THE ANTISIALOGOGUE EFFECT OF PHENOTHIAZINE DERIVATIVES: COMPARISON OF PROMAINE, LEVOMEPROMAZINE, TRIFLUOPERAZINE, PROCLORPERAZINE, METHDILAZINE AND PROTHIPENDYL

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THERE is a significant difference in the antisialogogue effect among phenothiazine drugs that are used for preanaesthetic medication.[1, 2] A high antisialogogue activity would add much to the efficacy of these drugs in preanaesthetic medication.[3] The present study reports on a comparison of several phenothiazine derivatives which were recently introduced or are undergoing screening tests. The effect of these drugs was compared with previous observations with the belladonna drugs and some anticholinergic drugs.

METHOD

Serial tests were done on 6 healthy adult subjects. Duplicate tests were done at least 24 hours apart with carbaminoylcholine chloride-epinephrine mixture (control), promazine (Sparine), levomepromazine (Nozinan), trifluoperazine (Stelazine), proclorperazine (Compazine, Stemetil) methdilazine and prothipendyl (Timovan). Each subject had at least fourteen tests. The intravenous dose of each drug was selected after preliminary trials to determine the dose which produced no subjective or objective effect except drowsiness and a dry sensation in the mouth, as was done in the previous studies.

In the control test, saliva was collected for 10 minutes before any drug was administered, and then for 30 minutes after the intravenous injection of the mixture containing carbaminoylcholine chloride and epinephrine. In the comparative tests, each drug was injected intravenously at the beginning of the experiment, and saliva was collected for 10 minutes. Then the mixture of carbaminoylcholine chloride-epinephrine was injected and saliva was collected for a further 30 minutes. The same parotid duct which was initially selected in each subject was used throughout the series, and the volumes collected were recorded at 10-minute intervals. The saliva was removed from the surface of the parotid duct by means of a cup that was applied over the area, and it was drawn into a calibrated trap by means of a tube connected to a Stedman pump.[1, 2, 4, 5]

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RESULTS

A summary of the data is shown in figure 1. The mean volume of saliva collected during the ten minutes immediately following the injection of the mixture of carbaminoylcholine chloride-epinephrine was taken as 100 per cent. All other volumes of saliva which were collected were then computed on this percentage basis. Standard deviations were calculated for the mean volumes of saliva secretion expressed as a per cent as noted above, with each drug, at each time interval. These are noted under each mean value in figure 1.

From the tabulated data, one may observe that none of the drugs caused suppression of salivation during the initial 10-minute period. There appeared to be a slight stimulation of salivary secretions at first with trifluoperazine and proclorperazine. After injection of the carbaminoylcholine chloride-epinephrine mixture, promazine reduced salivary secretion by about 25 per cent, while the other five drugs each reduced salivary secretion by about 50 per cent. Aside from moderate drowsiness, there were no subjective or objective side effects observed during these experiments.

DISCUSSION

The intravenous dose of these phenothiazine derivatives which produce drowsiness or sedation was not sufficient to reduce salivary secretions sufficiently to allow elimination of

