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Plasma Levels of Dosulepine and Heart Electric Field

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Summary

Antidepressants, particularly tricyclic (TCA) antidepressants, may have cardiotoxic effects, such as cardiac arrhythmias, especially in patients with cardiovascular diseases. For most of TCA, no exact correlation between dosage, plasma levels and changes of ECG parameters of standard ECG has been found. So far, no relationship between dosulepine plasma levels and heart electric field parameters has been studied. We selected 18 female outpatient subjects diagnosed with recurrent depressive disorders, currently in the remission phase (HAMD < 10), without any cardiovascular disease. Patients were treated with daily dosulepine doses of 25-125 mg for 4-8 weeks. 30 heart electric field parameters were analyzed by Cardiag 128.1 diagnostic system as part of BSPM (Body Surface Potential Mapping). Acquired data were correlated with dosulepine plasma levels by means of Spearman's rank order correlation test. Four ECG parameters showed a significant correlation with dosulepine plasma levels: QRS axis deviation in frontal plane ($p=0.01$), DIAM 40 max ($p<0.05$), QRS-STT angle in transversal and left sagittal plane ($p<0.05$). The demonstrated changes confirmed dosulepine influence on the early myocardium depolarization phase and the correlation of this effect with dosulepine dose (its plasma concentration). The higher the dosulepine level, the more marked are the changes of the QRS-STT angle in transversal and sagittal planes and the changes in the QRS axis deviation in frontal plane. Repeatedly recorded changes in the heart electric field were dosulepine-specific and dependent on its plasma levels.

Key words

Cardiotoxicity • Dosulepine • Plasma levels • ECG • Heart electric field

Introduction

Antidepressants, particularly tricyclic antidepressants (TCA), influence the cardiovascular system to a variable degree. Already at therapeutic daily doses of 100-200 mg and at plasma concentrations of 150-200 ng/ml, TCA cause sinus tachycardia (a marked atropine-like effect) and also a prolongation of intraventricular conduction (less marked quinidine-like effect). It is necessary to consider carefully their use particularly in depressive patients with concurrent cardiovascular diseases (Biggs *et al.* 1997, Crome 1982, Roose *et al.* 1991, Glassman 1997, Personne *et al.* 1997, Paclt and Kitzlerová 2000, Rodriguez 2001).

The prolongation of intraventricular conduction manifests itself by a prolonged ORS interval and may also be one of the bundle branch block manifestations. First-degree of atrioventricular heart block can by found in 70 % of young patients treated with TCA with serum concentrations of 350 ng/ml but only in 3 % of patients with concentrations below 350 ng/ml. The irregular ventricular depolarization and repolarization may lead to

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ventricular arrhythmia, tachycardia or even to fibrillation and the sudden death syndrome (Preskorn and Fast 1991). This effect is associated with prolongation of both the QT interval and the refractory period. At the membrane level, the therapeutic doses of TCA have restrictive effect on the fast sodium current influx into the cell during the action potential (Rawling and Fozzard 1979). TCA (e.g. amitriptyline) have been proved to lower the L-type calcium current (Ica) in the rat ventricular cell in culture (Hamplová-Peichlová *et al.* 2002).

For most TCA, no exact correlation between doses, plasma levels and changes of standard ECG parameters has been found. Doses and plasma levels of certain TCA (amitriptyline, nortriptyline, imipramine, desipramine, doxepine, clomipramine) correlate with the changes of ECG parameters of a 12-lead ECG. This is based on the studies of overdosage with the above mentioned drugs (Petit *et al.* 1977, Biggs *et al.* 1977, Braithwaite *et al.* 1979, Rawlings and Fozzard 1979, Crome 1982, Montgomery *et al.* 1989, Buckley *et al.* 1994, Singh *et al.* 2002).

TCA have a narrow range between therapeutic and toxic drug levels. Significant cardiovascular toxicity symptoms during TCA treatment appear after the use of 3-4 times higher daily doses (450-1000 mg). TCA doses of more than 1 g are toxic and potentially fatal. Generally, a serious TCA overdosage is characterized by plasma concentrations of 1000 ng/ml. QRS interval duration of 140 ms or more can be accompanied by grand mal type generalized seizures (Biggs *et al.* 1997, Crome 1982).

