

QT Dispersion Estimated from 80 Body Surface Potential Map Leads and from Standard 12-Leads ECG in Psychiatric Patients Treated with Dosulepin

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Abstract: The aim of the study was to detect changes of the QT dispersion (QTd) due to cardiotoxicity of tricyclic antidepressant dosulepin. Electrocardiographic and body surface potential mapping (BSPM) recordings were obtained using Cardiac 112.2 diagnostic system from 27 psychiatric outpatients treated with prophylactic doses of dosulepin and compared to those obtained from 37 healthy volunteers. From these recordings the QTd and the dispersion of heart rate-corrected QT interval QTc were evaluated. These parameters were estimated both from 80 BSPM leads and from 12 standard ECG leads. Acquired data were statistically correlated by Spearman rank order correlation coefficient with dosulepin plasma levels. The average QTd evaluated from BSPM leads (\pm SD) in the dosulepin group was significantly higher [70 (\pm 21) ms] than that in the control group [34 (\pm 12) ms] ($P < 0.001$). Moreover, the correlation between QTd and the dosulepin plasma level was statistically significant as well ($P < 0.001$) with the value of correlation coefficient 0.7871. The QTd evaluated from standard 12 ECG leads was increased in dosulepin group as well [46 (\pm 18) ms vs. 28 (\pm 10) ms – $P < 0.05$] but we have not found any significant correlation of the QTd with the dosulepin plasma level. According to the above-mentioned results we can conclude that the QTd estimated from BSPM leads (but not that estimated from 12-lead ECG) could be used as a marker of the dosulepin effect on the myocardium.

Key words: QT dispersion – Electrocardiography – Body surface potential mapping – Dosulepin – Tricyclic antidepressants

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Introduction

Many antidepressant drugs can influence either the electrical or mechanical function of the heart. In the case of tricyclic antidepressants (TCA) changes of the $\text{Na}^+\text{-K}^+$ pump activity were suggested to be the cause of these effects at a molecular level (Glassman et al. 1993, Rawlings et al. 1978, Weld et al. 1980, Hamplová et al. 2002). Frequent side effects of high doses of TCA on the electrical processes in the human heart were described, the most important was the prolongation of the heart intra-ventricular conduction – the so called “quinidine – like effect” (Warrington et al. 1989, Švestka 1994). As a consequence of this fact 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 Prescorn et al. (1991). The other well-known side effect of therapeutic doses of TCA is the decrease of the His-Purkinje and Purkinje-ventricular conduction time causing prolongation of the QRS complex.

Moreover, not only the aberrant electrical activation but also aberrant electrical repolarization in ventricles is one of the cardio-toxic effects of the TCA (Prescorn et al. 1991). It is well known that cardiac repolarization is delayed and consequently the duration of the QT interval is significantly prolonged in patients overdosed by TCA. Overdosing by TCA is supposed to be able to induce severe ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation and even the syndrome of sudden cardiac death (Prescorn et al. 1991). TCA overdosing and its cardio-toxic effects can be predicted accurately enough by 3 electrocardiographic markers: a prolongation of the intra-ventricular conduction (QRS duration time of 140 ms or more), a QRS axis deviation towards the right ($120^\circ\text{--}270^\circ$), and the increased R wave amplitude (R higher than 3 mm in lead aVR) (Singh et al., 2002).

In comparison to overdosing the cardio-toxic effects of therapeutic plasma levels of TCA (150–200 ng/ml in serum) is not quite so evident. 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 et al. 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 been found yet. In the recent study by Kitzlerova et al. (2003) 4 electrocardiological parameters were found to correlate significantly with dosulepin plasma levels when the method of body surface potential mapping (BSPM) was used: QRS axis deviation in the frontal plane ($p < 0.01$), maximal value of the isointegral map during the first 40 ms of the QRS complex $\text{DIAM40}_{\text{max}}$ ($p < 0.05$) and QRS-STT angles in the transverse and sagittal planes ($p < 0.05$).

