Physiol. Res. 52: 311-317, 2003

Electrocardiographic Dose-Dependent Changes in Prophylactic Doses of Dosulepine, Lithium and Citalopram

I. PACLT[1], J. SLAVÍČEK[2], A. DOHNALOVÁ[2], E. KITZLEROVÁ[1], K. PIŠVEJCOVÁ[1]

[1]Department of Psychiatry, and [2]Institute of Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic

Received July 23, 2002
Accepted October, 9, 2002

Summary

Tricyclic antidepressant drugs dosulepine (TCA), serotonin selective reuptake inhibitor (SSRI) and prophylactic agent with antidepressant effect lithium carbonicum (Li) have different cardiovascular side-effects. We compared them in the prophylactic therapy of periodic affective disorder in remission with TCA, SSRI and Li. Our previous papers confirmed the most prominent effects of heart electric field parameters in TCA patients (Slavíček *et al.*, 1998). In the present work we studied for the first time the dose-dependent changes of ECG, body surface potential maps (BSPM – parameter DIAM 30, 40) in 43 TCA dosulepine, 40 SSRI citalopram and 30 Li outpatients (Hamilton scale: HAMD≤10; age 40±5 years; treated for depressive disorders or bipolar disorders). The daily doses of dosulepine were 50-250 mg, citalopram 20-80 mg, Li plasma levels 0.66±0.08 meq/l. The electrocardiogram (ECG), vectorcardiogram (VCG), and BSPM were measured and calculated by the Cardiag 112.1 diagnostic system. The results have shown a relation between the dose of dosulepine and extremum (maximum and minimum) of depolarization isoarea map in dosulepine, but not in citalopram patients. The repolarization BSPM changes were most pronounced in SSRI patients. Lithium in long-term prophylaxy (1-22 years) caused only minimal ECG BSPM changes. The present results correspond with our previous observations.

Key words

ECG • Body surface potential maps • Dosulepine • Citalopram • Dose-dependent changes • Lithium • Prophylactic doses

Introduction

Many antidepressant drugs influence the cardiovascular system. The side effect of tricyclic antidepressants (TCA) is the prolongation of heart intraventricular conduction – the quinidine-like effect (Warrington *et al.* 1989, Švestka 1994). The therapeutic doses of TCA decrease the His-Purkinje and Purkinje-ventricular conduction time (P-V junctions). In conventional 12-lead ECG recordings, the QRS prolongation is observed. A prolongation of QRS higher than 140 ms can provoke the bundle branch block. The first degree of A-V block in 70 % of young patients with TCA blood serum level 350 ng/ml and in 3 % of persons with TCA blood serum level below 350 ng/ml was observed (Preskorn and Fast 1991). The aberrant activation and repolarization in the ventricles induce ventricular arrhythmia, ventricular tachycardia, fibrillation and syndrome of sudden death (Preskorn and Fast 1991). The Q-T duration and refractory period are

Fax+420 241 062 164
E-mail: physres@biomed.cas.cz http://www.biomed.cas.cz/physiolres

prolonged. The quinidine-like effect of therapeutic TCA doses (150-200 ng/ml in the serum) is less pronounced than their antimuscarinic atropine-like effect manifested by tachycardia. TCA alters the Na-K pump activity (Rawling and Fozzard 1979, Weld and Biggert 1980, Glassman *et al.* 1993, Hamplová *et al.* 2002) and the irregular ventricular repolarization is manifested by ST denivelation, different shape and polarity of T wave (Ray *et al.* 1987, Stoudemire and Fogel 1987, Kittzlerová *et al.* 2003).

Lithium side-effects upon the cardiovascular system were described, but only in higher than therapeutic serum levels (e.g. Mitchell and MacKenzie 1982, Kazmierczak and van Lente 1990). If serum lithium level is higher than 1.5 meq/l or reaches toxic values (2-3 meq/l), the sinus dysfunction, such as sinoatrial block, A-V block or atrial flutter, was observed. This is probably due to insufficient brain blood flow, with complex consequences, including disorders of consciousness etc. The heart irritability or bathmotrophy was increased especially in older persons above 60 years. The T wave abnormalities, such as isoelectric inversion, presence of the U wave at normal serum potassium levels, the bundle branch blocks etc., were described (Carmeliet 1964). In the cell membrane, the monovalent cation of sodium is substituted with lithium (Kazmierczak and van Lente 1990) and it influences the Na-Ca exchanger which is blocked by lithium (Enemark 1993).

