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CASE REPORT

A Case of Parkinsonism and Encephalopathy with Combined Lithium-Risperidone Therapy: Treatment with Pramipexole

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Abstract

Lithium is a drug that has been used in the treatment of bipolar disorder for many years. Due to its narrow therapeutic range, systemic side effects can be seen frequently. Serious side effects can occur even in non-toxic doses. We present a case of parkinsonism and encephalopathy developed in a patient with normal lithium blood level who used lithium and risperidone combination therapy for bipolar disease.

Keywords: Lithium, Risperidone, Parkinsonism, Encephalopathy, Lithium induced parkinsonism, Bipolar disorders

Abbreviations: CT: Computed Tomography; EEG: Electroencephalogram

Introduction

Lithium is a drug that has been used to treat bipolar disorder for over 60 years. Due to its narrow therapeutic range, the treatment is effective in the treatment of bipolar disorder, although it causes toxicity and serious side effects. Lithium can cause serious systemic side effects even before reaching the toxic dose [1].

Serious neurological findings such as encephalopathy, parkinsonism and ataxia may occur in lithium intoxication. Various drugs can be used in parkinsonism due to the combination of lithium and risperidone [2]. We tried pramipexole treatment in this case, and we found the case worth presenting because of the complete complete resolution of symptoms.

Case Report

A 57-year-old male patient was brought to the emergency room with drowsiness, blurred consciousness, slowed movements, and difficulty of walking. He had been using1200 mg/day lithium and 2 mg/day risperidone with the diagnosis of bipolar disorder for 6 years. In his neurological examination, the patient was in a confused state. He had bilateral resting tremor, bradykinesia and rigidity. His steps were short and slow. Acute pathologies were excluded in brain computed tomography (CT). The lithium level was 0.41 mmol/L (normal: 0.6-1.2 mmol/L). Renal and thyroid function and electrolytes, were normal. A moderate frequency slowing was detected in the electroencephalogram (EEG) examination.

Although the lithium level was normal, neurotoxicity developed. After immediate withdrawal of lithium clinical picture did not improve. As the extrapyramidal symptoms were changed after 10 days of lithium withdrawal, pramipexole 0.375 mg/day was administered.

Improvement was observed within three days and a complete resolution of symptoms within a week. Pramipexole therapy was stopped after one month without recurrence of parkinsonism.

Discussion

Lithium was first used in the 19th century to treat recurrent depression. It has been used for more than 60 years in the treatment of bipolar disorders after its

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effectiveness on manic symptoms has been observed. In this process, the growing doubts about the evidence-based efficacy of lithium decreased the frequency of use because previous studies on lithium could not meet new research standards. Fatal toxicity and difficulty of use also limited the use of the drug.

In addition, over the last 60 years, the prescription of lithium has decreased with the changes in the diagnostic criteria of bipolar disorder, the use of mood stabilizer antiepileptic drugs and antipsychotics. However, recent double-blind randomized controlled trials and meta-analyses have once again reported that lithium is effective in the treatment of bipolar disorder. Lithium is now considered the treatment of choice for the long-term prophylaxis of new episodes, regarded as the only agent to prevent both new depressive and new manic episodes. Also, lithium is the only drug with an established anti-suicidal efficacy in bipolar disorders [1,3].

Before initiating lithium treatment, patients should be subjected to a series of tests considering the potential side effects of the drug. First, kidney function tests should be studied, since lithium is metabolized by the kidneys. In the presence of renal dysfunction, the risk of toxicity will increase due to lithium accumulation. Renal function tests should be studied every 6 months. Since lithium can cause hypothyroidism, thyrotoxicosis and hyperparathyroidism, thyroid function tests, parathormone and calcium levels should be studied. In this respect, patients should be tested every 6 months. Since lithium causes weight gain, it is recommended to check weight and body mass index every 6 months. Furthermore, electrocardiograms may also be recommended as long-term lithium treatment has been associated with corrected QT(QTc) interval prolongation [4].