To contribute to the identification of possible electrocardiographic markers of the cardio-toxic effect of the prophylactic doses of dosulepin we studied

dispersion of QT interval (QTd) as a marker of attenuated repolarization pattern. The QTd seems to be a useful parameter in detecting repolarization abnormalities as many studies have demonstrated a direct relation between increased QT dispersion and different cardiovascular pathologies (Mirvis 1985, van de Loo et al. 1994, Cowan et al. 1988, Day et al. 1990, Linker et al. 1992, Priori et al. 1994, Hii et al. 1992, Hohnloser et al. 1993, Barr et al. 1994, Somberg et al. 1985, Sporton et al. 1997). That is why we measured QTd in patients treated with prophylactic doses of dosulepin and tested the possible relation between the QTd and the plasma dosulepin level.

Patients and Methods

Patients: Electrocardiographic recordings were obtained from 20 female and 7 male psychiatric outpatient subjects diagnosed with recurrent depressive disorder, currently in remission phase (DSM-IV). Hamilton Psychiatric Rating Scale for Depression (HAMD) score below 10, treated with a dosulepin 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 (Tab 1).

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 glycaemia, normal cholesterolaemia, a normal ECG, non-smoker, normal body weight, a negative neurological, psychiatric and endocrinological personal history and no cardioactive medication.

Measurement: The examination was done under standard conditions; electrocardiographic, vectorcardiographic and BSPM recordings were obtained simultaneously using the Cardiac 112.2 device (Kittnar et al. 1993). The QT interval was measured by 80 unipolar chest leads used for body surface potential mapping and by 12 standard ECG leads. The QT interval was measured from

Table 1 – Comparison of characteristics of dosulepin and control groups

	patients treated with dosulepin	healthy volunteers	significancy of difference
Age	44.1 ± 13.7	39.8 ± 11.2	no
Gender	20 women, 7 men	27 women, 10 men	no
Cardiovascular personal history	negative	negative	no
Tobacco smoking	no	no	no
Arterial hypertension	no	no	no
Hypercholesterolaemia	no	no	no
Diabetes	no	no	no

the start of the Q wave to the end of the T wave; each QT interval was corrected for the patient's heart rate (QTc) using Bazett's formula (van de Loo et al., 1994). QT dispersion was then defined as the difference between the maximal and minimal QT interval in any of the leads measured. Accordingly, QTc dispersion was defined as the difference between the maximal and minimal QTc interval. Plasma levels of dosulepin were determined by high-performance liquid chromatography (HPLC) (Balíková, 1992).

Evaluation of BSPM was used for locating the minimal and maximal values on the isointegral maps of both the depolarization and repolarization phases.

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 on 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 the curves on the device screen. Cursor was used to indicate the start of the Q wave and the end of the T wave. For the measurement, curves were displayed corresponding to the paper speed of 50 mm/s and a gain of 1 mV/cm. Excel tables containing QT intervals from all 80 leads were obtained and the difference between the longest and shortest interval in each table was automatically

