CARDIOVASCULAR EFFECTS OF SOME PHENOTHIAZINE DERIVATIVES FOLLOWING INTRACORONARY INJECTION IN DOGS

By

K.P. SINGH

Department of Pharmacology and Experimental Therapeutics,
R.N.T. Medical College, Udaipur

The cardiovascular effects of phenothiazine derivatives in general and chlorpromazine in particular are quite complex (4-6, 11, 13, 14, 17) because such drugs produce direct effects on the heart and blood vessels, and also indirect ones through actions on C.N.S. and autonomic reflexes. Hypotension most commonly seen, is primirily due to inhibition of cetrally mediated pressor reflexes, but peripheral adrenergic blockade may also play a role (7). Reflex tachycardia is commonly seen following administration of chlorpromazine because of lowered peripheral resistance and resulting hypotension.

In order to eliminate autonomic and central influences modifying drug effects on cardiovascular system, it was thought of interest to investigate and compare cardiovascular effects of some recently synthesized phenothiazine derivatives following intracoronary injection in dogs.

MATERIALS AND METHODS

The following compounds were studied :—

Chemical Name	*Code Name*
10-3-(Dimethyl amino-propyl)-2-Chlor, Phenothiazine Hydrochloride.	Chlorpromazine
10-Propyl phnothiazine tartrate	10-Propyl phenothiazine
10-Isopropyl phenothiazine tartrate.	10-Isopropyl phenothiazine
10-Tertiarybutyl phenothiazine tartrate	10-Tertiary butyl phenothiazine
10-Butyl phenothiazine tartrate	10-Butyl phenothiazine
10-(3-dimethyl-aminopropyl) Thiophenyl Pyridylamine Hydrochloride	Prothipendyl
10-Cyclopentyl phenothiazine Hydrochloride	10-Cyclopentyl phenothiazine
10-(3-dimethyl-aminopropyl)-2-methoxy phenothiazine dimaleate.	Methoxypromazine
10-(2-methyl, 3-dimethyl aminopropyl)-2-Methoxy phenothiazine hydrochloride.	Levomepromazine

Chemical Name	*Code Name*
10-(3-dimethyl-amino propyl 2-dimethyl) phenothiazine hydrochloride.	4595 R.P.
10-(Isopropyl trimethyl ammonium methyl) phenothiazine sulphate.	Multergan

All the drugs were soluble in distilled water except Methoxypromazine which dissolved on heating. To avoid deterioration, solutions were not kept beyond six days.

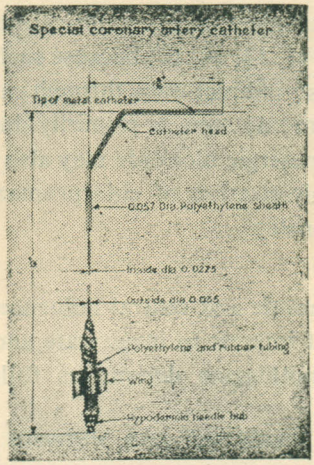

Fig. 1.

Showing the catheter used in the present study for administering drugs in different branches of coronary artery.

Catheterization of coronary artery : The technique of West *et al.* (18) was adopted with slight modification.

The coronary catheter made of stainless steel hypodermic needle (20 Gauze) was used. The tip was curved and covered with a section of soft flexible polythene tubing $2^1/_4$ inch length to prevent puncturing the vessel. The opposite end of the catheter was attached to the hub of the hypodermic needle as shown in Fi.g 1.

Mongrel dogs of both sexes weighing (15.0 to 21.0 Kg.) were anaesthetised with pentobarbitone sodium (30 *mg/kg*) given intravenously. The chest was opened by midsternal thoracotomy under positive pressure artificial respiration and retracted on either side. Pericardium was cut open and sutured to the thoracic wall to expose the heart.

The animal was placed first in left lateral position. The tip of the catheter was introduced into the left carotid artery at the level of the mid neck and was pushed towards the heart. The artery was ligated distally and a loose ligature was tied over the artery with catheter *in situ* to prevent blood leaking from the cut end. The tip of the catheter was advanced just

above the aortic valves. It was then gently turned towards the left and with slight digital manipulation, left coronary osteum was entered. Now the catheter could be passed either in the circumflex or anterior descending branch of the main left coronary artery.

It was more difficult to catheterise the right coronary artery. After the catheter reached the aortic cusps, it was rotated with the tip pointing towards right. It was then brought into the right coronary osteum by slightly lifting the right side of the heart.

