Inhaled loxapine: A novel treatment for agitation in psychotic disorders

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Summary

Psychomotor agitation is a widespread clinical problem both in patients with schizophrenia and BD. It is a highly hazardous condition, imposing significant risks in psychiatric emergency, as expressed by elevated ratios of adverse events and traumatic experiences (both for patients and medical staff). The available anti-agitation drugs have numerous disadvantages. The orally administered medications (even though preferable to patients) take hours or even days for the therapeutic effect to emerge (and also there is a risk of exacerbating agitation in between). Although rapid onset of action (15–45 minutes) is a noteworthy merit of intramuscular drugs, such an invasive strategy is far too often bound to patients’ anxiety, resistance, and traumatic experiences. The need for novel drug formulations (ideally, both integrating the benefits of injectable and orally administered tranquillizing medications, and free from their disadvantages) can be, therefore, clearly grasped. Development of inhaled loxapine exemplifies the attempts to overcome the above-delineated obstacles. As suggested by the available research base, inhaled loxapine seems to be an effective anti-agitation drug in treatment of patients with schizophrenia and BD (with the onset of action similar to the one observed in intramuscular antipsychotics). However, this formulation of loxapine is distinguished by its non-invasive route of administration, as accompanied by markedly low risk of side effects or adverse events.

Key words: loxapine, schizophrenia, bipolar disorder

Introduction

Agitation may occur in patients with either mental or medical disorders [1-3]. In some individuals, this clinical phenomenon (defined as a condition of motoric hyperactivity intertwined with the experience of inner tension) forms a part of a picture of a particular illness; others suffer from agitation as a specific complication of a primary condition. Furthermore, agitated patients may present with irritability, nervousness, anger (or, at times, anxiety), hostility toward others, hypersensitivity and over-reactivity to internal or external stimuli, rapid alterations of mental status,
as well as lack of rapport and loss of control over self-behaviour [3-5]. Therefore, agitation is a psychiatric emergency, and – as such – requires an urgent treatment, in order to manage the high risk of violence by a patient. This, in turn, is a prerequisite of providing safety for a patient him- or herself, as well as all the other individuals involved in the emergency situation (i.e. staff members, other patients, and hospital guests) [3-6]. It is also worth mentioning that both agitation and its consequences are significant sources of both distress, and stigma of psychiatric patients [7, 8].

Psychomotor agitation is commonly observed in individuals hospitalized due to bipolar disorder (BD) or schizophrenia [3, 9, 10]. As elaborated by Serretti and Olgiati [11], in a sample of 652 patients with BD as many as 87.9% of the subjects with BD type I have presented with the signs of agitated activity. This outcome has also been noticed in 52.4% of patients suffering from hypomania in course of BD type II, 29.2% of individuals with psychotic depression, and around 12% of subjects with non-psychotic major depression. According to the Orta et al.’s [12] cross-sectional survey of 503 inpatients (as admitted due to exacerbations of schizophrenia), non-aggressive agitation has been experienced by 38.4% of the individuals, while agitation with aggression has been exhibited by 23.5% of the patients.

Non-pharmacological de-escalation is the strategy of choice when treating a patient with mild-to-moderate agitation. Establishing verbal contact (in a polite way), minimizing abrasive sensory stimulation, offering help or food etc., and providing a patient with comfort and sense of safety – these are the elements forming the mainstay of the non-pharmacological interventions [13]. If effective, the strategy should be followed on by offering the possibility of voluntary medication (in order to obtain tranquillisation, instead of over-sedation). However, if the plan of action fails, or in cases of severe agitation and on-going deterioration of a patient’s mental status, the need for rapid pharmacological tranquillisation may become urgent. The established risk-control effectiveness and the potential for staving off coercive measures are the notable advantages of the treatment model discussed [4, 5, 14-17].

