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ANTI-EMETIC ACTIVITY OF PHENOTHIAZINES IN RELATION TO THEIR CHEMICAL STRUCTURE

BY

K. P. BHARGAVA AND OM CHANDRA

From the Upgraded Department of Pharmacology and Therapeutics, K.G. Medical College, University of Lucknow, India

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Twelve phenothiazine derivatives have been studied for anti-emetic potency in dogs against emesis induced by apomorphine. The PD_{50}s of all the compounds were determined and the activities compared with chlorpromazine hydrochloride as standard. Thioproperazine methanesulphonate was 300 times more active than chlorpromazine hydrochloride and twice as active as perphenazine sodium citrate. The anti-emetic activity of the compounds has been correlated with their chemical structure.

Courvoisier, Fournel, Ducrot, Kolsky & Koetschet (1953) reported that chlorpromazine abolished the vomiting induced by apomorphine in dogs. The site of its action was established as the chemoreceptor trigger zone (Brand, Harris, Borison & Goodman, 1954). Since the discovery of the value of chlorpromazine in the treatment of vomiting, numerous phenothiazine derivatives have been tested in search of a more potent anti-emetic agent with fewer side-effects. Although the anti-emetic activities of phenothiazine compounds have always been compared with that of chlorpromazine there are discrepancies in the results of different investigators (Rosenkilde & Govier, 1957 ; Wang, 1958).

The present investigation was undertaken to compare the anti-emetic activities of twelve phenothiazine derivatives under the same environmental and experimental conditions and to correlate activity with chemical structure.

The phenothiazine compounds selected for the study are listed in Table 1 ; they are classified according to the substituent (R_2) at position 10 in the phenothiazine nucleus.

A preliminary report of this study was presented before the Annual Session of the Association of Physiologists and Pharmacologists of India in 1962.

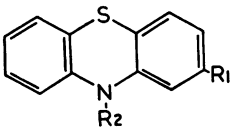
METHODS

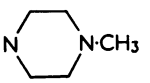
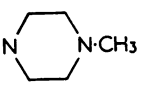
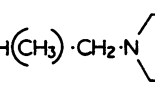
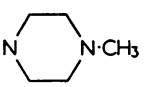
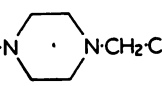
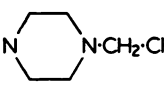
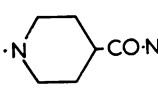
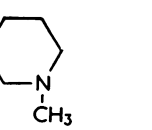
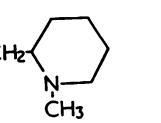
Adult dogs weighing from 8 to 16 kg were used. Only those dogs which vomited in response to the minimal effective intravenous dose of apomorphine hydrochloride (25 μg/kg) were used. The dogs were divided into groups of six and the challenging dose of apomorphine (100 μg/kg) was four times the minimal effective dose. Actual expulsion of the gastric contents was taken as the criterion for vomiting. Normally the dogs vomited within 2 to 5 min after the intravenous injection of apomorphine but positive responses were recorded up to 30 min.

TABLE 1

PHENOTHIAZINE DERIVATIVES

Phenothiazine ($R_1=R_2=H$)



Name	R_2	R_1
3-Dimethylpropylamines		
Chlorpromazine	$\cdot[CH_2]_3\cdot N(CH_3)_2$	Cl
Fluopromazine	$\cdot[CH_2]_3\cdot N(CH_3)_2$	CF_3
Chlorpromazine sulphoxide*	$\cdot[CH_2]_3\cdot N(CH_3)_2$	Cl
3-(4-Methylpiperazin-1-yl)propyl derivatives		
Prochlorperazine	$\cdot[CH_2]_3\cdot$ 	Cl
Trifluoperazine	$\cdot[CH_2]_3\cdot$ 	CF_3
Methyltrifluoperazine (SKF 5657–A_2)	$\cdot CH_2\cdot CH(CH_3)\cdot CH_2\cdot$ 	CF_3
Thioproperazine	$\cdot[CH_2]_3\cdot$ 	$.SO_2.N(CH_3)_2$
3-[4-(2-Hydroxyethyl)piperazin-1-yl]propyl derivatives		
Perphenazine	$\cdot[CH_2]_3\cdot$ 	Cl
Thiopropazate	$\cdot[CH_2]_3\cdot$ 	Cl
Piperidine derivatives		
Pipamazine	$\cdot[CH_2]_3\cdot$ 	Cl
Pecazine		H
Thioridazine		$.SCH_3$