Compared to TCA, the side-effects of SSRI (selective serotonine reuptake inhihitors) are minimal due to its small influence on noradrenergic, muscarinic and histamine receptors. Their effects on heart rate distinguish from TCA (bradycardia, prolongation of R-R interval, decrease of blood pressure) (Rawling and Fozzard 1978). In sensitive persons, the bradyarrhythmias after fluoxetine were observed. Bradycardia occured only in 2 % of citalopram patients and small tachycardia was observed in 5 %. In bradycardia of younger subjects, the PQ interval was not changed. QTc was slightly prolonged (a quinidine-like effect) and the T wave amplitude was decreased (Enemark 1993).

The ECG body surface maps (BSM) method was used in ontogeny of healthy persons (Green *et al.* 1985, Kozmann *et al.* 1989, 1999, Kittnar and Šťovíček 1993, Slavíček *et al.* 2001), in coronary artery disease (Kittnar *et al.* 1993), or in patients treated with antidepressants (prominent noradrenergic and serotoninergic action) in order to detect changes in the heart electric field (Slavíček *et al.* 1995, 1998, Paclt *et al.* 1995).

We found the influence of lithium and TCA (amitriptyline) on the parameters of early depolarization – depolarization isoarea map maximum (extremum) after 30 and 40 ms of depolarization – DIAM 30, 40 and also the influence of citalopram on the parameters of repolarization – repolarization isointegral – RIIM – and isoarea – RIAM – map maximum (extremum) – (RIAM, RIIM max) (Slavíček *et al.* 1995, 1998, Paclt *et al.* 1995). From these pilot studies we predict most prominent changes in parameter DIAM max 30 in patients treated with TCA (dosulepine), because we suppose that parameters DIAM 30, 40 are the most sensitive markers of quinidine-like effect. We hypothesize that these changes of DIAM 30 and 40 will be more prominent in patients with higher doses of TCA compared to higher doses of citalopram.

Methods

We compared 43 patients treated by dosulepine (TCA), 30 patients treated by lithium, 40 patients treated by citalopram, and 21 control subjects. Patients were treated by monotherapy for 6-8 weeks. The diagnosis of these patients was a periodic depressive disorder. These patients were compared with patients treated for bipolar disorder by lithium monotherapy. All patients were investigated by the Hamilton scale in remission (HAMD $\leq$ 10). The control group consisted of volunteers without any cardiovascular or psychiatric disease in their medical history.

The electrocardiogram (ECG), vectorcardiogram (VCG) in the frontal, transversal, and left sagittal plane were recorded and isopotential, isointegral and isoarea maps were registered using the diagnostic system CARDIAG 112.2 (Kittnar *et al.* 1993, Slavíček *et al.* 1995, 1998, Paclt *et al.* 1995). Forty-nine parameters were evaluated. The following characteristics were obtained: *ECG*: Heart rate (min^{-1}), PQ, QRS, QT, QTc, RR intervals duration (ms); *VCG*: the Frank orthogonal leads were used: (Frank 1956, Rutkay-Nedecký 1983). The QRS axis and QRS-STT angle in the frontal, transversal and left sagittal plane were measured. The spatial angle of QRS-STT was computed by diagnostic system Cardiag (Pišvejcová *et al.* 2002).

ECG body surface potential maps (BSPM) consist of depolarization, repolarization isopotential maps (DIPM, RIPM), their maximum and minimum in μV and also depolarization, repolarization and total isointegral maps, their maximum and minimum in μV (DIIM max, DIIM min, RIIM max, RIIM min, DRIIM max, DRIIM

min). Depolarization isoarea maps, their maximum and minimum in μV (isointegral maps from the beginning of QRS till 30 and 40 ms of depolarization - DIAM max 30, DIAM min 30, DIAM max 40, DIAM min 40), repolarization isoarea maps, their maximum and minimum in μVs (isointegral maps from the point J to 35^{th} and 80^{th} ms of repolarization – RIAM max 35, RIAM min 35, RIAM max 80, RIAM min 80). Maximum amplitude of R wave was measured in μV (IPMAM-R). Activation time (ms) was measured between the beginning of depolarization in an orthogonal lead and maximum of R wave in individual chest leads (ICHVAT). Map of Q duration is expressed in ms (Q-ICHM, Stojan, 1991a, 1991b, Stojan *et al.* 1993). The localization of maximum and minimum (extremum) on the surface of thorax were evaluated.