Only a partial prediction of more serious cardiovascular disorders such as ventricular arrhythmia, cardiac conduction abnormalities or exacerbation of ischemic changes is possible during the course of antidepressant (AD) therapy. Doses and plasma levels are not considered accurate enough for the purpose of clinical response prediction. According to the most recent study of TCA overdosage, possible cardiotoxicity can be more accurately predicted from the QRS duration time longer than 140 ms, indicating a prolongation of intraventricular conduction (Singh *et al.* 2002). ECG changes reflect cellular and subcellular myocardium impairment more accurately than drug plasma concentrations. QRS has a 100 % sensitivity and 98-100 % specificity in prediction of cardiac arrhythmias and seizures. This study revealed three additional more sensitive cardiac predictive factors, namely the QRS axis deviation (120-270 degree right deviation), R wave amplitude > 3 mm in lead aVR and systolic blood pressure below 100 mm Hg (Singh *et al.* 2002).

The mechanism of cardiotoxic changes during the course of TCA therapy remains unclear. The prediction of cardiotoxicity risks cannot be based solely on the recorded plasma levels and in some cases not even on the prolonged QTc interval. ECG mapping, which is more sensitive than the standard 12-lead ECG, has revealed new facts about manifestation of cardiotoxic changes. Thanks to the high density of precordial leads and their uniform distribution, ECG mapping is more suitable for analyzing local depolarization and repolarization changes during the course of antidepressant therapy. Due to simultaneous registration of vectors, it allows us to determine more exactly not only the QRS axis deviation in individual planes, but also the angles of maximum QRS and T wave vectors and to calculate the spatial angle.

Despite its potential cardiotoxicity, dosulepine is a frequently used TCA in the Czech Republic with good results in depressive disorders using the aggressive treatment with daily doses of 100-400 mg. So far no relationship between dosulepine plasma concentration and heart electric field parameters has been studied.

Methods

We examined 18 female psychiatric outpatient subjects diagnosed as a recurrent depressive disorder, currently in the remission phase, F 33.4 (according to ICD-10), Hamilton Psychiatric Rating Scale for Depression (HAMD) score below 10, treated with a dosulepine maintenance daily dose of 25-125 mg. Patients did not suffer from any cardiac disease. Therapy lasted for 4-8 weeks. The control group consisted of 27 women without any cardiovascular or psychiatric disease, aged 36.9±9.8 years, examined by a cardiologist.

The ECG (electrocardiogram), VCG (vectorcardiogram) and BSPM (ECG Body Surface Potential Mapping) were recorded and 30 parameters of heart electric field were analyzed by Cardiag 128.1 diagnostic system (Kittnar and Šťovíček 1993). ECG, heart rate, duration of PQ, QRS, QT, QTc, and RR intervals (ms) were assessed. Frank lead vectors for the VCG were recorded (Frank 1956). Deviation of the QRS axis was measured in the frontal plane with zero degree on the left horizontal lead and with a positive clockwise direction (parameter 8, Table 1, Fig. 1). QRS-STT plane vectors in frontal, transversal and left sagittal planes were measured with an anticlockwise direction of positivity (parameter 29-31, Table 1, Figs 2, 3). The spatial angle QRS-STT was measured, but not evaluated in this study (Ruttkay-Nedecký 1983).

Table 1. Basal characteristics female patients treated with dosulepine (DOS).

