Effect of dofetilide on QT dispersion and the prognostic implications of changes in QT dispersion for patients with congestive heart failure

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Abstract

Aims: Drug-induced changes in QT dispersion may be a way of detecting harmful repolarisation abnormalities for patients receiving antiarrhythmic drugs affecting ventricular repolarisation. Methods and results: In 463 congestive heart failure (CHF) patients enrolled in the Danish Investigations Of Arrhythmia and Mortality On Dofetilide-CHF (DIAMOND-CHF) study, both pre-treatment and on-treatment day 2–6 QT dispersion was available from standard 12-lead ECGs. Patients were randomised in a double-blind manner to receive either placebo or dofetilide, a new class III antiarrhythmic drug. During a median follow-up of 19 months (minimum 1 year), 179 patients (39%) died (135 patients from cardiac causes). Changes in QT dispersion did not predict all-cause or cardiac mortality for patients treated with dofetilide in multivariate survival analysis (Risk ratio: 1.02, 95% confidence interval: 0.97–1.08, P = 0.4). This finding was independent of pre-treatment QT dispersion. Dofetilide caused a small QT dispersion increment of 8 ms, not different from the changes seen in the placebo group (3 ms). Conclusion: For patients with CHF and reduced left ventricular systolic function, changes in QT dispersion following treatment with dofetilide do not predict all-cause or cardiac mortality. The dofetilide-induced QT dispersion changes are small and comparable to those seen in placebo treated patients. © 2002 European Society of Cardiology. Published by Elsevier Science B.V. All rights reserved.

Keywords: QT dispersion; Heart failure; Prognosis; Arrhythmia; Antiarrhythmic agents

1. Introduction

Repolarisation abnormalities of the ventricular myocardium may cause ventricular tachyarrhythmias and death. It has been speculated that one of the mechanisms of the antiarrhythmic effect of Vaughan Williams’s class III antiarrhythmic drugs is a homogeneous increase in the refractory period, while proarrhythmic events — primarily Torsade de Pointes ventricular tachycardia — caused by these drugs may be predicted from an inhomogeneous increase. QT interval dispersion (often defined as maximum minus minimum QT interval in a 12-lead standard ECG) is a marker of heterogeneity in the ventricular refractory period and therefore changes in QT interval dispersion induced by drugs affecting ventricular repolarisation may be a marker of future arrhythmia [1].

Dofetilide is a new ‘pure’ class III antiarrhythmic drug that increases repolarisation time by blocking the rapid component of the delayed rectifier I K of the potassium current [2]. Small-scale studies on the effect of dofetilide on QT dispersion in normal subjects [3] and in patients with stable angina pectoris [4] have shown insignificant changes. However, such lack of changes may be the sum of a decrease in QT dispersion in patients benefiting from dofetilide and an increase in QT dispersion in patients at increased risk from drug-induced proarrhythmias and death. The prognostic value on mortality of changes in QT dispersion for patients receiving dofetilide has yet to be established.

We have previously shown that, in spite of an overall neutral study outcome for patients with moderate to
severe congestive heart failure included in the Danish Investigations of Arrhythmia and Mortality on Dofetilide-Congestive Heart Failure (DIAMOND-CHF) study [5], the pre-treatment QTc interval was highly important in selecting a sub-group of patients that would benefit from subsequent treatment with dofetilide [6]. Pre-treatment QT dispersion could not differentiate between survivors and non-survivors [7], but one explanation for this could be that drug-induced changes in QT dispersion rather than pre-treatment QT dispersion itself holds the prognostic information.

We therefore prospectively evaluated the effect on mortality of changes in QT dispersion made by dofetilide for patients with CHF and reduced left ventricular systolic function.

2. Methods

2.1. Patients

The DIAMOND-CHF study population was the basis for our pre-defined sub-study. The DIAMOND-CHF study [5] was a double blind, placebo-controlled, randomised study conducted in 34 hospitals in Denmark from 1993 to 1996. The aim of the main study was to evaluate the effect of dofetilide on mortality for patients with CHF. Screening criteria were: age \( \geq 18 \) years and hospitalisation with CHF of all causes with New York Heart Association (NYHA) functional class III or IV within the last month prior to hospitalisation. Screening procedure was consecutive and included echocardiography. Randomisation required that patients had left ventricular systolic dysfunction with a Wall motion index (WMI) \( \leq 1.2 \), corresponding to an ejection fraction of \( \leq 35 \). Of the 5812 patient screenings, 1518 patients were enrolled, with a baseline ECG available locally in all patients. A 12-lead pre-treatment baseline ECG was available for our sub-study in 1319 patients, whilst an ECG taken within day 2–6 after initiation of study treatment was available in 1177 patients.

