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Brief Report

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A Single Dose of Asenapine for the Treatment of Bipolar Patients Affected by Withdrawal Syndrome Induced Psychomotor Agitation: A Pilot, Open-Label Study

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Abstract

Psychomotor agitation is a medical condition associated with a wide range of psychiatric and non psychiatric diseases including: mood disorders, schizophrenia, personality disorders and drug dependence. In our pilot, open-label study, we evaluated the effect of a single dose of sublingual asenapine in bipolar patients affected by withdrawal syndrome induced psychomotor agitation resistant to the treatment with agonist medicines (methadone, gamma hydroxybutyrate and benzodiazepines).

Keywords

Psychomotor agitation, Withdrawal syndrome, Addiction, Asenapine, Bipolar disorder

Introduction

Psychomotor agitation is a medical condition associated with a wide range of psychiatric and non psychiatric diseases including: mood disorders, schizophrenia, personality disorders and drug dependence [1]. The management of psychomotor agitation poses still important diagnostic, clinical, ethical and legal implications [2]. Second generation antipsychotics have been shown to be safe and effective in the treatment of psychomotor agitation in psychotic and non-psychotic patients [2, 3]. In recent studies, asenapine, a second generation antipsychotic acting as an antagonist at various dopaminergic (D2, D3 and D4), serotonergic (5HT2A, 5HT2B, 5HT2C, 5HT6 and 5HT7) and alpha adrenergic receptors (α1A and α2), showed to be safe and efficacious in the treatment of psychomotor agitation in psychotic and non-psychotic patients [4, 5]. Asenapine was approved in the USA for the treatment of adults affected by schizophrenia and in both USA and Europe for the treatment of adults with manic or mixed episodes associated with bipolar I disorder with or without psychotic symptoms [4, 5]. Psychomotor agitation is a serious manic phase symptom particularly resistant to the pharmacological treatment [6]. When inadequately treated, this symptom can escalate producing severe physical consequences for both patients and healthcare staff [6]. In our pilot, open-label study, we evaluated the effect of a single dose of sublingual asenapine in bipolar patients affected by drug withdrawal syndrome induced psychomotor agitation resistant to the treatment with agonist medicines (AMs) (methadone, gamma hydroxybutyrate and benzodiazepines).

Materials and Methods

Our sample was recruited from outpatients which referred to the Addiction Treatment Unit of Alba from January 2016 to January 2017. Inclusion criteria

were: (a) A diagnosis of drug or alcohol or benzodiazepines dependence in comorbidity with bipolar disorder as assessed by the Mini-International Neuropsychiatric Interview 5.0 (MINI); (b) a Visual Analogue Scale (VAS) score for craving ≥ 7; (c) a Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score ≥ 20; a Clinical Global Impression Scale (CGI) score ≥ 4. At baseline (T0), patients were assessed using: MINI, PANSS-EC, VAS and CGI. They received 30 milligrams of methadone, if they showed craving for opioids, 10 ml of gamma hydroxybutyrate, if they showed craving for alcohol, and 2.5 milligrams of oral lorazepam, if they showed craving for benzodiazepines. Two hours later (T1), they were reassessed using: PANSS-EC, VAS and CGI. Patients with a PANSS-EC score ≥ 15 were treated with 10 milligrams of sublingual asenapine. Two hours later (T2), they were reassessed using: PANSS-EC, VAS and CGI. ANOVA of repeated measurements was used for our statistical analysis. Where necessary, Bonferroni correction was applied. Considering the small size of our sample, a p-value < 0.01 was considered significant. A written informed consent was obtained from each patient. The study was conducted in accordance to the Declaration of Helsinki and it was approved from the Local Ethical Committee as part of the study approved with the following code: ASL CN2/SerD 1.

Results and Discussion

Thirty-one patients, nineteen males and twelve females with a mean age of 37.9 (SD = 9.1; range = 23-52) were enrolled in the study. All included patients had a history of bipolar disorder. Among them, eleven were affected by opioid dependence, ten by alcohol dependence and ten by benzodiazepine dependence. All patients completed the study. As shown in Table 1, the PANSS-EC score reduction induced by the AMs (T1) and asenapine (T2) was statistically significative ($p < 0.0001$) if compared with T0 score. However, clinical effect induced by the asenapine on PANSS-EC score was statistically significative in T2 if compared with the partial response induced by the AMs in T1 ($p < 0.0001$). Asenapine was also effective in reducing the CGI score ($p < 0.0001$) while AMs failed this target. On the other hand, AMs were effective in reducing VAS score ($p < 0.01$) while asenapine was ineffective. Comparison among subgroups highlighted that asenapine was effective in reducing the PANSS-EC score in heroin ($p < 0.0001$) and alcohol dependent ($p = 0.0041$) patients, but it was ineffective in benzodiazepine dependent patients. CGI score was significantly improved by the asenapine in heroin dependent patients ($p < 0.0001$), but our results were nonsignificant in alcohol and benzodiazepine dependent patients. AMs were ineffective in all subgroups. In T2, the CGI score in alcoholics was significantly improved by the sequential combination between AMs and asenapine ($p = 0.0052$). Finally, asenapine was ineffective in reducing the VAS score in all subgroups while AMs were effective in heroin ($p < 0.0001$) and alcohol dependent ($p = 0.0041$) patients. No serious adverse event was observed: three patients reported sedation while one patient signalled asthenia. No extrapyramidal side effect was evidenced during the clinical observation. To the best of our knowledge, this open-label study represents the first report in which the asenapine was used for the treatment of bipolar patients affected by withdrawal syndrome induced psychomotor agitation resistant to the treatment with AMs. In our sample, asenapine was safe and effective in reducing the PANSS-EC score in heroin and alcohol dependent patients. Furthermore, sublingual asenapine was effective in reducing the CGI score in heroin dependent patients. Finally, it was an effective augmentation therapy in reducing the CGI score in alcoholics. The main