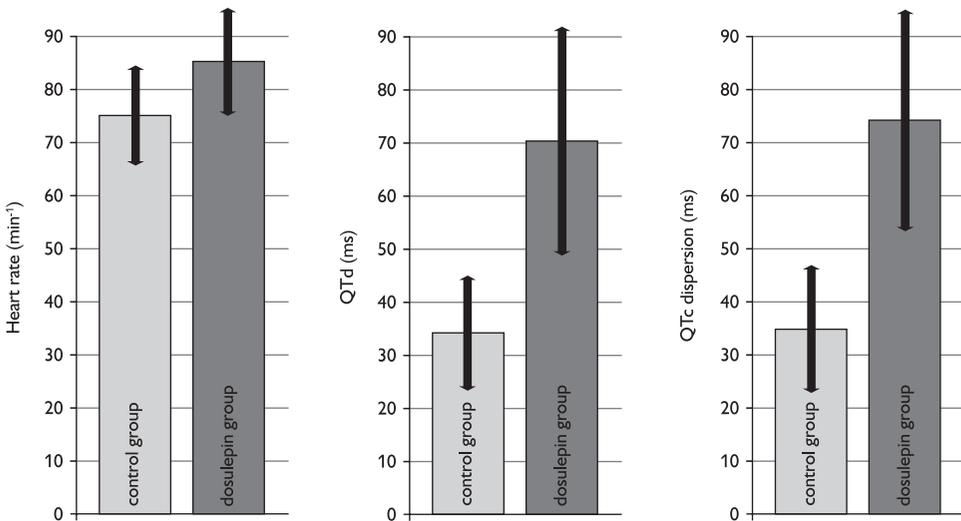


Fig. 1 – The comparison between the dosulepin and control groups in following parameters: heart rate, QT dispersion and QTc dispersion. In all cases the differences between the groups are statistically significant (heart rate: $p < 0.05$; QT dispersion: $p < 0.01$; QTc dispersion: $p < 0.01$).

computed. To check the reproducibility of measurement of QT interval both the intraobserver and interobserver variability was assessed. For determining the intraobserver variability, all ECG tracings were evaluated by the same investigator on two different occasions. To assess the interobserver variation, all ECG tracings were analysed by a second independent investigator who was blind to the results obtained by the first one.

To determine the correlation between the electrocardiographic data and the dosulepine plasma levels, Spearman rank order correlation coefficient was used.

Results

The dosulepin plasma level in the investigated group of psychiatric patients treated with prophylactic doses of dosulepin was in average 45.8 (± 18.2) ng/ml ranging from 5 to 164 ng/ml (Fig. 1).

Reproducibility of the determination of QT dispersion was high enough in both intraobserver and interobserver comparisons. In absolute numbers, the difference between the first and second determination of the QT dispersion in the same ECG tracing (intraobserver variability) ranged between 0 and 16 ms, with an average value of 7 (± 4) ms. The values for interobserver variability varied between 0 and 19 [± 5] ms].

The average QT dispersion (\pm SD) in the control group was significantly lower [33 (± 14) ms] than in psychiatric patients treated with dosulepin [70 (± 21) ms]

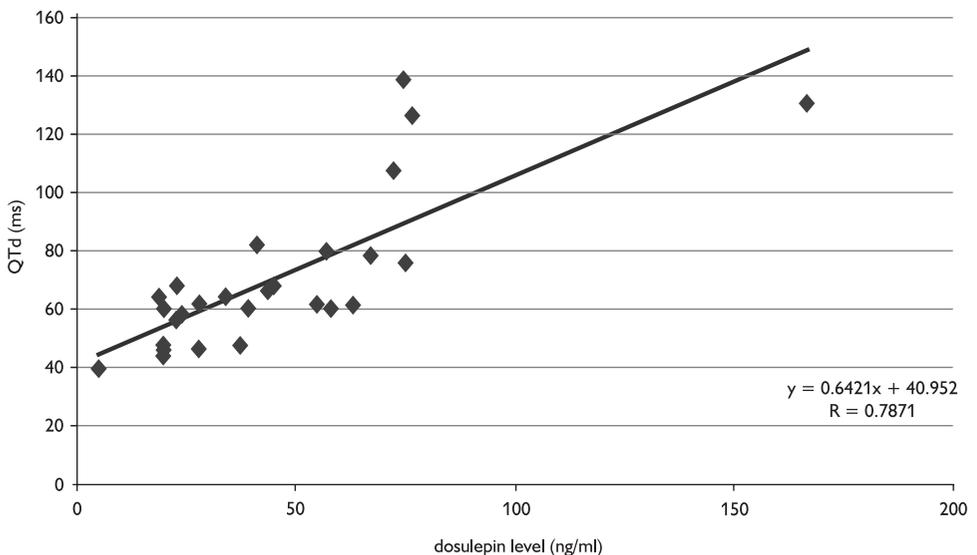


Fig. 2 – The correlation between the QT dispersion and the dosulepin plasma level.

