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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 5HT_{1A} 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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References

- [1] J. Kane, G. Honigfeld, J. Singer, and H. Meltzer, "Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine," *Archives of General Psychiatry*, vol. 45, no. 9, pp. 789–796, 1988.
- [2] A. Cipriani, M. Boso, and C. Barbui, "Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD006324, 2009.
- [3] R. R. Conley and D. L. Kelly, "Management of treatment resistance in schizophrenia," *Biological Psychiatry*, vol. 50, no. 11, pp. 898–911, 2001.
- [4] J. A. Lieberman, A. Z. Safferman, S. Pollack et al., "Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome," *American Journal of Psychiatry*, vol. 151, no. 12, pp. 1744–1752, 1994.
- [5] C. I. Mitsonis, N. P. Dimopoulos, P. A. Mitropoulos et al., "Aripiprazole augmentation in the management of residual symptoms in clozapine-treated outpatients with chronic schizophrenia: an open-label pilot study," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 31, no. 2, pp. 373–377, 2007.
- [6] F. Mouaffak, C. Tranulis, R. Gourevitch et al., "Augmentation strategies of clozapine with antipsychotics in the treatment of ultrasensitive schizophrenia," *Clinical Neuropharmacology*, vol. 29, no. 1, pp. 28–33, 2006.
- [7] R. C. Josiassen, A. Joseph, E. Kohegyi et al., "Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial," *American Journal of Psychiatry*, vol. 162, no. 1, pp. 130–136, 2005.

- [8] A. E. Anil Yagcioglu, B. B. Kivircik Akdede, T. I. Turgut et al., "A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety," *The Journal of clinical psychiatry*, vol. 66, no. 1, pp. 63–72, 2005.
- [9] W. G. Honer, A. E. Thornton, E. Y. H. Chen et al., "Clozapine alone versus clozapine and risperidone with refractory schizophrenia," *New England Journal of Medicine*, vol. 354, no. 5, pp. 472–482, 2006.
- [10] G. Remington, "Augmenting clozapine response in treatment-resistant schizophrenia," in *Therapy-Resistant Schizophrenia*, H. Elkis and H. Y. Meltzer, Eds., vol. 26 of *Advances in Biological Psychiatry*, pp. 129–151, Karger, Basel, Switzerland, 2010.
- [11] K. Karunakaran, T. E. Tungaraza, and G. C. Harborne, "Is clozapine-aripiprazole combination a useful regime in the management of treatment-resistant schizophrenia?" *Journal of Psychopharmacology*, vol. 21, no. 4, pp. 453–456, 2007.
- [12] D. C. Henderson, L. Kunkel, D. Nguyen et al., "An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 113, no. 2, pp. 142–147, 2006.
- [13] J. S. Chang, Y. M. Ahn, H. J. Park et al., "Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial," *Journal of Clinical Psychiatry*, vol. 69, no. 5, pp. 720–731, 2008.
- [14] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*, American Psychiatric Publishing, 4th edition, 2000.
- [15] W. Guy et al., *ECDEU Assessment Manual for Psychopharmacology*, U.S. Department of Health, Education, and Welfare, Rockville, Md, USA, 1976.
- [16] S. R. Kay, L. A. Opler, and A. Fiszbein, *Positive and Negative Syndrome Scale-Manual*, Multi-Health Systems, New York, NY, USA, 1992.
- [17] P. Baumann, C. Hiemke, S. Ulrich et al., "The AGNP-TDM expert group consensus guidelines: therapeutic Drug Monitoring in psychiatry," *Pharmacopsychiatry*, vol. 37, no. 6, pp. 243–265, 2004.
- [18] P. J. Perry, D. D. Miller, S. V. Arndt, and R. J. Cadoret, "Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients," *American Journal of Psychiatry*, vol. 148, no. 2, pp. 231–235, 1991.
- [19] K. Gao, D. Muzina, P. Gajwani, and J. R. Calabrese, "Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review," *Journal of Clinical Psychiatry*, vol. 67, no. 9, pp. 1327–1340, 2006.
- [20] R. A. Lorenz, C. W. Jackson, and M. Saitz, "Adjunctive use of atypical antipsychotics for treatment-resistant generalized anxiety disorder," *Pharmacotherapy*, vol. 30, no. 9, pp. 942–951, 2010.
- [21] M. A. Katzman, "Aripiprazole: a clinical review of its use for the treatment of anxiety disorders and anxiety as a comorbidity in mental illness," *Journal of Affective Disorders*, vol. 128, supplement 1, pp. S11–S20, 2011.
- [22] S. Pallanti, L. Quercioli, and A. Pazzagli, "Social anxiety and premorbid personality disorders in paranoid schizophrenic patients treated with clozapine," *CNS Spectrums*, vol. 5, no. 9, pp. 29–43, 2000.