Exclusion criteria included acute myocardial infarction (MI) within 7 days, a locally measured baseline QTc interval exceeding 460 ms [500 ms in patients with bundle-branch block (BBB)], severe non-cardiac disease, severe electrolyte abnormality, severe renal dysfunction, or patients receiving a class I or class III antiarrhythmic drugs. Written informed consent was obtained, and patients unwilling or incapable of participating were excluded [8].

The study was approved by the ethics committees of the hospitals involved and the Danish Board of Health.

2.2. QTc interval

Baseline QT dispersion could be measured in 630 ECGs (48%) of the 1319 ECGs recorded. The main reason for exclusion of baseline ECGs was atrial fibrillation (\( n = 371 \)). These ECGs were excluded as no studies have been performed to show the reproducibility of QT interval (and thus QT dispersion) and the relationship between QT interval/QT dispersion and survival in patients with atrial fibrillation. Other reasons for exclusion of ECGs were <nine readable leads (\( n = 259 \)), poor recording quality (\( n = 11 \)), pacemaker rhythm (\( n = 45 \)), and bigemini (\( n = 3 \)). Of the 630 patients with baseline QT dispersion, a measurable ECG taken within 2–6 days was available in 463 patients.

In all 12 leads of a standard ECG two consecutive QT intervals were measured by one of two experienced observers using a computerised digitiser tablet (Cherry, Mk III Graphic tablet, resolution 0.1 mm), and an averaged QT interval was calculated for each lead. The QT interval was measured from the beginning of the QRS-complex to the visual return of the T-wave to the isoelectric line. When a U-wave interrupted the end of the T-wave, the termination of the T-wave was defined as the nadir between the T and the U-wave. If this distinction was not possible, the lead was discarded from analysis. QT dispersion was defined for both baseline and on-treatment ECGs as maximum minus minimum QT interval.

2.3. Follow-up

All patients were followed for a minimum of 1 year (median follow-up 19 months), with no patient lost to follow-up.

2.4. Endpoints

Mortality endpoints from the main DIAMOND-CHF study were also endpoints in our sub-study. All-cause mortality was the primary endpoint. Secondary endpoints included death from cardiac causes and arrhythmic death. Members of an event committee evaluated on a blinded basis all available data in connection with an endpoint and classified the endpoint according to the CAPS criteria [9] (with the exception that successful resuscitation of cardiac arrest was not considered as death).

2.5. Statistical analysis

Median value and 5/95\% percentiles are reported for continuous data, with quartiles being used whenever grouping of a continuous variable was necessary. Comparisons between groups were made by non-parametric analysis of variance (Kruskal–Wallis test) for continuous data and by the \( \chi^2 \)-test for discrete data.

Survival analysis included univariate as well as multivariate Cox proportional hazard models [10,11].
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 244, 53%)</th>
<th>Dofetilide (n = 219, 47%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-years (perc)a</td>
<td>70</td>
<td>(53–84)</td>
<td></td>
</tr>
<tr>
<td>Male sex — (no)</td>
<td>70%</td>
<td>(171)</td>
<td></td>
</tr>
<tr>
<td>Duration of heart failure (months) (perc)b</td>
<td>9</td>
<td>(0.07–144)</td>
<td></td>
</tr>
<tr>
<td>Current smoker — (no)</td>
<td>42%</td>
<td>(101)</td>
<td></td>
</tr>
<tr>
<td>Medical history — (no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>55%</td>
<td>(135)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>71%</td>
<td>(173)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16%</td>
<td>(38)</td>
<td></td>
</tr>
<tr>
<td>Wall motion index (perc)b</td>
<td>0.9</td>
<td>(0.5–1.2)</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class 3 or 4 — (no)</td>
<td>55%</td>
<td>(133)</td>
<td></td>
</tr>
<tr>
<td><strong>Medications at randomisation — (no)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>12%</td>
<td>(30)</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>43%</td>
<td>(106)</td>
<td></td>
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<tr>
<td>Diuretics</td>
<td>96%</td>
<td>(234)</td>
<td></td>
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<tr>
<td>ACE inhibitorad</td>
<td>79%</td>
<td>(192)</td>
<td></td>
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<tr>
<td><strong>Laboratory results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum-potassium (mmol/l) (perc)a</td>
<td>4.2</td>
<td>(3.7–5.0)</td>
<td></td>
</tr>
<tr>
<td>Serum-creatinine (mmol/l) (perc)a</td>
<td>113</td>
<td>(81–188)</td>
<td></td>
</tr>
<tr>
<td><strong>ECG at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS ≥ 120 (ms) (no)</td>
<td>38%</td>
<td>(93)</td>
<td></td>
</tr>
<tr>
<td>QT interval (ms) (perc)b</td>
<td>395</td>
<td>(337–473)</td>
<td></td>
</tr>
<tr>
<td>QTc interval (ms) (perc)b</td>
<td>453</td>
<td>(398–518)</td>
<td></td>
</tr>
<tr>
<td>QT dispersion (ms) (perc)b</td>
<td>69</td>
<td>(34–142)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm) (perc)b</td>
<td>78</td>
<td>(57–103)</td>
<td></td>
</tr>
</tbody>
</table>

* All continuous variables are reported by median and 5–95% percentiles (perc).

b P-value > 0.1.

c New York Heart Association.

da Angiotensin-converting enzyme.

