Effects of Phenothiazine and Propranolol on ECG

The Effects of Propranolol on the Electrocardiographic Abnormalities Induced by Phenothiazine Derivatives

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The effect of propranolol on some ECG abnormalities induced by different kinds of the phenothiazine was investigated in 5 psychiatric patients. The ECG changes such as sinus tachycardia, depression of ST-segment and flattening of T-wave could be reverted toward normal with propranolol. This suggests that the drug is effective in preventing such undesirable effect of the phenothiazine on the heart. Theoretical importance of the favorable action of propranolol on these abnormal ECG's was discussed.

KELLY et al.¹ first described striking T-wave abnormalities and two fatal cases of ventricular tachycardia associated with complete A-V dissociation in a series of patients who were taking thioridazine. These observations were later extended by other investigators,²⁻⁴ who found similar electrocardiographic changes in psychotic patients receiving thioridazine or other drugs of the phenothiazine group.

In the preliminary papers,⁵⁻⁶ the authors reported that various somatic complaints and electrocardiographic abnormalities induced by the phenothiazines were able to be treated with the concurrent administration of the adrenergic β -receptor blocking agent, propranolol.⁷

Further investigations were undertaken to ascertain some desirable effects of propranolol on the electrocardiographic abnormalities, with special reference to ST-component and T-wave changes which were induced by the phenothiazines.

MATERIAL AND METHODS

Five patients, 2 males and 3 females, age range 26 to 43 years, were randomly selected from the psychotic patients who were admitted to the psychiatric division of Fukuma Hospital in Fukuoka Prefecture. A common electrocardiographic

feature was deformed T-wave with sinus tachycardia. In each case the presence of organic heart diseases was excluded on the basis of a detailed medical history, physical examination, and radiological studies of the chest.

The phenothiazines used in this study were as follows: chlorpromazine, levomepromazine, fluphenazine, and chlorprothixine. Each was administered orally at moderate to fairly high dosage; some patients received two or three derivatives of phenothiazine. To examine the effect of β -receptor-blockade on markedly deformed T-wave produced by the phenothiazines, propranolol was given orally in dosage of 30 to 40 mg daily; in one patient (Fig. 8), 2 mg of the drug were also used intravenously. In every case, the phenothiazine was continued uninterruptedly during the period of administration of propranolol.

The routine ECG, blood pressure, serum potassium level and reaction to eyeball pressure were examined and compared before and after administration of propranolol.

REPORT OF CASES

Case 1 (Fig. 1 and 2)—A 26-year-old man (J. T.) was admitted to the hospital in May 1965 because of delusions of reference and persecution. A diagnosis of acute schizophrenia was made. In

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CASE J.T. 26 yrs. (M)

Fig. 1. A series of ECG's (top to bottom) illustrating gradual return to normal T-wave when a daily dosage of levomepromazine was gradually reduced from 600 mg to 150 mg.

September 1965 the patient was treated with 100 mg of levomepromazine daily; this dosage was increased to 600 mg over the next three months, and thereafter gradually decreased.

Electrocardiographic changes during the latter 8 months when the drug was gradually reduced from maximal dosage (600 mg) to a maintenance level (150 mg) are shown in Fig. 1. The ECG during the administration of maximal dosage (uppermost trace in Fig. 1) showed a sinus tachycardia of 115 beats per minute as well as definitely lowered bifid T-waves. These findings were gradually eliminated by decrease in dosage of the drug (top to bottom in Fig. 1), i.e., the height of T-wave is inversely proportional to the daily dosage of the drug. The ECG during the administration of maintenance dosage (150 mg) reveals almost normal T-wave deflections (lowermost trace in Fig. 1).

