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A FOLLOW-UP STUDY ON ECG CHANGES DUE TO NEUROLEPTICS

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ABSTRACT

In a sample of 25 psychiatric in-patients at Tokyo Musashino Hospital, Institute of Psychiatry, Tokyo, ECG examination were performed before medication and followed up. The mean period of observation was ten weeks. The following were observed:

1) The heart rate was in the normal range at the examination before medition. The younger patients tended to increase heart rate, whereas the elder tended to stay at the same level. A few other mild arrythmias were found.
2) No marked change was found in PQ interval, but there was a slight tendency for PQ interval to increase in the older patients whereas it decreased in the younger ones. This is thought to be the result of heart rate dependency of PQ interval.
3) A slight tendency for the voltage to decrease was found in 60% of the patients even though there was no so-called "low voltage".
4) One ischemic change of ST was found.
5) T/R ratio was emphasized more than the height of T wave because of the marked voltage decrease. The decrease of T/R ratio was found amongst 60% of patients.
6) The possible causes and treatments of these ECG changes were discussed.

There have been many reports about neuroleptic-induced ECG changes which are summarized by Shader and his colleagues.[1] The majority of them, however, are cross-sectional studies; longitudinal ones are rare. The longest organized longitudinal studies were done by Huston *et al*[2] and Suwa *et al*[3]. Huston and

A summary of this paper was presented in front of the Hegistrar's Meeting, Section of Psychiatry, Birmingham Medical Institute on 7th December, 1976.

his co-workers[2] took prospectively three months as an interval of the first and second examinations, whereas Suwa and his colleagues[3] took retrospectively one half to three years as an interval. The present study, therefore, focussed on the longitudinal changes and also the interrelationship of the clinical and ECG factors.

PATIENTS AND METHODS

The sample consisted of 25 in-patients at the Tokyo Musashino Hospital, Institute of Psychiatry, Tokyo. Patients were excluded if they were older than 70, had severe physical illnesses, or had taken any kind of neuroleptics up twelve months prior to admission. Out of 25 patients, 15 were men (aged 31.9 ± 12.9, 19–66) and 10 were women (aged 41.0 ± 8.9, 21–54). The mean age of women was older than that of men ($P<0.1$). The mean period of observation was almost the same in both sexes, being approximately 10 weeks (mean ± SEM 10.0 ± 6.3 weeks). Seventeen (10 male, 7 female) were schizophrenics, and 8 were non-schizophrenics; the latter include 2 alcoholism, 1 alcohol dependancy, 1 amphetamine addiction, 1 postencephalitic syndrome, 1 arteriosclerosis, 1 paranoid reaction and 1 psychotic reaction. The medications used were phenothiazines, thioxanthenes, butyrophenones, benzodiazepines, antidepressants, barbiturates, antiepileptics, antiparkinson drugs and hypnotics. Every patient was given at least one neuroleptic that was either a phenothiazine, a thioxanthene or a butyrophenone.

All in-patients received psychiatric, physical and routine laboratory examinations. Other examinations were added if clinically indicated. The laboratory data was all normal. All patients received twelve lead ECG examinations on the first day of admission just before treatment, and were followed up at roughly monthly intervals. T-test was adapted for statistical analysis.

RESULTS

Heart rate—Heart rate was almost always in the normal range throughout the study for all patients; it went up slightly from the premedicational value (76.6 ± 16.3/min) to the fifth week value (85.9 ± 15.7/min), and showed some fluctuations afterwards.

The heart rate changes in this study were classified under three groups, namely the "increasing group", the "decreasing group" and the "stable group". The "increasing group" means the patients whose sequential heart rate was at least 20% higher than the premedicational value; the "decreasing group" those

whose sequential heart rate was at least 20% lower than the premedicational value; and the rest formed the "stable group" which includes those showing both higher and lower values in their courses.

The average age (27.5 ± 7.7) of the "increasing group" (N=8) was younger than the "decreasing group" (37, but N=1) and significantly younger than the "stable group" (39.5 ± 12.5, N=16, $p<0.05$).

More women were found in the "stable group" and more men in the "increasing group". No specific relationship was found with the patients' diagnosis (schizophrenic vs non-schizophrenic). The premedicational heart rate in the "stable group" (82.4 ± 16.2, N=16) was significantly higher than in the "increasing group" (64.8 ± 10.1, N=8, $p<0.02$). However, at the fourth week the "increasing group" (N=4) had a heart rate at 97.0 ± 19.9, significantly higher ($p<0.05$) than the "stable group" (N=8) where heart rate was 73.5±14.8.

