ECG Findings on Administration of Neuroleptics

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(Received April 10, 1977)

INTRODUCTION

In pushing ahead with treatment that makes use of neuroleptics or psychotropic drugs such as phenothiazine, butyrophenone and antidepressants mainly of the tricyclic group, the doctor can by no means make light of the powerful influence that these drugs , an exert on the cardio-vascular system.

Among the untoward side-effects of these drugs, certainly the most serious is "sudden death" which can sometimes be identified on ECG as serious arrhythemia or a block.

Recently, among patients who were taking so-called psychotropic drugs or neuroleptics we conducted an investigation with respect to age, sex, the duration of medication and the kinds of medication, for possible ECG abnormalities. The results are reported here.

SUJECTS AND METHODS

346 patients of the Psychiatry Ward of Kitsunan Hospital who were already receiving administration of psychotropic drugs were selected as subjects for our investigation. A study was made comparing the ECG records taken during November or December of 1976 with ECG records taken on admission or those taken one year prior to the present investigation.

If any changes in ECG were found, a check was made of atrial fibrillation, bundle branch block, ST changes, T changes, PQ prolongation, pulmonary P, mitral P, tachycardia and bradycardia.

The electrocardiograph used in this investigation was a Fukuda Denshi Model SCC-2.

RESULTS

1) Incidence of ECG abnormalities

As indicated in Table 1, 203 of the 346 subjects, or 58.7 per cent showed ECG findings that were abnormal in form or another.

120 (55.8%) of 215 male cases and 83 (63.3%) of 131 female cases showed abnormal ECG findings. There was an unusually high incidence of abnormalities in both males and females, but the incidence was slightly higher in females (Table 1).

Table 1. The number of subjects and sexratio

Sex	No. of Subjects	No. of ECG Abnormal(%)
M.	215	120 (55.8)
F.	131	83 (63.3)
Total	346	203 (58.7)

Table 2. Composition by age

Age	No. of Subjects	No. of ECG Abnormal(%)
-19	6	5 (83.3)
20-29	75	62 (82.7)
30-39	98	48 (49.0)
40-49	90	45 (50.0)
50-59	41	19 (46.3)
60-69	27	17 (62.9)
70-	9	7 (77.8)
Total	346	203 (58.7)

2) ECG abnormalities and age disribution

With regard to the relationship between age and the appearance of abnormal findings, abnormalities in one form or another were observed in 5 (83.3%) out of 6 patients under twenty years of age, 62 (82.7%) out of 75 patients in their twenties, 48 (49.0%) out of 98 patients in their thirties, 45 (50.0%) out of 90 patients in their forties, 19 (46.3%) out of 41 patients in their fifties, 17 (62.9%) out of 27 patients in their sixties and 7 (77.8%) out of 9 patients in their 70s or over as shown in Table 2.

Table 3. Classification by diseases

Diagnosis (psychiatric)	No. of subjects	No. of ECG Abnormal(%)
Schizophrenia	249	137 (55.0)
Senile Psychoses	30	24 (80.0)
Affective Disorders	13	13 (100.0)
Mental Subnormality	19	12 (63.2)
Epilepsy	10	3 (33.3)
Chronic Alcoholism	5	1 (20.0)
Others	20	13 (65.0)
Total	346	203 (58.7)

Table 4. ECG findings and period of administration of psychotropic drugs

ECG Findings	Period of Drug Administration (Year)				Total
	-1	2-5	6-9	10-	
Atrial Fibrillation	0	0	0	3	3
Bundle Branch Block					
incomplete	4	3	7	6	20
complete	0	0	2	2	4
ST-Changes	10	6	5	3	24
+Premature Beat	1	0	0	1	2
T-Changes	3	11	16	22	52
+AV Block	3	2	0	2	7
+PQ Prolongation	2	0	0	2	4
+ST Low	3	11	9	4	27
+Mitral P	0	1	0	0	1
+Tachycardia	8	4	6	2	20
+U Wave	3	5	4	1	13
PQ Prolongation	0	0	1	1	2
Pulmonray P	0	0	0	1	1
+PQ Prolongation	1	0	0	0	1
+Tachycardia	3	0	0	0	3
Mitral P	1	0	0	0	1
+Tachycardia	1	0	0	0	1
Tachycardia	10	4	0	0	14
Bradycardia	1	1	0	1	3
Total (%)	54 (56.8)	48 (51.1)	50 (78.1)	51 (54.8)	203 (58.7)
No. of Subjects	95	94	64	93	346

