CHEMICAL CONSTITUTION AND DRUG ACTION OF N-SUBSTITUTED PHENOTHIAZINE IN VENTRICULAR ECTOPIC TACHYCARDIA

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Following the study of antiarrhythmic action of chlorpromazine by Arora and Madan (1, 2), Courvoisier et al. (3) and Burn (4), several others phenothiazine derivatives have been found to possess arrhythmia combating properties (1-10). The correlation of chemical structure with antiarrhythmic activity among phenothiazine derivatives has been studied by Sato et al. (9), and Singh and Sharma (10). In the present study, 10-N substituted phenothiazines have been examined in ventricular ectopic tachycardia and an attempt has been made to find the essential structural features responsible for antiarrhythmic activity.

MATERIALS

The phenothiazine derivatives examined, with their formulae are given in Table 1.

Ventricular arrhythmias following acute myocardial infarction: The technique of two-stage ligation of the anterior descending branch of the left coronary artery as developed by Harris and Kokernot (11) was employed.

Mongrel dogs of both sexes (12 to 18 kg) were anaesthetized with pentobarbital, 30 mg/kg i.v. Under artificial respiration, the anterior descending branch of the left coronary artery was exposed via a small incision in the fourth intercostal space on the left side. The artery was freed from connective tissue and accompanying veins for a few mm. at a level of 2 to 5 mm. distal to the margin of the left auricular appendage. A doubled ligature was passed under the artery and cut, thereby becoming two ligatures. One of the ligatures was then tied snugly but not tightly around the artery, constricted but not closed. The second ligature was tightened 30 minutes later, totally occluding the artery. The chest wound was closed in layers and natural respiration restored. The animals were used in the unanaesthetized state 18-24 hours after the operation when their electrocardiogram indicated complete dissociation of atrial and ventricular activity with nearly all beats ventricular in origin. The test compounds were administered (dosage ranging between 3 and 15 mg/kg) intravenously, diluted in 20 ml of 5 percent glucose in normal saline over a period of 5 minutes. The drug was repeated after 30 minutes if necessary. Electrocardiograms, bipolar Lead II, were recorded.

TABLE 1. Chemical structure.

Compounds	Positions of substituents in phenothiazine structure		
	2	5	10
Chlorpromazine	Cl	S	$\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-N(CH}_3)_2$
10-Propyl phenothiazine	H	"	$\text{CH}_2\text{-CH}_2\text{-CH}_3$
10-Isopropyl phenothiazine	H	"	$\text{CH-(CH}_3)_2$
10-Tertiary butyl phenothiazine	H	"	$\text{C-(CH}_3)_3$
10-Butyl phenothiazine	H	"	$\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$
10-Cyclopentyl phenothiazine	H	"
Prothipendyl	N	"	$(\text{CH}_2)_3\text{-N=(CH}_3)_2$
Methoxypromazine	OCH_3	"	$\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$
Levomepromazine	OCH_3	"	$\text{CH}_2\text{-CH(CH}_3)\text{CH}_2\text{-N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$
4595 R.P.	Cl	"	$\text{CH}_2\text{-} \begin{matrix} \text{CH}_3 \\ \\ \text{C} \\ \\ \text{CH}_3 \end{matrix} \text{-CH}_2\text{-N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$
Multergan	H	"	$\text{CH}_2\text{-} \begin{matrix} \text{CH}_3 \\ \\ \text{CH} \\ \\ \text{SO}_4 \text{ CH}_3 \end{matrix} \text{-N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$

RESULTS

Only such dogs were selected for determining the antiarrhythmic activity in which over 75 percent of the heart beats were ventricular in origin and there was complete A.V. dissociation with little evidence of atrial activity as characterized by absence of P wave.

The test compounds were administered in unanaesthetized state 18 hours after the operation. A drug was considered to be effective if it produced and maintained reduction in ectopic rate by more than 50 percent for more than 15 minutes.

Generally the typical response was a reduction in total rate and ectopic ventricular rate first followed by appearance of small beats.

The comparative effectiveness of drugs is presented in Fig. 1.

10-Propyl phenothiazine, 10-isopropyl phenothiazine, 10-tertiary butyl phenothiazine and 10-butyl phenothiazine are more potent than chlorpromazine in suppressing ectopic activity and heart rate. Amongst these drugs, 10-butyl phenothiazine is of special interest. Its effect was characterized by immediate and prolonged suppression of ectopic impulses in all the five dogs in a dose of 3 mg/kg. The effect lasted for more than 24 hours. The typical response of 10-butyl phenothiazine is shown in Fig. 2.

FIG. 1. Comparative effects of drugs in ventricular ectopic tachycardia.

V.E.R. indicates ventricular ectopic rate.

H.R. means heart rate.

Ordinate : Heart beats/min.

Abscissa : Time in minutes.

DISCUSSION

Sato et al. (9) examined typical phenothiazines and concluded a possible relationship between their chemical structure and antiarrhythmic activity. Singh and Sharma (10) analysed the structural requirements for N-substituted phenothiazine derivatives from the point of view of their antifibrillatory activity and pointed out that the presence of a 3 carbon atom straight chain is possibly responsible for maximum activity.

