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The incidence of dysrhythmias after administration of the antipsychotic olanzapine
Výskyt dysrytmií po podaní antipsychotika olanzapínu

Original research article

Gulač P.✉, Vicen M., Hričáková S., 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*

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Abstract We evaluated the effect of the antipsychotic olanzapine on electrical activity of rat hearts under conditions of ischemic–reperfusion injury. We focused on the prolongation of the corrected QT interval as a risk factor for the incidence of different types of dysrhythmias. Pretreatment with olanzapine showed prolongation of the corrected QT interval as well as increased incidence of dysrhythmias in following order: ventricular premature beats > bigeminies > trigeminies > salvos. We also observed an increase in the frequency of episodes of ventricular tachycardia of about 64% and the average duration of ventricular tachycardia was more than doubled under the conditions of the ischemic–reperfusion injury.

Slovak abstract V našej práci sme hodnotili efekt antipsychotika olanzapínu na elektrickú aktivitu srdc potkanov v podmienkach ischemicko-reperfúzneho poškodenia myokardu. Zamerali sme sa na predĺženie korigovaného QT intervalu ako rizikového faktora pre vznik rôznych druhov dysrytmií. Predliečenie olanzapínom ukázalo predĺženie korigovaného QT intervalu ako aj zvýšenú incidenciu jednotlivých druhov dysrytmií a to v poradí predčasné komorové kontrakcie > bigemínie > trigemínie > salvy. Súčasne sme zaznamenali 64 % nárast početnosti epizód ventrikulárnej tachykardie a viac ako zdvojnásobenie ich priemerného trvania počas ischemicko-reperfúzneho poškodenia.

Keywords *olanzapine - heart – QTc interval - dysrhythmias*

Kľúčové slová: *olanzapín - srdce - QTc interval - dysrytmie*

INTRODUCTION

The studies from recent years have shown that patients with schizophrenia have a higher risk of developing cardiovascular diseases (Jones et al., 2013, Pasterbak et al., 2014, Wang et al., 2014) and increased risk of mortality after administration of antipsychotics drugs (Jones et al., 2013). Olanzapine (OLA) belongs to second generation of antipsychotic drugs and together with risperidone is currently the most commonly prescribed drug for the treatment of schizophrenia and other related diseases in spite of occurrence of cardiometabolic complications (Anastassion, 2012). In our experiment, we premedicated rats with single dose of OLA (10 mg/kg) s.c. After 24 h of premedication, we analysed heart function under condition of isolated spontaneously beating rat hearts. Our aim was to record the changes in electrical activity during stabilisation and during ischemic–reperfusion myocardial injury.

MATERIAL AND METHODS

For the experiments we used male Wistar rats with body weight of 230–270 g fed on standard pellet diet and water *ad libitum* period 12 h from 8 a.m. We divided rats into two groups. The first group was premedicated only with the aqua pro injectione s.c. (control (CTRL) group) (n = 6) and the second group was premedicated with olanzapine (OLA group) (n = 6) solubilised in aqua pro injectione. We applied OLA 10 mg/kg s.c. in a single dose. Animals were anesthetised 24 hours after premedication by thiopental i.p. (VUAB Pharma, Czech republic, 45 mg/kg). The chest was opened and anticoagulant heparin (0.2 ml, 500IU Lachema, Czech republic) was applied into vena cava inferior. The hearts were isolated and perfused under constant pressure 7.5 kPa with K-H solution gassed by pneumoxide, pH 7.4, t = 36–37°C according to the Langendorff method. Experimental protocol consisted of 20-min long stabilisation, 30-min ischemia and 40-min reperfusion. We

* *E-mail: patrik.gulac@gmail.com*

recorded the electrical activity of isolated spontaneously beating hearts by inserting needle electrodes (MLA1213 Needle Electrodes, ADInstuments, Spechbach, Germany) into the left ventricular wall and transferring the signal to module PowerLab 8/30 (ADInstuments, Spechbach, Germany). The analysis of these data was carried out by software LabChart 7 Pro version 7.3.7. (ADInstuments, Spechbach, Germany). Statistical comparison between the groups was done by the Mann Whitney test. The difference was considered statistically significant at a level $p \leq 0.05$. Normal distribution of data was done by Grubbs' test, and we did not record any outlier.

RESULTS

The analysis of electrocardiography (ECG) showed longer corrected QT interval durations (fig. 1a.) during stabilisation and also during reperfusion in OLA group. Direct effect of OLA caused increased incidence of dysrhythmias (fig. 1b.) during stabilisation as well as increased incidence of dysrhythmias during ischemic–reperfusion injury in the following order: ventricular premature beats > bigeminies > trigeminies > salvos (Table 1). The average incidence during whole experiment of non-lethal dysrhythmias (ventricular premature beats, bigeminies, trigeminies, salvos) in CTRL group was 96.4 ± 13.47, and in OLA group, the incidence of non-lethal dysrhythmias was 310.8 ± 64.77 (Table 1), which represents an significant increase of 322%. Administration of OLA caused spontaneously terminating episodes of ventricular tachycardia in the time between 10th and 25th minute in reperfusion, which represents an increase of 64% in the number of episodes and more than twice longer average duration compared to the CTRL group.

