

Case Report

Addition of Aripiprazole to the Clozapine May Be Useful in Reducing Anxiety in Treatment-Resistant Schizophrenia

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There exist many case reports and studies on the antipsychotic augmentation by aripiprazole in partial responders to clozapine, the most seem to be finding a slight difference in the PANSS and CGI scores after the aripiprazole addition. The results of our report are compatible with those of other studies but, we have found a considerable antianxiety action in both of the cases. The 5HT1A agonism of aripiprazole could be hypothesized as mechanism contributing to this effect.

1. Introduction

Clozapine is the drug of choice in treatment-resistant schizophrenia, but 40–70% of clozapine-treated patients continue to demonstrate suboptimal clinical response [1–4].

Various augmentation strategies have been tested, including the use of other atypical antipsychotics, but no clear recommendations can presently be proposed [5–10].

Augmentation with aripiprazole has been documented in case reports [11], in open trials [5, 12], and in a randomized controlled study [13].

In this paper, we report on 2 cases in which augmentation with aripiprazole had a beneficial impact on anxiety.

2. Case Presentation

2.1. Case Report 1. Ms. A, a 40-year-old woman diagnosed with a residual schizophrenia [14] was admitted following an exacerbation of psychotic symptoms with a predominance of anxiety despite 700 mg/d of clozapine for two years. The clinical scores and the trough plasma concentrations of clozapine

and norclozapine at admission were CGI: 5; total PANSS: 123; positive: 17/49; negative: 18/49; excited component: 12/35; general: 39/112; Hamilton-anxiety: 14/56; clozapine: 896 ng/mL; norclozapine: 551 ng/mL, respectively (clozapine therapeutic range: 350–600 ng/mL [15–17]). Because of the risks of seizures, the dose was reduced to 500 mg/d, and aripiprazole (10 mg/d) was added. Clozapine and norclozapine plasma concentrations measured after 10 days were decreased according to the reduction of the dose (615 ng/mL and 478 ng/mL, resp.). The aripiprazole plasma concentration after 10 days was 282 ng/mL. Following a clinical reduction of the anxiety, the patient was discharged from the hospital three weeks after the addition of aripiprazole.

A followup over 6 months did not reveal any change in the CGI and PANSS scores (at 6 months: CGI: 5; total PANSS: 125; positive: 18/49; negative: 23/49; excited component 10/35; general: 38/112). On the other hand, the Hamilton-anxiety score diminished progressively to 12, 7, and 8 after one, three, and 6 months, respectively. Clozapine and norclozapine plasma levels were stable over this

period (at the sixth month: 608 ng/mL, 443 ng/mL, and 75 kg, resp.), and the comedications (clorazepate 20 mg/d, valsartane 40 mg/d, zopiclone 7.5 mg/d, and tamsulosine 0.4 mg/d) were not modified. No reports are describing an impact on anxiety by the antihypertensive comedication by valsartane (an angiotensin II receptor antagonist) and tamsulosine (peripheral α 1-antagonist). There is no significant pharmacokinetic or pharmacodynamic interactions of that comedication and the antipsychotic/anxiolytic treatments.

2.2. Case Report 2. Mr. L, a 48-year-old man with a diagnosis of residual schizophrenia [14] treated for many years with clozapine 500 mg/d was admitted because of the worsening of his anxiety. The clinical scores and the trough plasma concentrations of clozapine and norclozapine were: CGI: 4; total PANSS: 88; positive: 20/49; negative 25/49; excited component: 9/35; general 40/112. Hamilton-anxiety: 24/56; clozapine: 594 ng/mL; norclozapine: 470 ng/mL, respectively. Aripiprazole 10 mg/d was added to clozapine (dose unchanged) and lorazepam (1 mg/d) was discontinued. The patient was discharged three weeks after the aripiprazole addition.

A followup over 3 months did not reveal any change in the CGI and PANSS scores (at 3 months: CGI: 4; total PANSS: 73; positive: 20/49; negative: 25/49; excited component: 7/35; general: 40/112), while the Hamilton-anxiety score diminished progressively to 19 and 15 after one and three months, respectively. The clozapine and norclozapine plasma concentrations at three months were 431 ng/mL and 343 ng/mL, respectively.

3. Discussion

In the present paper the augmentation did not result in a reduction of psychotic symptoms despite a treatment period of 3 to 6 months, which is in agreement with previous reports [5, 10–13]. Because a therapeutic window has been demonstrated for clozapine [17, 18], it is important to mention that therapeutic blood levels of clozapine were maintained during the whole observation period. An important reduction of anxiety was clinically observed in both cases, with a marked improvement of psychosocial functioning observed, which allowed a change of residential institution of both cases, three and six months after the discharge from the hospital, for a residential stay in more open environment with less psychosocial accompanying measures.

It has been suggested that in anxiety disorders, the adjunction of atypical antipsychotics to the current SSRI and/or benzodiazepine treatment could, through the modulation of the dopaminergic system, be beneficial but the data are not conclusive [19, 20].

The agonist action of aripiprazole on the 5HT1A receptors could eventually contribute to the antianxiety action that we have observed [21].

However, considering the present observations could be due to external factors or to the natural evolution of the illness, a randomized controlled study is required to evaluate the efficacy of the clozapine-aripiprazole combination in

cases of treatment-resistant schizophrenia with predominance of anxiety. Moreover, the anxiety observed in Case 1 could have been in part attributable to psychotoxic effects due to the high plasma concentration at the beginning of the followup [22].

Disclosure

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