Systemic blood pressure was recorded from femoral artery with a mercury manometer. Electrocardiogram was monitored by Grass-inkwriting oscillograph in conventional bipolar lead II. Myocardial contractility was recorded by the suspension method of Jackson (9) in some experiments when injections were made in the anterior descending branch of the left coronary artery.

Each drug was injected in microgram doses in the same animal through the coronary catheter. The volume of the fluid injected with each dose was 0·1 *ml.* As such the effect of each dose was studied on heart rate, rhythm, myocardial contractility, electro-cardiographic pattern and femoral arterial pressure. One drug was tried in one dog and such four experiments were done with each drug.

In order to avoid complexities following insertion of the catheter in all the experiments, care was taken to pull the tip of the catheter out of the lumen of the coronary artery immediately after the injection of the drug.

RESULTS

Control Observations:—In all our experiments, following insertion of the cather in different branches, there was an indication of the coronary insufficiency manifested by changes in T wave and S.T. segment of the electrocardiogram and sudden fall of femoral arterial pressure.

The electrocardiographic changes were of course of a transient nature lasting for half to one minute. Such control observations encountered presently differ with that of West *et al.* (18) who reported no indication of coronary insufficiency either in the electrocardiogram or in the behaviour of the femoral arterial pressure. This possibly could be explained on the basis of the fact that his experiments were done on intact dogs without thoracotomy.

The electrocardiographic effect were observed for 5 mts. by continuous monitoring and during this period effect was found to be exerted on heart rate, P wave, P.Q. interval, QRS complex, S.T. segment and T-wave of the Electrocardiogram. After 5 mts. continuous recording of *E.C.G.*, further records were taken every 5 mts. for half an hour which showed no significant changes.

A. (i) *Effect on E.C.G.* : The electrocardiographic effects following injection in the anterior descending branch of the left coronary artery are summarised in Table I. The effects

TABLE I

Electrocardiographic effects of phenothaizines following injection in the anterior descending branch of the left coronary artery in a dose of 1.0 μg/kg.

Drugs	*Time in min.*	*Heart beats/ min.*	*P*	*P—Q interval*	*QRS*	*ST segment*	*T*
Chlorpromazine	..	137	N	0.10	N	N	N
	1	135	N	0.10	N	N	N
	5	135	N	0.10	N	N	N
10-Propyl phenothiazine	..	173	N	0.08	N	1.8 mm*	IN
	1	160	N	0.08	N	1.5 mm*	IN
	5	210		0.09	Ext. Fib.	Sagging	IN
10-Isopropyl phenothiazine	..	192	N	0.12	N	N	N
	1	198	N	0.12	N	N	Termini lipping
10-Tertiary butyl phenothiazine	..	210	N	0.12	N	N	N
	1	220	N	0.12	N	N	N
	5	225	N	0.08	N	N	N
10-Butyl phenothiazine	..	150	N	0.10	N	N	N
	1	150	N	0.10	N	N	N
	5	141	N	0.10	N	N	N
10-Cyclopentyl phenothiazine	..	176	N	0.16	N	N	N
	1	162	N	0.12	N	N	N
	5	167	N	0.14	N	N	N
Prothipendyl	..	222	N	0.08	N	N	N
	1	225	N	0.08	N	N	N
	5	233	N	0.08	N	N	N
Methoxypromazine	..	198	N	0.12	N	N	N
	1	108	N	0.12	N	1.0 mm*	N
	5	218		0.12	Ext.	3.0 mm*	N
Levomepromazine	..	210	N	0.10	N	N	IN
	1	217	N	0.12	N	N	IN
	5	220	N	0.12	N	N	IN
4595 R.P.	..	215	N	0.08	N	N	Round
	1	210	N	0.08	N	N	,,
	5	202	N	0.08	N	N	,,
Multergan	..	200	N	0.16	N	N	N
	1	215	N	0.16	N	1 mm**	N
	5	235	N	0.02	N	1 mm**	N

**Positive

*Depressed

N Stands for particular component to be normal in all respects.

IN Inverted : Ex-Extrasystoles ; Feb-Ventricular fibrillation.

on the heart rate were variable. The cardiac rhythm became irregular with 10-propyl phenothiazine and methoxypromazine and ultimately resulted in ventricular extra-systoles and fibrillation.

The terminal portion of E.C.G., i.e. the S.T. segment and T wave were adversely affected by certain drugs (Table I); S.T. segment was mainly depressed by 10-propyl phenothiazine and methoxypromazine. A variety of changes influencing the configuration of the T wave in the form of inversion, terminal lipping and rounding of the peak were induced by 10-propyl phenothiazine, levomepromazine, 10-isopropyl phenothiazine and 4595 R.P. respectively. These E.C.G. changes give an indication of direct effect of these drugs on ventricular myocardium. The effect of 10-propyl phenothiazine on electrocardiogram is illustrated in Fig. 2.

