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Use of atypical antipsychotics and risk of hypertension: A case report and review literature

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Abstract

Atypical antipsychotics is being considered in the treatment of "negative" symptoms of psychoses, such as schizophrenia. In this case report, we presented a case of a patient with psychiatric disorder who developed hypertension soon after starting using atypical antipsychotic. A 53-year-old woman had reported having episodes of tachycardia, nausea, headache and high blood pressure. At the time of the doctor's appointment, the blood pressure was 210/110 mmHg. According to the patient, she made use of simvastatin for dyslipidemia and started taking aripiprazole, an antipsychotic for approximately 40 days before the symptoms. The initial treatment was 20 mg of olmesartan, and examinations were requested. After 2 months, the patient returned with the examinations: altered serum lipids and the other results were normal. Ambulatory blood pressure monitoring showed an average of 24 h of 150/100 mmHg. Blood pressure was measured at the doctor's office; in regular use of 20 mg of olmesartan, it was 156/92 mmHg. The dosage of olmesartan was increased to 40 mg and 1.5 mg of indapamide was initiated. The patient returned after 20 days with a blood pressure of 146/90 mmHg. After approval from the psychiatrist, the Aripiprazole was stopped, and the patient returned 15 days later with blood pressure of 120/80 mmHg. The ambulatory blood pressure monitoring control showed an average of 24 h of 130/78 mmHg. The Dopamine receptors play a role in the regulation of the blood pressure and the alterations in this system can lead to hypertension. D1, D3 and D4 receptors interact with the renin-angiotensin-aldosterone system, while D2 and D5 interact with the sympathetic nervous system in the regulation of PA. The case reported and the literature review bring to light the discussion of the use of atypical antipsychotics and its adverse events. If necessary, the use of these drugs should be followed by careful monitoring of blood pressure.

Keywords

Atypical antipsychotics, hypertension, renin-angiotensin system

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Introduction

In recent studies, we observed a high prevalence of mental illnesses that are associated, in particular, to the labor incapacity of the patient and mortality.[1]

While the majority of studies have reported a high risk of suicide and accidental death, more recent studies have shown that the greater part of this mortality was attributed to cardiovascular diseases, which is explained by several factors of risks related to psychiatric illness, such as lifestyle, low socio-economic level and adverse effects of pharmacological treatment of these diseases.[1–3]

This increase in the prevalence has led to growth in the use of atypical antipsychotics (AA) in the last decade—the most used being the Aripiprazole, quetiapine and olanzapine. For this reason, it is of vital importance to look at the effects that these drugs can induce in its users. Among these effects, we can highlight the higher incidence of weight gain, dyslipidemia, metabolic syndrome and hypercholesterolemia, and predisposing conditions such as hypertension, hyperglycemia and increased abdominal circumference. These repercussions significantly increase the cardiovascular risk in these patients.[4]

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AA have profiles of adverse effects that differ from typical antipsychotics, being considered in the treatment of "negative" symptoms of psychotic disorders, such as schizophrenia which is the most common serious psychiatric pathology. The AA produce extrapyramidal symptoms significantly lighter, due to their low affinity for D2 receptors and its pharmacology not yet being fully established, but based on three hypotheses: relation to the antagonism of 5-HT2 receptors for serotonin, D4 and D2 dopamine.[5]

Objective

This article is a case report of a patient with psychiatric disorder who presented hypertension soon after starting using AA.

Case report

Medical history

A 53-year-old woman has reported having episodes of tachycardia, nausea, headache and high blood pressure (BP) for approximately 10 days before the doctor's appointment. At the time of the appointment, the BP was 210/110 mmHg.

The patient reported no previous hypertension. According to the patient, she had used simvastatin for dyslipidemia and started taking 15 mg of Aripiprazole per day, an antipsychotic, for 40 days before the symptons.

Personal history

The patient reports two pregnancies without intercurrences.

Menopause in follow-up and without hormone replacement.

No smoking.

Family history

Patient's father has hypertension.

Patient's mother does not have cardiovascular diseases.

No history of psychiatric diseases in the family.