Antipsychotic drugs form the centrepiece of the guidelines for pharmacological treatment of agitation. The use of oral or intramuscular formulations has been recommended (with orodispersible tablets as the optimal solution). The utilization of benzodiazepines has also been advocated (either as an alternative to or in combination with antipsychotics) [4, 15-18]. Insights from the clinical practice suggest that while the patients are more likely to accept orally administered medications (therefore, compliance seems to be less of a problem), it takes hours or even days for the therapeutic effect to emerge. Ominously enough, there is a risk of exacerbating agitation in between. Although rapid onset of action (15–45 minutes) is a noteworthy merit of intramuscular drugs, such an invasive strategy is far too often bound to the patients’ anxiety, resistance, and traumatic experiences. This, in turn, may lead to deterioration in rapport between the patients and the staff members, paving the way to the poor adherence with the long-term treatment. Also, making an injection to an anxious and non-compliant patient puts healthcare professionals at risk of a needle-stick injury [5, 17, 18].

As elaborated above, the common modes of treatment for agitation are hampered by significant shortcomings, and impose significant risk of numerous side effects and com-
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The need for novel drug formulations (ideally, both integrating the benefits of injectable and orally administered tranquilizing medications, and free from their disadvantages) can be, therefore, clearly grasped.

This review summarizes the available clinical data on the use of inhaled loxapine for agitation associated with BD and schizophrenia. It is a new drug, possibly meeting the demand for improved formulations of anti-agitation drugs.

The Staccato system: An innovative method for administering inhaled loxapine

The Staccato system has been used to deliver inhaled loxapine. The name refers to the small, palm-sized, disposable device (see Figure 1) [19]. Once a patient sealed his or her lips around the mouthpiece, drawing a normal breath activates an airflow sensor, which instantaneously triggers the heating of the substrate, onto which a film of the drug is coated. Within the next 200 milliseconds the film transforms into aerosol that is delivered deep into a patient’s lungs [19-22]. It takes less than a second for the process to come the full circle (from activating the device, to loxapine inhalation into the bronchial tree) [19, 22-24]. This mode of administration enables a patient to achieve the peak plasma concentration of loxapine in as quickly as 2 minutes (i.e. with the pace comparable to those of the intravenous drug delivery systems) [25].

Fig. 1. System Staccato

Regardless of the environmental variables (e.g. breathing dynamics, aerial humidity, temperature fluctuations, placement of the inhaler, etc.) an individual being treated receives about 90% of the medication quantity stored in the device at baseline [22].
Unlike other inhalers (pulmonary drug delivery systems, for instance), one does not need to take a deep breath in order to activate the Staccato system (since breathing normally would be just fine), nor to synchronize the inhale with the pull of the drug-releasing trigger (making the device very friendly to its users). Thus, the system seems to fit the (highly specific and arduous) demands of treatment for agitated psychiatric patients [26].

Pharmacodynamics and pharmacokinetics of loxapine

Loxapine is a dibenzepine derivative, tricyclic antipsychotic agent [27]. As early as in 1975 it has been approved in the U.S., Canada, and Europe. With regards to taxonomy, it has been ascribed to the class of typical antipsychotics. What needs to be emphasized, however, is the fact that apart from dopaminergic antagonism (as expressed by the high affinity to D\textsubscript{2} receptors, but also D\textsubscript{1} and D\textsubscript{4} receptors) loxapine also displays high affinity to the postsynaptic 5-HT\textsubscript{2A} serotonergic receptors, and concurrently blocks the α\textsubscript{1}- and α\textsubscript{2}-adrenergic, H\textsubscript{1}- histaminergic, and M\textsubscript{1}- muscarinic receptors (thus closely resembling the other dibenzepine derivatives, classified as atypical antipsychotics: clozapine, quetiapine, and olanzapine) [28-32]. On the whole it combines the properties of both typical and atypical antipsychotic drugs [33].