	Parameter	MeanSD	Min; Max
1	*Age (years)*	46.0±12.5	19; 62
2	*F (min^{-1})*	84.4±11.7	63; 110
3	*PQ (ms)*	151±34.3	106; 224
4	*QRS (ms)*	94.2±16.6	70; 150
5	*QT (ms)*	363±33.6	308; 418
6	*QTc (ms)*	427±32.4	363; 495
7	*RR (ms)*	725±102.8	549; 958
8	*QRS axis deviation (°)*	37.3±54.8	–153; 93
9	*DIIM max (μVs)*	27.50±14.65	5.78; 65.04
10	*DIIM min (μVs)*	–27.93±15.32	–64.31; –7.09
11	*RIIM max (μVs)*	50.83±28.20	3.81; 93.21
12	*RIIM min (μVs)*	–27.46±23.86	–91.73; –2.36
13	*DRIIM max (μVs)*	43.17±28.09	4.42; 92.95
14	*DRIIM min (μVs)*	–22.84±16.48	–53.41; –3.95
15	*DIAM 30max (μVs)*	4.55±2.37	1.30; 11.76
16	*DIAM 40max (μVs)*	10.79±5.87	4.01; 29.74
17	*DIAM 30min (μVs)*	–2.29±1.61	–7.90; –0.84
18	*DIAM 40min (μVs)*	–7.09±7.85	–36.50; –2.59
19	*RIAM 35max (μVs)*	7.67±8.92	1.87; 34.95
20	*RIAM 80max (μVs)*	18.09±21.94	5.13; 88.06
21	*RIAM 35min (μVs)*	–4.91±4.30	–18.30; –1.04
22	*RIAM 80min (μVs)*	–12.46±12.44	–51.43; –1.16
23	*R-IPMAM (mV)*	4.27±4.28	0; 13.99
24	*Q-IIM min (μVs)*	–28.45±17.12	–68.38; –10.73
25	*Q-IPMAM (mV)*	–13.94±8.46	–38.40; –4.83
26	*QS-IPMAM (mV)*	–13.92±8.48	–38.40; –4.62
27	*ICHVAT (ms)*	70.1±20.6	0; 96
28	*Q-ICHM (ms)*	85.4±21.5	54; 150
29	*QRS-STT fron. (°)*	2.0±60.7	–193; 71
30	*QRS-STT tran. (°)*	–82.2±48.8	–153; –2
31	*QRS-STT sag. (°)*	–72.1±46.1	–152; 50
32	*Plasma DOS (ng/ml)*	35.0±17.3	5; 67

BSPM: depolarization, repolarization and total isointegral maps, their maximum and minimum (DIIM max, DIIM min, RIIM min, RIIM max, DRIIM max, DRIIM min). Isoarea maps, their maximum and minimum in 30th and 40th ms of depolarization and in 35th and 80th ms of repolarization (DIAM max 30, DIAM max 40, DIAM min 30, DIAM min 40, RIAM max 35, RIAM max 80, RIAM min 35, RIAM min 80). Maximum amplitude of R wave (IPMAM-R). Activation time between the beginning of depolarization in an orthogonal lead and maximum of R wave in individual chest leads (ICHVAT). Map of Q duration (Q-ICHM), QS wave amplitude maps (Q-IPMAM, QS-IPMAM).

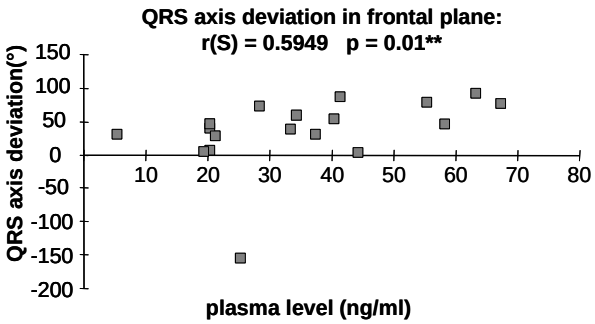

Fig. 1. *QRS axis deviation in frontal plane (degrees); r (S) – Spearman rank order correlation coefficient, axis x – dosulepine plasma level (ng/ml) , axis y – QRS axis deviation (degrees)*

Basal characteristics of studied patients, plasma dosulepine levels (determined by high-performance liquid chromatography according to Balíková 1992) and BSPM parameters (ECG Body Surface Potential Mapping according to Kittnar *et al.* 1993, Slavíček *et al.* 1998, Pišvejcová *et al.* 2002, Paclt *et al.* 2003) are shown in Table 1.

Spearman rank order correlation coefficient was used to determine the correlation between obtained data and dosulepine plasma levels.

Results

In this study the heart rate was higher (84.4±11.7/min) than the normal (71.9±8.7), even when maintenance doses of dosulepine were used. The R-R interval values were shortened (725±102.8 ms), when compared with controls (845.6±101.3 ms) (Table 1).

The assessment by Spearman rank order correlation coefficient showed significant correlation ($p<0.05$) between dosulepine concentrations and four ECG parameters: QRS axis deviation in frontal plane, DIAM 40 max and QRS-STT angles in transversal plane, QRS-STT in sagittal plane (Figs 1-4).

