Interactions between magnesium and psychotropic drugs

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Abstract. Psychotropic drugs (antidepressants, antimanics, antipsychotics, analgesic opioids, and others) are among the most frequently used medicines. Between these drugs and magnesium there are pharmacokinetic and pharmacodynamic interactions. Erythrocyte magnesium is decreased in patients with severe major depression (MD) vs normal subjects (44 ± 2.7 mg/L in MD group vs 59.1 ± 3.2 mg/L in control group, p < 0.01). Therapy with sertraline, 150 mg/day p.o. -21 days or with amitriptyline 3 x 25 mg/day p.o. 28 days increases significantly erythrocyte concentration of magnesium (56.9 ± 5.22 mg/L after sertraline vs 44 ± 2.7 mg/L before sertraline, p < 0.01). In patients with acute paranoid schizophrenia, erythrocyte magnesium concentration is decreased vs healthy subjects. Haloperidol, 8 mg/day, p.o. for 21 days or risperidone, 6 mg/day p.o. for 21 days have increased significantly erythrocyte magnesium concentration (46.21 ± 3.1 mg/L before haloperidol and 54.6 ± 2.7 mg/L after haloperidol, p < 0.05). Antimanic drugs (mood stabilizers) as carbamazepine, 600 mg/day, p.o., 4 weeks and sodium valproate, 900 mg/day p.o., 4 weeks, increased significantly magnesium in patients with bipolar disorder type I. Increased magnesium status positively correlated with enhancement of the clinical state. The existent data sustain the idea that an increase of erythrocyte magnesium is involved in the mechanism of action of some psychotropic drugs. Magnesium supply decreased the intensity of morphine-induced physical drug dependence. In heroin addicts, the plasma magnesium concentration is decreased.

Key words: psychotropic drugs, magnesium, major depression, bipolar disorder, carbamazepine, sertraline, amitriptyline

Psychotropic drugs represent some of the most important and frequently used drug categories. There are several psychotropic groups such as: anxiolytics, antidepressives, antipsychotics, hypomanics, etc.

Magnesium has complex actions at the central nervous system (CNS) level. Both pharmacodynamic and pharmacokinetic interactions have been noticed between plasma/tissue magnesium concentration and psychotropic drug actions. Interactions are in both directions. Data available about all these interactions are, on the other hand, non-concordant.

Our research was aimed to determine variations in magnesium and other bivalent cations in patients with major depression and the effects of some antidepressives on serum and tissue magnesium levels. Research was performed on a 76 adult patients of both sexes (primarily women). Pregnant women, alcoholics, patients with kidney or liver failure or those receiving medical drugs containing cations or diuretics were not included in the study. Depression severity was determined using the Hamilton rating scale of depression. Only patients with medium or severe major depression (MD) were included in the study (Hamilton score 17 or over). Determinations of
plasmatic and erythrocyte magnesium and copper, zinc, iron and manganese levels in plasma were performed before starting antidepressive therapy and after 28 days of treatment. Some of the patients received sertraline (Zoloft®, Pfizer, 150 mg/day per os at least for 28 days) while the other group received amitriptyline 3 x 25 mg/day per os at least for 28 days.

Our data show that the erythrocyte magnesium level was significantly decreased in the group with MD (44 ± 2.7 mg/L in MD group vs 59.1 ± 3.2 mg/L in control group, p < 0.01). In both sertraline and amitriptyline groups, the erythrocyte magnesium level increased (57.6 ± 4.5 mg/L in amitriptyline group and 56.9 ± 5.22 mg/L in sertraline group, p < 0.01 vs before treatment) [1]. The magnesium plasma level was significantly lower vs. controls only in the severe MD group (Hamilton score > 23) (17.8 ± 2.2 mg/mL vs 22.9 ± 1.9 mg/mL in healthy controls, p < 0.05) [1]. Meanwhile, the plasma copper concentration was found to be significantly increased in MD patients (0.86 ± 0.05 mg/L vs 0.63 ± 0.01 mg/L in control group). The zinc plasma level was decreased in the MD group [2, 3].

Also, we could establish a positive correlation between an increase in the erythrocyte and plasma magnesium concentrations and the patient’s clinical state. No changes in serum calcium concentration after sertraline or amitriptyline treatment could be established [4]. Our research showed partially concordant results with those of Schlegel-Zawadzka et al. [5], who observed a significant increase in zinc serum levels after amitriptyline therapy in an experimental model of depression in rats. Also, our results are concordant with Levine et al. [6], who reported a significant increase in the Ca/Mg ratio in cerebrospinal fluid (CSF) and in serum in patient with MD before beginning any treatment.

