EUROPEAN PHARMACEUTICAL JOURNAL

# Changes in electrical activity of heart during ischemic-reperfusion injury modified by the administration of antidepressants Zmeny elektrickej aktivity srdca počas ischemickoreperfúzneho poškodenia modifikované podaním antidepresív

Original research article

G

Vicen M.<sup>⊠</sup>, Gulač P., Stankovičová T.

Comenius University in Bratislava, Faculty of Pharmacy, Department of Pharmacology and Toxicology, Bratislava, Slovak republic Univerzita Komenského v Bratislave, Farmaceutická fakulta, Katedra farmakológie a toxikológie, Bratislava, Slovenská republika

Received 19 June, 2016, accepted 18 August, 2016

**Abstract** The aim of our work was to investigate the effect of amitriptyline, citalopram and venlafaxine on the heart during ischemicreperfusion (I-R) injury. Amitriptyline prolonged both QRS complex and QTc interval duration; citalopram and venlafaxine prolonged only QTc interval duration. Amitriptyline worked most proarrhythmogenic, citalopram least; venlafaxine increased the heart rate during ischemia; however, prolonged QTc interval at the beginning of reperfusion was followed by serious dysrhythmias.

Slovak Cieľom našej práce bolo objasniť efekt amitriptylínu, citalopramu a venlafaxínu na srdce počas ischemicko-reperfúzneho poškodenia (I-R) myokardu. Amitriptylín predĺžil trvanie QRS komplexu aj QTc intervalu, citalopram a venlafaxín predĺžil iba trvanie QTc intervalu. Amitriptylín mal najvýraznejší proarytmogénny efekt, citalopram najmenej výrazný, venlafaxín zrýchlil srdcovú frekvenciu počas štádia ischémie, ale predĺžil QTc interval na začiatku reperfúzie, pričom toto predĺženie bolo nasledované výskytom závažných dysrytmií.

 Keywords
 amitriptylin – citalopram – venlafaxine

 Kľúčové
 amitriptylín – citalopram – venlafaxín

slová:

### INTRODUCTION

It is well known that drugs such as antidepressants can affect the function of heart. According to WHO, ischemic heart disease was world's leading cause of death in 2012, so it is important to find out how the antidepressants modify hearts function during I-R injury. Some authors (Ma-Li et al., 2008, Waring et al., Leonard et al., 2011) described the increased risk of myocardial infarction and sudden death within the initial days of antidepressant therapy. Until now, the experimental data about the effects of drugs on heart function after the administration of single dose of antidepressant were missing. In our experiments, the effects of single dose (30 mg/kg) of representatives from main antidepressants' groups (TCA, SSRI and SNRI) were tested. Pretreatment of animals with drugs was followed by heart function analysis under conditions of spontaneously beating perfused hearts isolated 24 h after rats' premedication. The purpose of this study is to detect the changes in electrical activity of the hearts modified by antidepressants under conditions without or with ischemic– reperfusion myocardial injury.

#### **MATERIAL AND METHODS**

The experiments were carried out on male Wistar rats with body weight of 220–270g fed on standard pellet diet and water *ad libitum* with light period of 12 h from 8 a.m. Rats were divided into four groups: animals that received only vehicle s.c., ischemic–reperfusion injury (control, I-R) group (n = 12), and animals pretreated with selected antidepressants: amitriptyline (Ami) group (n = 6), citalopram (Cit) group (n = 6) and venlafaxine (Ven) group (n = 6). Substances of

<sup>©</sup> European Pharmaceutical Journal

		I-R	Amitriptyline	Citalopram	Venlafaxine
Incidence per heart	VPB forms	123.4 ± 47.7	356.2 ± 79.7*	238.8 ± 61.1	214.0 ± 53.9
	life-threatening	1.6 ± 0.9	15.6 ± 5.1	8.7 ± 4.0	9.2 ± 3.1*
Duration of episodes (s)	life-threatening	25.2 ± 13.2	296.6 ± 73.5*	66.3 ± 39.8	157.0 ± 82.0

Table 1. Incidence and duration of dysrhythmias during ischemic–reperfusion injury of spontaneously beating hearts isolated from the rats pretreated with single dose 30 mg/kg s.c. of selected antidepressants 24 h before heart isolation