QRS axis deviation in frontal plane significantly correlated with dosulepine plasma levels (10-70 ng/ml). The higher the plasma level of dosulepine, the higher was the value of QRS axis deviation (right axis deviation, Fig. 1). QRS-STT vectors plane angles in transversal plane (horizontal plane – Fig. 2) and also in left sagittal plane (Fig. 3) completed the findings shown in Figure 1 – gradual angles opening with increasing plasma levels. Maximum of the depolarization isoarea map at 40 ms

following QRS initiation (DIAM max 40) decreased in direct proportion to the increasing dosulepine plasma levels (Fig. 4).

The comparison of control group and dosulepine-treated patients is shown in Figure 5. QRS axis deviation in frontal plane was decreased ($p<0.05$), QRS-STT angles of planar vectors in transversal and left sagittal planes were more negative in dosulepine patients than in the controls ($p<0.01$).

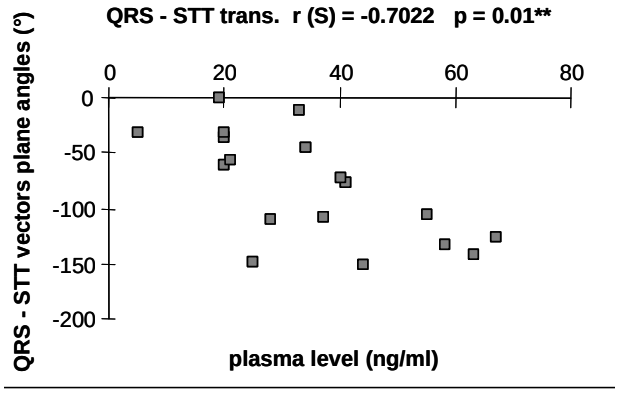

Fig. 2. *QRS-STT vectors plane angles in transversal plane (degrees); r (S) – Spearman rank order correlation coefficient, axis x – dosulepine plasma level (ng/ml), axis y – QRS-STT vector plane angles (degrees)*

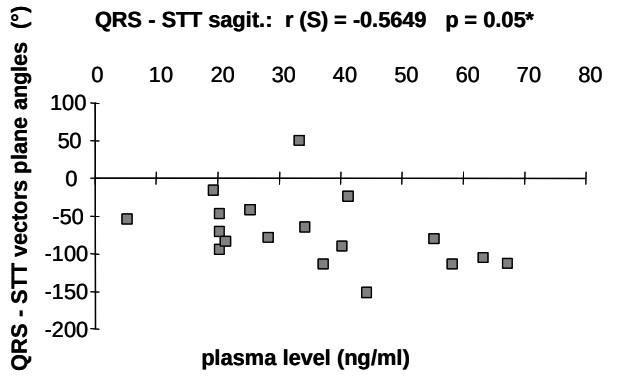

Fig. 3. *QRS-STT vectors plane angles in left sagittal plane (degrees); r (S) – Spearman rank order correlation coefficient, axis x – dosulepine plasma level (ng/ml), axis y – QRS - STT vector plane angles (degrees)*

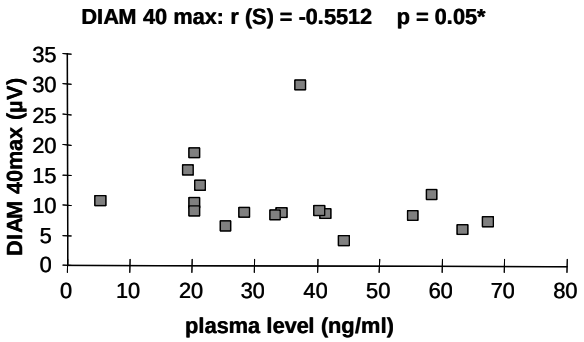

Fig. 4. *Maximum of the depolarization isoarea map at 40 ms following QRS initiation (DIAM max 40, µVs). Axis x – dosulepine plasma level (ng/ml), axis y – absolute value of maximum (µV), r (S) – Spearman rank order correlation coefficient.*