DISCUSSION AND CONCLUSION

The cardiovascular diseases and their complications are the most common causes of death amongst mentally ill people treated with antipsychotics. Bresee (2010) observed a higher incidence of cardiovascular disease amongst treated patients compared with non-treated patients.

The use of atypical antipsychotics (including olanzapine) is accompanied by breach of balance of ions, which also negatively affects the development of cardiovascular diseases (Khasawneh 2013). It seems that one of the crucial factors that cause QT prolongation and ventricular tachycardia is the blockade of the cardiac hERG channel and subsequent inhibition of Ikr channel (Gintant et al., 2011, Silvestre et al., 2007, 2014). Furthermore, there are a lot of receptors, such as muscarinic M_2 and α- and β-adrenergic receptors, which could be involved in cardiac autonomic tone, be influenced by olanzapine and participate in the effects on the QT interval prolongation (Fossa, 2008, Taggart, 2003).

Prolongation of the QT interval reflects delayed ventricular repolarisation, which is associated with Torsades de Pointes, a life-threatening ventricular tachyarrhythmia that may degenerate into ventricular fibrillation and lead to sudden death (Moss, 1999). We also observed the prolongation of the QT interval corrected on the heart rate in the stabilisation and also during ischemic–reperfusion injury. Furthermore, we noticed increased incidence of different types of dysrhythmias such as ventricular premature beats, bigeminies, trigeminies

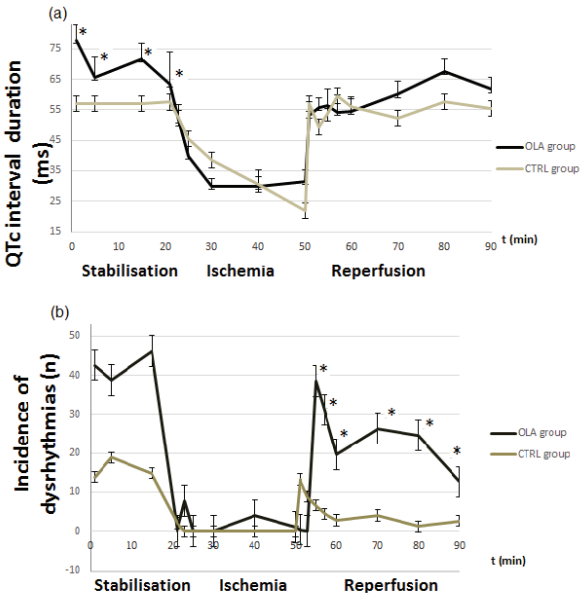

Figure 1. (a) Changes in QT interval duration during ischemic - reperfusion injury. (b) Average incidence of non-lethal dysrhythmias during each interval per one heart

Table 1. Incidence and duration of dysrhythmias during ischemic–reperfusion injury of spontaneously beating hearts isolated from the rats pretreated with olanzapine 10 mg/kg s.c. in a single dose 24 h before heart isolation

		CTRL group	OLA group
Incidence per heart	Ventricular premature beats	27 ± 2,01	271.8 ± 3.49*
	Bigeminies	61 ± 4.01	19 ± 0.28
	Trigeminies	7 ± 0.75	15,4 ± 0.22
	Salvos	1.4 ± 0.19	4,6 ± 0.08
	Life-treatening	1.4 ± 0.05	2.2 ± 0.06
Duration of episodes (s)	Life-treatening	16.4 ± 0.77	43 ± 1.93

*Incidence of different types of dysrhythmias expressed as mean ± SEM per heart, incidence and duration of life-threatening (ventricular tachycardia) dysrhythmias expressed as mean ± SEM per heart in CTRL group and OLA group; *p < 0.05, OLA group versus CTRL group*

and salvos as well as the development of severe episodes of ventricular tachycardia during reperfusion. Shafti examined the effect of olanzapine and risperidone on the ECG changes in patients with schizophrenia. He concluded that the occurrence of significant changes in the ECG recording was higher in patients in the olanzapine group than those in the risperidone group with respect to prolongation of the QT interval (Shafti, 2014). Lee et al. (2013) reviewed the cardiovascular risk of six atypical antipsychotics, namely, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, and also described the QTc prolongation and increased risk of serious life-threatening dysrhythmias. According to the results, OLA modified the electrical activity of the isolated spontaneously beating rat hearts and displayed the proarrhythmogenic effect during stabilisation and reperfusion.

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