Physiol. Res. 47: 297–300, 1998

SHORT COMMUNICATION

Antidepressant Drugs and Heart Electrical Field

J. SLAVÍČEK[1], I. PACLT[2], J. HAMPLOVÁ[2], O. KITTNAR[1], Z. TREFNÝ[3], B.M. HORÁČEK[4]

[1]Department of Physiology, [2]Department of Psychiatry, First Faculty of Medicine, Charles University, [3]Department of Medicine, Prague 7, Czech Republic and [4]Department of Physiology and Biophysics, Dalhousie University, Halifax, New Scotia, Canada

Received January 29, 1998
Accepted April 1, 1998

Summary

Some antidepressant drugs, especially tricyclic ones – (TCA), have cardiovascular side effects. To compare the effects of antidepressant drugs, the electrocardiogram (ECG), vectorcardiogram (VCG), and body surface maps (BSM) were recorded in psychiatric patients without cardiovascular diseases treated by a) TCA amitriptyline or dosulepin (daily dose 50–200 mg, 22 patients), b) lithium (serum level 0.66±0.08 meq/l, 21 patients), c) selective serotonine reuptake inhibitor citalopram (daily doses 20–60 mg, 30 patients), and in 23 control patients. In the TCA-treated patients, the heart rate was increased, QT and RR intervals shortened ($p<0.01$, antimuscarinic effect). This was not observed in lithium- and citalopram-treated patients. All antidepressants decreased the absolute maximum values of depolarization isointegral maps, lithium and TCA reduced the initial and citalopram the later phase of depolarization. Citalopram slightly diminished the amplitude of the R wave. The results confirm the antimuscarinic effects of TCA in therapeutic doses and specify the intraventricular effects of antidepressants.

Key words

Antidepressants – Tricyclic – Lithium – SSRI Citalopram – ECG body surface mapping – Cardiac depolarization – Repolarization

Some antidepressant drugs especially tricyclic (TCA) ones have cardiovascular side effects, e.g. anticholinergic (antimuscarinic), α_1-adrenoreceptor blocking, antihistaminic (H_1), and membrane stabilizing (quinidine-like) effects (Rawlings and Fozzard 1978). Their use in depressed patients is dangerous especially in connection with cardiovascular diseases (Glassmann *et al.* 1993). Amitriptyline decreased myocardial contractility after 6 days of treatment in healthy volunteers and an increase in mean arterial blood pressure was observed. Heart rate was raised with no alterations of ECG parameters (Wester and Siegers 1980).

It was demonstrated in 1977 that TCA imipramine provoked antiarrhythmic effect comparable with quinidine (Bigger *et al.* 1977, Bigger 1990). On the other hand, antiarrhythmic drugs, even though they suppress arrhythmias, may increase rather than decrease the mortality rate (Glassmann *et al.* 1987, Bigger 1990). TCA's exert a restricting effect on the fast inward sodium current during the membrane action potential (AP) which reflects the initial (zero) phase of depolarization (prolongation of AP duration, QRS, QT, and QTc prolongation) (Weld and Bigger 1978).

The selective serotonine reuptake inhibitor (SSRI) citalopram has a lower affinity to noradrenergic muscarinic and histamine receptors when compared with TCA. The heart rate is unchanged or slightly reduced. It is not quite certain if SSRI increases the tone of the parasympathetic, or decreases the tone of the sympathetic nervous system (Glassman *et al.* 1993). The side effect of lithium on cardiovascular apparatus was described as isoelectricity of the T wave with bundle branch blocks and the appearance of the U wave (Mitchell and Mackenzie 1982).

The question arises, how the different antidepressant drugs influence the spatial and temporal changes of depolarization and repolarization in the human heart registered by the method of BSM in relation to their cellular effects (Taccardi 1990).