Fig. 2 indicates T-wave changes in lead V₄ of the same patient by the use of propranolol during other courses of phenothiazine treatment in July 1966. Fig. 2A, which shows typical electrocardiographic changes due to phenothiazine, was recorded during administration of levomepromazine 250 mg in combination with fluphenazine 6 mg per day. This also shows a sinus tachycardia of 100 beats per minute and impressively lowered

J. T. 26 yrs. (M): V₄

Fig. 2. A typical electrocardiographic abnormality induced by the phenothiazine (A) and its restoration to normal by propranolol (B).

A: Lead V₄ while the patient J. T. was receiving levomepromazine 250 mg and fluphenazine 6 mg a day. B: 12 days after administration of propranolol 30 mg a day; the phenothiazine was continued. Note a drastic improvement of T-deflection associated with prolonged R-R interval.

CASE H.F. 43 yrs. (M)

Fig.3. Left column: ECG on admission without treatment. Middle: Changes produced by a combined administration of chlorpromazine 100 mg, levomepromazine 100 mg and chlorprothixine 100 mg a day. Right: 7 days after concurrent administration of propranolol 30 mg a day with these phenothiazines.

bifid T-waves that resembled lead V₄ registered during treatment with levomepromazine 600 mg (uppermost trace in Fig. 1).

On the other hand, Fig. 2B was recorded after 12 days of propranolol administration, 30 mg a day; levomepromazine and fluphenazine were

prescribed in the same dosage as in Fig. 2A. Here, the heart rate became slower and prominent and normal-shaped T-waves developed. In addition, no significant change in blood pressure was registered before and after administration of propranolol.

CASE Y.S. 40 yrs. (F)

Fig. 4. A review of ECG's taken during administration of chlorpromazine 150 mg daily (left column), without any drug (2nd column), during resumption of chlorpromazine 150 mg (3rd column), and during combined administration of propranolol 30 mg daily with chlorpromazine 150 mg (right column). Note a preventive effect of propranolol against the chlorpromazine-induced deterioration of T-wave.

Hence it is apparent that T-wave abnormalities induced by phenothiazine can be reversed by the application of the β -receptor blocking drug, propranolol, even if the phenothiazine is continued.

Case 2 (Fig. 3)—A 43-year-old male (H. F.) was

admitted to hospital with a diagnosis of manic depressive psychosis in December 1966. The ECG on admission (left column in Fig. 3) showed completely normal features with prominent T-waves followed by inconspicuous U-waves especially in

CASE E.O. 35 yrs. (F)

Fig. 5. Electrocardiographic changes produced by administration of chlorpromazine 200 mg and fluphenazine 6 mg daily (left column) and its modification by propranolol 30 mg a day (2nd and 3rd columns). The right two columns were registered in this sequence after interruption of propranolol; the phenothiazine was continued. They show gradual restoration to the control ECG (left column).

the chest lead.

In six months after combined application of the phenothiazine, i.e., chlorpromazine 100 mg, levomepromazine 100 mg, chlorprothixine 100 mg daily, the ECG findings changed to a sinus tachycardia of 100 beats per minute with lowering of T-deflection in every lead. (see middle column on Fig. 3).

Immediately after this observation propranolol was prescribed in a dosage of 30 mg daily and maintained for 7 days with the phenothiazine. The ECG was then registered again and is shown in the right hand column of Fig. 3. It is evident that the tachycardia was eliminated and the deflection of the T-waves sharply increased comparably to the control (left column). In other words propranolol eliminated absolutely an un-

desirable effect of phenothiazine on the ECG.

Case 3 (Fig. 4)—A 40-year-old woman (Y. S.) was admitted to the hospital in 1964 because of increasingly bizarre behaviour. A diagnosis of chronic schizophrenia was made. During her 4 years of hospitalization chlorpromazine in a daily dosage of 100 to 300 mg was administered intermittently.

