CAN ARIPIRAZOLE NORMALIZE YATROGENIC HYPERPROLACTINEMIA?

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OBJECTIVE

Aripiprazole is a second generation atypical antipsychotic (AAP), with properties of partial dopaminergic agonist and additional antidepressants effects, used in schizophrenia, bipolar disorder and depression¹, among others. Its mechanism of action differs from other AAPs, since it is a partial agonist of both D2 and 5-HT1A^{2,3} and, like the rest of AAP, an antagonist of 5-HT2A^{4,5}. It presents a linear kinetics with a half-life of approximately 75 h, reaching steadystate in 14 days, a bioavailability of 90% and undergoing extensive liver metabolism mainly through CYP2D6 and CYP3A4⁶.

The side effects associated with AAP treatment are drug-specific, with hyperprolactinemia and metabolic syndrome being one of the most important. Hyperprolactinemia is an adverse effect associated to the use of antipsychotics, with consequences both in the short term, alterations in gonadal function and parkinsonism, and in the long term, osteopenia-osteoporosis, metabolic syndrome and increased thromboembolic risk⁷. Being related to its ability to block D2 receptors in lactotrophic cells of the pituitary.

The prevalence of Diabetes Mellitus type II (DM II), as a component of the metabolic syndrome, in schizophrenic patients is double that in the general population⁸. There are numerous retrospective studies that associate DMII with the use of certain PAAs, many of them indicating that Drugs associated with weight gain are also at a higher risk of developing DM II^{9, 10, 11, 12}.

Therefore, normalization or reduction of prolactinemia is sufficient to restore gonadal function. Prolactin and the sex hormones estradiol and/or testosterone are normalized, in those patients to whom aripiprazole has been added to their treatment, enough to restore gonadal function. While the alteration of bone mineral density in patients older than 20 years on AAP treatment, those who have caused hypogonadism of duration greater than or equal to 1 year, will require at least 2 years of additional treatment with aripiprazole for its normalization.

The objective, therefore, has been to assess the decrease in prolactin induced by aripiprazole when it is part of different therapeutic schemes, alone or in combination with other PAAs, with a view to the important task of minimizing the side effects derived from hyperprolactinemia without affecting the efficacy of the treatment.

MATERIAL AND METHODS

Sample composed of 306 patients, from the outpatient psychiatric consultations of the Hospital Real de Nuestra Señora de Gracia in Zaragoza, undergoing treatment with different therapeutic schemes including atypical antipsychotics, alone or in combination. In 31 patients, the therapeutic scheme included aripiprazole in a dose of 17.3 (7.7) mg, 61% with a diagnosis

of schizophrenia (F. 20), 21% with Schizoaffective disorder (F. 25) and 13% with Bipolar disorder and 5% other diagnoses (according to DSM-IV, ICD-10), age 39. 5 (13 . 8) years, weight 70. 6 (20. 8) Kg and 63% women, in chronic treatment for an average of 5.1 years (12. 1-1. 3), who were weighed, tallied and carried out biannual analysis of cholesterol (COL), prolactin (PRL) and thyroid-stimulating hormone (TSH). As well as routine biochemical and hematological parameters.

All data are presented as mean (SD).

RESULTS

Body mass index (BMI) 30 (5) Kg/m², COL 202 (40) mg/dl, PRL 404 (441) µUI/ml and TSH 2.5 (1.1) µUI/ml.

Treatment with: atypical antipsychotics 84% (clozapine 26% and risperidone 24%), selective serotonin reuptake inhibitors (SSRI) 24% (s-citalopram 50%), benzodiazepines 26%, eutimizers 29% (lithium salts 15% and valproic ac 8%) and antiepileptics in 12% of patients.

The percentage of patients with PRL < lowest mean value of a control group composed of healthy men health care professionals (< 7 ng/mL x 27.6= 193 µUI/ml)¹³, was 45.1% in the aripiprazole group and 1.3% in the group that did not include aripiprazole.

The odds in favor of patients in the group exposed to aripiprazole (cases) presenting hypoprolactinemia lower than 193 µUI/ml, was 0. 83 in the group of patients that included aripiprazole and 0. 013 in that of the patients not exposed to aripiprazole (controls), with OR = 64, resulting in a 98% probability (p <0.001).

DISCUSSION

It is well established that antagonism of D2 receptors, mainly, together with agonism of 5HT1A receptors, leads to the release of prolactin. Dopamine maintains a predominant role in

the regulation of prolactin secretion, through a direct effect on the lactotrophic cells of the anterior pituitary. There is a wide variety of modulators of its secretion that act at the hypothalamic level, either by disinhibition of the dopaminergic tone, such as, for example. and, serotonin that acts through the 5HT receptors, among which is 5HT1A, or else reinforces it.

AAPs associated with sustained hyperprolactinemia, such as risperidone, paliperidone, or amisulpride, have a high affinity for the D2 receptor, exhibiting slow dissociation once bound to it. The resulting hyperprolactinemia has acute and chronic clinical consequences, being an option for its management, the change from antipsychotic to aripiprazole or the combination of this with the cause of hyperprolactinemia.

On the other hand, 5-HT1A receptors, the most widely distributed of all 5-HT receptors, appear in the CNS as presynaptic somatodendritic autoreceptors or as postsynaptic receptors in the hippocampus¹⁴. Stimulation of the 5-HT1A autoreceptors inhibits the release of serotonin at the nerve endings, and for this reason, 5-HT1A agonists such as aripiprazole tend to exert a biphasic mode of action; at low doses, they decrease the release of serotonin acting on presynaptic receptors and, therefore, decreasing its stimulatory activity on postsynaptic 5HT1A

receptors, for later, at moderate-high doses, continue to decrease the release of serotonin, acting on receptors presynaptic, but increasing activity on postsynaptic 5-HT_{1A} receptors by direct stimulation of aripiprazole on the postsynaptic receptor replacing serotonin. Therefore, with moderate-high doses of aripiprazole, activation of the postsynaptic receptor 5-HT_{1A} facilitates the release of dopamine in the mid-prefrontal cortex, striatum, and hippocampus, and may be useful both for the reduction of prolactinemia and for improvement of symptoms of schizophrenia and Parkinson's disease^{15,16}.

Aripiprazole would also facilitate its clinical efficacy^{16, 17,18} as an antipsychotic due to the anxiolytic and antidepressant effects it produces as a post-synaptic 5-HT_{1A} receptor agonist^{18,19}; since at high enough doses aripiprazole would replace serotonin in the direct activation of postsynaptic 5-HT_{1A} receptors.

According to our results, Aripiprazole would therefore be the ideal component for the combined treatment with those other antipsychotics that cause hyperprolactinemia, such as risperidone, reducing it and alleviating or eliminating the adverse effects derived from chronic hyperprolactinemia. At sufficiently high doses, it reduces prolactin, maintaining the stimulating effects of serotonin and, consequently, alleviating negative symptoms such as social isolation, causing fewer extrapyramidal adverse effects and, due to the anxiolytic and antidepressant effects it produces after receptor activation. Postsynaptic 5-HT_{1A}^{18,19}, increasing and facilitating its clinical efficacy^{16, 17,18}.

CONCLUSION

Aripiprazole, by reducing prolactinemia in more than 90% of patients, is useful alone or in combination with other atypical antipsychotics to avoid long-term thromboembolic risk and hypogonadism, and parkinsonism and gonadal function disorders.

Aripiprazole, due to its agonist effects on the postsynaptic 5-HT_{1A} receptor, constitutes a good alternative to the use of SSRIs and BZD in the treatment of anxiety and negative symptoms that accompany schizophrenia and depression.

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