QT Dispersion and Electrical Heart Field Morphology in Patients Treated with Dosulepin

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Summary

The aim of the study was to detect the changes of QT dispersion (QTd) due to cardiotoxicity of tricyclic antidepressant dosulepin. Electrocardiographic and vectorcardiographic recordings were obtained using Cardiag 112.2 diagnostic system from 28 psychiatric outpatients treated with prophylactic doses of dosulepin and compared to those obtained from 37 healthy volunteers. From these recordings following parameters were evaluated: QTd, spatial QRS-STT angle and amplitude of T-wave. The acquired data were correlated with the dosulepin plasma levels using Spearman´s rank order correlation test. The average QTd (±S.D.) in the dosulepin group was significantly higher (70±21 ms) than that in the control group (34±12 ms) (P<0.001). Moreover, the correlation between QTd and the dosulepin plasma levels was highly significant (r = 0.7871, P<0.001). Similar results were obtained when QTc dispersion was used. On the contrary, the QRS-STT space angle did not correlate with the dosulepin plasma levels. Furthermore, the T-wave amplitude was not significantly correlated to the QT-interval. Thus we can conclude that the QT dispersion could be used as a simple marker of the dosulepin effect on the myocardium.

Key words

Introduction

Many antidepressant drugs can influence either the electrical or mechanical functions of the heart. In the case of tricyclic antidepressants (TCA) changes of the Na^+-K^+ pump activity were suggested to be the cause of these effects at a molecular level (Rawling and Fozzard 1978, Weld and Biggert 1980, Glassman *et al.* 1993, Hamplová-Peichlová *et al.* 2002). The side effects of high doses of TCA on the electrical processes in the human heart were proven to be numerous, the most important

being the prolongation of the heart atrioventricular and intraventricular conduction - the so called "quinidine-like effect" (Warrington *et al.* 1989, Švestka 1994). Cconsequently, the first degree of A-V block in 70 % of young patients with a TCA blood serum level of 350 ng/ml and in 3 % of people with a TCA blood serum level below 350 ng/ml was described by Preskorn and Fast (1991). The other well-known side effect of therapeutic doses of TCA is the decrease of His-Purkinje and Purkinje-ventricular conduction time (P-V junctions), causing a prolongation of the QRS complex on a standard

12-lead ECG curve. A prolongation of the QRS higher than 140 ms can provoke a bundle branch block.

Moreover, not only aberrant electrical activation but also aberrant electrical recovery (repolarization) in ventricles is one of the cardiotoxic effects of the TCA (Preskorn and Fast 1991). Delayed cardiac repolarization could be detected on the basis of the QT interval prolongation. It is well known that the QT duration and consequently the refractory period are significantly prolonged in patients overdosed by TCA. Overdosing by TCA is supposed to induce severe ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation and even the syndrome of sudden cardiac death (Preskorn and Fast 1991). TCA overdosing and its cardiotoxic effects can be predicted accurately enough by three electrocardiographic markers: a prolongation of the intraventricular conduction (QRS duration time of 140 ms or more), a QRS axis deviation towards the right (120-270°), and an increased R wave amplitude (R higher than 3 mm in lead aVR) (Singh *et al.* 2002). Thus, ECG changes can detect cellular and subcellular myocardium impairments more accurately than a drug plasma concentration. QRS markers (especially QRS duration time) have 100 % sensitivity and 98-100 % specificity in the prediction of cardiac arrhythmias and seizures.

The cardiotoxic effects of therapeutic plasma levels of TCA (150-200 ng/ml in serum) are not quite so evident. The quinidine-like side effect of therapeutic TCA doses is less pronounced than the antimuscarinic one ("atropine-like effect") manifested in particular by tachycardia and repolarization changes. The irregular ventricular repolarization can be manifested by any of the following: an ST denivelation, a prolonged QTc interval, an abnormal shape and/or polarity of the T wave (Ray *et al.* 1987, Stoudemire and Fegel 1987, Kitzlerová *et al.* 2003). Nevertheless, no correlation between the TCA plasma levels and the standard ECG markers for therapeutic and particularly for prophylactic doses has yet been found. In the recent study by Kitzlerová *et al.* (2003) four electrocardiological parameters were proven to correlate significantly with plasma levels of dosulepine (the most frequently used TCA in Czech Republic) when the method of body surface potential mapping (BSPM) was used: QRS axis deviation in a frontal plane (p<0.01), the maximal value of the isointegral map during the first 40 ms of the QRS complex, the so-called $DIAM40_{max}$ (p<0.05) and the QRS-STT angles in the transverse and left sagittal planes (p<0.05).