The aim of the present work was to compare the electrocardiographic parameters in depressive patients without cardiovascular diseases, treated with TCA (amitriptyline or dosulepin), selective serotonine reuptake inhibitor (SSRI) citalopram or lithium, using ECG body surface potential mapping (BSM) for a more detailed analysis than can be performed by the 12-lead ECG (Taccardi, 1963, Kittnar *et al.* 1993, Slavíček *et al.* 1995). Due to the high number and density of leads in the precordial area, the BSM method permits to specify the origin of arrhythmias (Mitchell *et al.* 1992) and the local effects of antidepressants on the initial or later phases of activation (depolarization) and repolarization in the heart. The different results of antidepressants on heart electrical field parameters have been correlated with their membrane cellular effects.

Three groups of patients of both sexes aged 42 (27–58) years from the Department of Psychiatry, Prague and a control group were studied (Table 1).

Table 1
Characteristics of examined groups

	Controls	TCA	Lithium	Citalopram
Number	21	22	21	30
Age	40.8±9.2	42.5±16.8	45.9±10.9	41.2±14.7
Men/Women	12/9	5/17	13/8	6/24
Serum level (meq/l)			0.66±0.08	
Daily dose (mg)		50–300		20–60
Duration of therapy		4–5 weeks	1–22 years	4–5 weeks

Data are means ± S.E.M.

ECG, VCG and BSM (Stojan *et al.* 1993, Kittnar *et al.* 1993) were recorded using the diagnostic system Cardiag (Slavíček *et al.* 1995, Paclt *et al.* 1995). Thirty-two parameters of the heart electric field were measured – *ECG:* heart rate, duration of PQ, QRS, QT, QTc, RR. *VCG:* P, QRS, T loop direction, shape, in the frontal, transversal and left sagital planes, QRS-STT space angle, QRS axis deviation in the frontal plane. *Mapping:* isopotential, depolarization and repolarization (DIPM, RIPM) maps, their maximum (μV). Isointegral depolarization (DIIM), repolarization (RIIM), total (DRIIM) maps, their maximum and minimum (absolute values, μV). Isoarea depolarization (DIAM 30, DIAM 40) and repolarization (RIAM 35, RIAM 80) maps, their maximum and minimum (μV), isopotential maps of asynchronous maximum R wave (IPMAM-R, μV). Isopotential maps of asynchronous minimum Q and S wave (IPMAM-QS, μV). For the statistical evaluation ANOVA and the T-test were used. The results are summarized in Table 2.

The most pronounced effect in TCA patients was sinus tachycardia with a shortening of QT and RR intervals (anticholinergic effect). In depressed patients without cardiovascular diseases it seemed to be of little significance, but it was most prominent in patients with substantial vagal activity and slower pretreatment rates in the ECG (Vaughan-Williams 1991, Enemark 1993). Sinus tachycardia was not observed in lithium- and citalopram-treated patients. In TCA and lithium patients the parameter DIAM max 30, i.e. the initial phase of depolarization, was decreased. In our previous work, DIAM max was decreased although the heart rate was the same as in the control group without treatment, showing a "pure" quinidine-like effect without modification by an atropine-like effect (Slavíček *et al.* 1995). Lithium is a substitute for sodium in the membrane of heart cells (Carmeliet 1964). It suppresses the function of S-A and A-V node (Rosenqvist *et al.* 1993), and the inward i_{NaCa} current in the heart (Janvier and Boyett 1996). On the other hand, in citalopram-treated patients, the DIIM max

and RIIM max were decreased in the later phase of depolarization (a small quinidine-like effect). Furthermore, the maximum amplitude of R wave (IPMAM-R) was lower than in the controls (Table 2).

Table 2
Effects of antidepressant drugs on some ECG parameters in patients and controls.