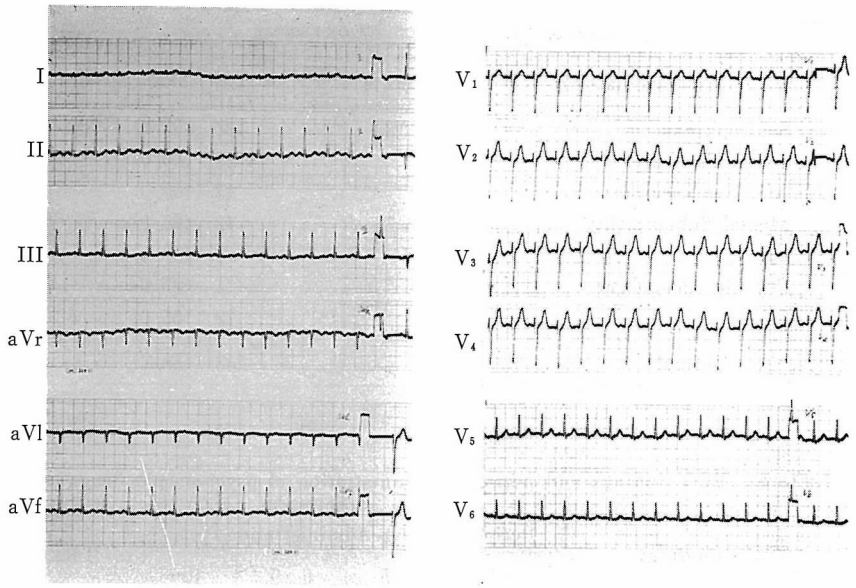

Fig. 1 25 years old Male
Sinus tachycardia, heart rate 130/min. On oral administration of haloperidol 9mg/day

Fig. 2 54 years old Male
Atrial fibrillation. On oral administration of clocapramine 150mg/day

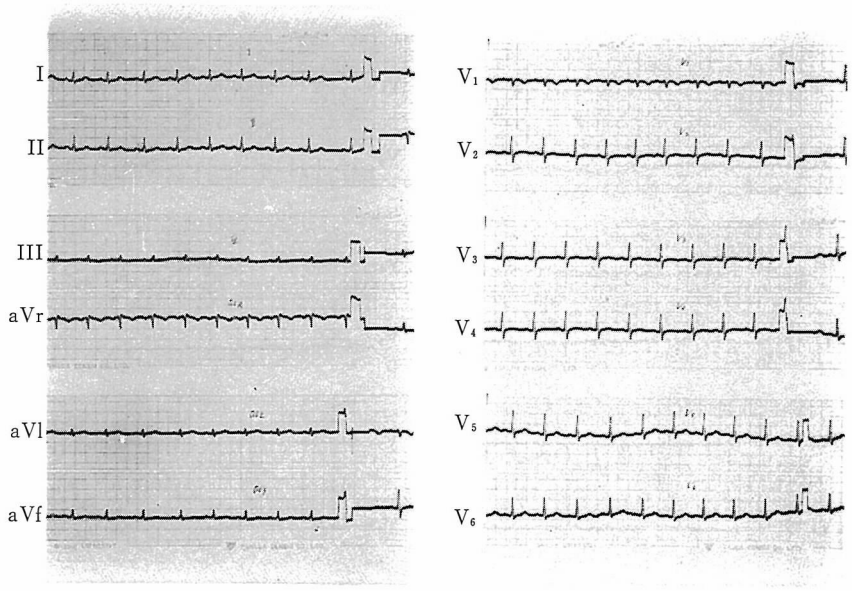

Fig. 3 20 years old Female
ST depression observed in leads V_{5-6}. On oral administration of pericyazine 60mg/day

