Switching Antipsychotics in HIV Patients
Focus on Aripiprazole

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Abstract

This article reports three cases of patients with dual diagnosis of HIV infection and schizophrenia, in which the antipsychotic they were given was changed to aripiprazole due to the emergence of hyperprolactinemia or prolonged QTc. The switching was performed in the context of antiretroviral drugs, taking into account the unique safety profile of aripiprazole without endocrinological toxicity and low cardiotoxic risk. To our knowledge, this report on a short series of cases is the first in the literature to focus on the switching of antipsychotics in HIV patients under cART with aripiprazole as a drug-target.

Keywords: HIV; Schizophrenia; Switching Antipsychotics; Aripiprazole; Hyperprolactinemia; QTc Prolongation

Introduction

HIV patients with serious mental illness as a comorbid condition require the use of psychotropic drugs, in many cases permanently. When it comes to schizophrenia, the long-term application of antipsychotics is proposed, in which case it is mandatory to take into account potential pharmacokinetic interactions (drug-drug) with antiviral drugs and the safety profile of the neuroleptics chosen [1-5].

In fact, the decision-making process may become even more challenging when the need arises in schizophrenic patients to switch an antipsychotic that is ineffective or causes undesirable effects for another drug with a more favorable profile in the context of antiretroviral treatment.

In this paper, we report a series of three cases of patients with dual diagnosis of HIV infection and schizophrenia who had to switch the second-generation antipsychotic they were receiving for aripiprazole due to the appearance of hyperprolactinemia or QTc prolongation.

Case 1


She presents a psychiatric diagnosis of paranoid schizophrenia [DSM IV-TR], stabilized with risperidone monotherapy, in doses of 3 mg per day. Due to the emergence of marked but asymptomatic hyperprolactinemia - highest serum level: 132.2 mcg/ml in April 2016 - aripiprazole addition was first decided in doses of up to 30 mg per day, without modifying risperidone during four weeks’ time. With the combination of both neuroleptics, there was no significant decrease in serum prolactin [6].

The discontinuation of risperidone was then attempted by a 50 per cent reduction of the dose in a first step, and then a tapering off of the drug till suspension; plus a reduction of aripiprazole dose up to 15 mg per day. This switching procedure could be completed in twelve weeks without any further complications.

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In September 2016, the patient was stable with aripiprazole monotherapy - 10 mg per day - and prolactinemia reached normal serum level: 14 mcg/ml.

Case 2
A 52-year-old female patient with HIV status known in 1992 - cART: tenofovir/emtricitabine/ efavirenz - with viral load < 40 RNA HIV copies and CD4 cells 287.7 [21%] dated in April 2016. Diagnosis of schizophrenia simple type [DSM IV-TR], stabilized with risperidone monotherapy, 3 mg per day. Treatment- emergent asymptomatic hyperprolactinemia was observed; maximum level 79.6 mg/ml dated in November 2015. A cross-taper switching to aripiprazole was decided on and completed in four weeks with a final dose of aripiprazole 10 mg per day. Six weeks after the switching procedure, aripiprazole titration dose to 30 mg per day was necessary due to a low intensity auditory hallucinations emergence [6].

Serum prolactin got normal level in March 2016 – 28.2 mcg/ml. The last psychiatric control dated in March 2016 showed a stabilized patient without hallucinations. Aripiprazole monotherapy was kept to 30 mg per day.

Case 3

Diagnosis of paranoid schizophrenia [DSM IV-TR] as a comorbid condition which was stabilized with risperidone monotherapy 3 mg per day. In September 2015, a QTc prolongation was observed: 465 mseg, for the first time in two years of the psychiatric follow-up. With the exception of the HIV disease, no other predisposing factor to QTc alteration was present [6].

A rapid switch from risperidone to aripiprazole was initiated immediately, with discontinuation of the first drug in two weeks plus the installation of the second antipsychotic drug up to the dose of 20 mg per day. This fast switching process was completed in October 2015. At the same time, the team of infectologists switched the patient’s protease inhibitor-based antiviral regime [with atazanavir/r] to another with the integrase inhibitor raltegravir for the purpose of releasing the hepatic cytochrome P 450 inhibitory effect of the first combination with ritonavir.

Positive psychotic symptoms reappeared two weeks after the end of the switching process, with paranoid delusions of influence and persecution. The dose of aripiprazole was titrated in 30 mg per day, being able to control the psychotic production.

The QTc interval decreased to 450 msec in February 2016, and to 439 msec a month later. In September 2016, the patient was stable with aripiprazole monotherapy - 30mg per day.

Discussion
In recent years, much attention has been paid in the psychiatric field to the design of strategies for switching antipsychotics, or to move from one to another. That is expected to be more effective, or to resolve the emergence of adverse events attributable to the first drug administered [7,8].