Another problem is that the plasma levels of TCA may not correspond to the doses used currently for treatment or prophylaxis, as about 6-10 % of the population have a slow metabolism of TCA antidepressants, whereas about 6 % of the population have a fast metabolism. The catabolic rate of the TCA in the human body is determined by genetic polymorphism of cytochrome P450 (Hollister 1989, Glassman *et al.* 1993). This is a reason why plasma levels of tricyclic antidepressants can be different in various subjects, even though the doses used are identical (Leonard 1994).

As the dispersion of the QT interval (QTd) was suggested by many authors to be a useful parameter in detecting repolarization abnormalities (Mirvis 1985, Somberg *et al.* 1985, Cowan *et al.* 1988, Day *et al.* 1990, Linker *et al.* 1992, Hii *et al.* 1992, Hohnloser *et al.* 1993, van de Loo *et al.* 1994, Priori *et al.* 1994, Barr *et al.* 1994, Sporton *et al.* 1997), we have tried to measure QTd in patients treated with dosulepin and to test the possible relationship between the QTd and the plasma level of dosulepin.

Methods

Patients

Electrocardiographic recordings were obtained from 20 female and 7 male psychiatric outpatient subjects diagnosed with recurrent depressive disorder, currently in the remission phase (DSM-IV). Hamilton Psychiatric Rating Scale for Depression (HAMD) score below 10, treated with a dosulepine daily maintenance dose of 25-125 mg. The patients did not suffer from any cardiac disease, all of them were non-smokers, aged 44.1±13.7 years. The therapy lasted for 4-8 weeks. The same recordings were obtained from the control group containing 37 healthy volunteers, 27 women and 10 men, aged 39.8±11.2 years.

A healthy person was defined for the purposes of this project according to the following findings and data: a negative cardiological family and personal history, a normal arterial blood pressure, normal glycemia, normal cholesterolemia, a normal ECG, non-smoker, normal body weight, a negative neurological, psychiatric and endocrinological personal history and no cardioactive medication.

Measurement

The examination was performed using standard conditions; electrocardiographic, vectorcardiographic and BSPM recordings were obtained simultaneously using the

Cardiac 112.2 device (Kittnar *et al.* 1993). All examinations were performed in the morning between 09:00 and 11:00 h in order to avoid any influence of circadian rhythms (Svorc *et al.* 1994, 2000). The QT interval was measured by 80 unipolar chest leads used for body surface potential mapping. The QT interval was measured from the start of the Q wave to the end of the T wave, QT dispersion was then defined as the difference between the maximal and minimal QT interval in any of the leads measured. T wave amplitude was similarly measured by the same 80 body surface leads. Vectorcardiographic parameters were used to evaluate the QRS-ST space angle (Ruttkay-Nedecký 1983). Evaluation of BSPM was used for locating the minimal and maximal values on the isointegral maps of both the depolarization and repolarization phases. Plasma levels of dosulepine were determined by high performance liquid chromatography (HPLC) (Balíková 1992).

Data analysis

For the processing of the electrocardiographic and vectorcardiographic data the computer program of the Cardiac 112.2 device was used. This program determines common wave onsets, offsets and amplitudes for all 95 leads in one representative beat. The set of leads comprises of: 12 standard ECG leads, 3 orthogonal Frank's vectorcardiographic leads and 80 regularly placed unipolar body surface leads (Kittnar and Šťovíček 1993).

QT intervals were measured manually by a single observer from curves on the device screen. The cursor was used to indicate the start of the Q wave and the end of the T wave. The curves were displayed on the screen in a measurement corresponding to a paper speed of 50 mm/s and a gain of 1 mV/cm. To check the reproducibility of measurement we have assessed both intra-observer and inter-observer variability. For determining the intra-observer variability, all ECG tracings were evaluated by the same investigator on two different occasions. To assess the inter-observer variation, all ECG tracings were analyzed by a second independent investigator who was unaware of the results obtained by the first one.