Incidence of VPB forms (ventricular premature beat + bigeminy + trigeminy + salvos) expressed as mean  $\pm$  SEM per heart, incidence and duration of life-threatening (ventricular tachycardia + ventricular fibrillation + bradycardia) dysrhythmias expressed as mean  $\pm$  SEM per heart in group of animals without pretreatment with antidepressant (I-R), or with pretreatment with amitriptyline, citalopram or venlafaxine. \*p < 0.05, pretreated group versus I-R group

antidepressants were solubilised in aqua pro injectione and applied s.c. in a single dose of 30 mg/kg. Rats were anesthetised after 24 hours using thiopental i.p. (VUAB pharma, Czech republic, 45 mg/kg). Chest was opened and anticoagulant heparin (0.2 ml, 1000IU Lachema, Czech republic) was applied into inferior vena cava. Heart was isolated into the ice cold K-H solution (NaCl (118 mmol/l), KCl (4.7 mmol/l), MgSO<sub>4</sub> × 7H<sub>2</sub>O (2.39 mmol/l), KH<sub>2</sub>PO<sub>4</sub> (2.35 mmol/l), CaCl × 2 H<sub>2</sub>O (9.73 mmol/l), NaHCO<sub>2</sub> (25 mmol/l) in distilled water). Subsequently, the heart was positioned into Langendorff apparatus and perfused under constant pressure 7.5 kPa using K-H solution gassed by pneumoxide at a pH of 7.4 and temperature (t) of 36-37°C. Electrical activity of isolated spontaneously beating hearts was recorded during 20-min stabilisation, 35-min ischemia and 45-min reperfusion. Electrical activity was recorded by the needle electrodes (MLA1213 Needle Electrodes) inserted into the free wall of left ventricle and connected to the module PowerLab 8/30 (all the equipments were from ADInstruments, Spechbach, Germany) by the amplifier (FE136 Animal Bio Amplifier). Obtained data were stored in computer (HP, Palo Ato, USA). Data analyses were carried out by using the LabChart 7 Pro version 7.3.7. software (ADInstruments, Spechbach, Germany). Statistical comparison between the groups was done by using oneway ANOVA with the Bonferroni test, and the difference was considered statistically significant at a level  $p \le 0.05$ .

#### RESULTS

Amitriptyline prolonged both QRS complex and QTc interval duration during I-R injury; citalopram and venlafaxine prolonged only QTc interval duration. Differences in the duration of QRS complex were significant according to the Bonferroni test between amitriptyline and control groups and amitriptyline and venlafaxine groups ( $p \le 0.05$ ) (Fig. 1b). Differences in the duration of QTc interval after the administration of antidepressant in a single dose was statistically significant after the administration of all antidepressants compared to control group ( $p \le 0.05$ ) (Fig. 1c). Amitriptyline worked most proarrhythmogenic,

citalopram the least. Venlafaxine significantly increased heart rate during ischemia and also prolonged QTc interval at the beginning of reperfusion, followed by serious dysrhythmias. Incidence of different forms of ventricular premature beats decreased in the order Ami > Cit > Ven > I-R. Duration of life-threatening dysrhythmias ventricular tachycardia (VT), ventricular fibrillation (VF) and bradycardia decreased in the order Ami > Ven > Cit > I-R (Table 1).

#### DISCUSSION AND CONCLUSION

The highest incidence and duration of life-threatening dysrhythmias was in amitriptyline group. At the beginning of reperfusion, there were typical VT and VF, during reperfusion bradycardia episodes. Citalopram caused the lowest amount of dysrhythmias, which suggests that this antidepressant is safer than amitriptyline and venlafaxine. After venlafaxine premedication were present typical episodes of VT, which are also in clinical practice biggest problem during therapy (Abozguia et al., 2006). Some drugs induce arrhythmias directly by affecting the conduction system of heart. Other drugs act on the heart indirectly, through their effect on the sympathetic or parasympathetic nervous system or by causing other physiological changes, such as hypotension, changes in metabolism or electrolyte disorders. Amitriptyline predominantly inhibit inward currents, such as  $I_{Na}$  and  $I_{Ca'}$ and also inhibits outward current, Ikr. Citalopram inhibits predominantly outward current, I<sub>kr</sub> (Sicouri et al., 2008). After venlafaxine premedication, minor blocade of ion currents was also observed (Pacher et al., 2004).