Fig. 4 shows a review of ECG's during about 1 year from July 1966 to August 1967. The left column was taken during administration of chlorpromazine 150 mg daily. It reveals a concave depression of ST-segments followed by low T-waves in leads II, V₄, V₅ and V₆. This pattern of ST-T changes is remarkably similar to that seen in the ECG's of the patients with sclerotic heart disease. The ECG in the 2nd column was taken

Fig. 6. Electrocardiographic changes (left to right) registered for about 10 months while levomepromazine treatment was begun and gradually increased to 1300 mg per day and tapered off.

about one month after the cessation of chlorpromazine. Abnormalities in the ST-T segments as well as a sinus tachycardia had almost disappeared.

Resumption of chlorpromazine, 150 mg again produced ST-depression and T-flatness accompanied with a sinus tachycardia as presented in the 3rd column, which was registered in 2 months after resumption.

The ECG in the right column was taken during administration of propranolol (30 mg a day)

while chlorpromazine was continued uninterrupted at a daily dosage of 150 mg. In this record, abnormal findings induced by chlorpromazine, for example sagging of ST-segments, lowering of T-waves and sinus tachycardia, were abolished by propranolol despite of continuous administration of chlorpromazine.

Case 4 (Fig. 5)—A 35-year-old woman (E. O.) was admitted to hospital with a diagnosis of acute schizophrenia because of auditory hallucinations, delusions and behaviour disorders in 1956.

During her 8 years of hospitalization she received various kinds of treatment—insulin shock, electric shock, psychotherapy as well as psychotropic drug therapy.

The ECGs in Fig. 5 were recorded between February 1968 and June 1968 when the patient was taking two phenothiazine derivatives, chlorpromazine 200 mg and fluphenazine 6 mg a day. In the left hand column the (control) ECG shows the characteristic changes of T-waves due to the phenothiazine, that is to say slightly lowered T-deflections with T-P fusions and a sinus tachycardia.

The 2nd and 3rd columns were registered while she was receiving propranolol 30 mg a day in addition to the phenothiazine for 7 days and 14 days respectively. Here the T-wave abnormalities mentioned above were eliminated.

The right two columns were recorded again 20 and 55 days after administration of propranolol had been stopped while the phenothiazine was still continued. The T-wave abnormalities and

tachycardia had reappeared.

No significant alteration in blood pressure or in the serum level of potassium were observed during the whole course of treatment. The values are given below in Fig. 5.

Case 5 (Fig. 6, 7 and 8)—a 27-year-old woman (N. K.) was admitted to hospital because of a severe attack of anxiety due to olfactory hallucinations in February 1968. Regardless of her emotional instability, ECG's taken on admission showed normal tracings, that is ordinary sinus rhythm and prominent T-deflections in almost all leads (left-hand column in Fig. 6). In the chest lead U-waves of normal amplitude were also present.

Because of severe anxiety, levomepromazine treatment (200 mg a day) was started in March 1968, and gradually increased to 1300 mg a day, then decreased to 100 mg and finally discontinued. Fig. 6 shows a review of ECG's during the course of this treatment.

It is apparent from this figure that the heart rate per minute increased almost proportionately to the daily dosage of levomepromazine; on the other hand the height of T-waves in every lead decreased. In some traces, the summit of the T-waves seemed flat with a somewhat bifid appearance. At the maximal dosage, 1300 mg of levomepromazine, the T-waves in V_5 and V_6 become almost straight. Terminal T-wave inversion is also seen in V_2 , V_3 and V_4 . One or two weeks after interruption of the drug, however, the T-waves attained a normal height and contour with ordinary sinus rhythm and consequently revealed an entirely normal appearance as shown in the right-hand column in this figure. In this patient the blood pressure increased slightly when the dosage was increased; the change in values is illustrated below in Fig. 6.

During administration of maximal dosage of levomepromazine, 1300 mg, propranolol in a daily dosage of 40 mg was prescribed in addition. Fig. 7 indicates the electrocardiographic changes in these circumstances, i.e., before (control) and after administration of propranolol. Flat and terminally inverted T-waves have changed to upward and prominent ones after propranolol had been given for 7 days (right in Fig. 7).

