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PRELIMINARY COMMUNICATION

EFFECT OF ZINC SUPPLEMENTATION ON ANTIDEPRESSANT THERAPY IN UNIPOLAR DEPRESSION: A PRELIMINARY PLACEBO-CONTROLLED STUDY

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Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. G. NOWAK, M. SIWEK, D. DUDEK, A. ZIĘBA, A. PILC. Pol. J. Pharmacol., 2003, 55, 1143–1147.

A growing body of evidence implicates a derangement of zinc homeostasis in mood disorders. In general, unipolar depression is connected with low blood zinc levels that are increased by effective antidepressant therapy. A placebo-controlled, double blind pilot study of zinc supplementation in antidepressant therapy was conducted in patients who fulfilled DSM IV criteria for major (unipolar) depression. Patients received zinc supplementation (6 patients; 25 mg of Zn^{2+} once daily) or placebo (8 patients) and were treated with standard antidepressant therapy (tricyclic antidepressants, selective serotonin reuptake inhibitors). Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) were used to assess efficacy of antidepressant therapy, and patients' status was evaluated before the treatment and 2, 6 and 12 weeks after its commencement. Antidepressant treatment significantly reduced HDRS scores by the 2nd week of treatment in both groups, and lowered BDI scores at the 6th week in zinc-treated group. Zinc supplementation significantly reduced scores in both measures after 6- and 12-week supplementation when compared with placebo treatment.

This preliminary study is the first demonstration of the benefit of zinc supplementation in antidepressant therapy. The mechanism(s) may be related to modulation of glutamatergic or immune systems by zinc ion.

Key words: *unipolar depression, antidepressant treatment, zinc, placebo, supplementation*

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INTRODUCTION

Zinc is an essential bio-element, which plays a fundamental role in a wide range of biochemical processes. This metal is a major component of various proteins and is an important modulator of the mammalian immune and nervous systems [13]. Alterations of blood zinc homeostasis may accompany mood disturbances as well as affect functions of the immune system (see [11] for review).

Current hypotheses of the mechanism underlying pathophysiology and treatment of depression are based on the alteration in neurotransmission, mostly in the monoaminergic and recently, in amino-acidergic systems [17, 19]. Moreover, recent data indicate that alterations in zinc (a natural modulator of amino-acidergic neurotransmission) homeostasis may contribute to mood disorders and may be involved in antidepressant-like actions in laboratory models [13].

Preclinical studies have demonstrated alterations in brain zinc concentrations by antidepressant drugs and electroconvulsive shock in rats [12]. Moreover, zinc exhibited antidepressant-like effects in animal tests/models of depression [5, 6, 14]. Further, low (and subeffective) doses of zinc administered together with low and ineffective doses of antidepressants enhanced antidepressant-like behavior in rodent forced swim test [5, 21]. These data indicate a significant role of zinc in the mechanism of antidepressant therapy and suggest a possibility to increase efficacy of antidepressant therapy by zinc supplementation in human depression. In addition, some clinical investigations have pointed to alterations in the blood zinc level as a potential marker of depression [8–10, 15].

In toto, these data prompted us to investigate the effect of zinc supplementation on antidepressant therapy in human unipolar depression.

MATERIALS and METHODS

The study was approved by the Ethical Committee of Collegium Medicum, Jagiellonian University, Kraków and the informed consent was obtained from all participants.

The patients admitted to the trial fulfilled DSM-IV diagnostic criteria for major depression. Twenty patients were randomly divided into two groups: placebo-treated (n = 10) and receiving zinc supplementation (n = 10, 25 mg Zn^{2+}, Zincas Forte, Farmapol, Poznań, Poland). All patients, after at least 1 week of washout period, received standard antidepressant therapy [clomipramine (125–150 mg), amitriptyline (125–150 mg), citalopram (20 mg), fluoxetine (20–40 mg)] and placebo or zinc supplementation according to a "double blind" procedure. The psychopathological status was assessed by the Hamilton Depression Rating Scale (HDRS, 17 items; [4]) and Beck Depression Inventory (BDI, [1]) at the time zero (before therapy), and after two, six and twelve weeks of the treatment.

Group differences were assessed using *t*-test, Fisher's Exact Test and the multiple analysis of variance with two between-subjects factors (placebo vs. zinc treatments and successive measures) followed by Fisher's LSD post-hoc test, where appropriate. Data were deemed significant when $p < 0.05$.

