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Letter to the Editor

Reversible pisa syndrome related to the interaction between lithium and clotiapine: Case report

Dear Editor,

Pisa syndrome, as lateral truncal dystonia, occurs most commonly in neurodegenerative disorders and adverse effects of medication treatment, like antipsychotics, and anti-cholingeric agents. The definite pathology mechanism remains unclear, but it is often attributed to an imbalance in cholinergic-dopaminergic systems, asymmetric basal ganglia function [1]. Clotiapine is an antagonist of D2 and D4 (dopamine) receptors and 5-HT2 (serotonin) receptor involved in both schizophrenia and bipolar disorder [2]._ENREF_2 Lithium is used as a mood stabilizer in bipolar disorder and impulsivity. A single report about Pisa syndrome associated with clotiapine abrupt discontinuation with several other antipsychotics switch [3] or chronic lithium treatment [4] exists, respectively.

Miss C, a 31-year-old woman with bipolar I disorder was admitted to our psychiatric department due to manic symptoms after discontinuation of all medication (valproic acid 1000—1500 mg/day, combined with long-term administration of quetiapine 400—600 mg/day). According to her past medical history, she had neither truncal dystonia under psychiatric medication nor other involuntary movement disorders before this treatment course. At first, we administered lithium 600 mg/day and quetiapine with slow titration to 600 mg/day. The unstable psychiatric state was not controlled with the lower therapeutic concentration of lithium (0.42 mmol/L). Quetiapine was switched to clotiapine 120 mg/day and lithium was titrated to 900 mg/day (Li: 0.61 mmol/L). To address the manic state, clotiapine was adjusted to 160 mg/day, and lithium was on maintenance dosage of 900 mg/day (Li: 1.07 mmol/L) in 2 weeks. After the manic state improved, pisa syndrome developed. The patient refused the anticholinergic medication treatment for dystonia, because of constipation. Neurological tests, biochemistry tests and brain computed tomography all gave inconspicuous results. To improve the Pisa syndrome, clotiapine was reverted to quetiapine 600 mg/day. Dystonia resolved 10 days after this change, with lithium concentration being 0.78 mmol/L. To assess the probability of a causal relationship, we applied the Drug Interaction Probability Scale (DIPS). A DIPS score of 5 out of 11 indicated a probable interaction of lithium (object drug) and clotiapine (precipitant drug) (Table 1). We hypothesize that the bi-directional interaction of lithium and clotiapine induced the side effect of truncal dystonia. However, only single direction interaction was shown in the DIPS adverse drug reaction scale. In the case, quetiapine is less likely the cause of Pisa syndrome, due to the repetitive quetiapine performance without truncal dystonia occurrence.

The first case report of Pisa syndrome during chronic lithium administration in bipolar disorder only suggested the involvement of the dopaminergic system [4]. It was found that prolonged lithium decreases pre-synaptic dopamine release, and interferes with post-synaptic dopamine receptor signaling[5] similar to antipsychotics, which may influence nigrostriatal pathway leading to dystonia [1,5]. _ENREF_5In contrast to the latter case with a 2-year lithium usage [4], our patient received only 3 weeks of lithium treatment with similar lithium plasma concentration (1.1 mmol/L). In our case, the concentration of lithium could be one of the causes of dopamine imbalance.

With regard to lithium-clotiapine combined therapy, while lithium is mainly metabolized by the kidney, 35% of clotiapine is excreted by the kidney, which may increase the level of lithium [2]. It cannot be excluded that lithium also affects pharmacokinetic interactions in renal clearance; such an effect has been described at elevated concentrations of drugs excreted by the kidney.

Clotiapine down-regulates cortical 5-HT2 receptors, blocks 5-HT3 receptors, and has high affinity for 5-HT6 and 5-HT7 receptors. Its ratio of D2 to 5-HT2 blockage is similar to that of clozapine [2]. There are several case reports that show

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Table 1 Drug Interaction Probability Scale (DIPS) and the present Pisa syndrome patient's scores.

	Answer	Score
1. Are there previous credible reports of this interaction in humans?	Yes	+1
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	Yes	+1
3. Is the observed interaction consistent with the known interactive properties of object drug?	Yes	+1
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	Yes	+1
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?	Yes	+1
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	No	−1
7. Are there reasonable alternative causes for the event?	Unknown	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	No	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	No	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	Yes	+1
Total score		5

Total Score: Highly Probable: >8, Probable: 5—8, Possible: 2—4, Doubtful: <2.

that clozapine-induced Pisa syndrome_ENREF_1 [1] is related to the downregulation of postsynaptic 5-HT2 receptors. Clotiapine may share the same mechanism. In our case, whether the individual effects or drug interaction of lithium and clotiapine could be the causes of dopamine imbalance is still an unresolved question, further experiments are necessary needed to address the underlying mechanisms.

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