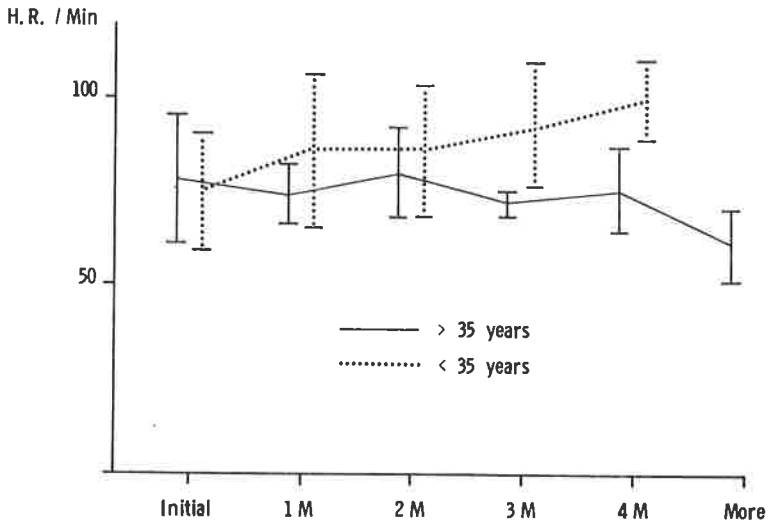

Fig. 1 Heart rate and age groups
The individual bars represent mean ±S. E. M.

If the average heart rate of those aged over and under 35 are depicted (Fig. 1), the younger patients increase gradually whereas the older remain steady and tend to fall only at the later stage. The premedicational value was the same in both age groups (under 35, 74.7 ± 15.5/min; over 35, 78.1 ± 17.2/min).

Many investigators have reported on clinical changes, such as of electrocardiogram, after combined administration of neutroleptics.[3,4,11,16,28,29,34,37] We

could not detect any relationship between the changes of the heart rate and contents of their medications, because almost all the patients were given more than two kinds of neuroleptics at the same time in the different doses according to their clinical states.

PQ interval—All measurements showed no abnormality, ranging from 0.12 to 0.20 msec. The change of the PQ interval was defined in this survey as follows: the "prolonged group" meant patients, at least one of whose sequential value was higher than the initial value; the "shortened group" meant the opposite ones; and the "stable group" meant those all of whose sequential values were about the same as the premedicational value. There was a significant tendency for the "prolonged group" to be older (40.3 ± 13.4 years old, $N=12$) whilst the "shortened group" was younger (27.9 ± 8.9 years, $N=7$) ($p<0.05$). The "stable group" lay between them, being 35.2 ± 8.9 years old ($N=6$). Sex had no influence on PQ interval changes.

The height of the voltage—The height of the voltage was measured in twelve leads although the second standard lead and the fifth precordial lead will be discussed for convenience sake. The fluctuation of voltage was defined in this investigation as increased or decreased when it was at least 20% higher or lower than the premedicational one. Lowering in the second lead was shown in 11 out of 25 patients, and lowering in the fifth precordial lead was shown in 12 patients. Lowering in the former and/or the latter was shown in 15 patients. Incidentally, no axis deviation nor axis change was observed. Nevertheless, there was no so-called "low voltage" (<0.5 mV in the standard leads, and/or <1.0 mV in the precordial leads). No significant relationships were found with the patients' age, sex, diagnosis or medication.

ST change—An ischemic type of ST change appeared in one case. This was a 42 year old male with alcoholism complicated by mild hypertension.

The height of the T wave—The fluctuation of the T wave height was defined here again as 20% higher or lower than the premedicational value. Nine patients showed lowering in the second standard lead ($9/25=0.36$), and 16 in the fifth precordial lead ($16/25=0.64$).

Taking it for granted that the height of the T wave varies in accordance with the voltage, attention should be paid to the T/R ratio, which might be a better indicator of myocardial repolarization. Although vectors of both T wave and R wave should be taken and compared, we believe this rather simple ratio expresses the ECG vector findings better than simple measurement of T wave height. Demarcation was given here again for convenience sake at $\pm 20\%$. Nine patients showed decrease of the T/R ratio in the second standard lead ($9/25=0.36$), fourteen in the fifth precordial lead ($14/25=0.56$) and fifteen in the former

and/or the latter (15/25=0.60). No significant relationships were found with the diagnosis, sex, PQ interval changes, or heart rate changes.

Arrhythmia—Apart from sinus tachycardia, one supraventricular tachycardia which disappeared during the course of the study, one incomplete right bundle branch block and one sinus bradycardia were observed.

DISCUSSION

As regards to neuroleptic-induced ECG changes, the majority of reports say that heart rate increases in human samples.[4–16] Suwa *et al.*[3] say that tachycardia is found more in younger patients than older, whereas Köhnel[14] says that the increase in age of patients is related to the increase of the frequency and intensity of the neurovegitative side effects presenting tachycardia as an example. Köhnel[14] has, unfortunately, shown no details.