($P < 0.001$). The results (Fig. 1) were very similar using rate corrected values with average QTc dispersion values of $34 (\pm 15)$ ms for healthy volunteers and $75 (\pm 18)$ ms for patients in the dosulepin group ($P < 0.001$). The correlation between the QTd and the dosulepin plasma level was statistically significant as well ($P < 0.001$) with the value of correlation coefficient 0.7871 (Fig. 2). Similar results were obtained when QTc dispersion was used.

The QTd evaluated from standard 12 ECG leads (Fig. 3) was increased in dosulepin group as well [$46 (\pm 18)$ ms vs. $28 (\pm 10)$ ms in the control group – $P < 0.05$] but we have not found any significant correlation of the QTd with the dosulepin plasma level.

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

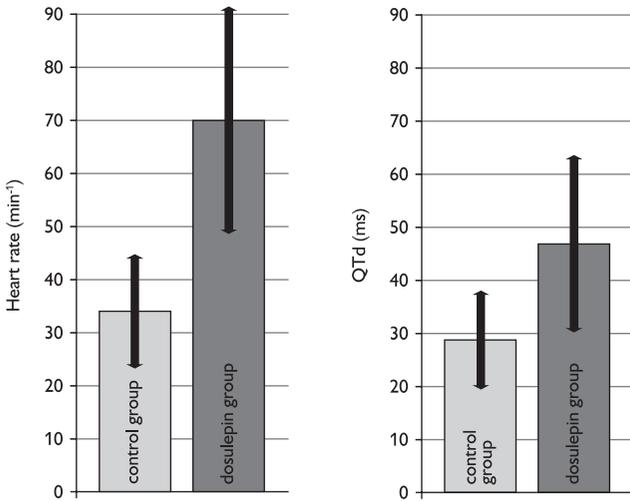


Fig. 3 – The comparison of QT dispersion estimated from 80 leads of Body surface potential map (BSPM) and from 12 leads of standard ECG

Table 2 – The distribution of the 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	19.0 %	28.6 %	19.0 %	33.4 %

groups (Tab. 2). The distribution of QT interval values in the third row of electrodes is demonstrated in the Fig. 4. The space that is close to standard precordial leads is highlighted.

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 (Tab. 3).

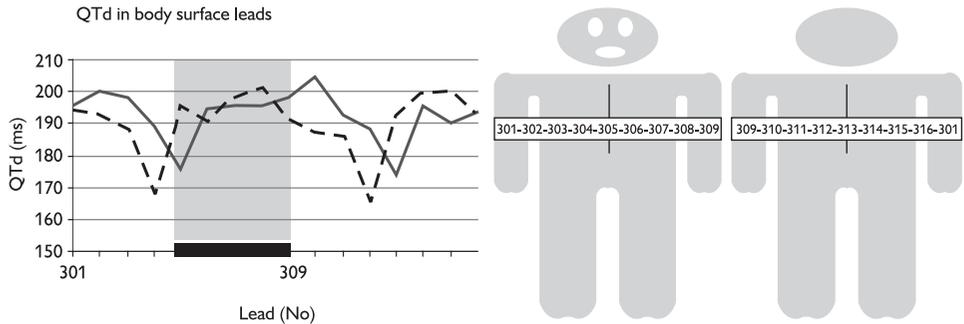


Fig. 4 - The distribution of QT interval values in the third row of electrodes (above), The space that is close to standard precordial leads is highlighted, the location of electrodes is simply shown on the lower picture: for instance electrode 301 is in the right axillar line, 305 in the central sternal line, 309 in the left axillar line, 313 in the central back line.

Table 3 – The locations of the 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 %

Discussion

The present study, aimed at determining the possible changes in QT and QTc dispersion in patients treated with dosulepin maintenance doses, used the method of body surface potential mapping. The decision to use a greater number of leads for the determination of the QT dispersion helps to determine the QTd more accurately than an assessment with only 12 or even 6 precordial leads. The use of the low number of leads was undoubtedly the main cause of the repeatedly described poor reproducibility (Kautzner et al. 1994, Day et al. 1990). Enhanced accuracy for QT dispersion assessment from the 12-lead ECG in comparison with only 6 precordial leads was reported as well (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 the important cause of the poor reproducibility (Glancy et al. 1996). Both the intra- and interobserver variability of QT and QTc dispersion assessed in this study permits the use of this method to determine changes in the QT dispersion, as the detected changes lie well above the errors encountered in this study. Also an influence of subjective evaluation of QT dispersion was prevented by a procedure of data processing: values of QT interval were written into specially designed Excel tables without possibility to follow values of other QT intervals. QT dispersion was then calculated automatically from these tables.