The atypical antipsychotic aripiprazole became a target-drug of the switching strategies due to its particular main profile characterized as being D2/5HT1A - partial agonist / 5HT2A - antagonist; with a significant advantage over first-generation neuroleptics or other atypical antipsychotics in terms of the power of induction of extrapyramidal phenomena or hyperprolactinemia in addition to having a smaller impact on the QT interval than its predecessors [9-11].

There are some publications in the literature on the use of aripiprazole in the HIV setting, but none in a focused way on the switching processes in which the drug could be included. This brief case-series paper would be the first of its kind [2,12-14].

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Case 1 shows the use of aripiprazole to resolve treatment-emergent asymptomatic hyperprolactinemia which is risperidone-related. In a first attempt, we added aripiprazole to risperidone, looking for a decrease of the prolactine level, in accordance with what can be found in the literature but it failed. Then, we considered switching the antipsychotic regime to aripiprazole monotherapy, with a fast risperidone-tapering off in two weeks’ time and aripiprazole in a 50 per cent dose reduction. It was at this point that we followed a similar model of the two-steps strategy (addition/switching) studied by ML Lu., et al. in a trial published in 2008. Similarly, to what these researchers think, the prolactin-normalizing effects of aripiprazole are probably caused by its singular profile of a dopamine partial agonist with high affinity for D2 receptors [15-18].

In case 2, hyperprolactinemia was resolved with a direct cross-taper switching to aripiprazole, without overlapping two antipsychotics. The reappearance of positive hallucinatory symptoms six weeks after the end of neuroleptic change could be related to the so-called supersensitivity psychosis, caused by the dopaminergic partial agonist effect of aripiprazole. If we take into account the seven criteria established by Chouinard and Jones for that entity in 1980, the psychosis of case 2 observed six weeks after switching intervention to aripiprazole, the only one that is not met is criteria 3, since in our patient the phenomenon of tardive dyskinesia associated by the authors with the supersensitivity of the neostriatal dopaminergic receptors did not appear [19,20].

As the work of Kumar., et al. shows, HIV invasion of the CNS reaches different regions of the brain, with the ganglia of the base being the most vulnerable. Related HIV-neuropathogenesis involves the degeneration of dopaminergic neurons in the substantia nigra and the loss of terminals of the same neurotransmitter in the ganglia of the base leading to a deficit of central dopaminergic activity and resulting in cognitive impairment and motor deficit. In the HIV setting it is possible to hypothesize then, that the depletion of dopamine levels in the striatum would act as a protector of the development of tardive dyskinesia induced by neuroleptic deprivation. In contrast, supersensitive psychosis is linked to the dopaminergic upregulation of the mesocortical and mesolimbic areas of the brain which are less affected by the HIV-related damage [21,22].

Case 3 shows the confluence of three conditions recognized in the literature as risk factors for torsade de pointes (TdP) or sudden cardiac death (SCD) due to the impact on QT interval duration: HIV infection, antiretroviral therapy with protease inhibitors [atazanavir boosted with ritonavir] and the use of the second-generation antipsychotic risperidone [23-28]. Aripiprazole was chosen as the target- switching drug in this case, due to the strong evidence founded on the cardiac safety of this antipsychotic. In the categorization of Fanoe., et al. based on the global clinical observation of healthy subjects, aripiprazole is considered as class A, without any risk on the involvement of QT. In the epidemiological study of Raschi., et al. it is classified as a class C drug with low - intermediate torsadogenic risk [29-31].

Here, aripiprazole was useful in a complex clinical setting, with several coexisting cardiac risk conditions. QTc was normalized slowly after four months of psychopharmacological monotherapy with this drug (< 450 msec dated in March 2016). The pharmacokinetic window for the application of aripiprazole (with CYP 2D6/ CYP 3A4 hepatic metabolism) could be opened by the rapid intervention of the team of infectologists by changing the antiviral regime to one based on the integrase inhibitor raltegravir (metabolized primarily by UGT 1A1 and which is not affected by P450 inhibitors or inducers) at the time of switching antipsychotics [2,3,9,32].

Conclusions

In this report of three cases of HIV-positive patients diagnosed with schizophrenia, the antipsychotic switching strategy is clearly exemplified, motivated by induction of hyperprolactinemia or QTc prolongation. In all of them, the target-drug chosen was aripiprazole, which because of its unique atypical safety profile does not raise serum prolactin levels and at the same time has a weak impact on cardiac repolarization with its marker: the QTc interval. As a result, with aripiprazole-monotherapy, adverse events were resolved without causing serious further complications in the mental status of these schizophrenic HIV- positive patients with cART. We believe that this inaugural series should be continued by well-designed clinical trials to obtain more potent evidence on the use of aripiprazole in complex settings, such as HIV patients receiving antiretrovirals and antipsychotics on a permanent basis.
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