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MIRTAZAPINE-INDUCED HYPONATREMIA IN A PATIENT WITH SYSTEMIC MASTOCYTOSIS AND GENERALIZED ANXIETY DISORDER

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INTRODUCTION

It is well known, that various psychopharmaceuticals, especially mood stabilizers and antidepressants, can cause hyponatremia. The majority of scientific works published until now, state that hyponatremia is most often caused by carbamazepine, oxcarbazepine and SSRIs (Letmaier et al. 2012). Some cases of hyponatremia may be a consequence of the mirtazapine use as an antipsychotic drug (Cheah et al. 2008, Verbalis et al. 2013, Lange-Asschenfeldt et al. 2013). This clinical case report shows mirtazapine-induced hyponatremia in a patient diagnosed with systemic mastocytosis, which is the rare chronic disease. Mirtazapine is known to be an antidepressant drug, with a combined, dual mechanism of action. As an antagonist of alpha2-adrenergic receptors, it specifically acts on noradrenaline and serotonin (NaSSA). By blocking presynaptic alpha2-adrenergic receptors on noradrenergic neurons, it increases the concentration of noradrenaline in the synaptic gap. By blocking alpha 2-adrenergic receptors on serotonergic neurons, where they function as heteroreceptors, it increases the concentration of serotonin in the synapse. Mirtazapine inhibits 5HT2A, 5HT2C and 5HT3 serotonergic receptors. It also has an antagonistic effect on H1. The cytochrome (CYP) P450 isoenzymes CYP1A2, CYP2D6 and CYP3A4 are mainly responsible for its metabolism.

CASE REPORT

The patient is 34-year-old woman, highly educated, with high socioeconomic status, mother of two boys. The patient has suffered from a chronic family stress. She was diagnosed with systemic mastocytosis at the age of 30, and has been in stable remission for three years, taking mast cell stabilizers as regular medication. In addition to regular medication with mast cell stabilizers, the patient always carries an adrenaline pen with her, so she can react with an intramuscular injection, in a possible case of dyspnea and acute respiratory distress syndrome. At the first psychiatric examination, the patient was diagnosed with generalized anxiety disorder GAD-7 scoring anxiety 9 (mild anxiety) and nonorganic insomnia of the initial and intermittent type. The patient was also assessed by a psychologist who determined the existence of an avoidant personality disorder (AVPD), as well as the dominant use of bad personality defense mechanisms, such as denial, repression, projection and rationalization. After the diagnosis has been made, Mirtazapine was introduced at a dose of 15 mg/d in the evening and the patient was included in psychotherapy sessions, or more precisely, cognitive behavioral therapy (CBT). After four days, the dose has been increased to 30 mg/d in the evening. On the fifth day, the patient has reported symptoms of restless legs, tingling fingers, blurry vision, irritability, dizziness, forgetfulness, nausea, vomiting, muscle weakness and unsteadiness while walking.

Laboratory test results were within reference values, except blood sodium level (120 mEq/l) and plasma osmolarity 269 mOsm/kg. Mirtazapine was immediately excluded from medication. The patient has received an intravenous infusion of NaCl 0.9% 1000 ml and sodium chloride tablets of 1 g, for the next two days. On the third day after the infusion of NaCl and sodium chloride tablets have been taken, all previously described symptoms disappeared. Blood sodium level on the third day of medication was 139 meq/l and the osmolarity of the plasma was 285 mOsm/kg. Due to existing insomnia and generalized anxiety (GAD-7 scoring anxiety 4), Quetiapine 50 mg/d and Clonazepam 1mg/d were introduced. After the new medicines have been taken, the patient didn`t have any of described symptoms at the follow-up examination, and a regulation of sleep was regained, as well as a significant reduction in anxiety-score. After re-checking the blood sodium level and plasma osmolarity (on the 10th day of the new medication), obtained values were in the reference range. Blood sodium level was 138 meq/l and plasma osmolarity 285 mOsm/l. The patient is still on the prescribed medication, with control tests of blood sodium level and plasma osmolarity have been done after every three months.

DISCUSSION

This clinical case report shows mirtazapine-induced hyponatremia in a patient with systemic mastocytosis. Using the Naranjo ADR Probability Scale, the score was 9, which indicates hyponatremia caused by the newly introduced drug – mirtazapine (Naranjo et al. 1981).

The value of sodium in the blood before the introduction of mirtazapine was 134 meq/L. Before the introduction of mirtazapine, the following assays were performed due to the existence of a rare chronic disease: complete blood count, electrolyte panel, liver function tests, urea, creatinine and ECG. Bearing in mind that it is a rare chronic disease, it is important to be careful when introducing a new drug for the patient, because it could lead to destabilization of the mast cell membrane and worsening, i.e. shifting chronic form of disease to acute one. In this patient, mirtazapine and then quetiapine were best-choice medications given, that induced sedation, sleep regulation, as well as H1 receptor blockade, and do not cause mast cell membrane destabilization. The use of other psychotropic drugs, especially SSRIs antidepressants, is not recommended in patients diagnosed with systemic mastocytosis, because these drugs can significantly destabilize, or damage the mast cell membrane, and release mediators such as histamine, serotonin and bradykinin (Valent et al. 2017). The mechanism of the development of hyponatremia is still unknown. There are reports from the literature related to SSRIs, carbamazepine, oxcarbazepine and other psychopharmaceuticals, that show this drugs can lead to hyponatremia (Giorlando et al. 2013, Mannesse et al. 2010). Mirtazapine-induced hyponatremia is most likely caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Famularo et al. 2009, Roxanas 2003). The way it occurs is still unknown, but it is assumed that SIADH is most likely triggered by the action of serotonin on 5HT and 5HT1C receptors, as well as by another unknown mechanism (Arinzon et al. 2002, Liu et al. 1996).

CONCLUSION

Hyponatremia is a well known emergency. In all psychiatric patients who have been diagnosed with some chronic disease, physician should always think about the possible occurrence of hyponatremia, both as a consequence of the chronic disease itself, and because of pharmacotherapy. Also, prior the introduction of psychopharmacotherapy in chronic patients, physician must take into account the possible interactions of psychopharmacotherapy drugs with current medications, used for chronic disease treatment.

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Contribution of individual authors:

Branislav Šakić: conception and design of the study, data collecting, interpretation of data, literature searches and analyses and manuscript writing.

Alen Greš: conception and design of the study, literature searches and analyses, interpretation of data, drafting of the article, critical revision of the article and manuscript reviewing.

Zoran Gajić: design of the study, statistical analyses, literaure searches and analyses, critical revision of the article and manuscript reviewing.

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