When inhaled from the Staccato system, the loxapine’s T\textsubscript{max} (i.e. the time to reach the peak plasma concentration) is as short as 2 minutes [25]. Following the absorption, 96.6% of the drug molecules are bound to the plasma proteins. Loxapine is the subject to fast tissue redistribution. The agent is metabolized primarily in the liver, with the cytochrome P450 isoenzymes (CYP3A4, CYP2D6, CYP1A2, CYP2C19, and CYP2C8), and flavin-containing monooxygenases (FMOs) playing the pivotal role in the process [26]. As a result, a number of metabolites are generated. The two active metabolites of loxapine have been identified: amoxapine (characterized by antidepressant and sedative properties) and 7-OH-loxapine (exhibiting five-fold higher antagonism towards D\textsubscript{2} receptors, as compared to loxapine) [27, 34]. The loxapine metabolites are eliminated with urine (in conjugated forms) and feces (in unconjugated forms). The drug’s elimination half-time ranges from 6 to 8 hours. As suggested by the current body of evidence, the pharmacokinetic properties of loxapine do not depend on gender, age, body mass index (BMI), race, tobacco smoking, or co-therapy with other antipsychotics. Finally, loxapine does not seem to exert any significant influence on the activity of the specific CYP450 isoenzymes [26].

Drug interactions of inhaled loxapine

No reports on the interactions between inhaled loxapine and other medications have been published so far. Thus, any considerations on the potential drug must be stem from the drug’s pharmacological properties, and have to be confined to some cautious extrapolation of data pertaining to intraoral or injectable loxapine. The current evidence base would then induce that concurrent intake of CNS-depressants (i.e. agents exhibiting the common feature with loxapine; such as benzodiazepines,
barbiturates, hypnotics, opiates, or alcohol) may elevate the risk of over-sedation, hypersomnia, hypotension, and – on the extreme – depression of the central nervous system. Also worth of attention is loxapine’s capacity to significantly decrease seizure threshold. Therefore, polypharmacotherapy with loxapine and the drugs with the similar property (e.g. clozapine, tricyclic antidepressants, bupropion, tramadol, or phenothiazines) may imply a higher risk of seizures [26]. Since loxapine is a substrate for the CYP450 isoenzymes, the use of some potent inductors of CYP (such as carbamazepine or rifampicin) or their inhibitors might lead to decrease of the loxapine plasma levels and loss of effectiveness, or – respectively – to increase of the plasma concentrations and toxicity. Due to the latter hazard, the producer has warned against the concomitant use of loxapine and the strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, propranolol, or rofecoxib) [26]. Notably enough, the fact that loxapine is metabolized along various pathways seems to mitigate the risk of such interactions.

Due to the possibility of hypotension loxapine should not be co-prescribed with adrenaline [26, 32]. One must also be cautious in cases of polytherapy involving loxapine and other anticholinergic medications, since such treatments are bound to the elevated risk of the development or exacerbation of the atropine-like side effects (e.g. dry mouth, tachycardia, urinary retention, and increase of the intraocular pressure in patients with glaucoma) [26, 27, 32].

The clinical effectiveness of loxapine

The intraoral formulation of loxapine (60–100 mg q.d.; the upper dose limit: 200–250 mg q.d.)\(^1\) is used primarily for the treatment of schizophrenia [32, 35]. Its effectiveness has also been proven both in the samples of individuals with psychotic depression, and BD [32, 36, 37]. Prior to the development of inhaled loxapine, the intramuscular formulation (used as an anti-agitation drug in psychotic patients) formed an alternative to other injectable antipsychotics [38-40].

The tranquillizing efficacy of inhaled loxapine in patients with mild-to-moderate agitation has been scrutinized in course of the phase 2 randomized controlled trial (RCT; trial N\(^o\) 4 004-201, encompassing 129 subjects diagnosed with schizophrenia or schizoaffective disorder [41]), and the two phase 3 RCTs (trial N\(^o\) 004-301, involving 344 patients with schizophrenia [42]; and trial N\(^o\) 004-302, comprising a sample of 314 individuals meeting the criteria for mania or mixed episode in course of BD type I [43]).

The participants of the phase 2 trial have been randomized to one of the three groups: loxapine 10 mg (single dose), loxapine 5 mg (single dose), and placebo. The severity of agitation has been assessed twice (prior to the medication intake, and 2 hours thereafter), and the following diagnostic measures have been used: the Positive and Negative Syndrome Scale–Excited Component (PANSS-EC), the Clinical Global Impression Scale (CGI), and the Behavioral Activity Rating Scale (BARS).

