ELECTROCARDIOGRAPHIC CHANGES IN CHRONIC SCHIZOPHRENIC PATIENTS

S. HAQUE NIZAMIE
SHRIDHAR SHARMA

SUMMARY

The electrocardiograms were compared in two groups of schizophrenic patients (Experimental group N=43, Control group N=60). The selected cases were given 4 mg of Trifluoperazine daily by IM route for five days. A 12 lead ECG was taken thrice in each case. A statistical analysis of the data showed definite changes in many of the ECG variables. Comparatively more changes were noticed in the experimental group and in patients beyond the age of 45 years.

Introduction

The antipsychotic drugs (APD) are known to produce various side-effects. The cardiovascular (CVS) side-effects are more common (Descotes et al. 1979) and are likely to be lethal. These side-effects are more likely to be missed. APD produce myocardial depressant effects which may result in prolonged conduction times, (Yoon et al. 1979) delayed refractory periods, diminished cell-membrane ionic permeability (Landmark 1971 & 1970), decreased myocardial contractility (Langer 1968) and repolarization abnormalities (Alvarez-Mena et al. 1973; Thornton and Wendkos 1971; Huston et al. 1966; Wendkos 1964). These changes usually lead to minor cardiotoxicity and electrocardiographic (ECG) abnormalities though chronic administration of APD may cause cardiomegaly, congestive cardiac failure, refractory arrhythmias (Alexander 1968) and even cardiomyopathy (Inoue 1979).

The APD-induced minor cardiotoxicity usually results in "benign" or "non-specific" ECG changes like prolongation of QT duration (Huston et al. 1966; Watanabe et al. 1973), T wave changes (Wendkos et al. 1969), appearance of U-wave (Ban et al. 1964), ST depression (Watanabe et al. 1973) and slight change in PR interval (Backman et al. 1964). These changes are seen even in patients without CVS pathology and they usually disappear with discontinuation of APD therapy (Huston et al. 1966). However, sometimes they may induce serious and potentially fatal arrhythmias e.g. occurrence of ventricular ectopics in a patient with prolonged QT duration may lead to R-on-T phenomenon resulting in ventricular tachycardia and fibrillation. In some instances the myocardial effects may combine with neuroleptic induced hypotension, autonomic and respiratory disturbances to cause sudden death.

The need to study the ECG correlates of longstanding APD therapy is obvious. Curiously enough there are not many ECG studies in patients on long term APD therapy (Fakuda et al. 1982; Schwalbe et al. 1978). Most of the studies reported are retrospective in nature with methodological

1. Assistant Professor of Psychiatry
2. Ex-Director, and Professor of Psychiatry | Central Institute of Psychiatry, Kanke, Ranchi.
flaws e.g. multidrug regimen and non-
homogenous sample in respect to age, 
diagnosis and duration of illness.

The present work was conducted with 
the aims- 1. To study the ECG changes in 
chronic schizophrenic patients and 2. to 
compare the ECG changes in chronic 
 schizofrenic patients on prolonged antipsy-
chotic medication with patients not on 
prolonged drug therapy.

Material and Methods

Sample: 103 ambulatory, chronic 
 schizofrenic in-patients of C.I.P., Ran-
chi were included in the study. They were 
divided into an experimental group of 43 
patients (23 male and 20 female), and a 
control group of 60 patients (44 male and 
16 females). Patients in experimental 
group were hospitalized continuously for 
two years or more, whereas control group 
patients were recently admitted in the hos-
pital.

Selection Criteria:
- Age 18-60 years.
- A diagnosis of schizophrenia by Re-
search Diagnostic Criteria (Spitzer et al. 
1978).
- A schizophrenic illness of at least 2 years 
duration
- The patients with evidence of heart dis-
 ease, either according to history or phys-
ical examinations were excluded.

Procedure

After preliminary screening, an in-
formed consent was obtained and possible 
side-effects of the drug was explained to 
the patients. A thorough clinical exami-
nation including pulse, blood pressure and 
cardiac status was done in every case. A 
routine hemogram and a random blood 
sugar estimation were also done, before 
the first ECG was taken. The patients in 
the experimental group were kept without 
antipsychotic drugs for at least 2 weeks to 
obtain a baseline ECG. No patient on in-
tramuscular fluphenazine decanoate was 
included in the study for the reason of a 
long washout period required. The pa-
tients included in the control group were 
only those cases who were on no drugs for 
2 weeks or more before their hospitaliza-
tion.