Table 1: Scales scores before (T0) versus after (T1 and T2) two hours from methadone and sublingual asenapine administration, respectively.

	T0	T1	p	T1	T2	p	T0	T2	p
PANSS-EC	25.05	22.2	**< 0.0001**	22.2	13.85	**< 0.0001**	25.05	13.85	**< 0.0001**
CGI	4.75	4.35	**NS**	4.35	2.5	**< 0.0001**	4.75	2.5	**< 0.0001**
VAS	8.1	4.85	**< 0.0001**	4.85	4.8	**NS**	8.1	4.8	**< 0.0001**
PANSS-EC- H	25.36	22	**< 0.0001**	22	12.27	**< 0.0001**	25.36	12.27	**< 0.0001**
CGI-H	4.63	4.36	**NS**	4.36	1.90	**< 0.0001**	4.63	1.90	**< 0.0001**
VAS-H	8.09	4.36	**< 0.0001**	4.36	4.27	**NS**	8.09	4.27	**< 0.0001**
PANSS-EC -A	24	21.4	**NS**	21.4	11.4	**0.0041**	24	11.4	**0.0044**
CGI-A	4.6	3.8	**NS**	3.8	2	**NS**	4.6	2	**0.0052**
VAS-A	7.6	3.6	**0.0041**	3.6	3.6	**NS**	7.6	3.6	**0.0041**
PANSS-EC-BDZ	25.5	23.75	**NS**	23.75	21.25	**NS**	25.5	21.25	**NS**
CGI- BDZ	5.25	5.25	**NS**	5.25	4.75	**NS**	5.25	4.75	**NS**
VAS- BDZ	8.75	7.75	**NS**	7.75	7.75	**NS**	8.75	7.75	**NS**

PANSS-EC = Positive and Negative Syndrome Scale-Excited Component; PANSS-EC-H = PANSS-EC heroin dependent patients; PANSS-EC-A = PANSS-EC alcohol dependent patients; PANSS-EC-BDZ = PANSS-EC benzodiazepine dependent patients; VAS = Visual Analogue Scale; VAS-H = VAS heroin dependent patients; VAS-A = VAS alcohol dependent patients; VAS-BDZ = VAS benzodiazepine dependent patients; CGI = Clinical Global Impression Scale; CGI-H = CGI heroin dependent patients; CGI-A = CGI alcohol dependent patients; CGI-BDZ = CGI benzodiazepine dependent patients

pharmacological characteristics underlying the rapid anti-agitation effect of sublingual asenapine are: a rapid Tmax estimated to occur in 30-90 minutes and a high D4/D2 receptor antagonist affinity ratio [4]. In particular, as hypothesized for clozapine, the high D4/D2 receptor antagonist affinity ratio could be the pharmacological mechanism associated with the anti-agitation effect produced by the asenapine in our sample [5] Unexpectedly, asenapine was ineffective in reducing the PANSS-EC score in patients affected by benzodiazepine dependence confirming the critical role of GABA-A receptor in the management of benzodiazepine withdrawal syndrome [7]. Although our sample was also resistant to the treatment with benzodiazepines, the absence of clinical response could be related with the low initial dose of benzodiazepines. As already demonstrated for other antipsychotics [8], asenapine has shown to be ineffective in reducing the drug craving in all subgroups. This data is in line with the currently available information correlating the Reward Deficiency Syndrome and the low D2 receptor density [9]. Consequently, the block of D2 receptors exerted by the asenapine could further compromise the dopaminergic transmission in brain areas involved in the regulation of reward increasing the drug craving.

Conclusion

In conclusion, although the small size of the sample, results emerged from our pilot study evidenced that a single dose of sublingual asenapine may be a safe and effective alternative for the treatment of psychomotor agitation in bipolar heroin/alcohol dependent patients showing a partial response to the treatment with AMs. Conversely, asenapine should be carefully used in agitated patients with benzodiazepine withdrawal syndrome.

Conflict of Interest

Authors declare no conflict of interest.

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