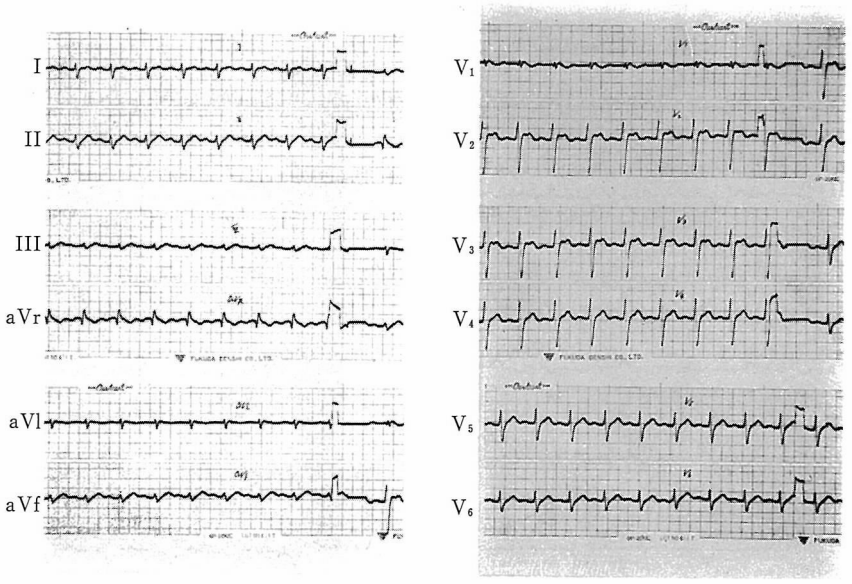

Fig. 4 42 years old Male
Complete RBBB. On adminlstration of chlorpromazine 75mg/day

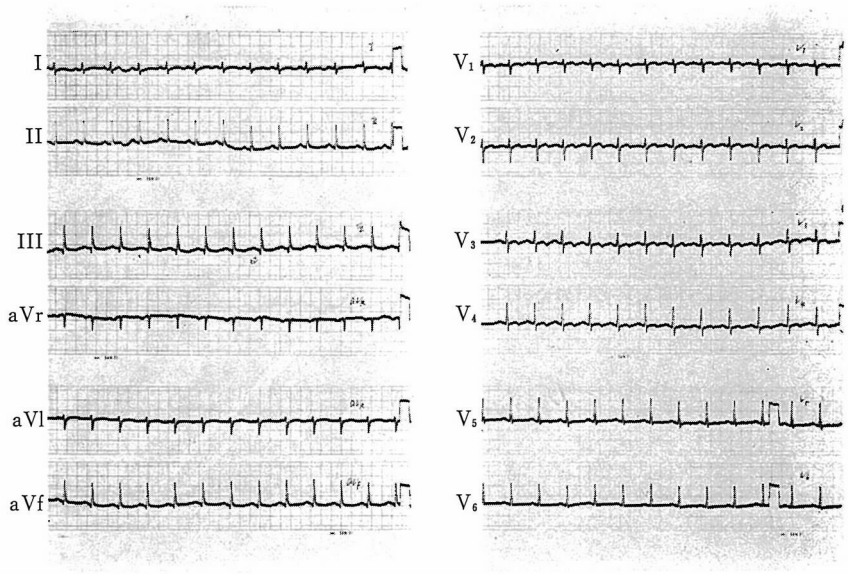

Fig. 5 32 years old Female

ST depression in leads V_{5-6} and appearance of diphasic T wave. On oral administration of thioridazine 150mg/day