In selected patients, two milligrams of 
trifluoperazine via intramuscular route 
were given twice a day for five days. No 
other drug was given to the patients during 
this five days period. A routine, 12 lead 
ECG in supine position, was taken thrice 
in each case. The first ECG was a baseline 
record taken during drug-free period i.e. 
just before the patient was put on in-
tramuscular trifluoperazine. The second 
ECG was taken within 24-36 hours of start-
ing the medication, and the last ECG was 
taken on the 5th day of the drug therapy. 
In each ECG a long strip was taken in the 
standard lead II and V1 in order to look for 
any rhythm variation. Each ECG was 
analysed for its various components, re-
polarization abnormalities and ar-
rhythmias. Repolarization abnormalities 
were graded using the criteria of Wendkos 
(1967).

Results

Different ECG variables were com-
pared within and between groups using 
mean, standard deviation, 't' test and per-
centage values. The results showed that 
88.37% of the patients in the experimental 
group had ECG changes in comparison to 
66.67% of the control group. The most 
common change noticed in the experi-
mental group was the prolonged QTC interval 
(88.37%). ST depression was found in the 
experimental group only (23.26%).
Ectopic beats were seen more in the experimental group (4.65%) than the control group (1.67%). Tachycardia and bradycardia were comparatively more common in the control group (Table 1).

Table 1
Percentage Value of ECG changes

| ECG changes          | Expt. Gr. (N=43) | Control Gr. (N=60) |
|----------------------|------------------|--------------------|
|                      |                  |                    |
| Tachycardia          | 16.28            | 31.67              |
| Bradycardia          | 25.58            | 31.67              |
| ST depression        | 23.26            |                    |
| T-wave abnormalities | 79.07            | 65.00              |
| QTC prolongation     | 88.37            | 66.67              |
| U-wave changes       | 39.53            | 36.67              |
| Ectopic beats        | 4.65             | 1.67               |

A consistently gradual decrease in the mean heart rate was noticed in both the groups in their successive ECG recordings. A statistically significant difference at .05 level has been found between the first and the third tracing and between the second and third tracing of the experimental group, though no such significant difference was noticed between the first and second tracing in the same group. A similar trend of decreasing mean heart rate was found in the control group also but it was not as conspicuous as in the experimental group (Table 2).

Table 2
Mean, Standard deviation and 't' value of Heart Rate (Per minute)

| E.C.G. Recordings | Experimental Group | Control Group |
|-------------------|--------------------|---------------|
|                   | Male Mean S.D.     | Female Mean S.D. | t  | Male Mean S.D. | Female Mean S.D. | t  |
| 1st               | 74.22 ± 15.79      | 88.3 ± 18.94   | 2.56 P<.05 | 78.70 ± 15.83 | 89 ± 11.99    | 2.63 P<.02 |
| 2nd               | 71.83 ± 11.26      | 85.7 ± 13.91   | 3.48 P<.01 | 77.73 ± 16.16 | 85.13 ± 18.21 | 1.99 NS |
| 3rd               | 67.69 ± 9.29       | 80.25 ± 12.67  | 3.69 P<.01 | 73.20 ± 14.76 | 84.69 ± 10.73 | 3.24 P<.01 |

Intra-group comparison in male subjects revealed statistically significant difference at .01 level between 1st and 2nd and 3rd ECG record of experimental group. The difference between 2nd and 3rd ECG was not found to be significant. However, in female subjects of the experimental group, this difference among the ECG tracing was not significant.

In both male and female control groups significant difference at .001 level was found between 1st and 2nd and 1st and 3rd ECG records. The difference between 2nd and 3rd ECG record of male group was significant at .02 level whereas in female group this was not found to be significant (Table 3).

