QT time in patients treated with alpenrolol or placebo after myocardial infarction

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SUMMARY  Studies were made on the effects of long-term beta-blockade on the QT interval in patients discharged alive from hospital after myocardial infarction. The patients (n = 230) in this study constituted all those who participated in the alpenrolol study on postmyocardial patients in Göteborg, Sweden. The study was double-blind (alpenrolol 200 mg b.i.d. or placebo) and randomised. The patients were divided into 4 risk groups (1-4) with different predicted mortality. The electrocardiograms before and after 8 weeks of treatment were analysed with respect to heart rate and QT time. There was a decrease in heart rate of about 10 per cent in the alpenrolol treated patients. The QT time was not significantly influenced by alpenrolol. The rate corrected QT time (QTcr) decreased in the subgroup of the most severely diseased patients (subgroup 4) treated with alpenrolol.

In recent years 2 controlled studies have shown that long-term beta-blockade after myocardial infarction reduces the rate of sudden deaths after discharge from hospital (Wilhelmsson et al., 1974; Multi-centre International Study, 1975). The specific mechanism of action has not been defined. The most likely explanation for this phenomenon is that lethal arrhythmias are prevented. The relations between the QT time and the duration of the action potential or the fibrillation threshold have been discussed (Schwartz et al., 1976; Raine and Vaughan Williams, 1978). The purpose of the present paper is to analyse the influence of long-term beta-blockade on the QT interval in patients discharged alive from hospital after myocardial infarction.

Patients and methods

The patients in this investigation constituted all those who participated in the study of alpenrolol treatment of patients with acute myocardial infarction after discharge from hospital. All men and women (n = 230) in Göteborg, Sweden, with acute myocardial infarction during 1970 to 1971 aged 57 to 67 years with no contraindication to beta-blocking drugs were included. The study was double-blind and started one week after discharge from hospital. The patients were divided into 4 risk groups with differing predicted mortality (Table 1).

Table 1  Criteria for homogeneous risk group allocation of patients with myocardial infarction

<table>
<thead>
<tr>
<th>Subgroup no.</th>
<th>Cardiac damage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No extensive cardiac damage</td>
<td>(1) Relative heart-volume: men, &gt; 450 ml/m² BSA; women, &gt; 400 ml/m² BSA</td>
</tr>
<tr>
<td>2</td>
<td>Mechanical damage to myocardium</td>
<td>(2) Alanine transferase &gt; 40 units (Karmen) during first 3 days</td>
</tr>
<tr>
<td>3</td>
<td>Electrical cardiac damage</td>
<td>(3) Body temperature &gt; 38°C during first 3 days</td>
</tr>
<tr>
<td>4</td>
<td>Combined electromechanical damage (subgroups 2 and 3)</td>
<td>(4) Transient atrial flutter and fibrillation</td>
</tr>
</tbody>
</table>

*BSA, body surface area.

before random allocation to placebo or active treatment with alpenrolol (200 mg b.i.d.; Wilhelmsson et al., 1974; Vedin et al., 1975). Routine examinations took place after every 6-week period. The patients took the tablets at 8 am and 8 pm, and the full dose was given from the beginning of treatment. At each control examination the patients were asked about the intake of tablets. The number of tablets taken was counted at each control examination and the
urine was assayed for alprenolol content.

Those patients who died, those who had non-fatal reinfarctions, or who developed contraindications against chronic beta-blocking therapy during the first 3 months of follow-up were excluded from this analysis. Predetermined criteria were used for treatment with digitalis and diuretics. No anti-arrhythmic drugs were used.

The number of reinfarctions and deaths between 3 months and 2 years after infarction was recorded (Wilhelmsson et al., 1974; Vedin et al., 1975).

Of the 114 patients receiving alprenolol and the 116 patients receiving placebo in the original report (Vedin et al., 1975), 105 on alprenolol and 107 on placebo were analysed (Table 2). For the remainder, one or both of the electrocardiograms needed was missing or the patient had reached an end-point before the second examination. The results will be given for each subgroup (1-4), as well as for all patients together. The numbers of patients in sub-

Table 2 Number of particles in each risk group: patients randomised to treatment (N) and analysed with regard to QT time (n)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Alprenol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>105</td>
</tr>
</tbody>
</table>

group 3 were too few to be analysed (alprenolol n = 2; placebo n = 3).