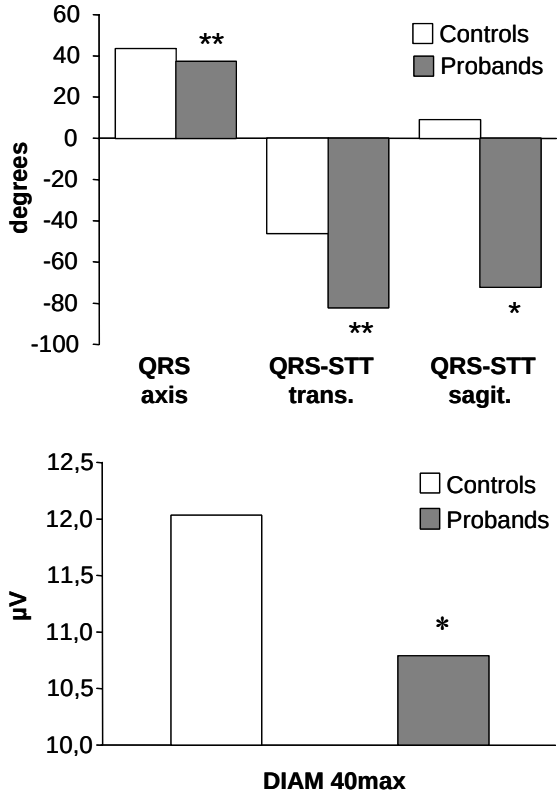

Fig. 5. *Upper part – comparison of dosulepine patients with controls: QRS axis deviation, QRS-STT angles of planar vectors in transversal and left sagittal planes (degrees). Lower part – maximum of depolarization isoarea map in the first 40 ms from the beginning of the Q wave (µVs).*

Discussion

The influence of treatment with TCA therapeutic doses on the onset of tachycardia was already reported previously (Slavíček *et al.* 1998). A comparison of patients treated with TCA and subsequently developing tachycardia with primarily tachycardic individuals with similar tachycardia (suffering from neurocirculatory asthenia) undergoing no treatment showed changes in isointegral and isoarea maps of heart electric field only in patients treated with TCA (Slavíček *et al.* 1995, Paclt *et al.* 1995). Tachycardia that occurs during the treatment with standard therapeutic TCA doses is caused by a blockade of biogenic amine reuptake (particularly noradrenaline, serotonine and dopamine) on presynaptic terminals in the CNS and the periphery (Merigian *et al.* 1991). This creates a hyperadrenergic state with initial hypertension and tachycardia. The subsequent blockade of α-adrenergic receptors on peripheral nerve terminals with noradrenaline depletion causes postural hypotension, which leads to reactive tachycardia (Singh *et al.* 2002). Tachycardia and heart electric field changes during the adrenergic system activation were observed in panic disorders without treatment (Pišvejcová *et al.* 2002).

In this work, we demonstrated that four ECG parameters (determined by the BSPM method) show directly proportional correlation with dosulepine plasma levels. The QRS axis deviation and maximum of depolarization isoarea maps in the first 40 ms of QRS (DIAM max 40) are related to the generally accepted thesis of TCA influence on early depolarization phase. In a previous study (Paclt *et al.* 1999), DIAM max 40 has been shown to be a dose-dependent parameter, which has been confirmed by the present study, revealing its dependence on plasma dosulepine levels. Values of the QRS-STT angles in sagittal and left transversal planes and QRS axis right deviation in frontal plane are increased together with increasing dosulepine plasma levels. The VCG spatial QRS-STT angle was increased during maximum inspiration (Beswick *et al.* 1961), in hypertensive patients (Dern *et al.* 1967) or during increased adrenergic myocardial activation (Andrasyová *et al.* 1998). Our work confirmed the adrenergic system activation. The QRS axis deviation described by Liebelt *et al.* (1997) and Singh *et al.* (2002) has been confirmed in our study (Fig. 1). The additional findings of the QRS-STT maximum vector angles opening in transversal and left sagittal planes (Figs 2, 3 and 5) generally show different depolarization and repolarization of ventricular myocardium with the increasing dosulepine plasma levels. The changes in QRS angles were also noted in advanced stages of gravidity and after the delivery (Lechmanová *et al.* 2002). Depolarization isointegral and isoarea maps, their maxima and minima, are changing during the ontogenesis of healthy individuals (Slavíček *et al.* 2001) and they are also altered in patients with cardiac hypertrophy (Kozlíková *et al.* 1998) or ischemia (Kittnar *et al.* 1993).

In the present work we extended our previous studies (Slavíček *et al.* 1998, Paclt *et al.* 1999, Pišvejcová *et al.* 2002, Paclt *et al.* 2003), in which we did not assess dosulepine plasma concentrations, but only the TCA daily doses in general (50-200 mg) in connection with changes in the heart electric field. We thus confirmed these changes in the present report.

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Reprint requests

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