When the ECG changes were correlated with age and duration of illness, a gradual rise in the ECG abnormalities were found with advancing age and
chronicity of the illness. A statistically significant difference at .01 level was found between the age range of 31-45 years and 46-60 years. A similar trend (but at .10 level) was noticed between the patients having illness for less than 10 years and those having it for more than 10 years (Table 4).

Table 4
ECG changes Correlated with age and duration of illness

| Range      | Percentage of patients with ECG changes | CR |
|------------|----------------------------------------|----|
| Age        |                                        |    |
| 15 - 30 yrs| 35                                     |    |
| 30 - 45 yrs| 50                                     | 3.24|
| 46 - 60 yrs| 88.39                                  | p<.01|
| Duration of illness |                               |    |
| < 10 yrs   | 40.91                                  |    |
| > 10 yrs   | 76.74                                  | 1.98|
|            |                                        | p<.1|

Discussion

A significant percentage of patients having ECG changes in both the groups clearly shows the CVS side-effects of APD. The ECG changes were found to be comparatively more in patients on prolonged APD therapy. Longterm APD medication has been found to cause more ECG abnormalities (Schwalbe et al. 1978 and Watanabe et al. 1973).

A gradual diminution in global heart rate was an interesting observation. A similar finding has not been reported in any of the studies though Appleton et al. (1980) mentioned a decrease in the heart rate in individual cases due to APD.

A very large number of patients showed QTC prolongation. It was seen more in chronic schizophrenic in-patients who were on APD for a long time. Even their basal record (after a washout period of two weeks) showed a prolonged QTC duration. Similar findings were reported by Watanabe et al. (1973) and Schwalbe et al. (1978). The increase in the QTC duration was much more marked in the first 24-36 hours and it slowed down by the fifth day. Other workers have reported similar finding (Nizamie et al. 1985; Yoon et al. 1979; Langslet 1969; Landmark et al. 1969). The gradual diminution in prolongation of QTC duration may be a physiological adaptation to the effect of drug (Beckman et al. 1964).
Presence of ST segment depression in the experimental group only may be due to prolonged APD therapy. Watanabe et al. (1973) reported ST depression to be the most common finding in a group of schizophrenic patients receiving long-term phenothiazines.

T-wave abnormality in both the groups showed that long term medication as well as exposure to APD for a short period, both can interfere with myocardial repolarization (Schwalbe et al. 1978; Wendkos et al. 1969).

Prolongation of myocardial repolarization may also lead to de novo appearance or prominence of existing U-wave (Ban et al. 1964; Backman et al. 1964). It is believed that phenothiazines shift potassium to the intracellular compartment (Alvez-Mena et al. 1973). This results in hypokalemia and consequent prominent U-wave (Goldman 1982). Oral potassium supplement reverses the repolarization abnormalities secondary to APD (Alverez-Mena et al. 1973). APD cause both atrial and ventricular ectopics (Langslet 1969; Landmark et al. 1969) albeit infrequently (Tatibouet et al. 1980). In the present study few cases developed ectopic beats. Presence of ectopics in male patients only is an interesting observation. There is some hormonal basis for it, since women have been found to show significantly less cardiac dysrhythmia than men (Van Diji et al. 1981).

A very large number of patients (88.89%) beyond the age of 45 years showed ECG changes. It suggested increased susceptibility to cardiotoxicity in older patients. Similarly, patients with longer duration of illness had more of ECG changes. These findings suggest that a patient with longer duration of illness who is in his 40's should be given APD more cautiously.

In conclusion, it may be said that a significant number of patients on APD develop features of cardiotoxicity which becomes more evident in middle aged patients with long duration of illness and on long term APD therapy.

References

ALEXANDER, C.S. (1968); Cardiotoxic effects of phenothiazines and related drugs, Circulation, 38, 1014-1015.

ALVAREZ-MENA, SERGIO. C. & FRANK, MARTIN, J. (1973); Phenothiazine-induced T-wave abnormalities: effects of overnight fasting, JAMA, 224: 1730-1733.

APPLETION, W.D. & DAVIS, J.M. (1980); Practical Clinical Psychopharmacology, 2nd Edn., London, Williams and Wilkins.