\(^1\) Not available in Poland.
The results suggest that loxapine used in the single dose of 10 mg has significant advantage over placebo in terms of the anti-agitation effect (regardless of the rating scale used). However, in the sample receiving 5 mg of loxapine the statistically significant difference between the active treatment and placebo could have been noted in the CGI scores only [41].

All the phase 3 RCTs have been identical in terms of the flow. Namely, the patients have been randomized to one of the three groups: placebo, loxapine 5 mg, and loxapine 10 mg. The severity of agitation has been assessed (with the use of the PANSS-EC) at the following time points: prior to the pharmacological intervention, and then after 10, 20, 30, 45, 60, 90 minutes, 2 hours, and – finally – 24 hours thereafter. Additionally, at baseline and after 2 hours following the drug application the efficacy has been evaluated with the CGI. Patients who failed to benefit from the first dose could have received the second (>2 hours after the first inhalation) and the third one (>4 hours after the second inhalation), if necessary [42, 43]. The post-treatment severity of agitation has been measured by the Agitation-Calmness Evaluation Scale (ACES) [42, 43].

In either of the two trials there have been significantly greater reductions on the PANSS-EC scores in the loxapine groups (5 mg or 10 mg), as compared to placebo. This effect has been noticeable as early as the first follow-up assessment (i.e. 10 minutes after the drug inhalation), and has been steady over time. Furthermore, the treatment outcome has not depended on age, gender, race, diagnosis, or the level of agitation at baseline [42, 43]. Loxapine has shown significant advantage to placebo in all the PANSS-EC dimensions of agitation, such as impulse control, hostility, uncooperativeness, tension, and psychomotor excitement. After 2 hours following the inhalation, the severity of agitation (as measured by the CGI scale) has also been statistically significant lower in the groups of loxapine (5 mg or 10 mg), as compared to the placebo samples (see Table 1) [42, 43].

Table 1. Clinical effectiveness of inhaled loxapine (a summary of the phase 3 clinical trials).

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia (Lesem et al. [42])</th>
<th>BD type I (Kwentus et al. [43])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=115)</td>
<td>Loxapine 5mg (n=116)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>43.9(9.5)</td>
<td>43.2(10.2)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>69.6%</td>
<td>75%</td>
</tr>
<tr>
<td>Mean severity of agitation at baseline: the PANSS-EC scores (SD)</td>
<td>17.4(1.8)</td>
<td>17.8(2.3)</td>
</tr>
</tbody>
</table>

The primary outcome has been defined as the therapeutic response after 2 hours following the medication. The response has been conceptualized as the ≥40% reduction in the PANSS-EC scores (as compared to the baseline level).
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| Mean change in the agitation severity after 2 hours of follow-up (as expressed by the effect size): the PANSS-EC scores (SD) | -5.5(4.9) | -8.1(5.2)^ | -8.6(4.4)# | -4.9(4.8) | -8.1(4.9)# | -9.0(4.7)# |
| Mean severity of agitation at baseline: the CGI-S scores (SD) | 3.9(0.5) | 4.0(0.6) | 4.1(0.6) | 4.1(0.6) | 4.0(0.5) | 4.0(0.5) |
| Mean change in the agitation severity after 2 hours of follow-up: the CGI scores (SD) | 3.0(1) | 2.1(1.1)^ | 1.9(1.1)# | 3.0(1) | 2.1(1.1)# | 1.9(1.1)# |
| The rates of the therapeutic response after 2 hours of follow-up (as expressed by the NNT): the CGI scores. | 35.7% | 57.4%^ | 67%# | 27.6% | 66.3%# | 74.3%# |
| The rates of the therapeutic response after 2 hours of follow-up (as expressed by the NNT): the CGI scores. | 38.3% | 62.9%^ | 69.6%# | 27.6% | 62.5%# | 73.3%# |
| Mean severity of sedation at baseline: the ACES scores (SD). | 2.3(0.5) | 2.2(0.6) | 2.2(0.5) | 2.0(0.4) | 2.1(0.4) | 2.1(0.4) |
| Mean severity of sedation after 2 hours of follow-up: the ACES scores (SD). | 3.9(1.8) | 4.7(2.1) | 4.9(2.0) | 3.3(1.7) | 4.7(2.0) | 5.1(2.1) |

All the data provided refer to the comparison between inhaled loxapine and placebo.

