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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Received: February 15, 2017
Accepted: May 11, 2017
Published: May 15, 2017


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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. ANOVAs 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
by 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
bipolar disorder. 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
significant (p < 0.0001) if compared with T0 score. However,
clinical effect induced by the asenapine on PANSS-EC score
was statistically significant 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 = 0.0041)
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  | < 0.0001 |
| 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 T\textsubscript{max} estimated to occur in 30-90 minutes and a high D4/D2 receptor antagonist affinity ratio \cite{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 \cite{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 \cite{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 \cite{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 \cite{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.

**References**


