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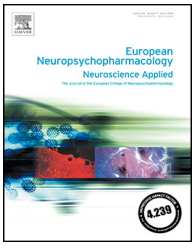

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Inhaled loxapine for agitation in patients with personality disorder: an initial approach

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Abstract
Inhaled Loxapine (IL) has demonstrated efficacy in the treatment of agitation in schizophrenic and bipolar patients, although data in patients with Personality Disorder (PD) are scarce. To evaluate the effectiveness and safety of IL in the treatment of agitation in PD, data from 41 patients who presented at our unit with acute agitation and were treated with 9.1 mg of IL were collected retrospectively. The results showed that IL significantly decreased agitation within 10 minutes and its effect was greater at 20 minutes (Positive and Negative Syndrome Scale-excited component: from 22.78 ± 4.39 at baseline to 11.14 ± 4.17 at 20 minutes; $p < 0.001$; Agitation and Calmness Evaluation Scale: from 1.80 ± 0.49 at baseline to 4.53 ± 1.05 at 20 minutes; $p < 0.01$) without any severe adverse reactions registered. IL led to fast, safe and well-tolerated control of agitation in patients with PD.

1. Introduction

Borderline Personality Disorder (BPD), one of the most frequent Personality Disorders (PD), is defined as "a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts" American Psychiatric Association, (2013). Patients may present a broad spectrum of symptoms such as severe behavioral dyscontrol, self-mutilation, psychosis-like symptoms and intense anger (Pascual et al., 2007).

The management of psychiatric agitation in BPD patients is challenging due to its complexity and high frequency in emergency departments (Koehne and Sands, 2008; Pascual et al., 2007). It becomes essential to rapidly address any acute symptoms of distress and to calm patients in order to prevent escalation to severe agitation, improve patient cooperativeness and the final clinical outcome (Garriga et al., 2016). In clinical practice, when verbal de-escalation is not enough, non-specific sedating medication (benzodiazepines or typical antipsychotics) could be recommended. However,

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severe adverse effects, such as strong sedation and extrapyramidal symptoms, limit their use (Shaikh et al., 2017). Due to their better tolerability, atypical antipsychotics, such as intramuscular (IM) olanzapine or ziprasidone, have been more frequently used (Damsa et al., 2007; Pascual et al., 2006). However, no specific treatment is indicated in agitated BPD patients.

Inhaled loxapine (IL), a new formulation of a previously extensively marketed antipsychotic, has demonstrated efficacy and safety in psychiatric agitation of schizophrenic and bipolar patients (Allen et al., 2012; Kwentus et al., 2012), although there is still little evidence in acute crises in BPD patients. Although classified as a typical antipsychotic, loxapine receptor binding and occupancy properties (high affinity antagonist of dopamine D2 and serotonin $5HT_{2a}$ receptors) are more characteristic of atypical antipsychotics, thus causing less extrapyramidalism and sedation (Singh et al., 1996). Moreover, IL is directly delivered to the alveoli providing IV-like pharmacokinetics (with C_{max} reached at 2 min) and, therefore, produces a rapid systemic effect (Spyker et al., 2010, 2015). These properties could improve the management of agitation in patients with PD.

The aim of this retrospective cohort study was to evaluate the potential value and safety of inhaled loxapine in the acute treatment of agitation in patients with PD.

2. Methodology

2.1. Patients and data collection

Both male and female patients between 18 and 55 years of age with a diagnosis of PD (according to the Diagnostic and Statistical Manual for Mental Disorders [5th ed.] criteria) and agitation (according to clinical judgment) were attended at inpatient unit of the psychiatric department of the General Hospital of Catalunya and treated with 9.1 mg of inhaled loxapine after evaluation of their agitation level by means of the Clinical Global Impression Scale-Severity (CGI-S) (Guy, 1976), the Agitation and Calmness Evaluation Scale (ACES) and the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) (Lindenmayer et al., 2004). To see if the level of agitation improved these scores were recorded again 10–20 min after administration of the treatment. Safety was evaluated by studying patients records for any recorded adverse reactions during the observation period after drug administration. The acceptability of the treatment was assessed by asking patients and physicians if they were satisfied with it.

Verbal de-escalation was applied to all patients before administering IL as per usual practice in our unit.

2.2. Statistical analysis

Effectiveness was evaluated according to the results of the three scales used. The ACES scale was analysed by means of a non-parametric Friedman test in order to assess if there were any within-group differences (at baseline, 10 and 20 minutes after IL administration), and a Wilcoxon non-parametric test was used to compare the score means corresponding to the three-time points with each other. To analyze the PANSS-EC scale, first a repeated measure analysis of variance (ANOVA) was performed to evaluate if there were any overall within-group differences in the score at the three time points and a paired *t*-test with Bonferroni correction was used to perform pairwise comparison of the means. As our data violated the assumption of sphericity, we used the Greenhouse-Geisser correction. Finally, descriptive statistics was used to evaluate baseline severity as per CGI-S and improvement (CGI-I).