Statistical comparison were performed by ANOVA, T-test, and Spearman correlation

Results

The results are summarized in Table 1 (mean values ± S.E.M.). The correlation of dosulepine prophylactic daily doses and parameters of heart electric field are described in Table 2. The same correlations with citalopram are presented in Table 3. Spearman's correlation was calculated only for patients where doses of drugs were not changed in the last 14 days (dosulepine and citalopram patients).

Table 1. Characterization of patients and controls.

Parameters	Patients treated by			Controls	ANOVA
	Citalopram	Dosulepin	Lithium		
Number of patients	40	43	30	21	
Age (years)	40.03 ± 14.43	41.33 ± 17.05	46.40 ± 10.55	40.81 ± 5.92	0.0002 ± 0.1744
Plasma levels (meq/l)	–	–	0.66 ± 0.08	–	
Daily dose (mg)	20-80	50-250	–	–	
Therapy duration	6-8 weeks	6-8 weeks	1-22 years	–	
Heart rate (min^{-1})	75.02 ± 12.80	89.47 ± 16.64***	75.20 ± 11.90	71.91 ± 8.69	0.0025 ± 0.0000
PQ (ms)	154.30 ± 46.23	138.05 ± 23.50	157.93 ± 30.93	151.43 ± 20.49	0.0423 ± 0.0125
QT (ms)	379.50 ± 36.73	347.49 ± 36.75*	393.53 ± 112.13	371.05 ± 21.50	0.0543 ± 0.0126
RR (ms)	822.30 ±144.33	696.09±139.49***	817.20 ± 152.21	845.62 ± 101.28	0.3893 ± 0.0000
Spatial angle QRS-STT (degrees)	47.58 ± 44.07	64.33 ± 45.45	30.83 ± 42.84	44.62 ± 20.04	0.0344 ± 0.0139
DIIM max (μV)	28.63 ± 13.12	29.87 ± 14.32	32.63 ± 15.02	39.50 ± 17.30	0.2998 ± 0.0424
RIIM max (μV)	46.45 ± 23.20*	49.99 ± 18.49	61.91 ± 28.08	67.19 ± 22.28	0.1074 ± 0.0016
RIIM min (μV)	–20.43 ± 11.85**	–28.41 ± 14.50*	–28.55 ± 16.94	–27.60 ± 13.40	0.6046 ± 0.0387
DRIIM min (μV)	–28.40 ± 16.40*	–38.25 ± 19.20	–26.11 ± 19.92	–33.15 ± 22.68	0.1625 ± 0.0345
DIAMmax30 (μV)	4.23 ± 1.54*	5.63 ± 4.55	4.17 ± 1.17*	5.65 ± 1.98	0.0068 ± 0.0089
DIAMmax40 (μV)	10.28 ± 3.51	12.11 ± 5.95	10.58 ± 4.26	13.01 ± 4.54	0.0180 ± 0.0723
RIAMmin35 (μV)	–1.42 ± 0.95	–2.33 ± 1.74	–1.58 ± 0.73	–1.63 ± 0.73	0.0007 ± 0.0407
RIAMmin80 (μVs)	–3.31 ± 1.71	–5.90 ± 4.24	–3.74 ± 1.57	–4.05 ± 2.09	0.0003 ± 0.0056
IPMAM-R (μV)	14.09 ± 5.01*	14.97 ± 5.05	16.37 ± 6.90	19.16 ± 7.04	0.1271 ± 0.0119
ICHVAT (ms)	72.85 ± 7.83	70.65 ± 8.52	75.20 ± 7.59	71.24 ± 4.58	0.2891 ± 0.0782
Angles QRS-STT Front. (degrees)	–22.05 ± 51.94	–47.05 ± 53.99**	–6.10 ± 42.58	–15.2 ± 19.25	0.0201 ± 0.0033
Angles QRS-STT Left Sagit. (degrees)	–44.08 ± 68.12	–2.84 ± 82.19	–49.97 ± 72.57	–44.43 ± 66.07	0.1669 ± 0.0198

*The significance of differences between patients and controls: * p<0,05; ** p<0.01; *** p<0.001.*

Table 2. Spearman coefficients – dosulepine.

