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The study of possible application of sodium selenite as an adjuvant in lithium treatment: an effect on oxidative processes in heart of rats

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Abstract. – OBJECTIVE: Despite numerous side effects, including heart disturbances, lithium is still used in medicine. Selenium treatment can protect against toxicity of harmful substances and side effects of other drugs. In this study possibility of sodium selenite application as an adjuvant in lithium treatment was studied.

MATERIALS AND METHODS: Male Wistar rats were treated with: control - saline; Li group - Li_2CO_3 (2.7 mg Li/kg b.w.); Se group - Na_2SeO_3 (0.5 mg Se/kg b.w.); Li+Se group simultaneously with Li_2CO_3 and Na_2SeO_3 (2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively) by stomach tube for a period of six weeks, once a day. In heart homogenates total antioxidant status (TAS), activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) as well as concentrations of ascorbic acid (AA), reduced glutathione (GSH) and malonyldialdehyde (MDA) were determined. SOD/GPx, CAT/GPx and SOD/CAT ratios were evaluated.

RESULTS: TAS was insignificantly increased, particularly in groups receiving selenium. GPx was slightly decreased in Li group and partially restored by Li+Se treatment. Selenium markedly enhanced AA concentration vs. control. MDA was increased significantly in Li and Se groups and restored in Li+Se treated. SOD/GPx and CAT/GPx. Ratios were slightly increased in Li group and restored by selenium co-administration.

CONCLUSIONS: As Li+Se treatment resulted in no significant differences vs. control and restored MDA, SOD/GPx and CAT/GPx ratios. Research on selenium application during lithium therapy seems to be worth continuation.

Key Words:

Antioxidants, Heart, Lipid peroxidation, Lithium carbonate, Sodium selenite, Rats.

Introduction

Lithium has been used in medicine for more than sixty years. It is applied in curing psychiatric and neurological diseases[1,2] as well as an adjuvant in therapy of thyroid disorders[3]. However, apart from beneficial effects, lithium treatment can result in numerous side effects. The harmful action of lithium can include disturbances of heart, kidney, glands and gastrointestinal system functions[4,5]. Clinical research has revealed electrocardiographic changes in patients undergoing lithium therapy, even with lithium being in the therapeutic dose range[5,6]. Cardiac injuries may also be involved into teratogenic effects of lithium treatment[7]. As the presented effects may considerably affect the living conditions and compliance of patients, the research on finding any protective adjuvant, whose administration could be efficient at alleviating side effects of lithium has been performed. The investigations have included different substances possessing antioxidant properties and the outcomes have seemed to be encouraging[8-11].

Despite of being a trace element, selenium plays an important role in the correct functioning of the organism. Among others, it has been found to affect the cardiovascular system. Selenium deficiency has been reported to increase heart dysfunctions observed in pathological conditions and cardiotoxicity of drugs as well as to induce cardiomyocyte injury[12-14]. The effect of selenium supplementation in form of sodium selenite has been studied in patients with coronary artery disease and the outcomes have been promising[15]. Since selenium is considered as belonging to antioxidants and oxidative stress is involved in pathogenesis of numerous severe diseases, the growing interest in possible application of selenium in medicine is still being observed. Among others, the protective effect of selenium treatment against toxicity of food and environment constituents has been found. Its beneficial action has been displayed in case of exposure to acry-

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lamide[16], mycotoxins[17,18] as well as toxic metals and their compouds[19-22]. Research on selenium application as an adjuvant protecting against side effects of some drugs e.g.: cisplatin or neuroleptics has also been performed, resulting in encouraging outcomes[23,24]. The studies have included different forms of selenium, both inorganic selenite[20] and organic compounds[19,21] as well as selenium enriched natural products[25]. Moreover, due to the development of nanotechnology, the attempts towards medical application of selenium nanoparticles have been made recently[26].

The present study was carried out with the aim of evaluating if selenium could be applied as a protective adjuvant in patients undergoing lithium treatment. An inorganic selenocompound sodium selenite was chosen because it is easily assimilated and still used in scientific studies[17,18,27].

Materials and Methods

Animals

The experiment was carried out on adolescent male Wistar rats (24 animals, 130-160 g body weight). Rats had free access to standard feed and drinking water. The study was performed according to statutory bioethical standards and approved by I Local Ethical Commission of Medical University of Lublin, acceptance no.1/2013.

Experimental Design

After acclimatization period of three days the animals were randomly divided into four groups (six animals each):

- K (control) – treated with saline;
- Li group – treated with lithium (as Li_2CO_3) at a dose of 2.7 mg Li/kg b.w.;
- Se group – treated with selenium (as Na_2SeO_3) at a dose of 0.5 mg Se/kg b.w.;
- Li+Se-group – treated simultaneously with lithium (Li_2CO_3) and selenium (Na_2SeO_3) at a dose of 2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively.