*p<0.01, ^p<0.001, #p<0.0001; SD – standard deviation, NNT – number need to treat, CGI-S – the Clinical Global Impression–Severity scale

In the loxapine samples from the both of the phase 3 trials, following the initial administration of the drug there have been significantly higher ratios of patients who had met the criteria for therapeutic response^3 (in comparison to placebo). Of note, the sta-

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^3 Here, the response has been defined as the ≥40% reduction in the PANSS-EC scores (in comparison to the baseline level), or by the rating of ‘much improved / very much improved’ (as captured on the CGI scale).
Statistically significant difference between loxapine and placebo has emerged at the first follow-up assessment, and has remained stable for the rest of the study. The number needed to treat (NNT; i.e. the number of patients who need to be treated in the predefined way, in order to achieve one additional positive outcome, or to prevent one additional negative outcome [44]) corresponding to the response rates noticed after 2 hours of observation, has turned out to be highly favourable for loxapine. Regardless of the response criteria utilized (PANSS-EC or CGI), in the sample of individuals diagnosed with schizophrenia NNT was equal to 3.2. Also, in the study encompassing patients with BD the NNT value was equal either to 2.1 (for the CGI criteria) or to 2.2 (the PANSS-EC criteria; see Table 1) [26, 42, 43].

It also needs to be emphasized that the anti-agitation effectiveness of loxapine has not been accompanied by the (poorly tolerated) over-sedation. Actually, after 2 hours of follow-up the mean ACES scores corresponded to the state of mild sedation [26, 42, 43].

The second dose of the drug was needed in 51.4% of patients randomized to the ‘5 mg’ sample, and in 38.1% of individuals from the group receiving 10 mg of loxapine. As compared to individuals receiving the active treatment, subjects ascribed to the placebo group needed to obtain the second dose significantly earlier. Also, the indications for the add-on tranquilization (with the intramuscular formulation of lorazepam) have been significantly less common in the loxapine group (in comparison to placebo). This has been the case both in the subgroup of patients with schizophrenia (receiving 10 mg of loxapine), and among the subjects with BD (treated with 5 mg or 10 mg of loxapine) [26, 42, 43, 45].

Of note, for the majority of patients the adherence to the novel mode of treatment has not been problematic at all. No participants have been excluded due to the inability to comprehend the instructions, unsurpassable difficulties of operating the inhaler, or setting improper dosage of the medication [42, 43].

Tolerability and side effects of inhaled loxapine

The current body of evidence lead to conclusion that inhaled loxapine is a fairly safe and well-tolerated drug. In the placebo-controlled phase 2 and 3 trials performed among the agitated patients with schizophrenia or BD (524 subjects who have received at least one dose of loxapine, and 263 individuals who have inhaled at least one dose of placebo), there have been similar overall rates of side effects or adverse events in the treatment and placebo groups (36.5% and 37.3%, respectively) [26, 41-43]. The treatment-related adverse events have been more widespread in the loxapine sample (for the dose of 5 mg: 32.8%; for the dose of 10 mg: 34.0%), as compared to the placebo group (25.9%). An in-depth analysis has revealed that the difference between loxapine and placebo had crossed the level of statistical significance only in the cases of dysgeusia (a transient distorted gustatory perception 12.8% vs. 4.9%), and sore throat (2.7% for the loxapine dose of 10 mg vs. 0.4% for placebo). Apart from distortions of the sense of taste, there are some other common adverse events of inhaled loxapine, e.g. sedation and hypersomnia (however, they are usually mild to moderate; 12% in the loxapine group vs. 9.5% in the placebo sample), as well as
vertigo (6.9% in patients treated with loxapine vs. 8.7% among individuals receiving placebo). There have been also reports on the rare cases of dry mouth, extrapyramidal symptoms (tremor, akathisia, dystonias, dyskinesias, etc.), and hypotension [26, 41-43].