The mechanism of neuroleptic-induced tachycardia is still unknown, but possible explanations may be given by the following facts. Many investigators demonstrate the drop of blood pressure with the increase of the heart rate.[7–9,12–15] Foster *et al.*[12] demonstrate that chlorpromazine increases the pulse rate and decreases blood pressure in ten conscious and twelve anaesthetized subjects. A few researchers also demonstrate by venous occlusion plethysmography that chlorpromazine has a powerful vasodilator action on vessels in the limbs and this vasodilator action is due to both central and local effects.[8,12,17]

Shikata[18] has, in an experiment on dogs, demonstrated that chlorpromazine-induced tachycardia can be inhibited by bilateral resection of their carotid sinuses, carotid bodies and vagul nerves, although a slight hypotension still results. Therefore it may well be concluded that neuroleptic-induced tachycardia is a physiological reaction to neuroleptic-induced hypotension.

From the result of the present investigation, it can be said as Suwa *et al.* reported,[3,16] that the heart rate is usually in the normal range on the admission day ("off" drug examination) and that after neuroleptic medication, the younger patients tend to increase their heart rate gradually while the older ones do not. Psychological overlay, which Suwa *et al.*[3,16] refer as a possible explanation of neuroleptic-induced tachycardia, is less significant than expected. Roughly speaking, every patient's psychological state was less stable on the day of admission. This was, incidentally, confirmed by their clinical notes. If, therefore, tachycardia is due to emotional disturbance, it should occur on the admission day. However, it appears, in fact, a few weeks later.

Suwa *et al.*[3] do not confirm this point because their investigation is retrospective, having no "off" drug examination, unlike the present study. The tenden-

cy of younger patients to show increment of heart rate is consistent with the above mentioned explanation that neuroleptic-induced tachycardia is a physiological reaction to hypotension.

PQ interval change has rarely been described in clinical studies. Langslet,[19,20] in his two animal experiments, shows that PQ interval is increased dose-dependently by phenothiazine drugs, while heart rate is decreased dose-dependently. In the present study, it is found that the PQ intervals are increased in the older patients and are decreased in the younger patients. It is also found that heart rate is increased in the young and decreased in the old. This phenomenon is likely to happen because the PQ interval will be shorter if heart rate is increased. Nevertheless, the group with increased heart rate and prolonged PQ interval consists of four patients, all, interestingly, schizophrenics.

The finding that the decrease of the R wave in the second standard and/or the fifth precordial lead was detected on 60% (15/25) patients, gives rise to the suggestion that the height of the R wave or the voltage should be measured when examining the ECG of the patients on any neuroleptics. This point has not been mentioned before. Only Langslet[19] demonstrates decrease of R wave (85% of the height before addition of neuroleptics) in the isolated perfused rat heart ECG. He also shows dose dependent coronary flow decrease. The decrease of the R wave can be explained partially as a result of the direct effect of neuroleptics upon cardiac muscle, but another explanation, or at least exaggerating factor may be the dilation of peripheral vessels which is followed by decrease of venous return causing a decrease of cardiac output. The above two factors, both the direct cardiac muscular effect and the decrease of the cardiac output, may lead to hypotension.

Some investigators[3,4,16,22] report ischemic heart diseases among patients on neuroleptics. From the present study, one case was found to be ischemic after treatment. Here, however, other factors, such as alcoholism, should be considered as important factors.

Decreased, blunted or inverted T waves are reported by many investigators.[2–6,10,11,16,21–26] Most of them, however, do not draw attention to voltage or T/R ratio. Both the height of the T wave and the T/R ratio decreased more in the fifth precordial lead than in the second standard lead in this study. This, however, does not necessarily imply the specific localization of the T/R change but further investigation of the relationship between the T/R change and the myocardial complications due to neuroleptics is required.

As far as arrhythmia was concerned, sinus tachycardia was prominent, while other kinds of arrhythmias were fewer than expected.[4,7,11,16,19,20,26–31]

As regards treatment of neuroleptic-induced ECG abnormalities, some

authors suggest the use of a beta blocker such as propranolol for neuroleptic-induced tachycardia.[3,32,33] This medication can not be recommended because firstly, from the above discussion, tachycardia due to neuroleptics is a physiological reaction which should not be suppressed, and secondly it is not wise to give two different kinds of negative inotropic acting drugs, beta blocker and phenothiazine simultaneously.

Granted that neuroleptic-induced T wave change is reversible by drug withdrawal or drugs,[24,25] neuroleptic treatment should be undertaken with care for the following reasons. Firstly coma, shock or sudden death may occur amongst psychiatric patients who have been on neuroleptics and their cause is still unknown.[26,28,34–38] Secondly, it is not infrequent that psychotic patients need long term neuroleptic maintenance, and therefore it is rather difficult to stop medication although T wave change appears.

What is now required is a long follow-up study to clarify the relationship between medication, ECG findings and cardiac complication which have been hinted at in this pilot study.

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