Data were expressed as means ± S.D. Spearman rank order correlation test was used to determine the correlation between the obtained electrocardiographic and vectorcardiographic data and dosulepine plasma levels.

Results

The dosulepin plasma levels in the studied group of psychiatric patients treated with prophylactic doses of dosulepin were 45.8 ± 18.2 ng/ml, ranging from 5 to 164 ng/ml (Fig. 1).
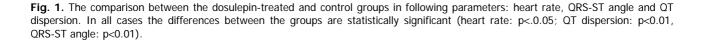

Fig. 1. The comparison between the dosulepin-treated and control groups in following parameters: heart rate, QRS-ST angle and QT dispersion. In all cases the differences between the groups are statistically significant (heart rate: $p<.0.05$; QT dispersion: $p<0.01$, QRS-ST angle: $p<0.01$).

Reproducibility of the determination of QT dispersion was high enough in both intra-observer and inter-observer comparisons. In absolute numbers, the difference between the first and second determination of the QT dispersion in the same ECG tracing (intra-observer variability) ranged between 0 and 16 ms, with an average value of 7 ± 4 ms. Values for inter-observer variability varied between 0 and 19 ms (8 ± 5 ms).

The average QT dispersion in the control group was significantly lower (33±14 ms) than in psychiatric patients treated with dosulepin (70±21 ms) (P<0.001) (Fig. 1). The correlation between the QTd and the dosulepin plasma level was also statistically significant (P<0.001) with the value of correlation coefficient 0.7871 (Fig. 2).
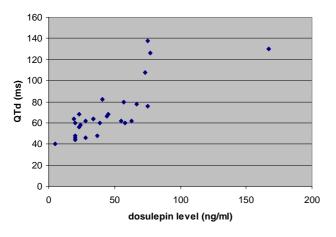

Fig. 2. The correlation between the QT dispersion and the dosulepin plasma level (r = 0.7871, n = 27, p<0.0001).

The distribution of the maximal and minimal values of QT interval on the torso surface quadrants was not significantly different between the dosulepin and control groups (Table 1).

The spatial QRS-ST angle differed significantly between the dosulepin and control groups (Fig. 1), but the correlation between the QRS-ST angle and the dosulepin plasma level was not statistically significant. The locations of the minimal and maximal values on the isointegral maps of both the depolarization and repolarization phases did not differ significantly between both groups (Table 2).

The general correlation between QT interval and T wave amplitude in all leads was not significant (P<0.08). Borderline significant correlation was found in the leads with high T waves (the left precordium) (P<0.03), but not in those with small T-wave amplitude. However, in the left precordial leads (with high T wave amplitude) there was no difference in T wave amplitudes between patients treated with dosulepin and control group (525.7 ±163.1 vs. 512.9±201.4 µV).

Table 1. The distribution of maximal and minimal values of QT interval in the dosulepin and control groups.

Maximal QT interval			
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	20.5 %	46.2 %	20.5 %	12.8 %
Control	22.7 %	50.0 %	9.1 %	18.2 %
Minimal QT interval			
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	19.0 %	43.0 %	19.0 %	19.0 %
Control	1.0 %	28.6 %	19.0 %	33.4 %

Discussion

The present study was aimed to determine the possible changes of QT dispersion in patients treated with dosulepin maintenance doses, using the method of body surface potential mapping. The use a greater number of leads for the determination of the QT dispersion helps to evaluate the QTd more accurately than the assessment with only 12 or even 6 precordial leads. The use of a low number of leads was undoubtedly the main cause of the repeatedly suggested poor reproducibility (Day *et al.* 1992, Kautzner *et al.* 1994). Enhanced accuracy for QT dispersion assessment from a 12-lead ECG in comparison

with only 6 precordial leads was also reported (van de Loo *et al.* 1994, Higham and Campbell 1994). Moreover, the reproducibility could be influenced by the scale of the ECG curve (the paper speed and the gain), and especially the lower time resolution (25 mm/s) was suggested to be an important reason for the poor reproducibility (Glancy *et al.* 1996). Both the low intra- and inter-observer variability of QT dispersion assessed in this study suggest that this method could be useful for determining changes in the QT dispersion, because the detected changes are well above the errors encountered in this study. Nevertheless, it is necessary to admit that in addition to measurement error the QT dispersion could be influenced

by many different factors (both intra- and extra-cardiac) as discussed in the following paragraphs.