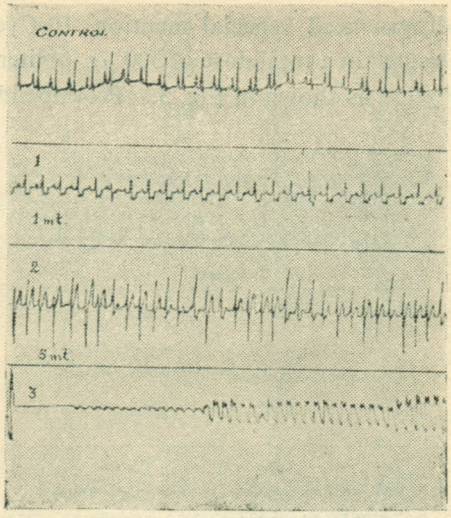

Fig. 2.

Illustrating the effect of 10-*propyl phenothiazine on ventricular complexes of the E.C.G. See notable depression of S.T. segment and T Wave after* 1 *mt. of drug administration. Excerpts* 2 *and* 3 *indicate ventricular extrasystoles and fibrillation.*

(ii) *F.A.P.* (*Femoral arterial pressure*) : Except 10-Cyclopentyl phenothiazine, levomepromazine and 4595 R.P., other drugs produced fall of femoral arterial pressure to the extent of 10-20 mm. Hg. Multergan surprisingly raised femoral arterial pressure by 10-15 mm. Hg.

(iii) *Ventricular contractility* : was decreased by chlorpromazine, 10-propyl phenothiazine, 10-tertiary butyl phenothiazine, 10-butyl phenothiazine, prothipendyl and methoxypromazine in a dosage of 1 $\mu g/kg$. Multergan on the other hand increased it. However, 10-Isopropyl phenothiazine, 10-Cyclopentyl phenothiazine, levomepromazine and 4595 R.P. had no effect in the said dose.

Chlorpromazine in a dose of 1 $\mu g/kg$. decreased F.B.P. (Femoral blood pressure) and ventricular contractility but heart rate and electrocardiographic pattern remained un-affected.

B. (i) *E.C.G.* : The detailed electrocardiographic effects of phenothiazine drugs injected in right coronary artery are given in Table II. Out of eleven phenothiazine derivatives, 10-propyl phenothiazine and 10-Isopropyl phenothiazine produced depression of S.T. segment and inversion of T wave. 10-Tertiary butyl phenothiazine and 10-Cyclopentyl phenothiazine also changed the normal pattern of T wave indicating myocardial hypoxia.

(*ii*) F.A.P. (Femoral arterial pressure) was decreased by 20 mm. of Hg. with prothipendyl and methoxypromazine in a dose of 0.5 $\mu g/kg$. following injection in the right coronary artery.

C. Catheterization and injection of drugs in left circumflex branch.

The effects of two drugs need special mention. 10-Cyclopentyl phenothiazine when injected into left circumflex branch in a total dose of 300 μg. obliterated sino-auricular dominance and produced A.V. nodal rhythm as shown in Fig. 3. Prothipendyl in a dose of 1.5 $\mu g/kg$. had

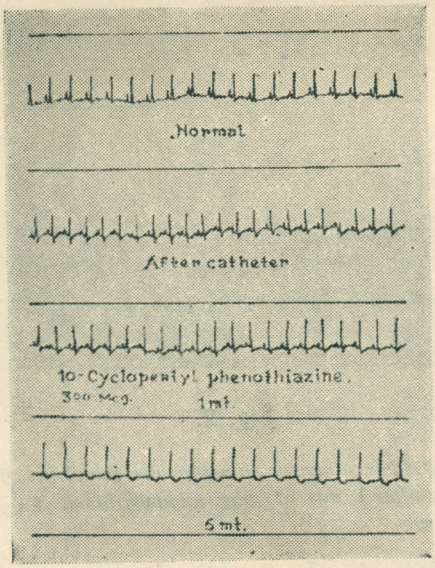

Fig. 3.

Depicts electrocardiographic effect of 10-*Cyclopentyl phenothiazine. The total drug injected into the left circumflex artery was* 300 μg.

Normal E.C.G. lead II.

After catheterization of the left circumflex artery.

One mt. after drug injection.