Measurements performed in the present study indicate that dosulepin causes an increase in both the QT and QTc dispersion. Surprisingly, these findings are in agreement with those from our previous study (Lechmanová et al., 2002),

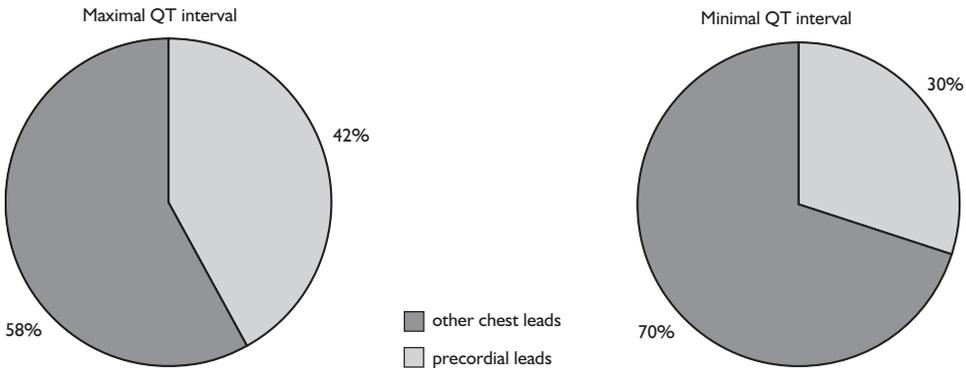


Fig. 5 – The distribution of maximal (above) and minimal (below) QT intervals in precordial leads and in other leads from the chest surface in all examined persons. In most cases both maximal and minimal values were not located in precordial leads.

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 ischaemia, but it can also be increased physiologically by a changed spatial arrangement of the chest organs, including the heart.

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 the changed course of repolarization, which reflects the cardio-toxic side effects of dosulepin. 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 Tab. 2), it does differ significantly in the case of minimal values of the QT interval in the late pregnancy group – $\chi^2 = 13.324$; $p < 0.05$, where the minimal QT intervals are predominantly in right frontal quadrant of the chest.

The correlation between QTd and the dosulepin plasma level was statistically significant, suggesting that the QTd estimated from increased number of ECG leads 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 even prophylactic plasma levels. Moreover the results of this study suggest that even prophylactic doses of dosulepin have considerable effect on repolarization pattern that could be well detectable from BDSM but not from standard 12-lead electrocardiogram. In our previous study (Slaviček et al., 1998) we have evaluated changes of electric heart field correlated to doses of tricyclic antidepressants in patients suffering from recurrent depressive disorders. Nevertheless, 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 whilst 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 (Glassman, et al., 1993, Hollister 1989). That is why plasma levels of tricyclic antidepressants can be different in various subjects, even though the doses used are identical (Leonard, 1994).

The difference between results obtained from body surface potential maps and those obtained from standard precordial leads could be explained by above mentioned lower sensitivity and accuracy of precordial leads. This fact is well demonstrated by the Fig. 5, where the distribution of both maximal (above) and minimal (below) QT intervals. In other words: the longest and the shortest QT intervals, that define the QTd, were detected in other regions of the chest than in the left precordium where standard ECG chest leads are located. In the case

(patient No 13) demonstrated in figure 4 it could be well recognized that QTd estimated from precordial leads is shorter than that estimated from the whole chest.

Present results support our previous conclusion (Lechmanova et al. 2002) that the prolonged QT dispersion is to be interpreted as “an unspecific sign of altered repolarization course”. The prolongation of QT dispersion reflects not only an increased risk of severe arrhythmias but undoubtedly it can result from some other factors (including physiological ones

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