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Short communication

Estimation of oxidative stress parameters in rats after simultaneous administration of rosuvastatin with antidepressants

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ABSTRACT

Background: Patients commonly receive statin drugs for the primary or secondary prevention of cardiovascular events and also commonly receive antidepressant drugs for the treatment of depression. A many-year polypharmacotherapy can lead to increased side effects of these drugs. It may lead to an oxidation–reduction imbalance and the growth of a generation of reactive oxygen species (ROS) which may induce cellular dysfunctions.
Methods: The aim of this study was to assess oxidative stress parameters in the blood of rats after simultaneous administration of rosuvastatin (10 mg/kg) with paroxetine (10 mg/kg) or citalopram (10 mg/kg). The activity of glutathione peroxidase (GPX) was determined in whole blood, and the activity of glutathione reductase (GR) and the total antioxidant status (TAS) were determined in the serum.
Results: The 14-day simultaneous administration of rosuvastatin with paroxetine or citalopram caused an increase in glutathione peroxidase and glutathione reductase activity and did not influence the level of the total antioxidant status. Rosuvastatin (10 mg/kg) or citalopram (10 mg/kg) administered alone to rats for 14 days did not affect the examined parameters. The 14-day application of paroxetine (10 mg/kg) significantly decreased a glutathione peroxidase activity, increased a glutathione reductase activity and did not affect the level of TAS.
Conclusions: The observed changes may indicate an increased activity of the enzyme system preventing oxidation, which appears to be the effect of the reaction on the severity of oxidative stress during the combined treatment with rosuvastatin and antidepressants.

Introduction

Depression is common with patients with a coronary heart disease (CHD) and is independently associated with an increased cardiovascular morbidity and mortality [1]. Several studies have shown depression and its associated symptoms to be a major risk factor for both the development of cardiovascular disease (CVD) and death after myocardial infarction [2]. Approximately one out of every five patients with CVD suffers from major depressive disorder [3]. The treatment of depressed patients with heart disease is crucial and often requires a simultaneous use of several drugs.

In CHD, dyslipidemia is a major risk factor. Statin drugs (3-hydroxy-3-methylglutaryl–CoA reductase inhibitors) are recommended for both primary and secondary prevention–independent of their cholesterol-lowering properties, they have a direct beneficial impact on cardiac functions. Statins have been reported to possess an intrinsic antioxidant activity, thereby protecting LDL from oxidation and further reducing progression of atherosclerosis [4]. Rosuvastatin has been widely accepted because of its efficacy, potency, and superior safety profile [5]. Some studies showed that a rosuvastatin therapy can reverse cardiac disorders, decreases biomarkers of oxidative stress (reducing reactive oxygen species) and has further beneficial immunomodulatory and thus anti-inflammatory effects [4,6,7].

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, paroxetine and citalopram, are the most commonly prescribed first-line antidepressant drugs in depression treatment

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nowadays [8]. These agents have replaced the former classic tricyclic antidepressant (TCA) drug since they are well tolerated and generally lack the anticholinergic and antihistaminic side effects [9]. They have benign cardiovascular profiles and are well tolerated in patients with cardiac disease [8]. Paroxetine is the most potent inhibitor of the reuptake of serotonin of all currently available antidepressants including the class of SSRIs [10]. Clinical trials suggest that paroxetine is as effective as other antidepressants. Serious adverse effects are, however, extremely rare even in overdose [11]. Moreover, paroxetine may have some cardio-protective effects, especially in cardiac patients [12]. One of the first-line antidepressant drug for patients with CHD is also citalopram. Citalopram is safe for patients with cardiovascular disease and effective for moderate or recurrent depression [1].

Although both rosuvastatin and the above-mentioned antidepressants are characterized by a high safety profile, however, a polypharmacotherapy lasting for many years can lead to increased side effects of these drugs. It may lead to an oxidation–reduction imbalance and the growth of a generation of reactive oxygen species (ROS) which may induce cellular dysfunctions [13]. Biochemical, as well as pharmacokinetics studies, reveal that during bioactivation of drugs, some reactive metabolites are produced very often which may contribute to ROS production [14,15]. Metabolism of a drug may generate a reactive intermediate that can reduce molecular oxygen directly to generate ROS [16]. Therefore, any potential drug interactions or adverse effects should be closely monitored.