Physical examination

Body mass index: 35.2

Blood pressure: 210/110 mmHg

Heart rate: 105 bpm

Respiratory rate: 22 ipm

Pulmonary auscultation: no changes

Cardiac auscultation: regular double rhythm without audible murmurs

Edema of the lower limbs not present

Diagnostic hypothesis

Hypertension of recent onset (secondary hypertension?)

Examinations

The initial biochemical data of the patient are presented in Table 1.

The ambulatory blood pressure monitoring (ABPM) showed an average of 24 h of 150/100 mmHg (no dipper). The mean blood pressure (MBP) for an average of 24 h was 105 mmHg (Figure 1).

Additional examinations

Renal ultrasound was done to the kidneys to find the dimensions and normal contours. Doppler of the renal arteries with normal speeds was found. In echocardiogram, ejection fraction was normal. Left ventricular hypertrophy and the valvular heart disease were absent.

Medical conduct

The patient received an initial treatment with 20 mg/day of olmesartan, and examinations were requested. The patient received guidelines for change of lifestyle: to start physical activity, to reduce calories and salt and to lower body weight.

Evolution and follow-up

After 2 months, the patient returned with the examinations: BP measured at the doctor's office, on regular use of 20 mg of olmesartan, was 156/92 mmHg. The dosage was increased to 40 mg of olmesartan and associated indapamide of 1.5 mg. The patient returned after 20 days with BP = 146/90 mmHg. The patient's psychiatrist believed it to be possible adverse effect, but he has no other cases so expressive like this. After approval from the psychiatrist, Aripiprazole was stopped, and the patient returned 15 days later with a BP = 120/80 mmHg. The ABPM control showed an average of 24 h of 130/78 mmHg and the MBP of 96 mmHg (Figure 2).

Discussion

According to Gonsai, the AA most often used for the treatment of schizophrenia are the dopaminergic antagonists of the family D2, D4 and some antagonists. Dopamine receptors, mainly of the kidneys, play a role in the regulation of BP, and alterations in this system can lead to hypertension.[6]

Table 1. Laboratory measures.

Examination	Values	Reference
Na+ (mEq/L)	142	135–145 mEq/L
K+ (mEq/L)	4.5	3.5–5.1 mEq/L
Mg++ (mg/dL)	2.1	1.3–2.1 mg/dL
Ionized calcium (mg/dL)	4.69	4.6–5.1 mg/dL
Total calcium (mg/dL)	9.2	8.4–10.6 mg/dL
Urea (mg/dL)	25	24–49 mg/dL
Serum Cr (mg/dL)	1.0	0.6–1.2 mg/dL
Glucose (mg/dL)	92	70–99 mg/dL
Hematocrit (%)	42	37–47% (females)
Hemoglobin (g/dL)	14	12–16 g/dL(females)
Leukocytes—Total (/mm³)	5200	3500–10,000 mm³
Segmented (%)	63	55–69%
Platelet count (/mm³)	280,000	150,000–400,000 mm³
Thyroid-stimulating hormone (TSH) mUI/L	1.33	0.4–4.8 mUI/L
Sodium urine (mEq/24 h)	100	40–220 mEq/24 h
Cholesterol (mg/dL)	254	<190 mg/dL
HDL cholesterol (mg/dL)	38	>40 mg/dL
Triglycerides (mg/dL)	291	<150 mg/dL

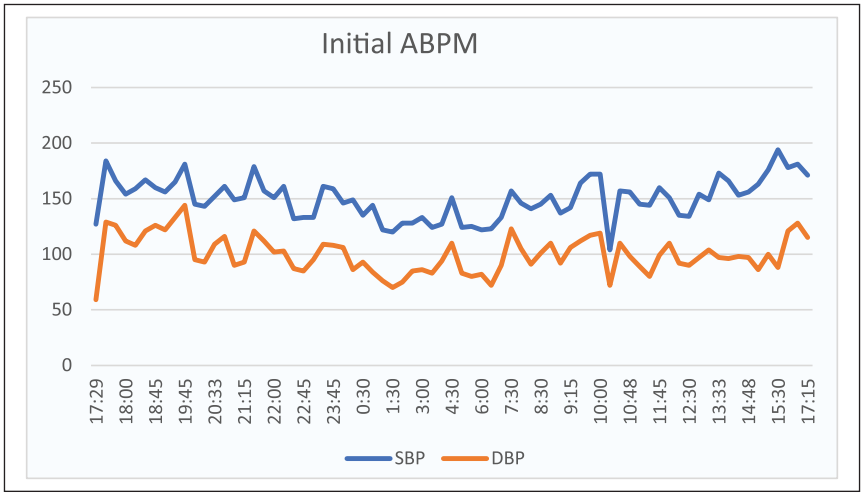

Figure 1. Initial ABPM. SBP: systolic blood pressure; DBP: diastolic blood pressure.