RESULTS

Some patients were excluded during the trial because of failure to complete all tests, delayed tests or serious family problems (spouse death). At the end of the study, groups consisted of 8 placebo-treated and 6 zinc-supplemented patients. Group characteristics are presented in Table 1. The mean age (± SD) in the zinc- and placebo-treated groups was 42.2 ± 13.7 and 43.4 ± 8.5 years, respectively, and the values were not significantly different ($p = 0.1204$, *t*-test). There were no significant differences in the male/female ratio between placebo (2/6) and zinc group (4/2) (Fisher's Exact Test). The mean ± SD of the HDRS score at the beginning of treatment was 24.5 ± 4.3 and 22.6 ± 3.9 in the zinc and placebo groups, respectively. Antidepressant therapy reduced the HDRS score in both groups beginning at the second week of the treatment (Fig. 1). The scores were significantly reduced in both groups over time: $F(3,28) = 5.091$; $p < 0.001$ in placebo and $F(3,20) = 29.578$; $p < 0.001$ in zinc group. The group effect [$F(1,48) = 4.275$; $p = 0.049$] and time effect [$F(3,48) = 21.683$; $p < 0.001$] were statistically significant. However, the group × time interaction did not reach significance [$F(3,48) = 1.836$; NS]. Zinc supplementation significantly augmented this reduction at sixth and twelfth week of treatment when compared with placebo administration (by ca. 55%, Fig. 1). The mean ± SD of the BDI score at the beginning of the treatment was 32.0 ± 5.4 and 33.3 ± 5.7 in the zinc and placebo groups, respectively.

Table 1. Characteristics of placebo and zinc-supplemented groups of patients

Treatment / Patient no.	sex	age	HDRS Baseline	HDRS Final	BDI Baseline	BDI Final
Placebo + ADs						
1	f	48	20	23	42	46
2	f	41	23	9	37	27
3	f	28	28	0	37	4
4	f	55	21	5	34	26
5	m	46	28	15	31	27
6	f	47	17	13	31	28
7	f	35	20	12	23	31
8	m	47	24	13	31	28
Zinc + ADs						
1	m	25	22	0	29	2
2	f	53	25	12	43	35
3	m	43	32	8	31	17
4	m	26	22	4	29	25
5	m	57	20	5	30	15
6	f	49	26	2	30	3

All patients received standard antidepressant therapy and placebo or zinc supplementation according to a "double blind" procedure. The psychopathological status was assessed by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) before treatment (baseline) and at 12th week of treatment (final); f – female; m – male; ADs – antidepressants

Antidepressant therapy reduced the BDI scores at sixth and twelfth week of treatment in zinc-supplemented group (Fig. 2). The scores were not significantly reduced over time, both in placebo group: $F(3,28) = 1.641$; NS, and in zinc group $F(3,20) = 2.687$; $p = 0.074$. The group effect [$F(1,48) = 3.486$; $p = 0.068$] lacked a significance, while the time effect [$F(3,48) = 4.025$; $p = 0.012$] was statistically significant. However, the group × time interaction was insignificant [$F(3,48) = 0.496$; NS]. Zinc supplementation significantly augmented the reduction in BDI scores at twelfth- week of treatment when compared with placebo supplementation (by 40%, Fig. 2).

DISCUSSION

The present results indicate a benefit of supplementation of the antidepressant therapy with zinc in unipolar depression. Although the effect is delayed, appearing at 6th week of co-treatment, its potency is quite robust.

A palliative effect of zinc in humans is consistent with converging lines of preclinical evidence. Zinc exhibits antidepressant-like activities in the forced swim test [5, 6, 14]. Low, ineffective doses of zinc administered together with low, ineffective doses of imipramine or citalopram exhibited antidepressant-like effects in mouse and rat forced swim test [5, 21]. Further, zinc exhibits antidepres-

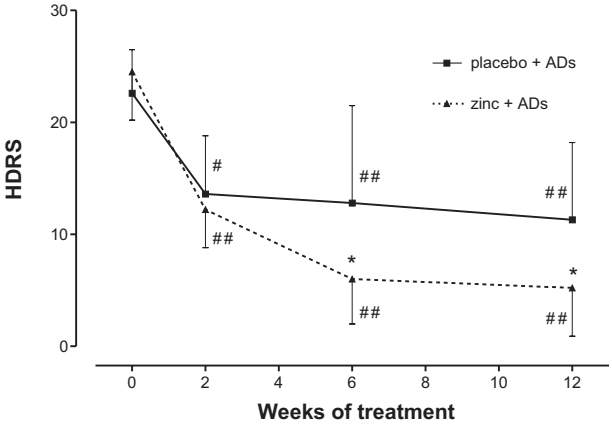

Fig. 1. The effect of placebo and zinc supplementation on antidepressant therapy evaluated by Hamilton Depression Rating Scale (HDRS) scores in patients with unipolar depression. Data represent the mean ± SD of 8 – placebo and 6 – zinc-supplemented subjects per group. * $p < 0.05$ vs. placebo; # $p < 0.01$, ## $p < 0.001$ vs. respective value at the beginning of the treatment (week 0)