Variables tested in multivariate Cox models were changes in QT dispersion, sex, age, smoking status, history of diabetes, ischaemic heart disease and hypertension, NYHA functional class, WMI, BBB, heart rate, serum creatinine, and serum potassium. As no intervention was made in the placebo group, no changes in QT dispersion and no prognostic value of changes in QT dispersion were anticipated in this group. Therefore the multivariate Cox analysis was performed comparing quartiles of QT dispersion changes in dofetilide-treated patients with the placebo group as a whole (with a default risk ratio of 1). Assumptions of the Cox models were tested (proportional hazards, interactions between variables, linearity of risk estimates for continuous variables). Results from the Cox analysis are expressed as relative risk (RR) with a 95% confidence interval (CI). A test was considered statistically significant with a P-value ≤ 0.05.

The Statistical Analysis System version 6.12 (SAS Institute, Cary Inc., NC) was used for all statistical analysis. Analysis was made on an intention-to-treat basis.

3. Results

3.1. Reproducibility of QT dispersion

Reproducibility was tested in a random sample of 90 patients. Interobserver difference was 14 (−39/78) ms (corresponding to a relative error of 28%), while intraobserver differences were 4 (−36/52) ms and 14 (−39/78) ms (corresponding relative errors 14 and 29%, respectively). Measurements by the two observers were evenly distributed in dofetilide/placebo treated patients and in survivors/non-survivors. All pairs of ECGs were recorded at the same paper speed, and all pairs of ECGs (except in 18 patients) were measured by the same observer.

3.2. Baseline characteristics and baseline QT dispersion

Baseline characteristics for placebo and dofetilide treated patients are shown in Table 1. Baseline QT dispersion was greater in the dofetilide group. Patients with ischaemic heart disease had greater QT dispersion...
3.3. Endpoints and changes in QT dispersion

One hundred and seventy-nine patients (39%) died during follow-up. Of these, 68 placebo-treated patients and 67 dofetilide treated patients suffered a cardiac death. For placebo treated patients, there was an increase in QT dispersion from baseline to day 2–6 (ΔQT dispersion) of 3 (–63/66) ms. ΔQT dispersion for dofetilide treated patients was 8 (–55/87) ms. ΔQT dispersion in the two treatment groups was not significantly different (P > 0.15). Table 2 shows ΔQT dispersion in survivors and non-survivors.

3.4. Univariate survival analysis

The following baseline variables reached a P-value ≤ 0.05 in univariate Cox analysis for placebo-treated patients: age per 10 years (1.47, 1.16–1.86, P < 0.001), use of digoxin (1.61, 1.08–2.42, P < 0.02), WMI per 0.3 unit’s decrease (1.35, 1.05–1.73, P < 0.02), and NYHA III or IV (1.53, 1.04–2.32, P < 0.05). For dofetilide-treated patients, only age per 10 years (1.63, 1.26–2.11, P < 0.0002) and serum creatinine > 130 mmol/l (2.29, 1.39–3.78, P < 0.001) contained prognostic information.

ΔQT dispersion did not hold any prognostic value in dofetilide-treated patients (all-cause mortality: 1.003, 0.998–1.008; cardiac mortality: 1.004, 0.998–1.010; arrhythmic death: 1.000, 0.993–1.008) or in placebo-treated patients (all-cause mortality: 0.997, 0.992–1.002; cardiac mortality: 0.997, 0.991–1.003; arrhythmic death: 0.997, 0.990–1.005). The relatively low number of arrhythmic deaths made multivariate survival analysis questionable for this endpoint, therefore this analysis was not performed.

3.5. Multivariate survival analysis

Results from multivariate survival analysis on all-cause mortality are shown in Table 3. As a continuous variable, ΔQT dispersion in dofetilide treated patients held a risk ratio of 1.02 (0.97–1.08, P < 0.4).

For cardiac death, survival analysis revealed a similar tendency as for all-cause mortality (with placebo serving as reference group with a default risk ratio of 1: NYHA III or IV as reference group with a default risk ratio of 1).
dofetilide group, lower to upper quartiles: RR: 0.9, 1.0, 1.0, 1.3. P-values: 0.9, 0.8, 0.9, 0.3).