Its pharmacology is mainly related to the renal hemodynamic action, as well as the transportation of ions and water. Dopamine exerts its effect through a family of BP receptors coupled to G protein of the cell surface (GPCRs), classified as D1-like (D1 and D5) and D2-like (D2, D3 and D4). Among these receptors, the D1, D3 and D4 interact with the renin-angiotensin-aldosterone system (RAAS), while the receptors (D2 and D5) interact with the sympathetic nervous system in the regulation of PA. Because of these factors, the clinical use of dopaminergic agonists or antagonists may disrupt the regulation of PA leading to hypotension or hypertension, respectively.[6]

This way, the dopamine participates in the renal tubular transportation of Na^+ and also regulates the intestinal transportation. Under normal conditions of ingestion of Na^+, dopamine decreases the renal transportation and decreases its reabsorption, unlike the function of the RAAS. In a deficient dopaminergic response, an increase in ingestion may result in an increase in BP by a failure in renal or jejunal transportation. If the dopamine receptor is uncoupled from the G protein, it alters the signal transduction to decrease the transportation of Na^+ (GI).[5,6]

The RAAS is activated after detecting low levels of BP in the afferent arterioles of the kidneys or hyponatremia, causing renin release by the juxtaglomerular renal cells with the objective of compensating for this loss. The renin is responsible for cleaving the angiotensinogen, thus forming the angiotensin I, which is then converted into the angiotensin II,

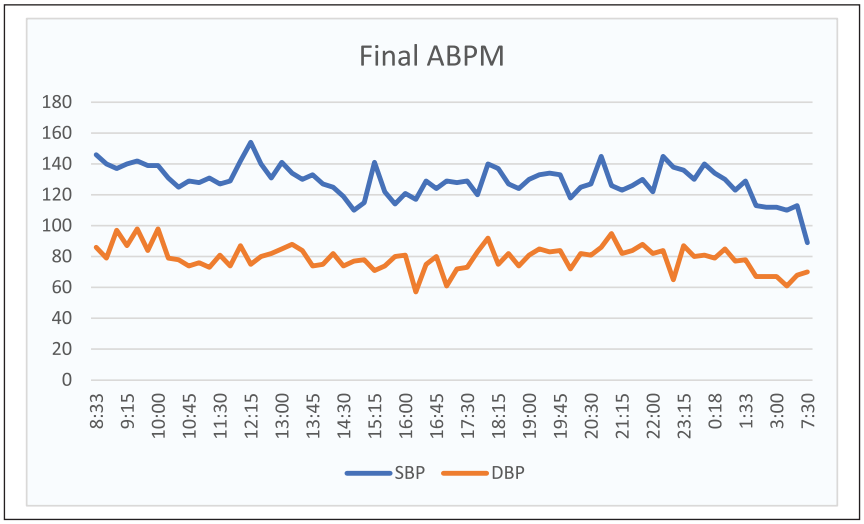

Figure 2. Final ABPM. SBP: systolic blood pressure; DBP: diastolic blood pressure.

leading to vasoconstriction, the increase of the peripheral resistance and, as a consequence, the increase of the BP, that the antipsychotic activates this system, even in normal BP conditions.[7]

Clozapine is the gold standard treatment for refractory schizophrenia, classified as an antipsychotic of second generation. Its main mechanism of action is the antagonism of D4 receptors, but it blocks D2 and 5-HT2A, a subtype of serotonin receptor. It is one of the main adverse effects of weight gain.[7]