Table 1 Comorbidity and Psychotropic Medication.

Comorbidity		
Axis I disorders comorbidity		
	N	%
No comorbidity	23	56.1
Anxiety Disorder	6	14.6
Affective Disorder	5	12.2
Schizophrenia and other psychotic disorders	4	9.8
SUD	3	7.3
Axis II disorders comorbidity		
	N	%
Borderline	21	51.2
PDNOS	13	31.7
Paranoid	3	7.3
Histrionic	2	4.9
Antisocial	1	2.4
Esquizoid	1	2.4
Psychotropic medication		
	N	%
SSRIs	34	82.9
Benzodiazepines	28	68.3
Mood stabilizers	14	34,1

SUD, Substance Use Disorder; PDNOS, Personality Disorder Not Otherwise Specified; SSRIs, Selective serotonin re-uptake inhibitors.

3. Results

The data from 41 PD patients (87.8% women, mean age 27.14 ± 8.21 years) were analyzed, the majority of them diagnosed as BPD (51.2%). Table 1 shows comorbidities and baseline treatment. None of the patients was intoxicated according to the patients' records. No data on interactions were observed between the basal concomitant psychiatric treatment of the patients and IL.

On average, patients were considered as moderately or markedly ill at baseline (CGI-S = 4.78, standard deviation = 0.52). At 10 minutes after the administration, 2.4% of patients were considered as "very much improved" (CGI-I = 1) and 9.8% as "much improved" (CGI-I = 2). This improvement was more evident at 20 minutes, when 29.3% of patients were considered "very much improved" and 48.8% "much improved".

Agitation level decreased significantly at 10 and 20 minutes after the administration of IL, according to the results of the PANSS-EC (from 22.78 ± 4.39 at baseline to 16.2 ± 4.93 and 11.14 ± 4.17 $p < 0.001$, respectively). The ACES scale showed an increase from 1.80 ± 0.49 at baseline to 3.75 ± 1.49 at 10 minutes and 4.53 ± 1.05 at 20 minutes; $p < 0.01$). The changes in these values during the observation period are shown in Tables 2 and 3. Only three patients needed additional medication with benzodiazepines due to lack of improvement.

Table 2 ACES values at each assessment and comparisons by time ($n = 41$).

	Basal	10 minutes	20 minutes
ACES(mean(SD))	1.80(0.49)	3.75(1.49)	4.53(1.05)
Comparisons ACES by time			
		p	
Basal vs 10 minutes		.000	
Basal vs 20 minutes		.000	
10 vs 20 minutes		.000	

ACES, Agitation-calmness Evaluation Scale; SD, Standard Deviation.

Table 3 PANSS-EC values at each assessment and comparisons by time ($n = 41$).

	Basal	10 minutes	20 minutes
PANSS-EC (mean(SD))	22.78(4.39)	16.2(4.93)*	11.14(4.17)*, **
Comparisons PEC by time			
	Mean differences		CI 95%
Basal vs 10 minutes	−6.49		−8.91, −4.07
Basal vs 20 minutes	−11.63		−14.05, −9.22
10 vs 20 minutes	−5.15		−7.56, −2,73

PANSS-EC, Excitement Component of Positive and Negative Scale;
* $p < 0{,}001$ versus basal;
** $p < 0{,}001$ between 10 min and 20 min.

The treatment was very well tolerated. Only one patient had an adverse reaction, described as respiratory distress controlled with a conventional bronchodilator (following the indications stated in its instructions of use). Physicians and patients reported high acceptability of the IL (97.6% in both groups).

4. Discussion

Our retrospective analysis showed that IL was rapid, effective, safe and well accepted in agitated PD patients. These results concur with other studies using IL in different situations of psychiatric agitation, such as in schizophrenic, bipolar, dual-diagnosis or intoxicated patients (Allen et al., 2012; Kwentus et al., 2012; Roncero et al., 2016, 2017; San et al., 2018). In all of them, IL significantly decreased agitation as fast as 10 minutes after administration, had no significant sedative effect and good tolerability, thereby confirming its pharmacologic properties. IL is directly delivered to the alveoli providing IV-like pharmacokinetics. Loxapine is removed rapidly from the plasma and distributed in tissues, including brain, thus reducing systemic exposure and the consequent risk of adverse reactions and improving efficiency. A 9.1 mg dose induces high response rates that could be otherwise attained with an IM dose more than 20 times higher. In France, IM loxapine is used as a first-line option to treat agitation, usually at a 200 mg dose, although some patients received doses of up to 300-600 mg (Bourdinaud and Pochard, 2003; Horn et al., 2015).