The administration was in form of water solutions given by stomach tube. The compounds were given for a period of six weeks, once a day. Body mass of each animal was measured every day before administration and the appropriate amount of selenium and/or lithium solutions was calculated. After the end of the treatment the animals were sacrificed under thiopental narcosis and samples of heart were collected. Ten per cent (w/v) tissue homogenates were prepared in 0.1 mol dm^{-3} Tris-HCl buffer, pH = 7.4. Supernatants were obtained by centrifugation at 5000 × g for 30 min.

Biochemical Investigations

The following oxidant parameters were determined in heart homogenates: total antioxidant status (TAS); activities of antioxidant enzymes: catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD); concentrations of low-molecular weight antioxidants: ascorbic acid (AA) and reduced glutathione (GSH) as well as concentration of a marker of lipid peroxidation malonyldialdehyde (MDA).

TAS values in plasma were assayed using diagnostic kit by RANDOX (Randox Laboratories Ltd, Crumlin, County Antrim, UK) and expressed in mmol of TAS/g of protein.

CAT activity was determined using a spectrophotometric method described by Aebi[28] and expressed in U of CAT/mg of protein. One unit of CAT was defined as such an amount of the enzyme which causes the decomposition of 1 mmol of H_2O_2/minute at 25˚C.

SOD and GPx activities were assayed using diagnostic kits RANSOD and RANSEL produced by RANDOX (Randox Laboratories Ltd, Crumlin, County Antrim, UK) and expressed in U of SOD/mg of protein and U of GPx/g of protein, respectively.

AA concentration was determined using modified Kyaw method[29] and expressed in mmol of AA/g of protein.

GSH concentration was determined using BIOXYTECH® GSH-400™ kit produced by Oxis-Research™ (OXIS Health Products, Inc., Portland, OR, USA) and expressed in mmol of GSH/g of protein.

MDA concentration was determined using Ledwożyw et al[30] method and expressed in μmol of MDA/g of protein.

Protein was assayed using Bradford method[31].

The measurements were performed with use of spectrophotometer SPECORD M40 (Carl Zeiss, Jena, Germany).

SOD/GPx, CAT/GPx and SOD/CAT ratios were evaluated.

Statistical Analysis

All statistical analyses were performed using STATISTICA program (version 10.0). The normality of data distribution was verified using Shapiro-Wilk test. The differences among the

studied groups were analyzed using one-way analysis of variance (ANOVA), followed by Tukey test (for normally distributed variables) or Kruskal-Wallis one way analysis of variance (for non-normally distributed variables). Values were considered significant with $p < 0.05$.

Results

TAS (total antioxidant status) was slightly increased in all the studied groups although no statistical significance was obtained vs. control. However, in Se and Li+Se groups this effect was more distinct ($p = 0.206$ and $p = 0.147$, respectively).

CAT (catalase) was not influenced by lithium and/or selenium administration.

GPx (glutathione peroxidase) was insignificantly depressed in Li group vs. control ($p = 0.147$) and slightly increased in Se group compared to Li alone group ($p = 0.213$).

SOD (superoxide dismutase) activity was slightly decreased in Se and Li+Se treated rats vs. control ($p = 0.151$ and $p = 0.242$, respectively) as well as vs. Li group ($p = 0.056$ and $p = 0.092$, respectively).

AA (ascorbic acid) concentration was markedly increased by selenium alone administration compared to control ($p = 0.019$). In Li+Se treated animals slight depletion vs. selenium alone group was observed ($p = 0.078$).

GSH (reduced glutathione) concentration values showed no distinct differences among the studied groups. MDA (malonyldialdehyde) concentration was significantly increased in both Li alone and Se alone groups compared to control ($p = 0.041$ and $p = 0.031$, respectively). In Li+Se treated animals, the obtained value was not different from the one noted in control ($p = 0.957$).

The obtained results are presented in Figure 1.

SOD/GPx ratio was insignificantly enhanced in animals treated with lithium alone vs. control ($p = 0.068$). In Se group the obtained value was markedly diminished compared to Li alone group ($p = 0.023$). In rats given Li+Se the obtained value was practically the same as that observed in control ($p = 0.998$).

CAT/GPx ratio was enhanced by Li treatment vs. both control and Se group but this effect was insignificant ($p = 0.211$ and $p = 0.294$, respectively). In all the other groups similar values were found.