*The bivalent sulphur of the phenothiazine nucleus is oxidized to $>SO_2$.

To determine the relative anti-emetic activities of phenothiazines against emesis induced by apomorphine a dose of the compound being tested was administered subcutaneously 30 min before the emetic test. The dogs were then fed and given the challenging intravenous dose of apomorphine. At least three doses of each compound which protected a proportion of the animals were tested and at least 5 days were allowed between tests. This period was considered sufficient to avoid cumulative effects or tolerance. Intravenous saline was occasionally given to test the development of a conditioned response to the procedure of injection. The results were subjected to probit analysis and the PD_{50} and the 95% fiducial limits were calculated for each drug by the method of Finney (1952).

TABLE 2

ANTI-EMETIC POTENCY OF PHENOTHIAZINES AGAINST EMESIS INDUCED BY APOMORPHINE

Compound	Subcutaneous PD_{50}(mg/kg)	95% fiducial limits	Relative potency
Chlorpromazine	2·10	2·00 –2·20	1·0
Fluopromazine	0·06	0·055 –0·065	35·0
Prochlorperazine	1·00	0·995 –1·005	2·1
Trifluoperazine	0·12	0·114 –0·126	17·5
Thioproperazine	0·007	0·0067–0·0073	300·0
Methyltrifluoperazine	1·55	1·42 –1·68	1·4
Perphenazine	0·013	0·008 –0·018	161·0
Thiopropazate	0·13	0·128 –0·132	16·2
Pipamazine	0·24	0·216 –0·264	8·8
Pecazine	3·36	3·34 –3·38	0·62
Thioridazine	—	—	Ineffective
Chlorpromazine sulphoxide	—	—	Ineffective

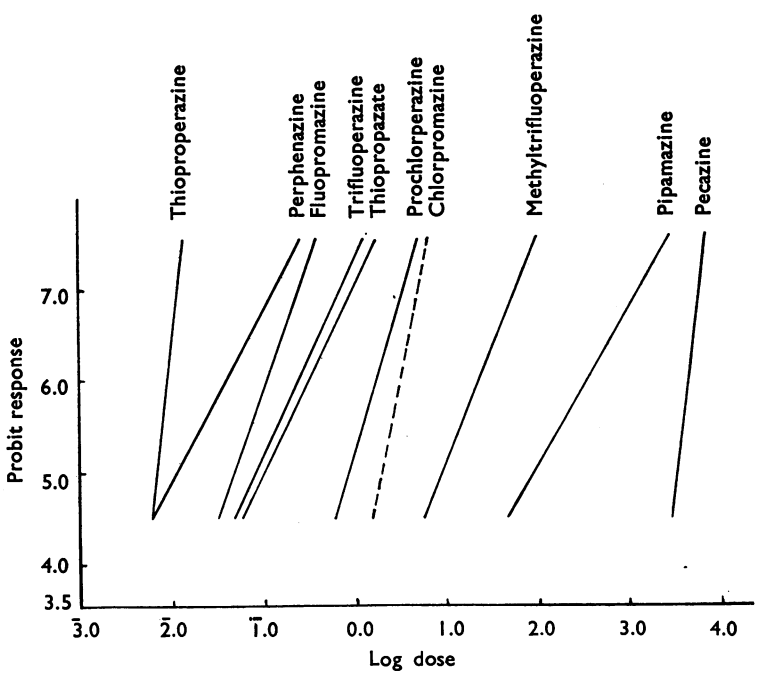


Fig. 1. Regression lines of phenothiazines showing their relative potencies in the anti-emetic test against apomorphine hydrochloride. Lines are arranged from right to left in order of increasing potency.

