

# Worsened hypertension control induced by aripiprazole

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**Abstract:** Aripiprazole is widely used in the treatment of schizophrenia and bipolar disorders. Although antipsychotics generally have hypotensive effects, two cases were identified that demonstrated hypertension during the switch from other antipsychotics to aripiprazole. The hypertensive state of these patients recovered after switching back to other antipsychotics, and these cases suggest that aripiprazole may lead to hypertension.

**Keywords:** hypertension, aripiprazole, dopamine antagonist, 5-HT1a

## Introduction

Hypotension is a known effect of atypical antipsychotics. In addition, the prevalence of orthostatic hypotension in the elderly is estimated to be between 5% and 33% and increases with age.<sup>1</sup> Orthostatic hypotension is a common side effect of a number of medications, including antipsychotic drugs, and a major contributing factor to the occurrence of falls with adverse consequences, such as bone fractures, injuries, functional decline, dependency, and death. Furthermore, the extent to which antipsychotic drugs cause hypotension differs, and low-potency conventional antipsychotics and clozapine are among the more problematic. However, there is little information on acute hypertension resulting from antipsychotic drugs.

Aripiprazole is a potent (high-affinity) partial dopamine D2 agonist, a serotonin 5-HT1A agonist and a 5-HT2A antagonist.<sup>2</sup> It acts as a functional antagonist of D2 receptors under hyperdopaminergic conditions but exhibits functional agonistic properties under hypodopaminergic conditions.<sup>3</sup> Here, two cases of acute hypertension during the switch from other antipsychotics to aripiprazole are reported.

## Case one

This patient was a 69-year-old woman with a 35-year history of schizophrenia. Her primary symptoms included auditory hallucinations, persecution mania, and self-talking. Her mental condition had been maintained with 2 mg/day of risperidone or 8–16 mg/day of perospirone for several years. Hypertension (systolic blood pressure > 180 mmHg) had developed 2 years previously and had been treated with a salt reduction policy and amlodipine at 5 mg/day. As a result, her blood pressure was controlled, and amlodipine was discontinued after 1 year. Due to akathisia, perospirone at 8 mg/day was changed to quetiapine at 100 mg/day or olanzapine at 5 mg/day; however, these drugs were withdrawn because of sedation. Thus, aripiprazole was initiated, but she suffered from dizziness, headache, and anacathesia as well

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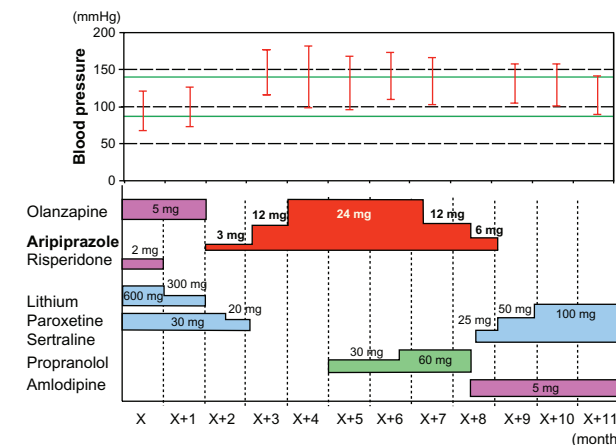
as hypertension (200/110 mmHg). Thus, aripiprazole was changed to risperidone at 2 mg/day, and her blood pressure immediately dropped to 130/80 mmHg. The clinical course is summarized in Figure 1.

### Case two

This patient was a 63-year-old man with a 9-year history of bipolar disorders. His primary symptoms included depressed mood, insomnia, appetite loss, concentration difficulty, and suicidal ideation. Manic episodes were also observed 2 years previously. He was diagnosed with hypertension (systolic blood pressure > 180 mmHg) 1 year previously and treated with a salt reduction policy and nifedipine at 10 mg/day. Consequently, his blood pressure was controlled, and nifedipine was discontinued after 3 months of treatment. His mental status was depressed with lithium treatment at 600 mg/day, paroxetine at 30 mg/day and olanzapine at 5 mg/day. Because of persistent depressive episodes, olanzapine at 5 mg/day was switched to aripiprazole at 3 mg/day. When the dose of aripiprazole escalated to 24 mg/day, his blood pressure increased to 180/90 mmHg with headache, and he was inarticulate. Although his hypertension was treated with amlodipine at 5 mg/day and propranolol at 60 mg/day, his blood pressure did not change. However, after aripiprazole withdrawal, his blood pressure dropped to 147/100 mmHg. The clinical course is summarized in Figure 2.

### Discussion

In the two cases presented here, hypertension after aripiprazole initiation but recovery after aripiprazole discontinuation was observed. Based on these clinical courses, it was concluded that the hypertension worsened due to aripiprazole, although withdrawal effects of previous antipsychotics cannot be ruled out.



