Phenothiazines and the electrocardiogram

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Introduction
Electrocardiographic abnormalities and sudden death have been reported in patients taking phenothiazines and closely related compounds such as imipramine and amitriptyline (Kelly, Fay and Laverty, 1963; Alexander and Nino, 1969). This paper records the incidence of ECG abnormalities in a large population of schizophrenic patients taking phenothiazine—chiefly chlorpromazine, thioridazine, fluphenazine and trifluoperazine—and provides new evidence of the effects of exercise on these changes.

Summary
Fifty-nine (42%) of 140 schizophrenic patients taking phenothiazines were found to have abnormal electrocardiograms. The abnormalities included T wave changes, S-T depression, P-R and Q-T prolongation, persistent sinus tachycardia (110 or more/min) and right bundle branch block.

In forty-eight (34%) of the fifty-nine patients, the ECG abnormalities disappeared after stopping the phenothiazine and reappeared on its resumption.

Patients and methods
This study population comprised 140 patients with schizophrenia under inpatient/outpatient treatment at Warley Hospital, Brentwood. One hundred and thirty-five were male (20-60 years, mean 36 years) and five female (34-42 years, mean 37 years). Details of their psychiatric drug treatment are shown in Table 1. None had evidence of heart disease, hypertension, general metabolic disturbance or anaemia. None was taking any other cardioactive medication.

Resting electrocardiograms were done on all patients. Recordings were repeated after 2-3 min treadmill-type running exercise in those found to have abnormal resting ECGs. The phenothiazine was then stopped and the resting and exercise ECG recordings repeated after 6 weeks. If the exercise ECG was still abnormal it was repeated after a further 4-6 weeks without the phenothiazine. Patients whose ECGs reverted to normal were given the same phenothiazine and the ECGs were recorded 4-6 weeks later.

Results
In fifty-nine of the 140 patients 101 ECG abnormalities were encountered. Two or more

<table>
<thead>
<tr>
<th>Phenothiazine</th>
<th>Daily dose (mg)</th>
<th>Duration of treatment (months)</th>
<th>No. of patients</th>
<th>No. with abnormal resting ECGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine (largactyl)</td>
<td>150-600</td>
<td>1-96 (mean 36)</td>
<td>49</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Thioridazine (melleril)</td>
<td>150-300</td>
<td>1-96 (mean 18)</td>
<td>20</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Trifluoperazine (stelazine)</td>
<td>15-60</td>
<td>6-60 (mean 18)</td>
<td>27</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Fluphenazine* (moditen)</td>
<td>2-4</td>
<td>6-24 (mean 12)</td>
<td>33</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Perphenazine (fentazin)</td>
<td>12-36</td>
<td>12-48 (mean 36)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Prochlorperazine (stelatil)</td>
<td>5</td>
<td>12-48 (mean 36)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Promazine (sparine)</td>
<td>150</td>
<td>24-48 (mean 36)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Periclavaine (neulactil)</td>
<td>10</td>
<td>24-48 (mean 36)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Given fortnightly.
abnormalities occurred in twenty-five of the fifty-nine patients. The incidence of resting ECG abnormalities in relation to the type of phenothiazine is shown in Table 1. There was no significant difference between groups on the four most used drugs and on correlation with age. The specific resting ECG abnormalities are listed in Table 2.

The tachycardia was unresponsive to carotid massage. Six weeks after stopping the phenothiazine the resting heart rate had fallen to 70–80/min in all cases. Recurrence of sinus tachycardia was noted in all cases when the phenothiazine was recommenced.

Low or flat T waves in standard and lateral chest leads (Figs 1 and 2) were seen in twenty-nine (49%) of those with abnormal ECGs. They were the earliest changes to regress after stopping the phenothiazine. Return to complete normality took 4–6 weeks.

Curiously notched, broad T waves (Fig. 3), usually in V3 and V4, were seen in nine cases (15%), eight of these patients being on thioridazine or fluphenazine. The duration and shape of the T wave reverted to normal 6 weeks after stopping the drug in all cases.

S-T depression of 2 mm or more (Figs 1 and 2) was seen in nineteen cases (33%). The S-T depression was best seen in the standard and lateral chest leads. Exercise increased both T wave abnormalities and S-T depression without causing chest pain or hypotension. The resting ECG 4–6 weeks after stopping the phenothiazine showed complete regression of S-T and T changes in all cases. However, the post-exercise ECG at that time continued to show minor S-T depression in all cases; after a further 4–6 weeks this also disappeared.

Prolongation of Q-Tc interval beyond 0.4 sec (Fig. 3) was seen in eight (13%) of those with abnormal ECGs; seven of these were on thioridazine. Regression to normal was seen in all cases within 6 weeks of stopping the drug.

A prolonged P-R interval (0.24 sec) was seen in one patient on chlorpromazine. No change was observed 6 weeks after stopping the drug.

In ten cases, the ECG abnormality was right bundle branch block. In no case had this disappeared 6 weeks after stopping the phenothiazine, which then

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### Table 2. The specific ECG changes

<table>
<thead>
<tr>
<th>Phenothiazine</th>
<th>Sinus rhythm over 109/min</th>
<th>Low or flat</th>
<th>Broad and/or notched</th>
<th>S-T depression</th>
<th>Q-T prolonged</th>
<th>RBBB</th>
<th>P-R over 0-20 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>14</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>4</td>
<td>6</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>–</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>29</td>
<td>9</td>
<td>19</td>
<td>8</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Male, 39 years. (a) Sinus tachycardia (125/min) and minor S-T depression in leads 2, 3, aVF, V3, and V7, and their regression in (b) 6 weeks after stopping chlorpromazine (200 mg t.i.d. for 2 years).
FIG. 2. Male, 37 years. (a) Low voltage T waves in leads 1, aVL, V- and V- before exercise; (b) sinus tachycardia (125/min) and S–T depression with T wave lowering in leads 2, aVF, V5–V6, minor T inversion in V5, immediately after exercise; (c) good recovery of S–T, T wave changes 6 weeks after stopping chlorpromazine (100 mg b.d. for 2 years).
had to be recommenced because of psychiatric relapse.

During the period of this study (9 months) there were no sudden deaths among the patients.

Discussion

The overall incidence of reversible ECG abnormalities in patients receiving phenothiazines in this series was 34%. This finding is in keeping with those previously published.

A causal relationship with sinus tachycardia, T wave abnormality, S-T depression and Q-T prolongation also seems likely. The underlying mechanism is not clear but interference with cellular potassium (Wendkos, 1967), or catecholamine metabolism has been suggested among other theories (Alexander and Nino, 1969; Richardson, Graupner and Richardson, 1966; Madan and Pendse, 1963).

Exercise increases phenothiazine-induced S-T depression and the drug must be stopped for at least 12 weeks to eliminate all exercise effect. This consideration could be of diagnostic importance where the physician is faced with the possibility of cardiac ischaemia in a patient taking one of these drugs.

The right bundle branch block may well have been purely coincidental; alternatively it may take longer to regress.

P-R prolongation has been associated with phenothiazines (Huston and Bell, 1966).

More severe effects reported by others (Alexander and Nino, 1969; Kelly et al., 1963; Orning, 1966; Poulsen, 1965) include left bundle branch block, intermittent A-V block, ventricular tachycardia and ventricular fibrillation. None of these was encountered in this study, possibly because of the generally lower dosage schedules used.

Acknowledgments

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References


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