Pulmonary side effects have been noticed in 0.4% of the patients. Accordingly, three cases of coughing or wheezing were reported, and one individual suffered bronchospasm (yet with no serious consequences, since the condition resolved with use of a standard dose of a β-mimetic [42]. Insights from the studies encompassing patients with pulmonary diseases suggest that individuals treated with inhaled loxapine are at the highest risk of bronchospasm within the initial 25 minutes after the medication [46]. The up-to-date body of evidence implies that tobacco smoking (currently or in the past) is an unlikely risk factor for bronchospasm following the loxapine inhalation. This piece of information seems to be an important one, given the high prevalence of nicotine abuse among the patients with mental disorders [26].

The results of the phase 3 clinical trials suggest that treatment with inhaled loxapine does not seem to impose additional risks of haematological side effects, biochemical alterations, abnormal results of urinalysis, or hepatotoxicity. There has been no clinical or pre-clinical [47] evidence hinting at loxapine’s arrhythmogenic potential (as implied by – inter alia – lack of reports of the loxapine-induced QT prolongation). Neither any significant differences (both in the statistical and the clinical meaning of the term) between the agent and placebo have been found in terms of their impact on the parameters of circulation (even though non-significant decrease in heart rate, and systolic/diastolic blood pressure have been noted) or ventilation (although some patients receiving loxapine have been presenting with mild decrease in the breathing frequency) [26, 41-43]. There have been two case reports of mild-to-moderate hypotension in patients treated with inhaled loxapine [43]. Finally, neither age, gender, race, body mass, nor tobacco smoking seem to mediate between the treatment with loxapine and the risk of side effects [26, 41-43].

For a summary of the most common adverse events observed in the phase 3 clinical trials of inhaled loxapine, see Table 2.

Table 2. A summary of the adverse events of inhaled loxapine, as observed in the phase 3 clinical trials.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=115)</th>
<th>Loxapine 5mg (n=116)</th>
<th>Loxapine 10mg (n=113)</th>
<th>Placebo (n=105)</th>
<th>Loxapine 5mg (n=104)</th>
<th>Loxapine 10mg (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients who have experienced any adverse events.</td>
<td>38.3</td>
<td>34.5</td>
<td>38.1</td>
<td>22.9</td>
<td>34.6</td>
<td>28.6</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2.6</td>
<td>8.6</td>
<td>10.6</td>
<td>5.7</td>
<td>17.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>9.6</td>
<td>5.2</td>
<td>10.6</td>
<td>7.6</td>
<td>5.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Sedation</td>
<td>9.6</td>
<td>12.9</td>
<td>10.6</td>
<td>2.9</td>
<td>6.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

*table continued on the next page*
Safety considerations in the specific clinical populations

One should not use inhaled loxapine in subjects presenting with acute respiratory symptoms or diagnosed with a pulmonary disease (asthma, chronic obstructive pulmonary disease {COPD}, etc.) [26]. Even though authors of the pre-clinical studies (encompassing healthy volunteers) [25] have found no evidence of interaction between the drug and spirometric parameters, and in the phase 2 and 3 trials (involving patients without any pulmonary conditions) just very mild respiratory symptoms have been observed [41-43], the data on the treatment outcomes in subjects with pulmonary diseases lead to different conclusions. Accordingly, inhaled loxapine has induced respiratory symptoms (episodes of bronchospasm, coughing, dyspnoea, wheezing, etc.) in as many as 53.8% of individuals with asthma (in comparison to 11.5% in the placebo group), and in 19.2% of patients diagnosed with COPD (as compared to 11.1% in subjects receiving placebo). However, the complications were mild or moderate, and tended to disappear (either spontaneously, or following inhalation of salbutamol) [46].