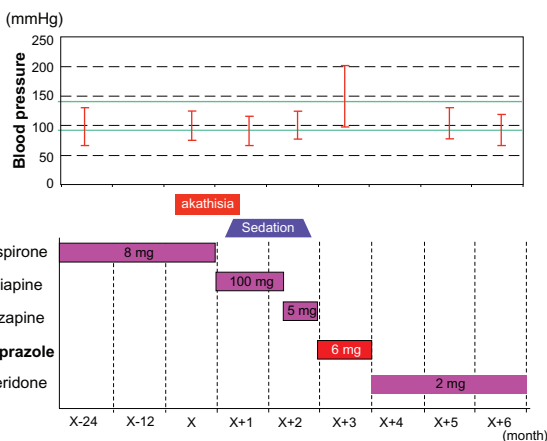
**Figure 2** Clinical course of case two. **Notes:** Upper green line indicates limit for systolic blood pressure; lower green line indicates limit for diastolic blood pressure.

zole, although withdrawal effects of previous antipsychotics cannot be ruled out.

Antipsychotics are known to cause the metabolic syndrome of insulin resistance, hyperlipidemia, and hypertension. Thus, addressing blood pressure as well as glycemia and lipid levels is an important step in the management of patients taking aripiprazole. In addition, according to the product information, the most frequently reported adverse reaction in clinical trials was headache (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan). Headache could have been a symptom of hypertension. In fact, the patients experienced headaches while having hypertension.

The dopamine receptor in vascular smooth muscle participates in vasodilatation, but the possibility that aripiprazole causes vascular smooth muscle to shrink as an antagonist under conditions in which dopamine is superabundant and high blood pressure is induced has been hypothesized. However, there is no D2 receptor in vascular smooth muscle, although there are D1 receptors. Because aripiprazole has extremely low affinity for the D1 receptor, it is unlikely that the high blood pressure observed with aripiprazole was mediated through the D1 receptor.

Although Hirose et al reported that aripiprazole acts as an antagonist for the 5-HT2A receptor,<sup>4</sup> Davies et al indicated that aripiprazole is a partial agonist for 5-HT2A.<sup>5</sup> Because the 5-HT2A receptor participates in the contraction of vascular smooth muscle, the possibility that vascular smooth muscle shrank as a result of aripiprazole acting as an agonist for 5-HT2A and inducing a rise in blood pressure has been hypothesized. The involvement of  $\alpha$ -1A adrenergic receptors cannot be ruled out because aripiprazole has high affinity for  $\alpha$ -1A adrenergic receptors,<sup>6</sup> which is related to



**Figure 1** Clinical course of case one. **Notes:** Upper green line indicates limit for systolic blood pressure; lower green line indicates limit for diastolic blood pressure.

malignant hypertension.<sup>7</sup> In addition, nitric oxide is known to suppress blood pressure. An *in vitro* study using brain macrophages has suggested that aripiprazole inhibits nitric oxide production from microglial cells.<sup>8</sup> Therefore, suppression of nitric oxide by aripiprazole may result in the patient's hypertension.

However, only four reports have demonstrated high blood pressure induced by aripiprazole. Borrás et al reported hypertension (220/110 mmHg) and tachycardia during aripiprazole treatment at 30 mg/day in a schizophrenic patient, which disappeared after aripiprazole discontinuation and propranolol administration.<sup>9</sup> Pitchot and Ansseau indicated that the addition of 5 mg of aripiprazole to 150 mg of venlafaxine in a patient with major depressive disorder led to hypertension (200/110 mmHg) and that aripiprazole discontinuation led to normalized blood pressure within 48 hours.<sup>10</sup> Hsiao et al showed high blood pressure (220/110 mmHg), headache, and dizziness after treatment with 90 mg of duloxetine and 5 mg/day of aripiprazole in a depressed patient.<sup>11</sup> Moreover, the administration of nifedipine and ramipril did not have an antihypertensive effect, and blood pressures were normalized with a reduction in aripiprazole from 5 mg/day to 2.5 mg/day. In addition, Bat-Pitault and Delorme reported hypertension (190/110 mmHg) in an adolescent patient, which was most likely induced by aripiprazole.<sup>12</sup> Although Pitchot and Ansseau and Hsiao et al discussed the influence of a concomitant drug,<sup>10,11</sup> case one in the current report received aripiprazole only, and high blood pressure developed after aripiprazole. Therefore, it is not likely that the influence of the concomitant drug induced hypertension. Pitchot and Ansseau suggested the association with a prior history of cardiovascular disease, including coronary disease,<sup>10</sup> and the two cases in the current report also revealed a history of hypertension. Therefore, blood pressure variation must be carefully monitored when administering aripiprazole to patients with a previous history of cardiovascular disease.

## Conclusion

This report presented two cases demonstrating high blood pressure after aripiprazole initiation, although blood pressures were normalized following aripiprazole interruption. Although the mechanism underlying the rise in blood pressure remains unclear, careful monitoring of blood pressure variations when administering aripiprazole to patients previously treated for high blood pressure is necessary.

## Disclosure

The authors report no conflicts of interest in this work.

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