Parameter	Controls	TCA	Lithium	Citalopram
Number of patients	21	22	21	30
Heart rate (min^{-1})	71.9±8.7	91.0±16.6***	74.9±13.0	75.6±13.7
QT (ms)	371.1±21.5	342.6±37.9*	401.6±131.3	375.0±33.8
RR (ms)	845.6±101.3	682.6±131.6**	827.3±172.0	821.1±152.0
DIIM max (μV)	39.50±17.80	31.94±14.36*	32.25±13.59	27.87±11.75*
RIIM max (μV)	67.19±22.28	50.50±18.80	62.50±27.41	43.38±24.41*
DIAM max 30 (μV)	5.65±1.98	4.21±1.32*	4.61±1.18*	4.73±1.70
IPMAM-R (mV)	1.91±0.70	1.59±0.50	1.69±0.70	1.39±0.45*

*DIIM max – maximum of depolarization isointegral map, RIIM max – maximum of repolarization isointegral map, DIAM max 30 – maximum of depolarization isoarea map, (isointegral map from the beginning of QRS to 30th ms of depolarization), IPMAM-R – maximum amplitude of R wave. Mean values ± S.E.M. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ in comparison with the controls.*

Thus, a decrease of the maximum was found in all groups of our patients in isointegral or isoarea maps (quinidine-like effect). The relatively low TCA ambulatory daily doses (50 mg) with an antidepressant effect provoked both an anticholinergic (tachycardia) and a small quinidine-like effect, which was also detectable by signal averaged ECG (Mladoševičová *et al.* 1996). The origin of negative dromotropic and inotropic effect of antidepressants probably depends on a decrease of the calcium current which is common to all three groups of antidepressants used in the present work (Minarovič *et al.* 1995). Amitriptyline blocked the neuronal uptake and prejunctional α_2-adrenoreceptors (Bradley and Doggrell 1983). It provoked the arrhythmias and released lactate dehydrogenase (Acosta and Ramos 1984). The decrease of contractility due to a depression of transmembrane AP and the slow calcium channels as well as the decreased rate and prolongation of contractions impaired calcium reabsorption from the sarcoplasma (Meledin *et al.* 1997).

In conclusions, the method of BSM is capable of detecting local changes in the activation and repolarization in the heart better than the classic 12-lead ECG. The isointegral and isoarea maps are sensitive enough to confirm the different cellular effects of antidepressant drugs on the heart muscle. While TCA and lithium decreased the initial phase of activation and repolarization, whereas citalopram decreased the later phase.

Acknowledgement
The authors wish to express their thanks to Miss H. Vašková for technical help in registration of electrical parameters with the Cardiag diagnostic system. The work was partially supported by grants 106/94/1554, 106/95/1164 and 106/96/1584 from the Grant Agency of the Czech Republic.

References

ACOSTA D., RAMOS K.: Cardiotoxicity of tricyclic antidepressants in primary cultures of rat myocardial cells. *J. Toxicol. Environ. Health* **14:** 137–143, 1984.

BIGGER J.T. Jr., GIARDINA E.G.V., PEREL J.M., KANTOR S.J., GLASSMAN A.H.: Cardiac antiarrhythmic effect of imipramine hydrochloride. *N. Engl. J. Med.* **296:** 206–208, 1977.

BIGGER J.T. Jr.: Implications of the cardiac arrhythmia suppression trial for antiarrhythmic drug treatment. *Am. J. Cardiol.* **65:** 3D–10D, 1990.

BRADLEY L., DOGGRELL S.A.: Effects of amitriptyline and mianserin on noradrenergic transmission in the rat isolated right ventricle. *J. Auton. Pharmacol.* **4:** 287–285, 1983.

CARMELIET E.E: Influence of lithium ions on the transmembrane potential and cation content of cardiac cells. *J. Gen. Physiol.* **47:** 501–530, 1964.

ENEMARK B.O.: The importance of ECG monitoring in antidepressant treatment. *Nord. J. Psychiat.* **47** (Suppl.): 57–65, 1993.

GLASSMAN A.H., ROOSE S.P., GIARDINA E.G.V., BIGGER J.T.Jr.: Cardiovascular effects of tricyclic antidepressants. In: *Psychopharmacology: The Third Generation of Progress*, MELTZER H.Y. (ed.), New York, Raven Press, 1987, pp. 1437–1442.

GLASSMAN A.H., ROOSE S. P., RIVELLI S.K., PREUD'HOMME X.A.: Cardiovascular effects of antidepressant drugs. *Nord. J. Psychiat.* **47** (Suppl.): 41–47, 1993.