Lithium has a relatively narrow therapeutic index, and individual differences should be accounted for when initiating treatment as lithium toxicity may occur if levels surpass 1.2 mmol/L. Lithium plasma levels greater than 1.2 mmol/L are potentially toxic, and in acute intoxication, plasma levels that exceed 2.0 mmol/L can be fatal [5]. Side effects can also be observed at normal serum lithium levels. Due to its small molecule structure and its ability to easily enter cells, it can cause side effects in almost any system.

These side effects usually respond well to dose reduction. It has been shown that lithium accumulates especially in nerve cells; It is known that side effects related to the nervous system occur even at normal serum lithium levels or even at non-therapeutic levels [6].

Nervous system symptoms are seen in 95% of patients in acute lithium poisoning. The picture related to the nervous system does not improve immediately after lithium is discontinued. Central nervous system symptoms include a state of confusion, encephalopathy, cerebellar signs such as tremor, dysarthria, ataxia, and nystagmus, extrapyramidal and neuromuscular signs such as fasciculations, fibrillations, and myoclonia, and polyneuropathy. In lithium-induced parkinsonism, symptoms such as bradykinesia, resting tremor, and cogwheel are seen. Although the mechanism of lithium-induced parkinsonism is not clear, some researchers have focused on factors such as a decrease in the amount of dopamine in the striatum, the cholinergic effect of lithium with its anticholinesterase effect, and the previous damage to the basal ganglia in patients with parkinsonism [2].

It has been studied by researchers that lithium or a combination of lithium and neuroleptics can cause irreversible neurotoxicity. Although the possible cause of this neurotoxicity is unknown, various hypotheses have been put forward. The most important hypothesis put forward is that lithium-neuroleptic therapy causes neurotoxicity by increasing dopamine receptor blockade. It has been reported that slow-wave EEG changes are the best indicator of neurotoxicity and can begin even with a serum level as low as 0.76 mEq/liters. Although lithium-neuroleptic combination therapy is largely safe, it has been shown that some patients are sensitive to this combination and are at high risk for disturbing side effects. It is still unclear who these patients are and why they should be more vulnerable to these side effects than other patients [7,8]. A case of encephalopathy associated with lithium-risperdal combination has been presented before [7], but our case is significant because it is the first case of parkinsonism and encephalopathy associated with this combination.

Treatment of lithium poisoning is chosen depending on the cause and severity of the poisoning and the rate of renal excretion of lithium. In all cases, after the cessation of lithium intake, regulation of the fluid-electrolyte balance and supportive treatment is the first mandatory step. For this, first of all, adequate hydration must be provided. After this point, the aim is to reduce lithium absorption and increase its excretion. Patients with severe clinical signs and symptoms, prolonged intoxication, high serum lithium levels, and impaired renal function should be treated with hemodialysis [9].

Studies have reported that benztropine is not effective on tremor and cogwheel symptoms in the treatment of lithium-induced parkinsonism. Drugs reported to be effective in these symptoms are primidone, β-blockers and amantadine [2].

In our case, pramipexole treatment was given because parkinsonism did not improve despite lithium discontinuation. Pramipexole has high affinity for D2, D3 and D4 dopamine receptors, which are distributed in the mesolimbic area, in the striatum, in the medial portion of globus pallidum, in the pars reticulata of the substantia nigra and in cortex. Pramipexole might also

act at the D3 subgroup level, where lithium may have no influence, and may be able to restore the balance in dopamine neurotransmission or the balance between dopamine and acetylcholine [10].

Conclusion

This case suggests that lithium can cause neurotoxicity and parkinsonism when administered as monotherapy or in combination with neuroleptics, and neurological symptoms do not always improve with lithium discontinuation. The temporal profile of improvements in symptoms indicates a beneficial effect of pramipexole. More clinical studies are needed to explore this hypothesis.

Sources of Support

None.

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