Pleurothotonus (Pisa syndrome) Induced by an Association of Clozapine and Mirabegron

To the Editor: Pleurothotonus or Pisa syndrome is a postural deformity occurring most commonly in the coronal plane defined by an abnormal lateral trunk flexion of more than 15°.[1,2] Pisa syndrome can be classified by the angle of lateral trunk flexion as mild (< 20°) or severe (≥ 20°) and can present in a chronic or subacute form.[3,4]

Case report. A 56-year-old woman with bipolar disorder (*DSM-5* criteria), borderline personality disorder (*DSM-5* criteria), hypercholesterolemia, and hypothyroidism presented to our clinic in February 2017 reporting left trunk flexion present for the past 2 days. Neurologic examination showed no other abnormalities. The patient's medications included levothyroxine, bupropion, topiramate, clonazepam, lithium, clozapine, atenolol, and atorvastatin, with no reported adverse effects over the last few months. There had been no adjustment to these medications, with the exception of mirabegron, which was started 5 days ago for urinary incontinence. The patient scored 5 on the Naranjo scale,[5] indicating a probable correlation between mirabegron and her symptoms.

The dose of clonazepam was increased (from 1 to 2 mg/d), mirabegron was discontinued, and the patient was sent to the emergency department. During the hospital admission, clozapine was discontinued while maintaining the other medications. No neurologic lesions were identified on brain magnetic resonance imaging, and there was spontaneous symptomatic remission of Pisa syndrome. One month later, the patient presented for follow-up in complete remission despite the reintroduction of mirabegron and clozapine.

Mirabegron is a selective β_3-adrenoceptor agonist that acts as a moderate time-dependent inhibitor of cytochrome P450 2D6 (CYP2D6) and a weak inhibitor of CYP3A.[6] Clozapine is an atypical antipsychotic recommended for treatment-resistant schizophrenia[7] and has been associated with Pisa syndrome.[8] Clozapine is almost completely metabolized before excretion by CYP1A2 and CYP3A4 and to some extent by CYP2C19 and CYP2D6. Concomitant administration of medications known to inhibit the activity of some CYP isozymes may increase the levels of clozapine, with eventual need for dose reduction due to undesirable events.[9]

This case report suggests that the association of mirabegron and clozapine may have led to an increase in clozapine levels, which may have caused Pisa syndrome. Clonazepam dose adjustment may have induced symptomatic remission. Psychiatric patients are frequently polymedicated. These patients are at high risk for adverse reactions triggered by an interaction between psychiatric drugs and medications for treatment of nonpsychiatric disorders.

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