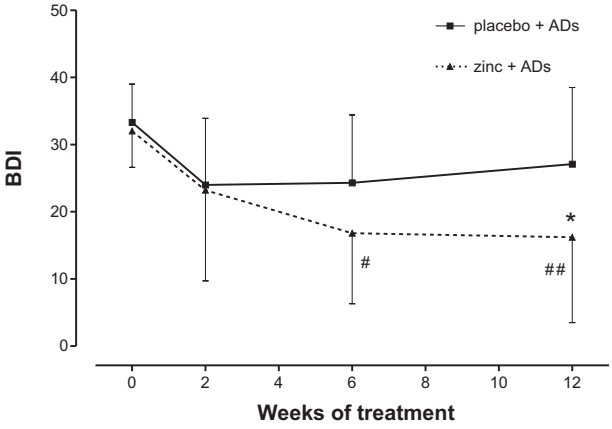

Fig. 2. The effect of placebo and zinc supplementation on antidepressant therapy measured by Beck Depression Inventory (BDI) scores in patients with unipolar depression. Data represent the mean ± SD of 8 – placebo and 6 – zinc-supplemented subjects per group. * $p < 0.05$ vs. placebo; # $p < 0.02$, ## $p < 0.01$ vs. respective value at the beginning of the treatment (week 0)

sant-like actions in olfactory bulbectomy, chronic unpredictable stress and chronic mild stress animal models of depression in rats ([14, 16], unpublished). Further, repeated administration of imipramine or citalopram induced a 20% increase in the ratio of zinc concentration in the hippocampus and other regions of the brain [12]. This finding may indicate a significant "redistribution" of the brain zinc pool following chronic antidepressant treatments favoring the hippocampus. Chronic electroconvulsive treatment (ECT) induced an increase in zinc concentrations in the hippocampus with a similar, although less robust effect in the cortex and cerebellum [12]. It has also been demonstrated (using Timm's method for zinc staining) that chronic ECT induces hippocampal mossy fibre sprouting [22]. The later data suggest an increase in the vesicular zinc level in the hippocampus following ECT.

Several clinical studies have examined blood (serum or plasma) zinc level in major depression (see [11] for review). A lower zinc blood concentration was demonstrated in depressed patients, which was normalized by effective antidepressant treatment [8–10, 18]. Most studies have reported that in unipolar depression, the severity of the illness measured by the Hamilton Depression Rating Scale (HDRS) is negatively correlated with the serum level of this ion [8, 10, 15, 18]. However, another study of Maes et al. [9] did not find a correlation between these two parameters (HDRS score and zinc). It may be supposed that the latter study included a different, mostly treatment-resistant, population of patients. These treatment-resistant patients exhibited the lowest serum zinc level, a characteristic which according to Maes et al. [9], is a sensitive and specific marker of treatment-resistant depression. Therefore, we can expect that a lower serum zinc level accompanies depression, while its relationship with the severity of the illness varies with the population of depressive patients.

According to recently introduced hypotheses of antidepressant action, one of major goals to be modified by an antidepressant is the NMDA glutamate receptor [17, 19]. The mechanism of antidepressant activity of zinc might be related to its direct antagonism at NMDA receptor [13]. In fact, antagonists of the NMDA receptor complex exhibit not only antidepressant-like effect in animal models (see [17, 19] for review) but also are effective in human depression [2, 3, 20]. Further, the indirect effects of zinc, viz. antagonism at group I metabotropic (mGlu) glutamate receptors or potentiation of AMPA receptors which both may attenuate the NMDA receptor function, should be considered as a potential mechanism of antidepressant action of this ion [13]. Besides the central nervous system, zinc is also involved in the immune/inflammatory regulation in depressive disorders, and this mechanism may be considered either [7, 11, 13].

The limitation of our trial is the small sample size, thus the study suggests the need to conduct a larger trial of zinc supplementation to further examine the effectiveness of zinc treatment in human depression.

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