Due to loxapine’s significant potential for decreasing the seizure threshold, caution is needed when it comes to using the agent in patients with history of seizures or diagnosed with epilepsy. Having in mind the antimuscarinic features of loxapine, clinicians should pay particular attention to the patients with glaucoma or prostatic hyperplasia, not to mention the individuals receiving antiparkinsonian drugs with anticholinergic properties [26, 27, 32].

Thus far, no data are available on the use of inhaled loxapine in the elderly, in agitated subjects with delirium, patients with renal failure, nor in pregnant or breastfeeding women [26]. No cases of inhaled loxapine overdose have been reported. The extrapolation of both the data on the pharmacological properties of the agent, and the evidence

<table>
<thead>
<tr>
<th>Oral hypoaesthesia</th>
<th>0</th>
<th>0.9</th>
<th>3.5</th>
<th>-</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.9</td>
<td>3.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Headache</td>
<td>13.9</td>
<td>2.6</td>
<td>2.7</td>
<td>8.6</td>
<td>3.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>2.6</td>
<td>2.6</td>
<td>2.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.2</td>
<td>0.9</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6</td>
<td>0.9</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Agitation</td>
<td>3.5</td>
<td>0.9</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.9</td>
<td>2.9</td>
<td>1</td>
</tr>
<tr>
<td>Sore throat</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>3.8</td>
</tr>
</tbody>
</table>

The data refer to the adverse events with the point prevalence of >2%. As provided by: Lesem et al. [42], Kwentus et al. [43], and EMEA [26].
on the alternative formulations of loxapine, leads to the conclusion that the intoxication with inhaled loxapine would likely manifest itself in the CNS depression, hypotension, disturbances of consciousness, seizures, and extrapyramidal symptoms [26].

General indications for inhaled loxapine: Clinical utility and dosing strategies

In the European Union, inhaled loxapine is indicated for the rapid tranquilisation of the patients diagnosed with schizophrenia or BD, presenting with mild-to-moderate agitation. The agent shall be administered in the hospital setting only, under the supervision of mental health professionals. Due to the respiratory hazard (notably, the risk of bronchospasm), a patient should be monitored throughout the first hour following each of the consecutive doses of inhaled loxapine. Consequently, the access to the β-agonist bronchodilator agents must be provided. The course of inhaled loxapine must be preceded by a triage, in order to screen for the contraindications, namely: ongoing pulmonary conditions (e.g. asthma or COPD), and acute respiratory symptoms.

In Poland, inhaled loxapine has been recently approved. The drug is already available, at the single dose of 9.1 mg (i.e. the dose equivalent of approximately 10 mg of loxapine, as deposed in the inhaler container). If necessary, a second dose can be delivered after 2 hours. (of particular note, no more than two doses should be administered) [26].

Summary

Psychomotor agitation is a widespread clinical problem both in patients with schizophrenia and BD. It is a highly hazardous condition, imposing significant risks in psychiatric emergency, as expressed by elevated ratios of adverse events and traumatic experiences (both for patients and medical staff). Overall, agitation poses a significant therapeutic challenge. The available medications fall short of meeting the criteria outlined by the expert authors of the ‘Consensus Guidelines for Treatment of Behavioral Emergencies’. Accordingly, the optimal anti-agitation drug should be characterized by rapid onset of action, effective control of aggressive behaviours, and reliable route of administration (as the prerequisite for a repeatable delivery of a standardized dose of a drug). Furthermore, such a medication should be acceptable for an affected individual (thus making it possible to safeguard a firm rapport between a patient and their physician) [5].

As suggested by the available research base, inhaled loxapine seems to be an effective anti-agitation drug in treatment of patients with schizophrenia and BD (with the onset of action similar to the one observed in intramuscular antipsychotics). At the same time, the medication discussed is distinguished by its non-invasiveness, and markedly low risk of side effects or adverse events.
References


Inhaled loxapine: A novel treatment for agitation


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