Shows shift of the pacemaker from S-A rhythm to A-V nodal rhythm after 5 *mts.* (*Characterised by absence of P wave*)

no appreciable effect on the vital segments of the electrocardiogram. However, a dose of 2.5 μg/kg. produced marked rising of R.S.T. segment indicating myocardial damage. This was followed by occasional ventricular extrasystoles.

TABLE II

Electrocardiographic effects following injection in right coronary artery in a dose of 0.5 μg/kg

Drugs	*Time in min.*	*Heart beats/ min.*	*P*	*P—Q interval*	*QRS*	*ST Segment*	*T*
Chlorpromazine	..	185	N	0.14	N	N	N
	1	190	N	0.14	N	N	N
	5	200	N	0.12	N	N	N
10-Propyl phenothiazine	..	173	N	0.08	N	0.5 mm*	IN
	1	153	N	0.08	N	2.0 mm*	IN
	5	160	N	0.04	Ext.Fib.	4.0 mm*	IN
10-Isopropyl phenothiazine	..	130	N	0.10	N	1.0 mm*	IN
	1	128	N	0.08	N	2.0 mm*	IN
	5	148	N	0.08	N	2.0 mm*	IN
10-Tertiary butyl phenothiazine	..	190	N	0.12	N	N	Round summit
	1	190	N	0.12	N	N	,,
	5	190	N	0.12	N	N	,,
10-Butyl phenothiazine	..	144	N	0.16	N	N	N
	1	138	N	0.16	N	N	N
	5	150	N	0.16	N	N	N
10-Cyclopentyl phenothiazine	..	144	N	0.16	N	N	N
	1	155	N	0.12	N	N	IN
	5	160	N	0.12	N	N	IN
Prothipendyl;	..	196	N	0.14	N	N	N
	1	190	N	0.16	N	N	N
	5	186	N	0.14	N	N	N
Methoxypromazine	..	192	N	0.10	N	N	N
	1	180	N	0.12	N	N	N
	5	180	N	0.12	N	N	N
Levomepromazine	..	218	N	0.12	N	N	N
	1	210	N	0.10	N	N	N
	5	206	N	0.12	N	N	N
4595 R.P.	..	160	N	0.14	N	N	N
	1	170	N	0.14	N	N	N
	5	170	N	0.14	N	N	N
Multergan	..	200	N	0.10	N	N	N
	1	245	N	0.08	N	N	N
	5	250	4 mm**	0.08	N	N	N

**Positive

*Depressed

N Stands for particular component to be normal in all respects.

IN Inverted; Ext.-Extrasystoles; Fib-Ventricular fibrillation.

Discussion

Moyer *et al.* (12) reported flattening of the T wave following chlorpromazine administration to anaesthetised dogs. Marked T wave changes were also noted following the administration of chlorpromazine in dogs under similar conditions (11). The results obtained in the present study give an indication of the fact that some of the 10-n substituted phenothiazine derivatives when injected in microgram doses produced electrocardiographic changes on T waves, ST segment and QRS complex. The effects were pronouncely observed with 10-propyl phenothiazine, 10-Cyclopentyl phenothiazine, methoxypromazine, levomepromazine, 4595 R.P. and multergan as summarised in the text Table I and II.

This shows that besides chlorpromazine other phenothiazine derivatives have a propensity of producing electrocardiographic changes due to their direct myocardial effects. These changes can well be compared with those produced by the administration of quinidine (3). Further, electrocardiographic changes reported earlier (2, 8) in patients on thioridazine, fluphenazine and trifluoperazine are in consonance with the present observations. The E.C.G. changes produced by these drugs were reversible.

Femoral arterial pressure and ventricular contractility were decreased by 10-propyl phenothiazine, 10-tertiarybutyl phenothiazine, 10-butyl phenothiazine and prothipendyl following injection in the anterior descending branch of the left coronary artery.

This decreased in femoral arterial pressure observed under present experimental conditions can be attributed to the negative inotropic effect of these drugs. 10-Isopropyl phenothiazine on the other hand produced hypotensive response without affecting ventricular contractility. Unlike other drugs, multergan raised F.A.P. (Femoral arterial pressure) which can be explained on the basis of its positive inotropic effect.

The method of intracoronary injection has the advantage of application of drugs directly to the pace-makers, myocardium and conducting tissues. It permits the injection of drugs into the individual coronary branches in doses too small to have generalised effects but large enough to produce localised responses as revealed by electrocardiographic monitoring.

On the basis of these findings, it will not be inappropriate to mention that electrocardiograms of chronically phychotic patients receiving prolonged or high doses of phenothiazine derivatives should be recorded from time to time for detection of any abnormality.