Parameters	Number	Spearman coefficient	Significance level
DIAM max 30	39	–0.3299	0.05
DIAM max 40	39	–0.2181	–
DIAM min 30	39	0.5044	0.01
DIAM min 40	39	0.2232	–

Table 3. Spearman coefficients – citalopram.

Parameters	Number	Spearman coefficient	Significance level
DIAM max 30	38	–0.2505	–
DIAM max 40	38	–0.2293	–
DIAM min 30	38	0.2740	–
DIAM min 40	38	0.0205	–

ECG and BSPM, show the acceleration of heart rate (tachycardia) only in patients with dosulepine (TCA 89.47±16.64, $p<0.001$). RR, heart rate, QT angles of plane vectors QRS-STT in the frontal plane were significantly increased (–47.05±53.99°, $p<0.01$) in dosulepine-treated patients compared to controls (–15.2± 19.25°). Space angle QRS-STT was also increased (64.33 ±45.45°), but this was not significant compared to the controls (44.62±20.04°). The influence of parameter DIAM 30 (5.63±4.55), corresponding to early depolarization, was dependent on the doses of used antidepressants only in dosulepine, but not in citalopram. Doses of lithium were not correlated to DIAM 30 or DIAM 40 because lithium plasma levels of all the patients were very similar (0.66 ± 0.08).

Patients treated by citalopram demonstrated higher influence on the repolarization phase. (RIIM max 46.45±23.20, $p<0.05$; RIIM min –20.43±11.85, $p<0.01$; DRIIM min –28.40±16.40, $p<0.05$). This repolarization phase was more affected in citalopram than in dosulepine patients, which showed only RIIM min –28.41±14.50 ($p<0.05$). Parameter IPMAM-R was decreased (14.09±5.01, $p<0.05$) in citalopram patients compared to the controls.

Patients treated with lithium (plasma level 0.66 ±0.08) for a long time manifested small changes in the investigated BSPM and ECG parameters compared to all used drugs (only DIAM max 4.17±1.17, $p<0.05$). The dose-dependent decrease in maximum and minimum (extremum) of depolarization isoarea map in the first 30 ms of QRS (DIAM max 30, DIAM min 30, $p<0.05$ in DIAM max, $p<0.01$ in DIAM min) were observed in dosulepine-treated patients (Table 2). In citalopram-treated patients no significant dose-dependent relationship was observed (Table 3).

Discussion

Patients of both groups (dosulepine and citalopram) were comparable in age and period of therapy (6-8 weeks). Prophylactic treatment by lithium lasted 1-22 years. These results are comparable with our previous studies (Slavíček *et al.* 1995, 1998, Paclt *et al.* 1995, 1999). This study, performed in a greater group, suggested the evidence for the small quinidine-like effects in all of the used drugs (dosulepine, citalopram, lithium). In the present report, we studied for the first time dose-dependent changes of ECG body surface potential maps (BSPM) – parameters DIAM 30, DIAM 40. The dependence of changes in early depolarization upon prophylactic doses of antidepressants was significant only for dosulepine but not for citalopram. Our companion study (Kitzlerová *et al.* 2003) will elaborate the present results with plasma levels of dosulepine for more exact quantification of heart electric field changes.

Tricyclic antidepressants exhibit arrythmogenic effects, blocking of Tawara conduction, orthostatic

hypotension, prolongation of QR, QT, QRS, supraventricular tachycardia, tachycardia, and abortive ventricular contraction (Bennet and Plum 1996, Braunwald 1996). At the levels below 300 ng/ml sinusoid tachycardia, prolongation PQ, QRS or QT, or sinusoid arrhythmia (Robertson and Katona 1997) may be present. Tricyclic antidepressants may also manifest significant cardiovascular complication in healthy individuals. These above mentioned changes of ECG parameters including QT_C exhibit no correlation with plasma levels during commonly used doses (Pidrman and Krpálek 1993). Our observation of a correlation of parameters DIAM 30, 40 with dosulepine (TCA) doses probably enables a significantly accurate prediction of cardiovascular complication danger in these patients. Further study of plasma TCA levels is necessary for more precise confirmation of our results.