The following drugs were used: chlorpromazine hydrochloride, fluopromazine hydrochloride, chlorpromazine sulphoxide, prochlorperazine acid maleate, trifluoperazine dihydrochloride, methyltrifluoperazine dihydrochloride, thioproperazine methanesulphonate, perphenazine sodium citrate, thiopropazate dihydrochloride, pipamazine hydrochloride, pecazine hydrochloride and thioridazine hydrochloride.

RESULTS

Table 2 summarizes the relative anti-emetic potencies of the phenothiazines tested. Thioproperazine, the most active, was 300 times as potent as chlorpromazine. The PD_{50} for each compound is shown in Table 2 and regression lines for active drugs are drawn in Fig. 1. Thioridazine and chlorpromazine sulphoxide, a metabolite of chlorpromazine, were inactive.

DISCUSSION

The most active compound in this series was thioproperazine, followed by perphenazine which was 160 times more potent than chlorpromazine. Other workers have found a lower ratio for this last pair of compounds: 24.2, 27.8 and 31 by Rosenkilde & Govier (1957), Wang (1958) and Janssen & Niemgeers (1959) respectively. The potency of fluopromazine, which we found to be less than one-quarter that of perphenazine, accords with the finding of Laffan, Papandrianos, Burke & Craver (1961).

Correlation of chemical structure with anti-emetic activity

(i) Since chlorpromazine sulphoxide, the major metabolic product of chlorpromazine, is inactive it would seem that activity is to be found only in the parent compounds containing bivalent sulphur.

(ii) An aminoalkyl chain attached to the nitrogen atom of the phenothiazine nucleus is essential for anti-emetic activity. In all the compounds tested there were three carbon atoms interposed between the terminal and phenothiazine ring nitrogen atoms. Branching of this chain, as in methyltrifluoperazine, reduces activity as compared with the unbranched chain found in trifluoperazine. Incorporation of part of the chain into a piperidine ring, as in thioridazine and pecazine, greatly reduces activity.

(iii) Of compounds with the optimum three carbon atom side-chain the 3-piperazin-1-ylpropyl derivative (perphenazine) is more active than the corresponding 3-dimethylaminopropyl compound (chlorpromazine). Of the 3-piperazinylpropyl phenothiazines the 4-(2-hydroxyethyl)piperazin-1-yl group of perphenazine conferred greater activity than the corresponding 4-methyl group of prochlorperazine. Acetylation of the free hydroxy group of perphenazine, as in thiopropazate, reduced activity by a factor of ten.

(iv) Replacement of the hydrogen atom at position 2 (R_1) in the phenothiazine nucleus by radicals possessing increasing electronegativity enhances anti-emetic potency in the same order. This is borne out by the results with the following piperazinyl derivatives listed in increasing order of potency: prochlorperazine ($R_1=Cl$), trifluoperazine ($R_1=CF_3$) and thioproperazine ($R_1=.SO_2.N(CH_3)_2$).

Fluopromazine ($R_1 = CF_3$) is more active than chlorpromazine ($R_1 = Cl$) in the dimethylamino series.

It would seem that the dimethylsulphonyl substitution at position 2 is particularly favourable for anti-emetic activity ; it may be possible to increase further the potency of thioproperazine by alterations in the aminopropyl side chain.

We are indebted to Dr Nitya Nand and Mr Kesari Kishore for discussions on chemical structures in relation to activity. We gratefully acknowledge gifts of chlorpromazine, prochlorperazine, thioproperazine and chlorpromazine sulphoxide from May & Baker ; trifluoperazine and methyltrifluoperazine from Smith Kline & French ; fluopromazine from Sarabhai Chemicals ; perphenazine from Schering ; pecazine from Warner-Chilcott ; thioridazine from Sandoz ; and pipamazine and thiopropazate from Searle Laboratories.

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