Summary

Intracoronary injection of 10-n substituted phenothiazine derivatives in anaesthetised dogs reveal the following.

1. Control observations give no indication of coronary insufficiency.
2. 10-Propyl phenothiazine and methoxypromazine changed the normal pattern of

cardiac rhythm which ultimately resulted in ventricular extrasystoles and fibrillation when injected in the anterior descending branch of the left coronary artery. Terminal position of S.T. segment and T wave were adversely affected by some drugs.

3. Femoral arterial pressure was maximally decreased by prothipendyl when injected both in anterior descending branch and right coronary artery.

4. 10-Cyclopentyl phenothiazine produced A-V nodal rhythm after injection in the left circumflex branch.

ACKNOWLEDGEMENTS

Grateful acknowledgements are made to the Director, Medical Research Department, Rhone Polu-lence, Paris and Averst Laboratories, U.S.A. for generous supply of compounds.

REFERENCES

1. Ban, T.A. and A. St. Jean. The effect of phenothiazine on the electrocardiogram. *Canad. M.A.J.*, **91**:537, 1964.

2. Ban, T.A. and A. St. Jean. Electrocardiographic cnanges induced by phenothiazine drugs *Am.H.J.*, **70**:575, 1965.

3. Ballet, S. Clinical Disorders of the Beat. Lea. and Febiger; **2**:869, 1968.

4. Courvoisier, S., J. Fournel, R. Ducrot, M. Kolsky and P. Koctschet. Properties pharmacodynamiques due chlorhydrate de-Chloro-3 (Dimethyl amino-3-propyl)-10 phenothiazine (4560 R.P.) etude experimental dun non veau corps utilise dans. 1. Anaesthese. Potentialise et daus, 1 'hibernation artificielle.' *Arch.Int.Pharmacodyn.*, **92**:305, 1953.

5. Dobkin, A.B., R.G.B. Gilbert and K.I. Melville. Chlorpromazine : Review and investigation as a premedicant in anaethesia. *Anaesthesiology.*, **17**:135, 1956.

6. Foltz, E.L. Cardiovascular observations following use of Dibenzylene and chlorpromazine singly and in combination. *Fed.Proc.*, **14**:339, 1955.

7. Goodman, L.S. and A. Gilman. The Pharmacological basis of Therapeutics, The MacMillan Company, New York, 3rd Ed. P. 170, 1955.

8. Hassert, Jun. G.L., A.E. Peterson and J.C. Burke. Comparision of T-wave changes in the dog following intravenous administration of chlorpromazine and Fluphenazine. *Nature.*, **207**:765, 1965.

9. Jackson, D.E. Experimentsl Pharmacology and Materia Medica. C.V. Mosby & Co., London., **2**:285, 1938.

10. Kelly, H.G., J E. Fay and S G Laverty. Thioridazine Hydrochloride (Mellaril) : Its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. *Canad. M.A.J.*, **89**:546, 1963

11 Melville, K.I. Studies on the cardiovascular action of Chlorpromazine 1. Antiadrenergic and antifibrillatory actions. *Arch.Int.Pharmacodyn.*, **115**:278, 1958.

12. Moyer, J.H., B. Kent, R. Knight, G. Morris, R. Huggins and C.A. Handley. Laboratory and clinical observations on chlorpromazine (SKF-2601-A)-Hemodynamic and toxicological studies. *Am.J.M.Sc.*, **227**:283, 1954.

13. Sato, T. and Y. Tanabe. The antiarrhythmic action of phenothiazine dervivatives. *Jap. Circul.J.*, **26**:216, 1962.

14. Sharma, P.L. and R.B. Arora. Antiarrhythmics Part XII Antiarrhythmic activity of some phenothiazine derivatives in experimental cardiac arrhythmias. *Ind.Jour.Med.Res.*, **49**: 1099, 1961.

15. Sharma, V.N. and Vijai Singh. Cardiovascular action of two thiophenyl pyridylamine. *Ind.Jour.Med.Res.*, **53**:545, 1965.

16. Singh, K.P., V.N. Sharma and D.S. Rathore. Pharmacological actions of some recently syntehesized phenothiazine derivatives. *Ind.Jour.Med.Res.*, **55**:889, 1967.

17. Stone, G.C., B.M. Bernstein, W.E. Hambourger and V.A. Drill. Behavioral and pharmacological studies of Thiopropazate, A potent tranquilizing agent. *Arch.Int.Pharmacodyn.*, **127**:85, 1960.

18. West, J.W., T. Kobayashi and S.V. Guzman. Coronary artery catheterization in the intact dog. *Circulation Res.*, **6**:383, 1958.