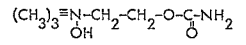
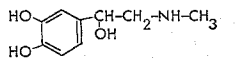
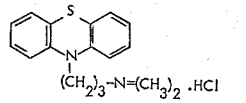
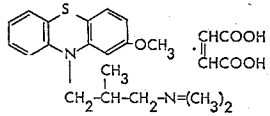
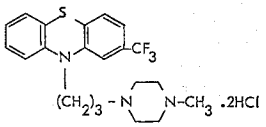
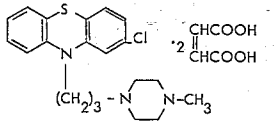
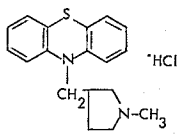
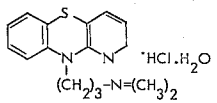
DRUGS	OFFICIAL & CHEMICAL NAME	FORMULA	Intravenous DOSE mg.	SECRETION OF SALIVA % OF CONTROL TEST RESPONSE BEFORE 10 min.	AFTER 10 min	AFTER 20 min.	AFTER 30 min.	% REDUCTION OF SALIVARY SECRETION
CARBACHOL	Carbaminoylcholine chloride		0.12	6	100	17	6	
ADRENALIN (CONTROL)	Epinephrine		0.06	± 7	44	14	4	
SPARINE	Promazine (Wyeth) 10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride		10	7 ± 12	73 58	15 16	7 9	27
NOZINAN	Levomepromazine (Poulenc) 1-methoxy-3-(dimethylamino-3'-methyl-2'-propyl)-10-phenothiazine acid maleate		5	6 ± 8	55 42	4 3	3 3	45
STELAZINE	Trifluoperazine (SKF) 10- 3-(1-methyl-4-piperazinyl) propyl - 2-(trifluoromethyl) phenothiazine dihydrochloride		0.5	14 ± 23	49 38	11 14	6 7	51
STEMETIL	Proclorperazine (Poulenc, SKF) 2-chloro-10-(3-1-methyl-4-piperazinyl-propyl)-phenothiazine dimaleate		3	10 ± 20	54 34	8 7	9 10	46
MJ 5022	Methdilazine (Mead Johnson) 10-(1-methyl-3-pyrrolidyl-methyl)-phenothiazine hydrochloride		5	5 ± 5	63 37	4 3	3 4	37
TIMOVAN AY 56031	Prothipendyl (Ayerst) Dimethylaminopropyl - thiophenylpyridylamine		5	4 ± 3	52 40	12 16	4 6	48

FIGURE 1.

other drugs which are used for this purpose. Atropine (0.6 mg.) scopolamine (0.2 mg.) and bellafoline (0.3 mg.) reduce salivary secretion reliably by more than 90 per cent, whereas none of the phenothiazine derivatives tested could consistently reduce the secretions by more than 50 per cent. Therefore, in order to assure adequate reduction of secretions before induction of anaesthesia, it would appear necessary to administer one of the belladonna derivatives together with the phenothiazine derivative which may be chosen.

Summary and Conclusions

The effect on salivary secretions of intravenous promazine, levomepromazine, trifluoperazine, proclorperazine, methdilazine and prothipendyl was compared in 6 healthy adult subjects. A mixture of carbaminoylcholine chloride and epinephrine was injected to stimulate the secretion. The dose selected for each drug was that which produced no undesirable effects except drowsiness. Promazine had a very weak unreliable antisialogogue effect, whereas the other five drugs reduced the secretion of saliva by about 50 per cent.

The data from these experiments indicate that when these drugs are used for preanaesthetic medication, it is advisable to combine them with a therapeutic dose of either scopolamine, atropine or bellafoline.

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TETANUS Two main objectives must be attained in order to arrest the progress of tetanus: (1) the neutralization of circulating toxin (antitoxin), and (2) the elimination of the focus of infection (surgical excision, antibiotic therapy). Meanwhile the neuromuscular manifestations of the disease must be controlled. A regimen is advocated which employs a sedative (either secobarbital or pentobarbital) and a muscle relaxant (methocarbamol—Robaxin) together with chlorpromazine, which is believed to potentiate the sedative-relaxant effects of the other two drugs. Methocarbamol is an interneuronal depressant agent and as such has a more specific and logical pharmacological action than the neuromuscular blocking agents in the control of the reflex muscle spasm of tetanus. Methocarbamol acts centrally at the internuncial pool of neurons by depressing the polysynaptic reflex arcs. There is no direct influence on the motor nerve, skeletal muscle, or myoneural junction. Electromyographic monitoring together with determination of end-expiratory carbon dioxide concentration and tidal volume demonstrates adequate suppression of spasm without impairment of pulmonary ventilation. Special emphasis is placed on constant, expert nursing care, the prevention of secretional airway obstruction, and the maintenance of adequate alveolar ventilation (early tracheotomy in severe cases, mechanical ventilatory assistance). (*Crandell, D. L., and Whitcher, C. E.: Control of Neuromuscular Manifestations of Severe Systemic Tetanus, J. A. M. A. 172: 15 (Jan. 2) 1960.*)