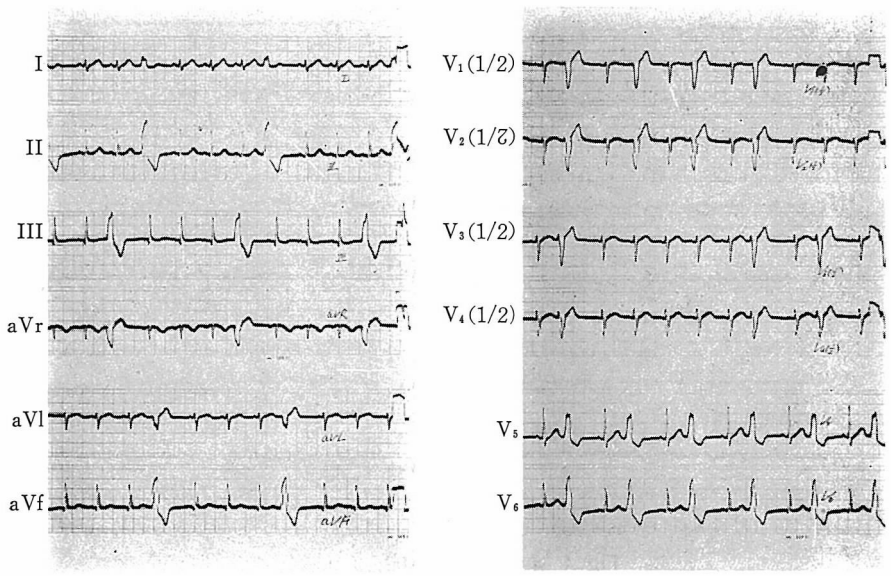

Fig. 6 26 years old Male

Bigeminal pulse and trigeminal pulse. On oral administration of clocapramine 75mg/day

3) Distribution of ECG abnormalities by diesease

When the patients were classified by disease, as shown in Tabel 3, ECG abnormalities were found in 137 out of 249 cases of schizophrenia, 24 out of 30 cases of senile psychoses, 13 out of 13 cases of affective disorders, 12 out of 19 cases of mental subnormality, 3 out of 10 cases of epilepsy, 1 out of 5 cases of chronic alocoholism and 13 cases of abnormalities were found in various disorders. It is worth noting that all patients suffering from affective disorders showed abnormal ECG findings in one form or another.

4) Changes in ECG

With respect to changes in ECG, ST and T changes accounted for a considerable percentage of the total; in particular, T changes was associated with AV block, PQ time prolongation, ST depression and tachycardia in many cases. Also, U wave was seen in association with T changes in some cases, as shown in Table 4.

In addition, bundle branch block, especially incomplete BBB was noted in many cases.

Tachycardia was also one of the abnormalities which was often observed. For our purposes a heart rate of over 110 beats per minute was dicided upon as the standard for tachycardia.

The ECG abnormal findings mentioned above are shown in Figs. 1 to 6.

5) Relationship between ECG findings, duration of medication and age of patients.

ECG findings were classified with reference to the period of administration of psychotropic drugs by dividing the patients into four groups, depending upon the length of time that they had received medication: under 1 year, 2 to 5 years, 6 to 9 years and over 10 years. No especially significant differences were observed between the groups, although somewhat more abnormalities appeared in the 6-9 year group, as shown in Table 4.

However, tachycardia appeared more often the shorter period of administration. As the period of administration became longer, abnormalities in T wave that indicated myocardial impairment increased, BBB tended to increase, and atrial fibrillation also increased. Furthermore, abnormalities in the stimulus-producing system and the excitement-transmitting system were also increased with an increasing period of drug use.

As for T changes, T depression, circular T, inverted T, nodular T

Table 5. ECG findings and patients' age

ECG Findings	Age (Year)							Total
	-19	20-29	30-39	40-49	50-59	60-69	70-	
Atrial Fibrillation	0	0	0	0	1	1	1	3
Bundle Branch Block								
incomplete	0	4	9	4	2	1	0	20
complete	0	0	1	1	1	0	1	4
ST-Changes	0	4	5	6	3	5	1	24
+Premature Beat	0	0	0	0	0	2	0	2
T-Changes	1	16	13	15	4	3	0	52
+AV Block	0	2	2	1	2	0	0	7
+PQ Prologation	0	0	0	3	0	1	0	4
+ST Low	2	5	3	8	4	3	2	27
+Mitral P	0	0	1	0	0	0	0	1
+Tachycardia	1	10	7	2	0	0	0	20
+U Wave	0	3	4	3	1	0	2	13
PQ Prolongation	0	1	1	0	0	0	0	2
Pulmonary P	0	1	0	0	0	0	0	1
+PQ Prolongation	0	1	0	0	0	0	0	1
+Tachycardia	0	3	0	0	0	0	0	3
Mitral P	0	1	0	0	0	0	0	1
+Tachycardia	0	1	0	0	0	0	0	1
Tachycardia	1	9	2	1	1	0	0	14
Bradycardia	0	1	0	1	0	1	0	3
Total (%)	5 (83.3)	62 (82.7)	48 (49.0)	45 (50.0)	19 (46.3)	17 (62.9)	7 (77.8)	203 (58.7)
No. of Subjects	6	75	98	90	41	27	9	346