The level of potassium in the blood 4.6 mEq/L before, and 4.9 mEq/L after the propranolol administration were both within normal limits. Hence it is possible that the change in potassium level may play little part in the improvement of T-deflection by propranolol.

Fig. 7. T-wave abnormalities of the patient N. K. induced by levomepromazine in a daily dosage of 1300 mg (left column) and its modification by a concurrent administration of propranolol 40 mg daily for 7 days (right column).

CASE N. K. 27 yrs. (F) : V5

Fig. 8. Effects of slowing the heart rate on the amplitude of T-deflection in the patient N. K. Slowing of the rate was made by eyeball pressure (top trace), intravenous injection (middle trace) and oral administration (bottom trace) of propranolol. Note that no improvement in T-deflection occurred with eyeball pressure; on the contrary, salient upward T-wave appeared with application of propranolol either intravenously or orally.

Further in Fig. 8, the effect of eyeball pressure and intravenous injection of 2 mg of propranolol on T-wave deformities induced by long-term administration of levomepromazine were examined and compared with the effect of oral propranolol in the same patient.

As shown in the top trace of Fig. 8, eyeball pressure induced significant slowing of the heart rate, but could not improve the depressed T-waves. On the other hand, intravenously applied propranolol brought about a considerable improvement in T-deflection as well as slowing of the rate (middle trace in Fig. 8). The improvement of T-deflection attained by intravenous injection of propranolol was comparable with that attained by oral administration of the same drug (bottom trace in Fig. 8).

DISCUSSION

Recently much attention has been focussed on the electrocardiographic effect of the phenothiazines, especially thioridazine and chlorpromazine.^{1-6,8-11}

It has been demonstrated that the phenothiazine and, to a lesser extent, chlorpromazine can produce the following: prolongation of the P-Q interval and the Q-T interval; rounding, notching, or splitting of the T-wave; lengthening of the QRS complex; depression of the ST segment;

splintering of the R wave, ventricular and atrial tachycardia; bigeminal rhythm; atrial premature beats; ventricular fibrillation; and variable degree of heart block.¹² Similar phenothiazine effects (nonspecific repolarization defects) have also been demonstrated in experimental animals.^{8,11}

Firstly, in this paper, the phenothiazine effect on ECG's has been reported in 5 patients receiving levomepromazine, chlorpromazine, fluphenazine and chlorprothixine. The repolarization changes and the shortening of the R-R interval in the ECG can be produced by the phenothiazines and are not artefacts because previously normal ECG's of nonmedicated patients can be altered by the administration of the phenothiazine and they can revert to normal within a week or so after the drugs are stopped or reduced (Fig. 1, 3, 4 and 6).

Secondly, the investigation has shown that if the patients exhibiting the phenothiazine induced abnormality in ECG were given either oral or intravenous propranolol, a specific β -receptor blocking agent according to pharmacological investigations performed by BLACK et al.⁷ in 1964, the electrocardiographic abnormalities were also blocked and the ECG's became normal in appearance.

Since this normalization occurred concurrently with a reduction in the heart rate it is necessary

to reconsider the assumption made by SJÖSTRAND that the changes in rate per se caused the changes in the ECG.¹³ This probability may be ruled out by the facts that the phenothiazine induced T-wave abnormalities still remained although the heart rate was reduced by eyeball pressure (Ashner's test) (Fig. 8), and that the degree of normalization of the T-waves due to propranolol seemed too conspicuous or drastic to ascribe the improvement to a decreased heart rate alone.