Depressive disorders are undoubtedly a dangerous factor for the development of cardiovascular diseases (Musselman *et al.* 1998, Roose and Spatz 1998). In the course of depressive or panic disorder (Coryell *et al.* 1986), decreasing variability of heart frequency due to an imbalance in autonomic nervous system were observed (Enemark 1993, Paclt *et al.* 1998). This effect was studied by means of heart rate variability, but it is limited due to the absence of a correlation with age and gender (Volkers *et al.* 2000). Tricyclic antidepressants also show the same effect, i.e. the loss of full variability of heart rate frequency (Lehofer *et al.* 1999). Our results indicate BSPM changes in untreated patients with panic disorder (Pišvejcová *et al.* 2002) and in patients with depressive disorder in remission (Slavíček *et al.* 1995, Paclt *et al.* 1995). These changes (tachycardia; DIAM 30, DIAM 40; opening of angle printed vectors QRS-STT) agree with results shown in the studies of heart rate variability with regard to the enhancement of the adrenergic system (Lehofer *et al.* 1999, Volkers *et al.* 2000).

Our results show a direct relationship between panic disorder and the influence of TCA therapy upon myocardial functions. The used method is sufficiently sensitive to allow the serious assumption regarding the immediate influence of strong emotion upon myocardial functions. This method is also able to register minimal changes caused by low clinical doses of antidepressants.

Acknowledgements

This study was supported by Grant MSM 11110000 1.

References

BENNET CJ, PLUM F: *Cecil Textbook of Medicine*. WB Saunders, Philadelphia, 1996, pp 166-367.

BRAUNWALD E: *Heart Disease. A Textbook of Cardiovascular Medicine*. WB Saunders, Philadelphia, 1996.

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

CORYELL W, NOYES R, HOUSE JD: Mortality among outpatients with anxiety disorders. *Psychiatry* **143:** 508-510, 1986

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

FRANK E: An accurate, clinically practical system for spatial vectorcardiography. *Circulation* **13:** 737-749, 1956.

GLASSMAN AH, ROOSE SP, RIVELLI SK, PREUD'HOMME XA: Cardiovascular effects of antidepressant drugs. *Nord J Psychiatry* **30** (Suppl): 41-47, 1993.

GREEN LUX RL, HAWS CW, WILLIAMS RR, HUNT SC, BURGESS MJ: Effects of age, sex and body habitus on QRS and ST-T potential maps of 1100 normal subjects. *Circulation* **71:** 244-253, 1985.

HAMPLOVÁ J, KRŮŠEK J, PACLT I, SLAVÍČEK J, LISÁ V, VYSKOČIL F: Citalopram inhibits L-type calcium channel current in rat cardiomyocytes in culture. *Physiol Res* **51:** 317-321, 2002.

KAZMIERCZAK SC, VAN LENTE F: Cardiac effects of therapy with lithium an enzymatic study. *Lithium* **1:** 157-161, 1990.

KITTNAR O, ŠŤOVÍČEK P: Contemporary body surface potential mapping in electrocardiology and its perspectives. *Physiol Res* **42**: 141-143, 1993.

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.

KITZLEROVÁ E, PACLT I, SLAVÍČEK J, PIŠVEJCOVÁ K, ANDERS M, DOHNALOVÁ A, BALÍKOVÁ M: Plasma levels of dosulepine and heart electric field. *Physiol Res* **52:** 319-325**,** 2003.

KOZMANN G, LUX R.L, GREEN LS: Sources of variability in normal body surface potential maps. *Circulation* **79:** 1077-1083, 1989.

KOZMANN G, FARKAS N, SÁNDOR G: Statistical characterization of QRST integral maps of normal subjects. In: *Electrocardiology ´98,* I PREDA (ed), World Scientific, Singapore, New Jersey, London, Hong Kong, 1999, pp 119-122.

LEHOFER M, MOSER M, HOEHN-SARIC R, MCLEOD D, HILDEBRANDT G, EGNER S, STEINBRENNER B, LIEBMANN P, ZAPOTOCZKY HG: Influence of age on the parasympatholytic property of tricyclic antidepressants. *Psychiatr Res* **85:** 199-207, 1999.

MITCHELL JE, MACKENZIE TB: Cardiac effects of lithium therapy in man: a review. *J Clin Psychiatry* **43:** 47-51, 1982.

MUSSELMAN DL, EVANS DL, NEMEROFF CHB: The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* **55:** 580-592, 1998.