JANVIER N.C., BOYETT M.R.: The role of Na-Ca exchange current in the cardiac action potential. *Cardiovasc. Res.* **32:** 69–84, 1996.

KITTNAR O., SLAVÍČEK J., VÁVROVÁ M., BARNA M., DOHNALOVÁ A., MÁLKOVÁ A., ASCHERMANN M., HUMHAL J., HRADEC J., KRÁL J.: Repolarization patterns of body surface potential maps (BSPM) in coronary artery disease. *Physiol. Res.* **42:** 123–130, 1993.

MELEDIN V.Y., ANTYUFIEV V.F., MASHANOV G.I.: Effect of amitriptyline on the contractility of a cardiac muscle. Dobutrex as a positive inotropic agent. *Anesthesiol. Reanimatol.* **1:** 76–79, 1997.

MINAROVIČ I., ZAHRADNÍK I., ZAHRADNÍKOVÁ A.: Effect of antidepressants on Ca-current in rat ventricular myocytes. *J. Mol. Cell. Cardiol.* **27:** A130, 1995.

MITCHELL J.E., MACKENZIE T.B: Cardiac effects of lithium therapy in man: a review. *J. Clin. Psychiat.* **43:** 47–51, 1982.

MITCHELL L.B., HUBLEY-KOZEY C.L., SMITH E.R., VYSE D.G., DUFF H.J., GILLIS A.M., HORÁČEK B.M.: Electrocardiographic body surface mapping in patients with ventricular tachycardia: assessment of utility in the identification of effective pharmacologic therapy. *Circulation* **86:** 383–393, 1992.

MLADOŠEVIČOVÁ B., HULÍN I., POGADY J., MARTISOVÁ D., PETRÁŠOVÁ H., HUBKA P.: Signal-averaged ECG in patients with antidepressant therapy. *Int. J. Cardiol.* **54:** 27–31, 1996.

PACLT I., SLAVÍČEK J., KITTNAR O., DOHNALOVÁ A.: Electrocardiological changes during the treatment with antidepressants in man. *Homeostasis* **36:** 223–227, 1995.

RAWLINGS D., FOZZARD H.A.: Electrophysiological effects of imipramine on cardiac Purkinje fibres. *Am. J. Cardiol.* **41:** 387–390, 1978.

ROSENQVIST M., BERGFELD L., AILI H., MATHE A.A.: Sinus node dysfunction during long-term lithium treatment. *Br. Heart J.* **70:** 371–375, 1993.

SLAVÍČEK J., PACLT I., KITTNAR O., DOHNALOVÁ A.: Some electrocardiographic side effects of antidepressant drugs. *Cor Vasa* **37:** 212–216, 1995.

STOJAN M., BOUDÍK F., ANGEL J.: The methodology of clinical analysis of electric heart field. *Physiol. Res.* **42:** 85–90, 1993.

TACCARDI B.: Distribution of heart potentials on the thoracic surface of normal human subjects. *Circ. Res.* **12:** 341–352, 1963.

TACCARDI B.: Body surface mapping and cardiac electric sources. A historical survey. *J. Electrocardiol.* **23** (Suppl.): 150–154, 1990.

VAUGHAN-WILLIAMS E.M.: Significance of classifying antiarrhythmic actions since the cardiac arrhythmia suppression trial. *J. Clin. Pharmacol.* **31:** 123–135, 1991.

WELD F.M., BIGGER J.T.: Effects of imipramine hydrochloride on electrophysiological properties of sheep cardiac Purkinje fibers. *Am. J. Cardiol.* **41:** 386–392, 1978.

WESTER H.A., SIEGERS C.P.: Cardiovascular effects of mianserin and amitriptyline in healthy volunteers. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **18:** 513–517, 1980.

Reprint requests
Dr. J. Slavíček, Institute of Physiology, First Faculty of Medicine, Charles University, Albertov 5, 128 00 Prague 2, Czech Republic.