivatives: Comparison of Promazine, Levomepromazine, Trifluoperazine, Proclorperazine, Methdilazine and Prothipendyl. Anesthesiology *21*: 260 (1960).