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

PACLT I, KITTNAR O, SLAVÍČEK J: Antidepressant drugs and ECG body surface maps. In: *Electrocardiology 97*, L BACHÁROVÁ, PW MACFARLANE (eds), World Scientific, Singapore, New Jersey, London, Hong Kong, 1998, pp 214-217.

PACLT I, SLAVÍČEK J, DOHNALOVÁ A, KITTNAR O, PIŠVEJCOVÁ K: Electrocardiographic changes during antidepressant therapy. In: *Neurobiology of Psychiatric Diseases*, Galén, Prague, 1999, pp 172-178.

PIDRMAN V, KRPÁLEK P: Amitriptyline and its metabolites in plasma and saliva in depressive patients. *Homeostasis Health Dis* **34:** 24-25, 1993.

PIŠVEJCOVÁ K, PACLT I, SLAVÍČEK J, KITTNAR O, DOHNALOVÁ A, KITZLEROVÁ E: Electrocardiogram, vectorcardiogram and body surface maps in patients with panic disorder. *Physiol Res* **51**: 401-406, 2002.

PRESKORN SH, FAST GA: Therapeutic drug monitoring for antidepressants: efficacy, safety and cost effectiveness. *J Clin Psychiatry* **52** (Suppl): 23-33, 1991.

RAWLING DA, FOZZARD HA: Effects of imipramine on cellular electrophysiological properties of cardiac Purkinje fibers. *J Pharmacol Exp Ther* **209**: 371-375, 1979.

RAY WA, GRIFFIN MR, SCHAFFNER W, BAUGH DK, MELTON LJ: Psychotropic drug use and the risk of hip fracture. *N Engl J Med* **316:** 363-369, 1987.

ROBERTSON MM, KATONA CLE: *Depression and Physical Illness*. John Wiley, Chichester, 1997, 564 p.

ROOSE SP, SPATZ BS: Depression and heart disease. *Depress Anxiety* **7:** 158-165, 1998.

RUTKAY-NEDECKÝ I: *Electric Field of the Heart* (in Slovak). Veda, Bratislava, 1983.

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

SLAVÍČEK J, PACLT I, HAMPLOVÁ J, KITTNAR O, TREFNÝ Z, HORÁČEK BM: Antidepressant drugs and heart electrical field. *Physiol Res* **47:** 297-300, 1998.

SLAVÍČEK J, KITTNAR O, NOVÁK V, TREFNÝ V, HORÁČEK BM: ECG Body surface isointegral and isoarea maps (BSM) in 30- and 60-years-old healthy humans. *Sb Lek* **102:** 369-374, 2001.

STOJAN M: *General Analysis of Heart Electric Field for Clinical Use* (in Czech). Vol. 2 (Atlas), ZPA Čakovice, Prague, 1991a.

STOJAN M: Body surface maps of electric cardiac activity. *Cardiag 91. International Symposium, November 19-21, 1991, Carlsbad, Czech Republic,* ZPA Čakovice, Prague. 1991b, Abstr. 42.

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

STOUDEMIRE A, FOGEL BS: Psychopharmacology in the medically ill. In: *Principles of Medical Psychiatry.* A STOUDEMIRE, BS FOGEL (eds), Grune & Stratton, Orlando, 1987, pp 79-112.

ŠVESTKA J: Third-, fourth- and fifth- generation antidepressants (in Czech). *Cesk Psychiatr* **90:** 3-19, 1994.

VOLKERS AC, TULEN JHM, BROEK WW, BRUIJN J, PASSCHIER J, PEPPLINKHUIZEN L: Autonomic neurocardiac regulation in major depressive disorder. In: *13th ECNP European College of Neuropsychopharmacology*, Munich, Germany, September 9-13, 2000, pp 235-236.

WARRINGTON SJ, PACHAM C, LADER M: The cardiovascular effect of antidepressants. *Psychol Med* **16** (Suppl): 1-40, 1989.

WELD FM, BIGGERT JT: Electrophysiological effects of imipramine on ovine cardiac Purkinje and ventricular muscle fibres. *Circ Res* **46:** 167-175. 1980.

Reprint requests

MUDr. Ivo Paclt, CSc, Department of Psychiatry, First Faculty of Medicine, Charles University, Ke Karlovu 11, 128 02 Prague 2, Czech Republic, e-mail: pacltovi@email.cz