The prognostic value of ΔQT dispersion on all-cause mortality and cardiac death was found not to be related to baseline QT dispersion (test for interaction between ΔQT dispersion and baseline QT dispersion in dofetilide treated patients: all-cause mortality: \( P > 0.8 \); cardiac mortality: \( P > 0.9 \)).

4. Discussion

The finding of this study is that independent of baseline QT dispersion itself, neither all-cause nor cardiac mortality can be predicted from dofetilide-induced changes from baseline QT dispersion in patients with CHF and reduced left ventricular systolic function. The changes in QT dispersion in dofetilide-treated patients are not different from those seen in the placebo group.

Although several studies point towards a greater predictive power of drug-induced changes in QT dispersion rather than of changes in QTc interval, the exact importance of these changes for both QT parameters remains insufficiently elucidated.

In 1991, Day et al. [12] showed a reduction in QT dispersion in 39 post-MI patients treated with sotalol compared to placebo-treated patients. Analysis of endpoints was not performed. In another study, Hii et al. [13] compared changes in QT dispersion in 38 patients receiving chronic amiodarone treatment secondary to quinidine treatment for ventricular tachyarrhythmias or atrial fibrillation. Nine of these patients had developed Torsade de Pointes ventricular tachycardia on quinidine treatment. In all patients, maximum QTc interval was prolonged, but for both drug regimes, only the nine patients with an episode of Torsade de Pointes ventricular tachycardia on treatment had increased QT dispersion compared to baseline QT dispersion. For the rest of the patients, on-treatment QT dispersion was unchanged from baseline QT dispersion. Cui et al. [14] found that though on-treatment QTc interval increased in both patients receiving amiodarone \((n = 26)\), sematilide \((n = 26)\), and sotalol \((n = 26)\) due to supra-ventricular or ventricular arrhythmias, only in the amiodarone group did QT dispersion change from baseline (a reduction). The study did not compare these QT dispersion changes to endpoints. Gillis et al. [1] compared drug-induced (including quinidine, sotalol and sematilide) QT dispersion changes to the probability of inducing sustained ventricular tachycardia or ventricular fibrillation in 72 patients with coronary heart disease and baseline inducible sustained ventricular tachycardia or ventricular fibrillation. For both patients with and without on-treatment inducible arrhythmias, on-treatment maximum QTc interval was prolonged. An increase in QT dispersion was only seen in the treatment failure group.

For our patients, dofetilide caused an increase in QTc interval and no significant increment in QT dispersion, a finding that is in agreement with other studies evaluating the effect of dofetilide on QT parameters in other patient categories [3,4]. The changes in QT dispersion were similar for survivors and non-survivors. Multivariate analysis confirmed that changes in QT dispersion following treatment with dofetilide did not predict mortality.

It is not obvious why changes in QT dispersion induced by dofetilide do not predict mortality. Perhaps the initial assumption that the beneficial effect of class III antiarrhythmic drugs lies in making spatial ventricular repolarisation homogenous is wrong. However, if this assumption is true one has to look for reasons why QT dispersion does not reflect these repolarisation changes. Recent studies indicate that QT dispersion is merely an incomplete marker of T wave morphology rather than of repolarisation itself [15]. Being both a crude as well as an indirect marker of ventricular repolarisation in combination with a low reproducibility [16,17] could explain the many contradictory studies made on this parameter. Also, QT dispersion is dependent on how QT intervals are measured, and the fact that there is no consensus on how to measure if the QT interval is reflected in the different ways QT dispersion is measured.

Patients with congestive heart failure (CHF) are at high risk of dying, including from sudden death [18]. In several observational studies for patients with CHF, increased QT dispersion has been associated with increased mortality [19–23], although this has not been a consistent finding [24–26]. For the DIAMOND-CHF population, we have recently shown that pre-treatment baseline QT dispersion did not hold any prognostic value on mortality irrespective of the patient subsequently receiving placebo or dofetilide [7]. The additional finding of this study, that changes in QT dispersion do not hold any predictive value on mortality, emphasises the need for other predictive repolarisation measurements.

4.1. Limitations

Patients were withdrawn from study medication if the QTc interval increased extensively. This may have affected the interpretation of the prognostic value of changes in QT dispersion. However, for the ECGs available, there was only a partial correlation between QTc interval prolongation and QT dispersion increment (a Pearson correlation coefficient of 0.32).

5. Conclusion

Dofetilide-induced changes in QT dispersion are comparable with changes seen in placebo-treated patients...
and do not predict all-cause or cardiac mortality in patients with moderate to severe congestive heart failure and reduced systolic left ventricular function. This finding is independent of baseline QT dispersion itself.

Acknowledgments

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References