The present investigations were undertaken in an attempt to define in more exact terms the structural features of phenothiazines contributing towards their effectiveness in ventricular ectopic tachycardia. In terms of molar activity (Table 2), 10-butyl phenothiazine ranks first and has more than double the activity of chlorpromazine. This suggests that a straight chain 4 carbon atom is most effective in influencing ventricular ectopic activity.

Next in decreasing order of activity are 10-isopropyl phenothiazine, 10-tertiary butyl phenothiazine, 10-propyl phenothiazine, levomepromazine, 4595 R.P., prothipendyl, 10-cyclopentyl phenothiazine, methoxypropazine and multergan respectively.

The decreased activity of 10-isopropyl, 10-tertiarybutyl and 10-propyl phenothiazine can be accounted for the presence of 3 carbon atom straight chain. The 4 carbon atom straight side chain present in 10-butyl phenothiazine on branching gives a less potent compound as illustrated by 10-tertiary butyl phenothiazine in Table 2. Between 10-iso-

FIG. 2. Illustrates the effect of 10-butyl phenothiazine in ventricular ectopic tachycardia. One to 10 are excerpts from the electrocardiographic record.

Note the complete suppression of ectopic activity in 4, 5, 6, 7, 8, 9 and 10.

The drug was injected at the arrow in a dose of 3mg/kg.

TABLE 2

Compounds	Dose mg/kg	% reduction in ventricular ectopic rate	Molecular weight	Relative molar activity
Chlorpromazine	3	50	318.46	23.8
10-Propyl phenothiazine	6	50	241	8.8
10-Isopropyl phenothiazine	3	50	241	17.6
10-Tertiary butyl phenothiazine	5	50	255	11.19
10-Butyl phenothiazine	1	50	255	55.9
10-Cyclopentyl phenothiazine	20	50	267	2.9
Prothipendyl	15	50	285	4.17
Methoxypromazine	30	50	314	2.3
Levomepromazine	9	50	328	3
4595 R.P.	10	50	346.46	7.9
Multergan	9	50	410	1

propyl and 10-tertiary butyl phenothiazine, 10-isopropyl is more active because it consists of a less branched side chain and propyl derivative with 3 carbon atom straight chain is still less active than the other two. If the straight chain of 3 carbon atoms (10-propyl phenothiazine) is branched; the activity of the compound is enhanced (10-isopropyl phenothiazine). The increased activity of 10-butyl phenothiazine (without any substitution at position 2) as compared to standard chlorpromazine suggests that the substitution at position 2 is not necessary to effect the ventricular ectopic activity, although it modifies the degree of activity as in case of methoxypromazine. In this compound, the methoxy group occupies the position 2 and the activity of this compound is nearly 1/10 of the chlorpromazine and 1/27 of the butyl derivative. Substitution by nitrogen at position 2 also decreases potency as in case of prothipendyl. A close study of compounds reveal that a side chain containing only carbon atoms enhances the activity. The introduction of amino group in the side chain reduces the activity considerably as observed with prothipendyl, methoxypromazine, levomepromazine, 4595 R.P. and multergan. The activity of these compounds varies in respect to the substitution at position 2 or alteration in the side chain. Out of the five amino derivatives of phenothiazine, levomepromazine and 4595 R.P. exhibit maximum activity. In them position 2 is occupied by OCH_3 and Cl atom respectively. At position 10 a disubstituted (dimethyl) amino group with three C atom chain in between the 'N' atom at position 10 and 'N' atom of amino group and carbon chain is branched at C atom No. 2 either by one methyl group as in levomepromazine and by 2 methyl groups as in 4595 R.P. The other two compounds i.e. prothipendyl and methoxypromazine are less active. The only alteration in the substitution at position 2 accounts for the difference in the activity of two compounds.

The variation in the activities of the compounds, prothipendyl, methoxypromazine, levomepromazine and 4595 R.P. can be explained by B-methyl branching in the side chain among these phenothiazine derivatives. Thus compounds, levomepromazine and 4595 R.P. possessing B-methyl group are more active than the compounds, methoxypromazine and prothipendyl possessing no B-methyl group in the side chain. Multergan although possessing B-methyl group in its structure is least active in ventricular ectopic tachycardia due to the pentavalent ammonium group and methyl sulphonyl group.

Further a 5-carbon atom side chain closed system is also found to be an important factor in the reduction of the activity as shown by 10-cyclopentyl phenothiazine.

SUMMARY

10-N substituted phenothiazine derivatives were examined in ventricular ectopic tachycardia and their structural features responsible for antiarrhythmic activity elicited.

A 4 carbon atom straight side chain is possibly responsible for maximum activity. Next a 4 carbon atom branched chain, although quite active, is less than compounds with 4 carbon atom in a straight side chain. A 3 carbon atom branched chain is more active than the 3 carbon atom straight chain. A 5 carbon atom cyclic ring reduces the activity of the compound. The compounds possessing no substitution at position 2 are more

active. Next in order of potency are those which have OCH_3 or Cl group at position 2. Among amino derivatives compounds possessing B-methyl group in the side chain are more active, the presence of a pentavalent nitrogen atom possessing sulphonyl methyl group in the molecule decreases activity to a marked extent.

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