The lack of data on the effects of a simultaneous treatment of commonly used statin–rosuvastatin and SSRIs has inspired our research. The study aims to evaluate the influence of a 14-day simultaneous intraperitoneal application of rosuvastatin with paroxetine or rosuvastatin with citalopram on the oxidative stress parameters in rats. The activity of glutathione peroxidase (GPX) was determined in whole blood and the activity of glutathione reductase (GR) and total antioxidant status (TAS) were determined in the serum.

Materials and methods

Animals

The study was carried out on male Wistar rats (200–250 g) purchased from a licensed breeding farm in Brwinów, Poland. The animals were kept under standard laboratory conditions and maintained on a 12 h day/12 h night cycle. They had access to food and water *ad libitum*. The study was approved by the Ethical Committee on Animal Experimentation of the Medical University of Lublin.

Drugs and chemicals

The following substances were used in the study: rosuvastatin (rosuvastatin calcium salt, Romazic, Polpharma SA - Starogard Gdański, Poland), paroxetine (paroxetine hydrochloride semihydrate, Seroxat, GlaxoStmithKline - Uxbridge, United Kingdom), citalopram (citalopram hydrobromide, Citabax, Ranbaxy - Warsaw, Poland), *aqua pro injectione* (Baxter - Warsaw, Poland). Ready-made diagnostic kits (RANDOX Laboratories Ltd. - Crumlin, United Kingdom) were used to determine: the glutathione peroxidase (GPX) and reductase (GR) activities and the total antioxidant status (TAS).

Treatments

Aqueous solution of rosuvastatin, paroxetine and citalopram were prepared *ex tempore* and injected intraperitoneally (*ip*) once a day for 14 days, separated or combined, in a constant volume of 0.5 ml/100 g of body weight. Six (I–VI) groups of rats, each consisting of eight animals, were administered sequentially: I. control animals—*aqua pro injectione*, II. rosuvastatin, III. paroxetine, IV. citalopram, V. rosuvastatin and paroxetine, VI. rosuvastatin and citalopram. 24 h after the last injection, the animals were decapitated and the blood was taken and divided as follows: one part was stored in heparin tubes (whole blood) and the other was left to clot. The whole heparinized blood was used to estimate the GPX activity by kinetic methods. From the other part of blood that was allowed to clot, the serum fraction was separated and taken to determine the GR activity and the total antioxidant status (TAS) by the kinetic method according to the instructions supplied with the respective kit (RANDOX Laboratories Ltd.).

Statistical analysis

Results were expressed as mean ± SEM. Groups of single drugs (2–4) were compared to the control group and one-way analysis of variance (ANOVA) was used (followed by Dunnett test). Double-drug groups (5–6) were compared with groups of single drug and two-way ANOVA with Tukey's *post hoc* test was used to determine statistical significance. A value of $p < 0.05$ was considered statistically significant. The statistical significance among the groups was determined by one-way analysis of variance (ANOVA) followed by the Kruskal–Wallis test. All parameters were considered statistically significantly different if p-values were less than 0.05.

Results

The 14-day simultaneous administration of rosuvastatin (10 mg/kg) with paroxetine (10 mg/kg) causes an increase in the GPX activity in rat blood compared with the group of animals receiving paroxetine these drugs alone (Fig. 1). The combined administration of rosuvastatin with citalopram to rats causes a significant increase of the activity of GPX compared with the groups of animals receiving only citalopram. In the blood of rats receiving paroxetine, we note a decreasing activity of GPX in comparison with the control group. In animals treated with rosuvastatin or citalopram separately, the activity of GPX remains unaffected.

Rosuvastatin administered to rats with paroxetine increases the activity of GR compared with the group of rats receiving only rosuvastatin (Fig. 2). The simultaneous application of rosuvastatin and citalopram increases the GR activity in comparison with rodents receiving only rosuvastatin or citalopram. In the serum of rats pretreated with paroxetine alone, we observe an increase in the activity of GR in comparison with the control group. In the groups of rats receiving separately rosuvastatin or citalopram GPX, the relevant activity does not change.

The conducted experiments have shown no significant changes in the total antioxidant status after two-week administration of rosuvastatin in combination with paroxetine or citalopram as compared with groups receiving these drugs alone (Fig. 3). However, a change of non-statistical relevance in the level of TAS in rats subjected to the simultaneous application of rosuvastatin with citalopram should be noted as confronted with the level in the control group. In the serum of rats pretreated alone with rosuvastatin, paroxetine or citalopram no change in TAS was observed.

Discussion

A drug-induced oxidative stress is implicated as a mechanism of toxicity in numerous tissues and organ systems, including liver, kidney, cardiovascular and nervous systems [16]. Several enzymes