and diphasic T were commonly found.

When ECG findings were examined by dividing the patients into 7 age groups; under 19 years of age, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and above 70 years of age many of the elderly patients showed abnormal findings in one form or another as expected, but it is worthy of note that abnormal T and tachycardia were often found in young patients in their teens and twenties (Table 5)

6) Abnormalities in ECG and kinds of psychotropic drugs

In general, two or more kinds of psychotropic drugs are used concurrently as pharmacotherapy for psychosis; administration of only one kind of psychotropic drug is, in fact, rather exceptional.

For the purposes of this report we noted only those drugs which were administered to act upon a specific target symptom among various

Table 6. Kinds of psychotropic drugs and ECG findings

ECG findings	Neuroleptica										Total
	Haloperidol	Levomepromazine	Pericyazine	Thioridazine	Clocapramine	Thiothixene	Chlorpromazine	Tricyclic Antidepressant	Perphenazine	Others	
Atrial Fibrillation	0	0	0	0	1	2	0	0	0	0	3
Bundle Branch Block											
incomplete	4	4	2	0	1	2	5	0	1	1	20
complete	2	0	1	0	0	0	1	0	0	0	4
ST-Changes	8	8	1	3	1	1	0	2	0	0	24
+Premature Beat	1	0	1	0	0	0	0	0	0	0	2
T-Changes	9	8	10	15	5	3	0	2	0	0	52
+AV Block	3	0	2	0	1	0	0	1	0	0	7
+PQ Prolongation	1	1	1	0	0	0	1	0	0	0	4
+ST Low	2	5	5	9	3	2	0	1	0	0	27
+Mitral P	0	0	0	0	0	1	0	0	0	0	1
+Tachycardia	2	4	2	1	2	2	2	4	1	0	20
+U Wave	2	1	1	4	2	2	0	1	0	0	13
PQ Prolongation	0	1	0	1	0	0	0	0	0	0	2
Pulmonary P	0	0	0	1	0	0	0	0	0	0	1
+PQ Prolongation	0	1	0	0	0	0	0	0	0	0	1
+Tachycardia	1	0	0	0	1	1	0	0	0	0	3
Mitral P	0	0	0	0	0	1	0	0	0	0	1
+Tachycardia	1	0	0	0	0	0	0	0	0	0	1
Tachycardia	2	2	1	0	3	1	2	2	1	0	14
Bradycardia	0	0	0	0	0	0	1	0	0	2	3
Total (%)	38 (55.1)	35 (60.3)	27 (48.2)	34 (87.2)	20 (60.6)	18 (58.1)	12 (41.4)	13 (86.7)	3 (50.0)	3 (33.3)	203
No. of Subjects	69	58	56	39	33	31	29	15	6	10	346

symptoms of the psychopathic patient or those drugs administered in combination.

Accordingly, interaction between the drugs was disregarded. We have no intention of ascribing the ECG abnormalities exclusively to the drugs mentioned in Table 6. However, there is evidently a general trend.

As for drugs very likely to cause ECG abnormalities, mention can be made first of thioridazine, a tricyclic antidepressant, followed by clocapramine, levomepromazine and thiothixene. In addition, haloperidol, perphenazine, pericyazine and chlorpromazine were observed to be likely to cause ECG abnormalities, in the order listed.

DISCUSSION

Of the 346 patients who were the subjects of this investigation, 203 patients (58.7%) showed ECG abnormalities in one form or another, making it clear that abnormalities appeared at a rather high incidence in patients who were receiving psychotropic drugs or neuroleptics.