The effects of amitriptyline on heart function are well known (Nezafati et al., 2015, Ueterecker et al., 2015, Noordam et al., 2015, Vicen et al., 2015). This is the reason why we decided to use this antidepressant as a reference drug and compare its effects with those of venlafaxine and citalopram on heart. Amitriptyline increased heart frequency and prolonged the duration of QTc interval. This effect was the most intensive in reperfusion. Citalopram decreased heart frequency during reperfusion of I-R experiment. Some studies suggest that this effect of citalopram may positively affect patients' quality







of life (Thase et al., 2013, Hanash et al., 2012). Interesting is the increase in heart frequency in phase of ischemia after venlafaxine pretreatment, which is followed by prolongation of QTc interval at the beginning of reperfusion and increase in the amount of dysrhythmias. This might be caused by energy depletion of the heart (Wang et al., 2005). The results suggest that single dose of antidepressants is enough to induce significant changes in electrical activity of heart.

## ACKNOWLEDGEMENT

This work was supported by grants VEGA, SR 1/1342/12 and UK/430/2015.

#### References

- Abozguia K, Chudley S., Gammage M. Dose-dependent venlafaxine-induced sinus tachycardia. Int J Cardiol. 2006;113:E9–E10
- [2] Hanash JA, Hansen BH, Hansen JF, Nielsen OW, Rasmussen A, Birket-Smith M. Cardiovascular safety of one-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome: results from the Depression in patients with

Coronary Artery Disease (DECARD) trial. J Cardiovasc Pharmacol. 2012;60(4): 397-405.

[3] Leonard C.E., Bilker W.B., Newcomb C., Kimmel S.E., Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. Pharmacoepidemiol. Drug Saf. 2011;20: 903-913.

#### Changes in electrical activity of heart during ischemic-reperfusion injury modified by the ...

- [4] Ma-Li, Wong D.CH., Esporito K., Thakur S., Liu W., Elashoff R.M., Licinio J. Elevated Stress-Hemoconcentration in Major Depression is Normalized by Antidepressant Treatment: Secondary Analysis for a Randomized, Double-Blind Clinical Trial and Relevance to Cardiovascular Disease Risk. PLOS ONE. 2008;7: 1-6.
- [5] Nezafati M, Vojdanparast M, Nezafati P. Antidepressants and cardiovascular adverse events: A narrative review. ARYA Atherosclerosis. 2015;11(5):295-304.
- [6] Noordam R, Van den Berg M, Visser L, et al. Assessing Prolongation of the Heart Rate Corrected QT Interval in Users of Tricyclic Antidepressants: Advice to Use Fridericia Rather Than Bazett's Correction. Journal Of Clinical Psychopharmacology. 2015;35(3):260-265.
- [7] Pacher P. and Valeria K. Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, Old Concerns? Curr. Pharmac. Des. 2004;10.20: 2463–2475.
- [8] Sicouri S. and Charles A. Sudden Cardiac Death Secondary to Antidepressant and Antipsychotic Drugs. *Expert opinion on drug* safety 2008;181–194.

- [9] Thase ME, Larsen KG, Reines E, Kennedy SH. The cardiovascular safety profile of escitalopram. Eur Neuropsychopharmacol 2013;23(11): 1391-400.
- [10] Unterecker S, Pfuhlmann B, Kopf J, Kittel-Schneider S, Reif A, Deckert J. Increase of Heart Rate and QTc by Amitriptyline, But Not by Venlafaxine, Is Correlated to Serum Concentration. Journal Of Clinical Psychopharmacology. 2015;35(4):460-463
- [11] Vicen M, Gulač P, Stankovičová T, et al., . Efekt jednodňovej premedikácie antidepresívami na funkciu srdca potkanov. Farmaceutický obzor, 2015, 1-2, 21-25 (in slovak)
- [12] Wang J, Ke D, Lin M. Heat shock pretreatment may protect against heatstroke-induced circulatory shock and cerebral ischemia by reducing oxidative stress and energy depletion. Shock. February 2005;23(2):161-167.
- [13] Waring W.S. Clinical use of antidepressant therapy and associated cardiovascular risk. Drug Health cPatient Saf. 2012;4: 93-101.
- [14] WHO, The top 10 causes of death (http://www.who.int/ mediacentre/factsheets/fs310/en/) Revised May 2014 Accessed December 20, 2015