

Fabiola Méndez-Sánchez¹
Itziar Baltasar-Tello¹
Antonio Leal-Micharet¹
Belen Gómez-Tovar¹
Juan A. Guisado-Macías¹

Concurrence of multiples factors in the occurrence of ventricular arrhythmia in patient treated with aripiprazole

¹Psychiatry Department
Hospital Infanta Cristina de Badajoz

Introduction. The Importance of the cardiovascular effects, fundamentally the ventricular arrhythmias, produced by the antipsychotic ones, is discussed.

Clinical case. 28 year old patient with morbid obesity, operated by bariatric surgery, with good result, suffers a ventricular no supported polymorphic tachycardia while he was heightening treatment with aripiprazole and fluoxetine.

Conclusions. To value the influence of diverse factors for the production of ventricular arrhythmias emphasizing fundamentally the interactions of aripiprazole and the loss of weight.

Key words: Arrhythmias, Aripiprazole, Interactions, Morbid obesity

Actas Esp Psiquiatr 2012;40(6):346-8

Concurrencia de múltiples factores en la aparición de arritmia ventricular en paciente en tratamiento con aripiprazol

Introducción. Importancia de los efectos cardiovasculares, fundamentalmente las arritmias ventriculares, producidos por los antipsicóticos.

Caso clínico. Paciente de 28 años con obesidad mórbida, por la que fue intervenido obteniendo buenos resultados, sufre una taquicardia ventricular no sostenida polimórfica mientras realizaba tratamiento farmacológico con aripiprazol y fluoxetina.

Conclusiones. Valorar la influencia de diversos factores en la producción de arritmias ventriculares, destacando fundamentalmente las interacciones de los antipsicóticos y la pérdida de peso.

PALABRAS CLAVE: Arritmias, aripiprazol, Interacciones medicamentosas, Obesidad mórbida

Correspondence:
Servicio de Psiquiatría del Hospital Infanta Cristina de Badajoz
Avenida de Elvas s/n, 06021 Badajoz, Spain
E-mail: fmendezsanchez@yahoo.es

INTRODUCTION

It is well known that both typical and atypical antipsychotics cause adverse cardiovascular effects, even when used at therapeutic doses. These reactions include orthostatic hypotension, myocarditis, alterations in cardiac conduction (sinus node, bundle of His block), left ventricular dysfunction and arrhythmias, as non-sustained polymorphic tachycardia (torsades de pointes) and ventricular fibrillation, although uncommon. They have also been associated with the appearance of unexplained sudden death syndrome.¹

The appearance of severe arrhythmias is related to the use of an elevated dose of antipsychotics, with rapid increase, with intramuscular administration and fundamentally with intravenous administration, and with the characteristics per se of the patient, such as age (elderly patients are more susceptible) or comorbidity, since these factors can be associated to the prolongation of the QRS and QTc intervals.² Ventricular tachycardia stands out within this type of arrhythmias. This is defined by the presence of three or more consecutive beats from the ventricle, a frequency of at least 100 beats per minute (bpm), which appear in the electrocardiogram with a wide QRS, with ventricular-atrial dissociation initiated generally with a ventricular extrasystole. It may be sustained, if it lasts more than 30 seconds, or produce circulatory collapse, above all if there is previous organic heart disease; and non-sustained, if its duration is less than 30 seconds. It is not generally associated to organic heart disease and, on the contrary to the sustained, it is almost always asymptomatic.¹

On the other hand, the long QT syndrome is a congenital or acquired disorder, produced by alterations in the membrane ionic currents that lengthen the duration of the action potential in the cardiac conduction cells, creating a great dispersion in the ventricular repolarization. It can be congenital due to mutations that affect the ion channels; acquired, related with ion alterations, intracranial processes and drugs, generally in predisposed individuals, as antiarrhythmics, antihistamics, macrolides, tricyclic antidepressants and antipsychotics.¹

Finally, the importance of the metabolism pathways, fundamentally the hepatic one (cytochrome P450) should be stressed to the degree that the confluence of drugs by said pathways may cause interactions, with the consequences thus entailed, normally lack of efficacy or toxicity.²

A CASE REPORT

The case of a 28-year old male patient who was being monitored in the Obesity Outpatient Clinic in the Hospital Infanta Cristina of Badajoz is reported.

His personal backgrounds were Not otherwise specified Eating Behavior Disorder, Schizoid Personality Disorder and morbid obesity. He underwent bariatric surgery in July 2008 (his obesity had begun in childhood, his weight reaching up to 100 kg during adolescence. This subsequently increased progressively). He also had asymptomatic bradycardia due to a syncopal episode 4 years earlier.

His family backgrounds were: mother and maternal grandmother were overweight, and a male first cousin on his father's side with sudden death at about 30 years of age.

The patient began to be monitored in the Obesity Outpatient clinic for pre-operative evaluation for bariatric surgery in February 2008, with weight of 125 kg and height 1.72 m (BMI 42.23). He had undergone treatment in the Eating Behavior Disorder Unit with Topiramate (100 mg) and Fluoxetine (60 mg) for the last 3 months. In spite of this, the patient had problems for daily functioning, eating control and some social withdrawal/isolation. Therefore, it was decided to modify the treatment, prescribing Fluoxetine (40 mg/day), Topiramate (150 mg) and Aripiprazole (10 mg), attempting to improve his eating pattern and low mood status with apathy - abulic characteristics.