SOD/CAT ratio was slightly decreased in Se group rats compared to control and Li group, but the differences were not significant ($p = 0.168$ and $p = 0.063$, respectively).

The obtained results are presented in Figure 2.

Discussion

In the present study no significant effect of lithium on elements of antioxidant barrier as well as on the ratios of antioxidant enzymes activities in rat heart was observed. This fact could be connected with rather short period of experiment and possibly with a small dose of lithium, too. However, insignificant depletion of GPx as well as slight increase in SOD/GPx and CAT/GPx ratios were found. According to some authors[32] the increased SOD/GPx is regarded as a symptom of oxidative stress. MDA concentration was markedly increased in Li treated group, which is consistent with other studies[33-35] which have revealed the occurrence of oxidative stress in animals exposed to lithium. Co-administration of selenium proved to be efficient at restoring of these parameters, at least to some degree. Furthermore, no significant differences were found between control and Li+Se treated group.

The available data concerning oxidative processes in heart of experimental animals exposed to lithium are scarce. In heart of rats receiving lithium orally significantly decreased adenosine triphosphate (ATP) level was found. It could be linked with oxidative status as ATP is an energy storage and major part of energy in heart comes from mitochondrial oxidative processes[9].

In the current study TAS was not influenced by any treatment vs. control, although slight enhancement, particularly in Se and Li+Se groups, was observed. Wu and Huang[36] observed that neither Se deficit in diet nor Se supplementation exerted any effect on total antioxidant capacity in the heart. Selenium given in drinking water caused no significant alterations of this parameter in aorta and arterial walls, either[36,37].

We observed no significant influence of selenium alone or given together with lithium on heart CAT activity. Similarly, no effect of dietary sodium selenite on heart CAT was noted by Ben Amara et al[38].

Despite the fact that selenium is a constituent of GPx, in the current experiment in Se group a slight decrease in GPx activity was found. These outcomes are consistent with the findings reported by Romanowska et al[39] who revealed that in