There is little information about agitation in BPD patients, although it is a common psychiatric condition (approximately 9-27% of agitated emergency patients) and consumes high levels of health care and social resources (Pascual et al., 2007; Paris, 2005). Its treatment continues to be a challenge as a consequence of its difficult diagnosis, its risk of concurring with severe agitation and the adverse attitude that general hospital staff display toward BPD patients (Shaikh et al., 2017). Several treatments have been used to manage agitation in BPD, such as benzodiazepines or typical antipsychotics, but side effects like sedation, hypotension and extrapyramidalism limit their use in clinical practice (Shaikh et al., 2017). Recently, a few studies have found atypical antipsychotics to be an option to treat these patients because of their good tolerance. Pascual et al. (2006) showed in a case report series that the use of IM olanzapine or ziprasidone led to a significant improvement in the PANSS-EC and ACES scores compared to baseline. On the other hand, Damsa et al. (2007), in a small observational study done in 25 patients with severe agitation and BPD, demonstrated significant reductions in agitation levels 2 hours after the administration of 10 mg of IM olanzapine, with good tolerance. Nevertheless, there is no drug approved with the indication of agitation in BPD patients and no rigorous evidence is available to select the best treatment.

Data on IL in agitation in BPD are even more scarce. Recently, Khal et al. (2015) published a small case series report of 3 consecutive patients who presented with high levels of agitation and whose previous episodes were characterized by serious self-harm injuries and poor response to treatment. They received intensive dialectic behavioral therapy prior to medication. The results showed that IL (9.1 mg) reduced agitation in an average of 60% as compared with baseline. No adverse events were reported.

Our data, with the largest number of BPD patients analysed to our knowledge, is in line with these results. IL significantly reduced the level of agitation within the first 10 minutes and maintained this effect 20 minutes post-administration when assessed by ACES and PANSS-EC scores. Moreover, a clear clinical effect was seen when the CGI scale results were reviewed. It is important to note that calmness was achieved without sedating patients, as observed through the ACES results. Moreover, a 97% treatment acceptability rate was reported by both patients and psychiatrists. This high acceptability could be due to the non-invasive route of IL administration, which enables patient autonomy to be preserved, maintains the patient-physician alliance and avoids any physical coercion. These aspects are essential in the management of agitation in BPD patients as showed in different studies (Pascual et al., 2007; Shaikh et al., 2017). There is a general consensus in establishing calmness without rapidly sedating the patient as a priority, in order to prevent staff or self-injuries and obtain the patient's collaboration to achieve quick discharge, and to avoid physical or chemical restraint, with the aim of maintaining patient alliance (Holloman and Zeller, 2012). Indeed, in our case, patients who have previously been

treated with IL ask for such treatment under similar conditions.

In relation to tolerability, inhaled loxapine was well accepted and only a non-severe respiratory distress was found, which was well controlled with standard measures (Adasuve, SmPC, Ferrer Internacional S.A.). It should be noted that no data on interactions between the basal concomitant psychiatric treatment of the patients and IL were found in patients records. It was no surprising giving its acute administration.

Moreover, it is important to note that it was possible to administer medication in all patients, in spite of the finding that all of them presented moderate to severe agitation. As reported in other studies, IL is self-administered under medical supervision, and minimal cooperation from patients is required. In our unit, appropriately training hospital staff on intensive verbal de-escalation could have facilitated the management of these patients.

While this retrospective study reports a new approach to the acute treatment of agitation in BPD, some limitations should be discussed. It was a retrospective revision of the patient cohort and not a clinical trial. Therefore, treatment was administered according to usual clinical practice. The lack of an active control prevents any direct comparisons from being made. Furthermore, we could not find data on patients follow-up beyond 1 h that impeded to determine whether this reduction in agitation persisted over time. On the other hand, it should be taken into account that patients included in the revision were heterogeneous being the majority diagnosed with BPD. Finally, as a retrospective study in the usual clinical practice patients with different concomitant treatment or associated comorbidities were included.

In conclusion, our retrospective study suggests that IL could be a good option to treat agitation in BPD and other PD patients, after prior verbal de-escalation.

Authors' disclosure

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Ferrer Internacional S.A. contributed to medical writing and editing.

Contributors

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors. BP and MG contributed to the study design and concept. BP, and MVN-H contributed to data acquisition and to analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

Conflict of interests

BP, MVN-H and MG did not receive direct compensation related to this work. No conflict of interests is declared.

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