Schizophrenia is considered the most severe psychosis. Our data, referring to intra- and extra-cellular magnesium concentrations in patients diagnosed with schizophrenia, are relatively contradictory. Some authors found increased levels of magnesium in CSF and serum [7, 8]. We studied serum and erythrocyte magnesium concentrations in a group of 56 adult patients (32 women and 24 men) with paranoid schizophrenia (DSM IV) admitted with psychiatric attacks to the clinical psychiatric hospital in Socola Iași (Romania) and who received antipsychotic treatment before hospitalisation. Patients with chronic renal failure, cardiac failure, chronic ethanol intake, malabsorption syndromes, and patients treated with diuretics or magnesium containing drugs were not included in the study. Plasma and erythrocyte magnesium concentrations were determined on admittance and after 30 days of therapy. Patients received, in a randomised manner, haloperidol 8 mg/day, for 21 days or risperidone (Rispolept®, Janssen Cilag), 6 mg/day for 21 days. Serum and erythrocyte magnesium levels were also determined in a group of healthy people, with the same sex and age distribution pattern as the studied groups. Previous studies showed no statistically significant differences between serum magnesium levels in patients with schizophrenia vs controls [9, 10]. On the other hand, there is a significant decrease in magnesium erythrocyte levels (59.2 ± 4.1 mg/L in control vs 46.21 ± 3.1 mg/L in schizophrenic patients, p < 0.05). After 3 weeks of antipsychotic treatment, in both haloperidol and risperidone treated patients, the magnesium erythrocyte concentrations expressed a significant increase (up to 54.6 mg/L in haloperidol treated patients and up to 52.8 mg/L in the risperidone treated group, p < 0.05 vs before treatment levels).

Together with a significant increase in magnesium erythrocyte levels, we also demonstrated a significant decrease in serum copper levels in both risperidone and haloperidol treated groups (0.8 ± 0.15 mg/L before treatment vs 0.62 ± 0.08 mg/L after risperidone treatment, p < 0.01) [9].

Bipolar disorder (BD) (also called manic-depressive psychosis) is included in the group of affective psychosis. BD is a heterogeneous disease with many clinical aspects. There is more than one form of BD. Data existing about changes in plasmatic and cellular levels of magnesium are contradictory. It is possible that the heterogeneity of data about magnesium in patients with BD results from studies on different types of BD.

The number of drugs used in the therapy of this disease has markedly increased from lithium salts to new mood stabilizers (such as sodium valproate, lamotrigine, carbamazepine, etc) [11]. There is a competition between Li+ and Mg2+ for some intraneuronal binding sites [12]. Administration of lithium salts increases intracellular concentration of magnesium. We searched for the influence of carbamazepine (600 mg/day per os for 4 weeks) and sodium valproate (Orfifil®, Desitin Arzneimittel GmbH; 900 mg/day per os for 4 weeks) in patients with BD admitted in an acute manic episode, without previous therapy. Both carbamazepine and sodium valproate in the above mentioned doses significantly increased concentrations of intracellular magnesium after 4 weeks (initial Mg concentration 45.01 ± 1.87 mg/L vs 52 ± 0.9 mg/L after sodium valproate, p < 0.05) [13]. Total magnesium concentrations in erythrocytes in BD patients during the acute episode were significantly decreased vs control group (45.01 ± 1.87 mg/L vs...
in BD group vs 59.15 ± 2 mg/L in control group, p < 0.01) [14]. Increasing intracellular brain levels of magnesium determines a decreasing glutamate-induced activation of NMDA receptors and consequently alleviates maniac psychomotor hyperactivity (figure 1). Because psychotropic drugs with different chemical structures and different mechanisms of action increase magnesium concentrations in the erythrocytes of BP patients, we consider this increase an important element in mechanism of action of mood stabilizers in BD.

There are interactions between magnesium and opiate analgesics. We searched for the influence of magnesium in morphine-induced experimental drug dependence in rat. We administrated morphine for 11 days in a group of rats in progressively increased doses (5 mg/kg/day s.c. on the first day to 90 mg/kg/day s.c. on the eleven day). A second group received morphine (as the first group) and magnesium acetaminate (MgAcx) 0.5 mEq/kg i.p. daily, 1 h before the morphine for 11 days. Withdrawal syndromes were induced after the 11th day with naloxone (1 mg/kg i.p.) and symptoms were followed. Our results [15] show a significant decrease in the intensity of withdrawal syndromes (especially grooming, locomotor activity, aggressive postures) in the group that received magnesium during morphine-induced dependence. We consider that this indicates that magnesium decreased the intensity of morphine-induced dependence. It is not a direct action of magnesium during the withdrawal syndrome, magnesium intake ceasing before the naloxone administration. Our results correlate with data showing that the plasmatic level of magnesium is decreased in heroin addicted patients [16, 17]. We consider that magnesium may modulate the intensity of psychotropic drug-induced dependence.

We consider that magnesium-psychotropic drug interactions play an important role in the pharmacodynamic effects of this group of drugs, although the proven number of psychotropic drugs that influence plasmatic and intracellular magnesium level is relatively limited. This effect might play a role in their therapeutic effect.

**Figure 1.** Drugs – Mg$^{2+}$ relations in psychoses (+ stimulating effect) (from [10]).
References