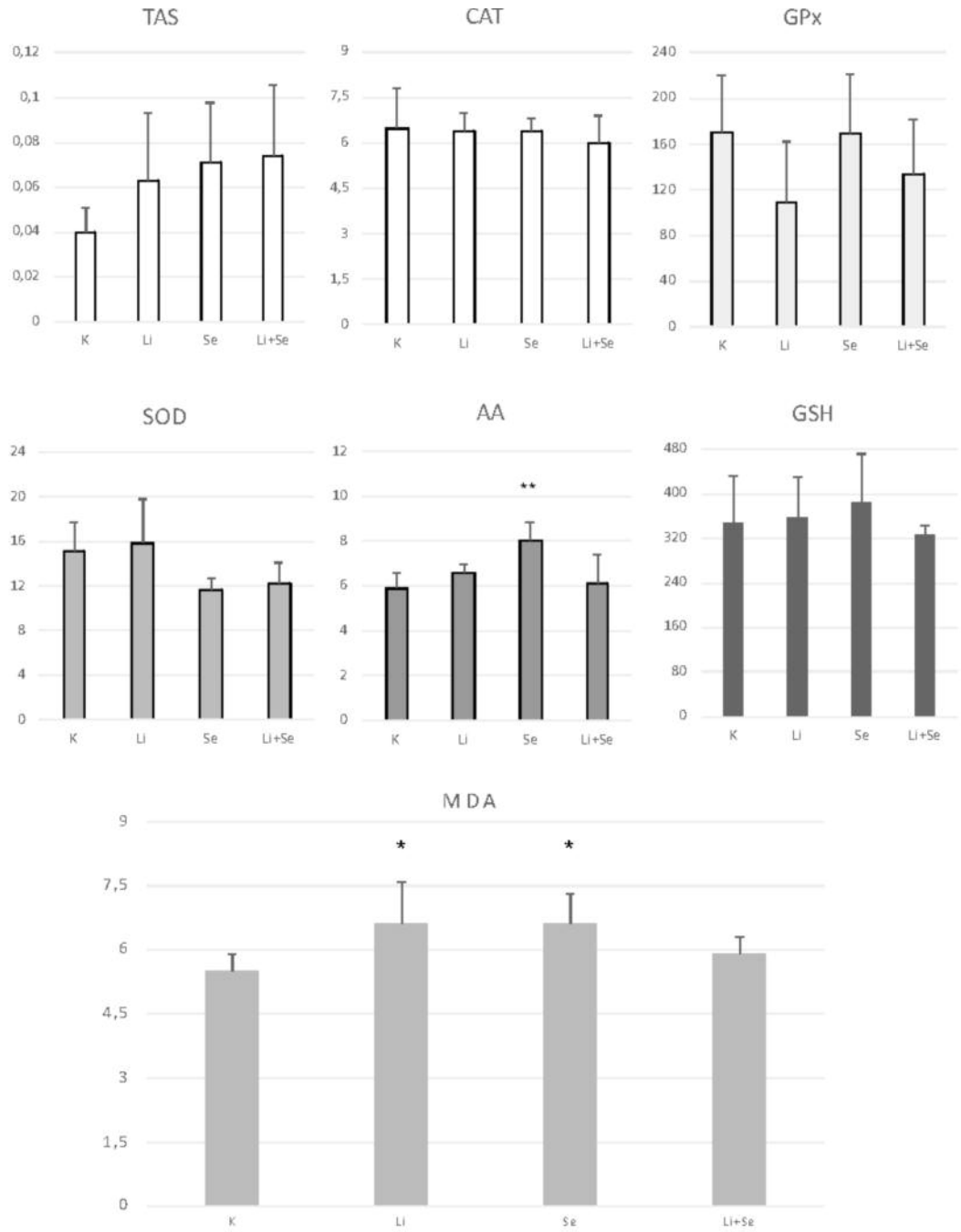

Figure 1. Effect of lithium and/or selenium supplementation on oxidative parameters in rat heart. K (control) - treated with saline; Li group – treated with lithium (as Li_2CO_3) at a dose of 2.7 mg Li/kg b.w.; Se group – treated with selenium (as Na_2SeO_3) at a dose of 0.5 mg Se/kg b.w.; Li+Se-group – treated simultaneously with lithium (Li_2CO_3) and selenium (Na_2SeO_3) at a dose of 2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively. Parameters are expressed: TAS (total antioxidant status) in mmol/g of protein; CAT (catalase) in U/mg of protein; GPx (glutathione peroxidase) in U/g of protein; SOD (superoxide dismutase) in U/mg of protein; AA (ascorbic acid) in μmol/g of protein; GSH (reduced glutathione) in μmol/g of protein; MDA (malonyl dialdehyde) in μmol of MDA/g of protein. $^{*}p < 0.05$ vs. control; $^{**}p < 0.01$ vs. control.

cells incubated in the presence of selenium, GPx was enhanced at first with the increase in Se concentration up to some level, but then the "saturation" occurred. Venardos et al[40] showed, in turn, that in hearts taken from rats fed Se free or deficient diet and subsequently subjected to is-

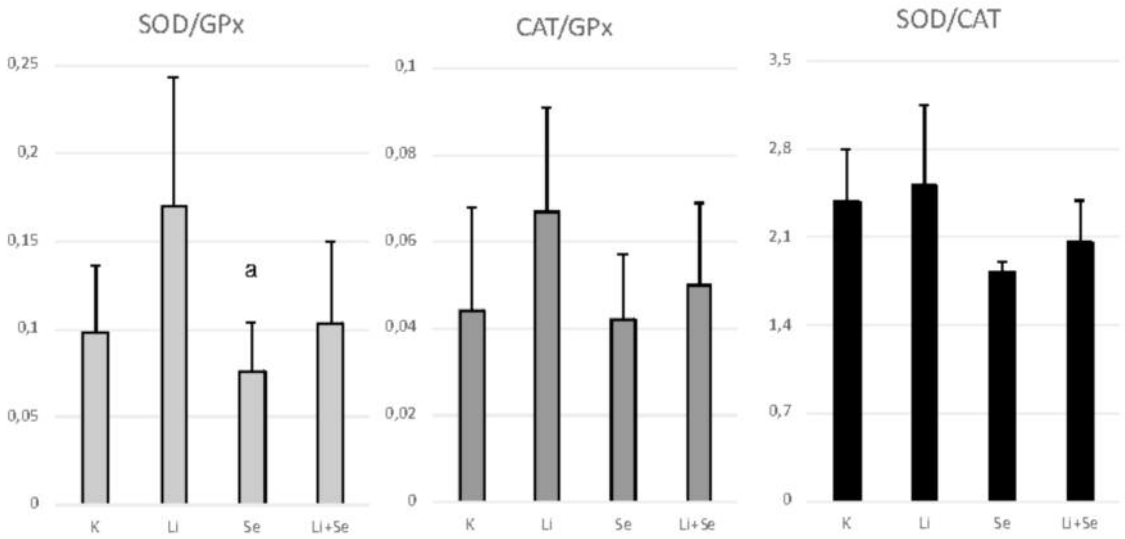

Figure 2. Effect of lithium and/or selenium supplementation on SOD/GPx, CAT/GPx and SOD/CAT ratios in heart of rats. K (control) – treated with saline; Li group – treated with lithium (as Li_2CO_3) at a dose of 2.7 mg Li/kg b.w.; Se group – treated with selenium (as Na_2SeO_3) at a dose of 0.5 mg Se/kg b.w.; Li+Se-group – treated simultaneously with lithium (Li_2CO_3) and selenium (Na_2SeO_3) at a dose of 2.7 mg Li/kg b.w. and 0.5 mg Se/kg b.w., respectively. $^a p < 0.05$ vs. Li-group.