The electrocardiograms from the day before treatment started (one week after discharge) and the electrocardiogram at the 12-week examination were analysed with respect to RR interval, QT interval, and QTc (rate-corrected QT interval according to Bazett, 1920). Thus, the patients had been treated for approximately 8 weeks. The resting electrocardiogram was recorded using a 4-channel ink recorder (Elema Schöndanger 81). The average recording time was 30 seconds at each examination. The values averaged were usually 5 but there were always at least 3 cycles of the strips which had been recorded at 50 mm/s after supine rest for 5 minutes.

The electrocardiograms were analysed by one observer (G.N.) without knowledge of the identities of the patients, the treatment given, or the time of the recording. After completion of the analysis the code was broken. Student’s t test, paired or unpaired, was used (two-tailed) for statistical analysis. Significant differences were defined for P < 0.05.

Results

In all the patients on alprenolol, the heart rate fell by 6.4 beats/minute (P < 0.01). The heart rate was consistently lower at 12 weeks in the alprenolol groups compared with the placebo groups. The difference failed to reach significance in subgroup 1 (Table 3). No consistent changes were observed in

Table 3 Heart rate, QT interval, and QTc before and after treatment (mean, standard deviation in brackets)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Heart rate beats/min</th>
<th>QT interval ms</th>
<th>QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Alprenol</td>
<td>69.8 (12.8) 75.1 (12.4)</td>
<td>-5.25* (13.23)</td>
<td>368 (32) 357 (33)</td>
</tr>
<tr>
<td>Placebo</td>
<td>72.1 (14.5) 68.0 (13.5)</td>
<td>+4.15* (12.42)</td>
<td>365 (43) 368 (39)</td>
</tr>
<tr>
<td>Significance for difference between drugs</td>
<td>NS NS NS NS NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Alprenol</td>
<td>66.5 (12.6) 73.7 (12.8)</td>
<td>-7.14* (8.6)</td>
<td>366 (36) 357 (36)</td>
</tr>
<tr>
<td>Placebo</td>
<td>70.2 (14.2) 74.8 (14.2)</td>
<td>-6.65* (20.74)</td>
<td>365 (39) 360 (39)</td>
</tr>
<tr>
<td>Significance for difference between drugs</td>
<td>NS NS NS NS NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Alprenol</td>
<td>69.1 (11.2) 74.1 (14.3)</td>
<td>-6.0* (14.0)</td>
<td>364 (37) 368 (33)</td>
</tr>
<tr>
<td>Placebo</td>
<td>78.8 (15.5) 76.0 (14.7)</td>
<td>+2.8 (11.3)</td>
<td>353 (39) 359 (43)</td>
</tr>
<tr>
<td>Significance for difference between drugs</td>
<td>P &lt; 0.01 NS P &lt; 0.02 NS NS P &lt; 0.01 NS</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.1; † P < 0.05; ‡ P < 0.001.
the placebo groups though a small increase was noted in subgroup 1.

The uncorrected QT interval is not significantly influenced by any of the treatments in any subgroup (Table 3). After correction for the influence of heart rate a significant shortening of the QTc was observed in risk group 4 of the alprenolol-treated groups and a non-significant shortening in risk group 2 (Table 3). No changes were seen in the placebo groups or in risk group 1 of the alprenolol group. Generally, before treatment at the start of the trial the QTc tended to be longer in risk group 4 than in risk groups 1 and 2 and this difference is significant when the results of the alprenolol and placebo groups are analysed together.

The reduction of QTc in patients with a QTc above 0.420 (considered normal for a heart rate of 55) was analysed in the alprenolol (n = 26) and in the placebo group (n = 27). The reduction was particularly pronounced in the alprenolol-treated group (−36 ms vs 23 ms for placebo) and the difference in change between the alprenolol and placebo-treated groups was significant.