Measurements performed in the present study indicate that dosulepin causes an increase in the QT dispersion. This finding is in agreement with that from our previous study (Lechmanová *et al.* 2002), where QT dispersion was measured using the same method on healthy female volunteers in a late phase of pregnancy. In that study, we concluded that QT dispersion can reflect not only an increased risk of serious tachyarrhythmias, especially due to myocardial ischemia, but it can also be increased physiologically by altered spatial arrangement of the thoracic organs, including the heart.

Table 2. The locations of minimal and maximal values on the isointegral maps of both the depolarization and repolarization phases.

Maximal value on a depolarization isointegral map				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	0 %	63.0 %	29.6 %	7.4 %
Control	0 %	45.5 %	54.5 %	0 %
Minimal value on a depolarization isointegral map				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	22.2 %	77.8 %	0 %	0 %
Control	9.1 %	77.3 %	0 %	13.6 %
Maximal value on a repolarization isointegral map				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	0 %	92.6 %	0 %	7.4 %
Control	0 %	86.4 %	9.1 %	4.5 %
Minimal value on a repolarization isointegral map				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Dosulepin	37.0 %	11.1 %	7.4 %	44.5 %
Control	40.9 %	27.3 %	0 %	31.8 %

Table 3. The distribution of maximal and minimal values of QT interval in late pregnancy and control groups

Maximal QT interval				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Pregnancy	0 %	51.9 %	19.2 %	28.9 %
Control	22.7 %	50.0 %	9.1 %	18.2 %
Minimal QT interval				
Group	Right frontal quadrant	Left frontal quadrant	Left dorsal quadrant	Right dorsal quadrant
Pregnancy	40.0 %	13.0 %	34.2 %	12.8 %
Control	19.0 %	28.6 %	19.0 %	33.4 %

In the present study, the results are very similar, but in the latter case, we suppose that the increased QT dispersion is a non-specific sign of a changed course of repolarization, which reflects the cardiotoxic side effects of dosulepin. A different explanation for these two findings is supported by the different distribution of the maximal and minimal values of the QT interval in the dosulepin group and in the group of pregnant women.

Although spatial distribution of these parameters on the chest in the case of dosulepin group does not differ from the control group (see Table 1), it does differ significantly in the case of minimal values of the QT interval in the late pregnancy group (χ^2 =1.324; p<0.05) (Table 3).

Non-specifity of the QTd is supported by the correlation between QT interval and T wave amplitude in left precordial leads. We suppose that altered T-wave shape does reflect the same abnormality as QTd does, because both of them could be non-specific signs of an attenuated repolarization pattern (and flattening of T wave is well known as a non-specific sign of the defective course of repolarization). This could also be explained by the fact that imprecision in the detection of T wave offset can contribute to the inaccuracy of QTd. However, since there was no difference between both groups with different QTd concerning T wave amplitude it does not support such an explanation. No correlation between QT interval and T wave amplitude in the leads with low T wave amplitudes might be explained by the frequent exclusion of measurement in these leads so that small amplitudes are eliminated from the analysis.

The QRS-STT space angle was not significantly correlated to the dosulepin level in spite of the fact that the QRS-STT angle correlated significantly with the dosulepin level (p<0.05) (Kitzlerová *et al.* 2003), when calculated only in the transverse and in the left sagittal plane. This could be explained by the significant angle deviation (toward the right) in the frontal plane (Kitzlerová *et al.* 2003).

On the contrary, the correlation between QTd and the dosulepin plasma level was statistically significant, suggesting that the QTd could be used as a simple marker for the elevated plasma level of dosulepin and thus also for an increased risk of toxic side effects of dosulepin on the myocardium at therapeutic or prophylactic plasma levels.

Acknowledgment

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