A recent meta-analysis demonstrated the weight gain in individuals from the ages of 18–35, with a body mass index (BMI) between 19 and 35 and without antecedents, noting an increase in the caloric intake of 25% and having, as a consequence, a weight gain of 1.4% after the use of antipsychotics for 4 weeks.[6]

This weight gain also relates to leptin, an anorexic hormone which controls the food intake; it is possible that the antipsychotics affect gene expression of leptin, inducing the fat gain. This mechanism is still not well established, but it is believed that it occurs due to an increased storage peripheral fat, and by consequence increased release of leptin in adipose tissues. Some studies also argue that this increase occurs because the antipsychotics interrupt the track of leptin in the hypothalamus, weakening its sensitivity.[6–8]

The weight gain significantly interferes in the lifestyle of individuals causing significant systemic and psychological effects. The psychological effects, such as the reduction of self-esteem and the phenotypic alteration of the body, are more concerning in children and adolescents who are more sensitive to the negative effects of the medication.[9]

These effects of antipsychotics converge in one common factor: the increased risk of hypertension. This disease is considered the most prevalent circulatory disease and an important risk factor for cardiovascular events such as stroke and acute myocardial infarction, affecting around 80 million American adults. Longitudinal studies such as the Minnesota Heart Survey, the National Health and Nutrition Examination Survey and the China Stroke Primary Prevention trial proved that the excess body fat is one of the main factors responsible for the development of hypertension.[10–12]

For the treatment of schizophrenia and other psychiatric disorders, Aripiprazole, a second-generation antipsychotic and a partial agonist of D2 and 5-HT1A receptors, has been used. This drug is considered safe because it has few adverse effects. The most commonly observed effects are mild, among them headaches, agitation, anxiety and sleeplessness.[13]

The postural hypotension has been reported to be the most frequent cardiovascular effect of this group of drugs.[14] Nevertheless, there is little information in the literature on the appearance of hypertension due to antipsychotics.

It is well established that second-generation antipsychotics can result in prolonged QT interval, arrhythmia, and postural hypotension in patients without structural disease in the heart.[14] Since 2005, cases that suggest the development of hypertension with aripiprazole have been reported in the literature.[15–17]

For example, Borras et al. have published a case in which a patient using 30 mg/day of aripiprazole developed tachycardia and hypertension (220/110 mmHg) and had normalized BP after withdrawal of aripiprazole.[15]

Bat-Pitault et al. in 2009 have described the development of hypertension in adolescents using aripiprazole. Another case report showed elevated BP with 150 mg/day of venlafaxine and 5 mg/day of aripiprazole, also with normalization of BP in 48 h after withdrawal of aripiprazole.[17]

In all of these reported cases, we observed that, in most of them, there was an association between cardiovascular disease and the use of concomitant drugs.

In the case reported here, hypertension was initiated soon after starting using aripiprazole and normalized after withdrawal. In this case, there was no systemic disease or other medication that could explain the mechanism of hypertension. Based on the clinical findings, we believe that this patient developed hypertension as an adverse effect of aripiprazole, corroborating the finding of Borras et al.[15] and Bat-Pitault and Delormes,[17] whose patients used only aripiprazole without a history of previous hypertension or cardiovascular disease.

It is necessary to have a better understanding of the mechanisms of hypertension induced by aripiprazole. We know that 5-HT2A and alpha-1 receptors play an important role in the genesis of hypertension. Perhaps the explanation is due to high affinity for the α-1A adrenergic receptor.[18] In the literature, the studies are controversial, while Michel et al.[18] suggest elevation of BP by aripiprazole; when compared to placebo, there are others that showed no relationship between aripiprazole and hypertension.[19] Future studies should clarify these diverse results.

By the exposed earlier, we saw the need to assess, based on a systematic review of the literature, the relationship between the use of antipsychotic medications and risk of developing hypertension.

Final considerations

The reported case and the publications raised bring to light the discussion about the use of AA and its adverse events.

We believe that hypertension, although rare, is an adverse effect that should not be neglected and, where necessary, the use of these drugs should be followed by careful monitoring of the BP, regardless of the presence of cardiovascular diseases.

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Ethical approval

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Informed consent

Informed and written consent were obtained from the patient of this reported case.

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