chaemia-reperfusion before measurements GPx was decreased, whereas in Se supplemented animals no enhancement of GPx was found, despite using the diet of selenium content fourfold increased compared to control. Selenium supplementation did not either cause any increase in GPx activity in heart and aorta or GPx and GPx mRNA level in arterial walls of rats[36,37]. Ben Amara et al[38] reported no changes of GPx activity in heart of rats receiving dietary selenite.

We did not observe any significant influence of selenium on heart SOD compared to control. Similarly, no significant effect of selenium on SOD in heart, aorta and arterial walls was obtained in rats supplemented orally with selenium. The same authors[36,37] reported that selenium deficiency in diet did not influence heart SOD in a significant way, whereas in aorta and arterial walls significant depletion compared to rats fed with normal diet was displayed. Ben Amara et al[38] also reported no influence of inorganic dietary selenium on heart SOD.

In the current experiment selenium given to rats significantly increased AA concentration in heart. In contrast, sodium selenite given in diet resulted in no changes of vitamin C in rat heart, whereas in animals exposed to a pesticide a significant increase was shown[38].

The present study revealed no well-marked influence of selenium on heart GSH. Similar observations were reported in rats fed with Se enriched diet[38].

According to the results of some investigations toxicity of lithium can be connected with the occurrence of oxidant stress in blood[33,35] and different organs[34]. Due to these outcomes the attempts towards finding any adjuvant which could alleviate side effects of lithium, have been performed to date, including different substances possessing antioxidant properties. Zinc was shown to be effective in improving of the disturbances of oxidant parameters, resulting from lithium exposure, in erythrocytes[11] and partially in liver[10]. The similar beneficial effect was revealed by substances of natural origin, possessing the antioxidant properties, in kidney[8] and liver[9]. Natural substances of plant origin were also found to prevent oxidative damage occurring in lithium-pilocarpine induced status epilepticus[41,42].

The present work revealed that co-administration of selenium restored, at least to some degree, the parameters disturbed by lithium treatment. Other authors observed the similar inhibition of oxidant stress caused by different forms of selenium in animals exposed to toxic substances. Selenium prevented oxidative stress in retina of rats exposed to acrylamide[16]. Sodium selenite partially inhibited lipid peroxidation as well as prevented depletion of antioxidant enzymes in liver of cad-

mium treated chickens[20]. Significant improvement of patulin-induced deterioration in brain oxidative status caused by sodium selenite was reported by Song et al[18]. Ben Amara et al[38] reported that inorganic selenite given to rats was fully efficient at restoring heart antioxidant enzymes and low-molecular antioxidants altered as a consequence of the exposure to a pesticide. Diphenyl diselenide, the organic form of selenium, was efficient at reversing changes of lipid peroxidation but not those of antioxidant enzymes[21]. Selamoglu Talas et al[43] showed that the disturbances of pro- and antioxidant parameters caused by a carcinogenic substance were reversed by administration of selenoorganic compounds. Danesi et al[25] observed that increase in reactive oxygen metabolites in lipid fraction of heart, caused by adriamycin, was reversed by selenium administration, although organic form was more effective. Pretreatment with selenium proved to be effective in preventing the damage of oxidant barrier as well as in inhibition of lipid peroxidation in animal heart, induced by isoproterenol[44]. Similarly as in our study, CuZn SOD/GPx ratio in rat liver, increased by cadmium exposure, was restored by sodium selenite co-administration[45].

Conclusions

The period of the current experiment was fairly short compared to those used in curing psychiatric disorders. No severe impairment of heart antioxidant barrier caused by lithium was observed. However, a tendency towards disturbances of antioxidant enzymes connected with lipid peroxidation induction was found. Selenium co-administration displayed protective action, to some positive degree. Having considered the obtained results as well as the other scientists' reports, the research on selenium application as an adjuvant in lithium therapy seems to be worth continuing. Selenium both alone and in combination with other antioxidants has already been reported to display beneficial effect in pathological condition[46]. Further investigations should include other forms of selenium as well as different lithium and selenium doses.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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