Follow-up was conducted twice a month, observing clear improvement in both eating control and on the affective and sociability level. The possibility of bariatric surgery was then considered, which was performed in July 2008. After the surgical intervention, the patient remained stable, achieve a weight of 88 kg (BMI 29.7), continuing with the same pharmacological treatment.

Approximately 12 months after the surgery, and during a routine check-up in Cardiology to monitor the already mentioned bradycardia, a non-sustained polymorphic ventricular tachycardia was observed in the long QT, with good response after drug treatment with beta blockers.

- Complete blood test, renal function, lipid profile and thyroid hormones - normal.
- Electrocardiogram: sinus rhythm at 45 beats per minutes (bpm) and prominent U waves.

- Echocardiogram: left ventricle not dilated or hypertrophic, without segmental contractility and conserved systolic function. Left atrial and aortic roots - normal. Valves- morphological and functionally conserved. Transmitral flow pattern - normal. Right cavities - normal.
- Holter electrocardiography: sinus rhythm with heart rate of 62 bpm with spurts of paroxysmal atrial fibrillation with complete right bundle branch block, probably focal (preceded by supraventricular extrasystole). Ventricular extrasystoles very frequent with abundant periods of ventricular bigeminism, some duple and some spurts of scarce beats of non-sustained polymorphic ventricular tachycardia. Some non-conducted p waves.

Based on these results, no evidence of organic heart disease was found. Therefore, a low salt and animal fat diet was recommended, as well as the maintenance of the same dose of beta-blocker. The patient continues with monitoring in psychiatry and the most important measure taken was the suspension of aripiprazole.

DISCUSSION

Aripiprazole is an antipsychotic drug, called third generation, due to its potent partial agonist activity on the D2 dopamine receptors. It is modulated based on the amount of existing dopamine, that is, if there were an excess, it would act as a complete antagonist of the D2 receptors and on the contrary, as an agonist. It also has an agonist activity on the 5-HT1A receptors and antagonist on the 5-HT2A, 5-HT2C, D3, D4, α 1-adrenergic and histaminic receptors.²

It is a compound with good oral absorption, with 87% bioavailability, whose principal metabolism mechanism is hepatic cytochrome p450 (2D6 and 3A4 enzymes) that is transformed to dehydroaripiprazole, responsible for most of the pharmacological effects. In this way, it may have interactions with other substrates of these enzymes, the compounds that they induce, such as la carbamazepine, that increase the elimination of aripiprazole, thus decreasing their plasma levels. However, with the simultaneous administration of 2D6 and 3A4 inhibitors, such as fluoxetine, the aripiprazole dose must be reduced to avoid increasing the risk of adverse effects. This takes on special clinical importance in drugs with narrow therapeutic margin.³ In the case of aripiprazole, overdoses up to 180 mg have been registered without significant repercussions, the most common effects being sedation, nausea, and vomiting, hypotension, syncope, sinus tachycardia and dystonic reactions.⁴

In 2006, Egger et al. described the case of a female patient diagnosed of schizophrenia, without cardiac history, who developed incomplete bundle block with gradual increase of

aripiprazole and that disappeared once the therapy was interrupted.⁵ In 2008, Torgovnick et al. reported the appearance of supraventricular tachycardia, with response to vigil maneuvers and calcium antagonists in an HIV positive female patient (without antiretroviral treatment) who had previously had syncopal episodes, and who was being treated with aripiprazole for her bipolar disorder.⁶ In 2010, Suzuki et al. reported a case of aripiprazole (30 mg/day) dose-dependent prolongation of the QTc interval. Even so, as occurs in our case, it is difficult to establish a direct relation between aripiprazole and the QTc interval, since the serum levels of aripiprazole are not measured and the QTc can be affected by many other factors, such as pharmacokinetic interactions and age.⁷ For example, specifically, in our case, one variable that should be considered is the influence of weight loss on the decrease of cardiac output. In this way, the loss of 1 kg of weight would entail a decrease of 100 ml/min in it. This could predispose to the appearance of cardiac arrhythmias and very restrictive diets favor the prolongation of the QTc interval and increase in risk of sudden risk.⁸

In spite of these descriptions, in the most recent literature, aripiprazole is recognized as one of the antipsychotics associated to the least cardiovascular effects in addition to having a low incidence of long QT.^{6,9}

The QTc interval serves to evaluate the risk of ventricular arrhythmias and it measures both cardiac depolarization and repolarization. In patients with left bundle block, depolarization is basally increased, so that the utility of this interval decreases. In these cases, Mukherji and Bauer propose using the JT interval (QT duration minus QRS duration is calculated) and the JT index (heart rate + 100)/518, as parameters that may contribute to determining the safety of drugs that prolong repolarization and crease QT dispersion. However, they admit it would be necessary to accurately know the relation between the JT, QTc and QRS index to avoid the underevaluation of antipsychotics in patients with alterations in cardiac conduction.¹⁰

In our case, the appearance of ventricular arrhythmia is probably due to a confluence of several factors: the influence

of restrictive diets and significant weight loss,⁸ previous existence of cardiac alterations,¹ treatment with aripiprazole, and interaction with a metabolism inhibitor, such as fluoxetine.² Thus, it is recommended to take the greatest precaution in patients with known cardiovascular diseases or predisposing conditions (dehydration, hypovolemia and treatment with antihypertensives) who received antipsychotic treatment, optimizing their doses and carrying out baseline and follow-up electrocardiographic controls.^{5,10}

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