

Severe orthostatic hypotension after adding low-dose aripiprazole to clozapine

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Received: 12/31/2016 – Accepted: 5/10/2017

DOI: 10.1590/0101-6083000000125

Lin YS et al. / Arch Clin Psychiatry. 2017;44(3):84

Dear Editor,

Antipsychotics can cause orthostatic hypotension (OH) by blocking adrenergic receptors¹. OH is easily under-recognized as it can be asymptomatic. In clinical practice, combination treatment of two or more antipsychotics is common; however, little attention has been paid to OH in this scenario. Here, we presented a patient who developed severe OH after adding aripiprazole 5 mg/d to clozapine 400 mg/d.

A 33-year-old man with a 15-year history of schizophrenia presented because of severe auditory hallucination and persecutory delusion. After admission, the dose of clozapine was gradually increased to 400 mg/day, and the psychotic symptoms were improved. Over the following 4 weeks, the patient still exhibited negative symptoms, including alogia, avolition, asociality, and poor self-care. Aripiprazole 5 mg/day was added, and the negative symptoms were improved. However, 2 weeks later, the patient fell down twice on a sudden rise from supine position. Physical and neurological examinations and the results of laboratory tests were negative. Notably, the lying-to-standing orthostatic test caused a remarkable change in blood pressure (BP). The patient showed 118/83 mmHg with pulse rate (PR) 90 beats per minute (bpm) in supine position and 70/36 mmHg with PR 122 bpm in standing position. Aripiprazole was discontinued, and the OH was relieved. After careful consideration of the risks and benefits, aripiprazole 5 mg/d was added again. However, OH recurred 2 weeks later. Therefore, aripiprazole was switched to escitalopram, and OH did not recur.

OH is defined as a drop in BP (> 20/10 mmHg) within in 3 minutes of standing. The OH is associated with aripiprazole because of the temporal relationship between its occurrence and the commencement of aripiprazole, its resolution upon aripiprazole discontinuation, and its recurrence with aripiprazole rechallenge. An animal study suggested that both clozapine and aripiprazole could block α_1 adrenoceptors, while the potential to cause OH is higher in clozapine². There are few data addressing OH under the combination therapy of aripiprazole and clozapine. A review article reported no pharmacokinetic interaction between aripiprazole and clozapine³. Considering the pharmacodynamics, aripiprazole and clozapine might act together to antagonize the α_1 receptors, thereby increasing the risk of OH. Moreover, 5-hydroxytryptamine 2A (5-HT_{2A}) antagonism could induce vasodilation⁴, and central 5-HT_{1A} stimulation could produce hypotension and bradycardia⁵. Being a 5-HT_{2A} antagonist and a 5-HT_{1A} partial agonist, aripiprazole may increase the risk of OH.

In this case, the combination of aripiprazole and clozapine increased the risk of OH that was considered to be principally related to clozapine. However, the patient did not develop OH under high-dose clozapine treatment (400 mg/d). We suggest that the high-dose clozapine treatment have primed his vulnerability to OH. Therefore, even though the dose of add-on aripiprazole was low (5 mg/d), it increased the extent of α_1 antagonism, negatively affecting the vascular smooth muscle cells' postsynaptic α_1 adrenergic vasoconstriction.

Adverse effects occurring during the combination of two or more antipsychotic treatment is an under-recognized area. Our case reminds clinicians that several potential adverse effects may occur during antipsychotic combination treatment, even though the dose of add-on antipsychotic drug is relatively low.

Disclosure statement

The authors report no conflicts of interest.

Acknowledgement

None.

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