The action of the phenothiazine on the cardiovascular system is complex because the drug produces direct effects on the heart and blood vessels, and also indirect ones through an action on the central nervous system and autonomic reflexes. The cause of the phenothiazine-induced tachycardia is considered as to be the hypotension, which is primarily due to inhibition of centrally mediated pressor reflexes, and partly due to slight atropine-like action, peripheral adrenergic α -receptor blocking action and direct depressant action on the heart.¹⁴

Moreover, another site of action of the phenothiazine has been demonstrated in the medullary portion of the adrenal.¹² As VON EULER and others have shown for reserpine, it is now clear that chlorpromazine and other phenothiazines have the ability to effect a biphasic action on the secretion of catecholamines from the adrenal.¹⁵

In cases of long term administration reported here (Fig. 5 and 6), however, tolerance seemed to develop to the phenothiazines' hypotensive effect. Especially in case N. K. (Fig. 6), the heart rate was progressively increased by increasing daily dosage of levomepromazine, while the blood pressure value was not reduced but somewhat elevated. Therefore, hypotension is not considered to be an important cause of phenothiazine-induced tachycardias in these cases.

The atropine-like action of the drug¹⁴ may not play a significant role in producing tachycardia, because eyeball pressure intended to enhance vagal tone caused marked slowing of the heart (Fig. 8). Furthermore there was no obvious abnormality in serum electrolytes to explain observed electrocardiographic changes, particularly flattening or splintering of T-wave, which resembled to some extent the T-wave change induced by hypopotassemia. This has been reported by other investigators.²

Thus the most likely explanation for the phenothiazine-induced electrocardiographic changes seems to be a direct effect upon the

myocardium. Moreover this effect may also be due to stimulation of the autonomic nervous system by the drug, thus secondarily affecting heart rate and ventricular repolarization.¹⁶ In these respects it is very interesting that reserpine, amphetamine, imipramine and chlorpromazine should all markedly reduce the uptake of circulating H³-norepinephrine by several tissues as well as heart muscle and elevated the plasma concentration of the H³-catecholamine.¹⁷

The authors propose that the interrelationship between the phenothiazines and the sympathetic system including cardiac β -receptors may be significant, because severe electrocardiographic abnormalities have been drastically abolished by short term administration of the β -blocker, propranolol, probably due to its direct blocking action of β -receptors at the myocardial site. A similar result has been obtained by NORDENFELT,¹⁸ that is, orthostatic changes in ECG such as depressed T-waves and increased heart rate, which might be due to the increased sympathetic tone inherent in the standing position, were reported to disappear after injection of propranolol.

An alternative explanation is that propranolol may have a direct effect on the central nervous system tending to correct electrocardiographic abnormalities. LESZKOVSKY and TARDOS¹⁹ reported sedative and anticonvulsant properties of propranolol in rats and mice, but only in doses far larger (100 mg/kg or more) than those used in the present investigation. Moreover, GRANVILLE-GROSSMAN and TURNER²⁰ stated that propranolol 20 mg q.d.s. was found to be more effective than placebo in the treatment of anxiety.

Since propranolol definitely eliminates T-wave abnormalities as well as tachycardias induced by the phenothiazines it is suggested that propranolol has an important role in distinguishing the functional or transient T-wave abnormalities due to the phenothiazine from the other so-called primary T-wave changes due to organic myocardial damage among psychiatric patients who are receiving a considerable dosage of phenothiazines. T-wave abnormalities due both to the phenothiazines and sclerotic heart disease could not be corrected at all by the administration of propranolol as previously described.^{5,6}

In addition propranolol may possibly be useful in preventing myocardial degeneration and fatal arrhythmias which have been reported^{1-3,12} as associated with large doses of the phenothia-

zine drugs.

SUMMARY

Six cases of the phenothiazine (chlorpromazine, levomepromazine, fluphenazine, chlorpromazine)-induced electrocardiographic abnormalities are presented. T-waves were flattened, broadened, notched, and inverted in many leads, and sinus tachycardia was also recognized. These changes reverted to normal in a week or so after concurrent administration of a β -blocker, propranolol (30–40 mg per day) or immediately after an intravenous injection of the drug (2 mg). Both blood pressure and potassium level of the serum were within normal limits throughout. Some possible mechanisms explaining favourable effects of propranolol on the phenothiazine-induced electrocardiographic abnormalities are discussed.

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