These findings closely agree with the results of studies by Suwa et al.[1] and Okamoto et al.[2].

While as of yet there is no research that refutes the claim that "sudden death"[3,4] occurs with a higher than normal frequency during the administration of psychotropic drugs, there are quite number of reports that deal with the adverse influence of psychotropic drugs on the heart.

Regarding changes in ECG due to chlorpromazine, reports by Kupatz (1956)[6], Eliakim et al. (1958)[7] and Teitelbaum (1963)[8] have been filed since Moyer et al. (1954)[5] first published on this topic over twenty years ago.

As for thioridazine, it has been attracting attention since Kelly et al. (1963)[9] rendered a rereport on it. Sakai et al. (1971)[10], reported two cases which developed Adams-Stokes syndrome following thioridazine administration of 300 mg to 600 mg/day, doses not necessarily deemed as large.

There have also been reports on the changes caused by trifluoperazine (Ban et al. 1964)[11] and perphenazine (Huston et al. 1966)[12].

The types of ECG changes considered attributable to the administration of these drugs of the phenothiazine group include the prolongation of PQ intervals, changes in T wave (becoming circular, flat, inverted, nodular, diphasic, etc.), appearance of U wave, prolongation of QRS, ST depression, ventricular and auricular tachycardia, bigeminal pulse, sinus tachycardia, atrial extrasystole, ventricular fibrillation and various degrees of heart block.

Among these changes, ST depression, abnormalities in T wave and appearance of U wave, that is, the disorder of repolarization are said to be most characteristic of the abnormalities found in patients using phenothiazines[11-13].

These abnormalities in ST and T waves are nonspecific changes. Therefore if these abnormalities alone are all that constitute changes in ECG then their appearance for a short period of time cannot be considered serious.

According to our investigation, only three cases complained of

subjective symptoms such as "oppression in the chest," abnormalities in ST and T waves appeared without subjective symptoms in most cases.

Tricyclic antidepressants, when administered in usual doses, are said to be more likely to cause prolongation of QT and changes in ST and T waves on the ECG compared with drugs of the phenothiazine group[14-16]. In this respect, clocapramine which is similar to the tricyclic group in its chemical formula is presumed to cause similar changes in ECG.

Regarding ECG changes caused by those drugs of the butyrophenone group which are used frequently in the field of psychiatry, a report by Sawa et al.[1] outlined the dangers of these drugs.

The fact that tachycardia is often found in the younger age brackets and in patients who have been in the hospital for less than one year and the fact that more serious changes in ECG are observed in the advanced age brackets and in patients who have been in the hospital over a long period of time are statistics that the doctor should carefully consider when administering psychotropic drugs.

In trying to elucidate a possible mechanism by which ST and T waves change following administration of drugs of the phenothiazine group, our observations indicated a mechanism similar to that observed in hypopotassemia.

In exploring this hypothesis we measured serum Na, K, Mg and Cl in patients who showed marked changes in ST and T waves but we were unable to obtain results which provided a correlation of ionic level and changes in ECG.

SUMMARY

Electrocardiographic examination was performed on 346 patients who were in the hospital for psychiatric treatment and who were receiving psychotropic drugs; of these patients, 203 (58.7%) showed abnormalities in ECG findings in one form or another.

The highest percentage of abnormal ECG finding were obseved in young patients in their teens and twenries and in patients of the advanced age group.

Tachycardia was observed most often in the young age group and in patients who had been in hospital for less than one year, while the more serious symptoms suspected of myocardial impairment were evident mainly in the advanced age group and in patients who had been in the hospital over an extended period of time.

The most characteristic abnormalities of ECG were changes in ST and T waves; particularly circular, flat, nodular and diphasic T weve were common, also a large percentage of aberrant U waves were observed.

ECG abnormalities appeared at high incidence in patients receiving tricyclic antidepressants such as thioridazine, clocapramine and levomepromazine.

ACKNOWLEDGEMENT

We should like to thank Hideo Fujii M.D., Instructor of the 2nd Department of Internal Medicine, Yamaguchi University School of Medicine for the guidance he gave us concerning ECG findings.

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