Patients with and without concomitant treatment with digitalis were analysed separately in all groups. No significant differences were found between the patients treated with digitalis and those who were not. If anything, digitalis tended to decrease QTc both alone and especially when used together with alprenolol.

Deaths and reinfarctions were not related to initial QTc and changes thereof during the remainder of the follow-up time.

Discussion

Previous studies have shown that continued alprenolol treatment has lowered mortality when given to patients with acute myocardial infarction after they have left hospital. The design of the study has been discussed extensively by Wilhelmsson et al. (1974) and Vedin et al. (1975).

Recently, the QT interval has been studied as a predictor of sudden death in patients with myocardial infarction (Wolf and Schwartz, 1976). Other studies using multivariate techniques have failed to show an independent contribution of the QT time when other variables were considered (Vedin et al., 1977).

Conflicting results are available regarding the influence of chronic beta-blockade on the QT interval. In studies using acute administration of a beta-blocker the QT interval remains unchanged. QTc, however, is shortened, reflecting the lowering of the heart rate (Stern and Eisenberg, 1969; Seides et al., 1974). Our findings indicate the same effect after chronic administration.

The absence of influence on the QT interval may have several explanations. The patients may not have taken their medication. However, pill counting and urine analysis have shown that more than 80 per cent of the patients took more than 90 per cent of the tablets. The use of other drugs such as digoxin was initially suspected to counteract a further change induced by the beta-blocker. On entry 50 per cent of all patients in the present study were treated with digitalis (Vedin and Wilhelmsson, 1975). In practice concomitant drug usage must be expected. However, propranolol and digoxin have both been shown to lower QTc. Combining the two drugs led to a further reduction (LeWinter et al., 1977). This observation is supported by our findings. Furthermore, the beta-blockade may influence both the duration of the action potential and the impulse propagation in various regions of the myocardium to produce a constant QT interval.

These findings are in contrast to those of Raine and Vaughan Williams (1976) who found a prolongation of the QT interval in rabbits after beta-blockade. In their work they found that the QTc began to lengthen after 5 days of treatment, and by 15 days had reached a constant prolongation of 11 per cent, as compared with saline. This change was present after 24 hours when the beta-blocker effect on the heart rate had vanished. Subsequent microelectrode studies on atria and ventricles from the hearts of these rabbits removed after 6 weeks of treatment showed a significant prolongation of action potential duration in the animals receiving active beta-blockade, which paralleled the increase in QTc. Since such a prolongation is known to be antiarrhythmic the authors propose that this is responsible for the effect seen on survival rate in patients with myocardial infarction. The same authors reported similar findings in a non-randomised study of cardiac patients (Raine and Pickering, 1977) though QT measurements were made with ongoing beta-blocking therapy and not, as in the animal studies, 24 hours after the last dose. The authors suggested that these findings might cause an antiarrhythmic effect of the beta-blockers explaining a mortality reduction in patients treated after myocardial infarction. Differences in study populations could partly explain the differences between those studies and the present one. Focal lesions, for example old myocardial scars in infarction patients, may influence the transmission of the repolarisation vector which can also affect the QT interval regardless of effects on the action potential.

However, the mortality reduction in the postinfarction studies need not be based on a pure anti-
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arrhythmic action of the drug. A beneficial effect of beta-blockers on the balance between regional myocardial demand and supply of oxygen may be important. In pathological states the conditions may indeed vary. For instance, in the so-called long QT syndrome a normalisation of the QT interval has been reported after resection of the left stellate ganglion (Moss and McDonald, 1971; Schwartz et al., 1976). Further clinical improvement together with varying effect on the QTc is reported after addition of beta-blockers in this condition.

The present findings indicate no effect of long-term beta-blockade on the QT interval in a controlled study, despite a favourable influence on sudden cardiac mortality. The reported change in QT could simply result from the fact that the beta-blocker directly influences the RR interval but it is not clear why this is not seen in all patients. Further studies are needed using a more direct method such as recordings of monophasic action potentials.

References


Requests for reprints to Dr A. Vedin, Department of Medicine, Östra Hospital, S-416 85 Göteborg, Sweden.
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