BACKMAN, M. ELUOSO, R. (1964); Electrocardiographic findings in connexion with a clinical trial of chlorpromazine, Ann. Med. Int. Finn., 53, 1-8.

BAN, T.A. & JEAN, A.S. (1964), The effects of phenothiazines on the electrocardiogram, Journal of Canadian Medical Association, 91, 537-540.

DESCOTES, J. LIEVRE, M. OLLAGNIER, M. et al. (1979); Study of Thoridazine Cardiotoxic effects by means of His bundle activity recording, Acta Pharmacologica et Toxicology, 44, 370.

FUKUDA, I. KISO, T. KUROKAWA, Y. et al., (1982); EKG findings of patients with schizophrenia and atypical psychoses, Japanese Heart Journal, 23 Suppl. (1), 49-551.

GOLDMAN, M.J. (1982); Principles of Clinical Electrocardiography, pp. 302. Lange Medical Publications Maruzen Asia (Pte) Ltd.

HUSTON, J.R. & BELL, G.E. (1966); The effect of Thoridazine Hydrochloride and chlorpromazine on the electrocardiogram, JAMA, 198, 16-20.

INOUE, F. (1979); Adverse reactions of antipsychotic drugs, Drug. Intel. Clin. Pharm., 13, 198.

LANDMARK, K.H. (1970); Cardiac effects of Phenothiazines, Nord. Med., 83, 617-620.

LANDMARK, K.H. (1971); Changes in rat atrial potentials induced by Promazine and Thoridazine. Acta Pharmacol. Toxicol., 30, 465-479.
LANGER, G.A. (1968); Ion fluxes in cardiac excitation and contraction and their relation to myocardial contractility. *Physiology Reviews*, 48, 708-757.

LANGSLET, A. (1969); Changes in coronary flow and ECG in the isolated perfused rat heart induced by phenothiazine drugs. *Acta Pharmacol. Toxicol.*, 27: 173-182.

NIZAMIE, S. HAQUE & SHARMA, SHRIDHAR (1985); Electrocardiographic changes due to Trifluoperazine and Haloperidol. Paper presented in the 37th Annual Conference of Indian Psychiatric Society at Vishakhapatnam.

SCHWALBE, H. ECKMANN, F. VAN EIMEREIN, W. (1978); ECG changes in psychiatric patients under longterm therapy with psychopharmaco. *Fortschr. Neurol. Psychiatr. Ihrer. Grenzgeb.*, 46, 484-490.

SPITZER, ROBERT, L. ENDICOTT, JEAN AND ROBINS, ELI (1978); Research Diagnostic Criteria for a selected group of functional disorders.

TATIBOUET, L. HENRY, R. BENOSTON, J. QUILLEC, A. GERMA, D. & GRANATALLI, D. (1980); Retentissement Cardiovasculaires des neuroleptiques, *Quest. Med.*, 33, 45.

THORTON, C.C. & WENDKOS, M.H. (1971); EKG T-wave distortion among thioridazine treated psychiatric in-patients. *Diseases of Nervous System*, 32, 320-323.

VAN DIJK, R.B. & TROMMEL, J. (1981); Cardiac arrhythmias in psychogeriatric patients, *Tijdschr. Geneskd.*, 125, 1032-1034.

WATANABE, S. EDAMATSU, K. EHARA, T. OBA YASHI, M (1973); Electrocardiogram of patients receiving longterm phenothiazine therapy. *Journal of Clinical Psychiatry*, 2, 369.

WENDKOS, M.H. (1964); Abnormal Cardiac repolarization in schizophrenics, *Diseases of Nervous System*, 25, 359-365.

WENDKOS, M.H. (1967); Cardiac changes related to phenothiazine therapy, with special reference to thioridazine, *Journal of American Geriatric Society*, 15, 20-28.

WENDKOS, M.H. & THORNTON, C.C. (1969); An ECG Survey of thioridazine treated patients. *Behavioural Neuro psychiatry*, 1(9), 18-23.

YOO, M.S. HAN, J. DERSHAM, G.H. et al., (1979); Effects of thioridazine (Melleril) on Ventricular electrophysiologic properties, *American Journal of Cardiology*, 43, 1155-1158.