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Case Report

Extremely High Dose Lorazepam in The Treatment of Catatonia

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Abstract

Catatonia is a neuropsychiatric syndrome characterized by symptoms such as stupor, mutism, and autonomic dysfunction. Benzodiazepines, particularly lorazepam, are considered first-line treatment for catatonia, but the optimal dosing strategies, especially at higher doses, remain unclear. This case report presents the treatment of a 27-year-old male with schizophrenia and chronic catatonia, requiring extremely high doses of lorazepam up to 130 mg per day. The significant increase in dosage led to gradual improvement of the catatonic symptoms, without any notable side effects. Especially, the patient showed no signs of sedation or respiratory depression. This case suggests that lorazepam can be safely administered at much higher doses than typically recommended, provided close monitoring for adverse effects. The findings advocate for the consideration of higher doses in patients not fully responding to standard doses and emphasize the need for further research into dosing strategies, safety, and long-term outcomes in the treatment of catatonia with benzodiazepines.

Key Words: catatonia; lorazepam; treatment; psychopharmacology

Introduction

Catatonia is a neuropsychiatric disorder first described by Karl Ludwig Kahlbaum in 1874 [1]. It is a syndrome characterized by a range of symptoms, including stupor, mutism, negativism, staring, autonomic dysfunction [2]and is a potentially life-threatening condition. The prevalence of catatonia is not well established. Within clinical psychiatric populations, prevalence is estimated at approximately 9.0% [3]. When catatonia is suspected, a comprehensive diagnostic evaluation is essential to identify potential underlying causes. This includes a medical screening to assess for somatic conditions that may contribute to the disorder. The most common psychiatric condition associated with catatonia is a mood disorder, particularly bipolar disorder [4].

Benzodiazepines are considered the first-line treatment for catatonia [5]. These medications exert their effects by modulating GABA-A receptors, which are ligand-gated ion channels. Upon GABA binding to the GABA-A receptor, the frequency of chloride channel opening increases, allowing more chloride ions to enter the cell, resulting in an inhibitory effect through hyperpolarization of the cell membrane. The ion flow is also influenced by the ion concentration gradient and the membrane potential of the cell. Benzodiazepines function as positive allosteric modulators by binding to a specific site on the GABA-A receptor, enhancing the effect of GABA. The presence of benzodiazepines increases the frequency of chloride channel openings beyond the effect of GABA alone [6]. Notably, benzodiazepines have no intrinsic activity and require the presence of GABA to exert their therapeutic effects [6]. The efficacy of benzodiazepines in treating catatonia supports the hypothesis that GABA hypoactivity plays a vital role in the pathophysiology of the disorder.

Electroconvulsive therapy (ECT) is another highly effective treatment for catatonia, especially in life-threatening situations or when pharmacological interventions fail [4]. Prognosis is generally favorable if treatment is initiated promptly [5].

Although lorazepam is the primary treatment option in catatonia, little is known about optimal dosing strategies in cases exceeding maximal recommended dosages of lorazepam. This report describes a 27-year-old man of Somali descent with schizophrenia, who presented with catatonia. The primary objective of this case is to raise awareness about the potential for administering extremely high doses of lorazepam in the treatment of catatonia and to encourage further research into optimizing treatment strategies for this condition.

Case presentation

Investigations

We present the case of a 27-year-old male with a history of schizophrenia, intellectual disability (total IQ between 53-58, 95% confidence interval), childhood maltreatment, and cannabis use, who was admitted to the critical care ward at the Dr. S. van Mesdag Centre in Groningen, a high-security forensic psychiatric hospital. The patient had previously been incarcerated in a psychiatric penitentiary facility following a conviction for attempted manslaughter. During his incarceration, he experienced multiple episodes of violent physical aggression, psychosis, and catatonia. The psychosis was primarily characterized by paranoia, disorganized thoughts and behavior, and negative symptoms. The first diagnosis of catatonia was established 2-years prior to his admission to our critical care ward. Symptoms were not well recorded. According the patients' medical record, his catatonia was successfully treated with clozapine 125mg and lorazepam (unknown dose). The lorazepam was later on tapered off. One year later there was a relapse in psychosis and catatonia. The symptoms of catatonia included: immobility (standing and sitting still) and mutism. The lorazepam was restarted at 7,5mg per day. After, the patient was admitted to our critical care ward.

Diagnosis

Upon admission, the patient, a small-statured man of Somali descent, presented with a frightened and anxious demeanor, as evidenced by his facial expressions and affect. He made brief eye contact but subsequently resisted further engagement. Mental status examination revealed signs of immobility, mutism, catalepsy, mitgehen, gegenhalten, ambivalence, and negativism. The Bush-Francis Catatonia Rating Scale (BFCRS) was scored at 28 points (see table 1). A neurological examination was conducted, but no abnormalities were found, although the assessment was limited by the severity of the catatonia. Vital signs indicated mild tachycardia (108 bpm), other vital signs were within the normal range. The patient was administered lorazepam 2.5 mg orally. Approximately 45 minutes after administration, some improvement in his mental state was observed. He became more responsive to commands and he expressed desires, such as requesting coffee and tobacco.

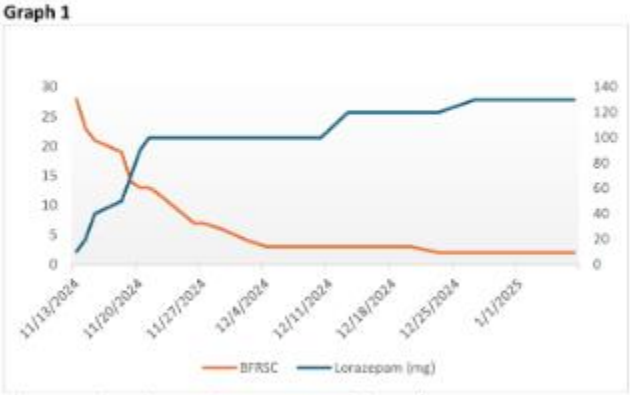
Catatonic Sign	Initial Presentation (Steady state 7,5mg)	50mg during titration	steady state 100mg	steady state 130mg
Excitement	0	0	0	0
Immobility/stupor	2	1	1	1
Mutism	2	1	1	1
Staring	3	1	0	0
Posturing	2	1	0	0
Grimacing	1	0	0	0
Echolalia/echopraxia	1	1	0	0
Stereotype	1	0	0	0
Mannerism	0	0	0	0
Verbigerations	1	1	1	0
Rigidity	1	1	0	0
Negativism	3	1	0	0
Waxy flexibility	0	0	0	0
Withdrawal	2	2	2	0
Impulsivity	0	0	0	0
Automatic obedience	0	1	0	0
Mitgehen	1	0	0	0
Gegenhalten	3	3	0	0
Ambitendency	3	3	0	0
Grasp reflex	0	0	0	0
Perseveration	0	0	0	0
Combativeness	0	0	0	0
Automatic abnormalities	2	2	1	0
Total score	28	19	6	2

Table 1: BFCRS scores recorded at the time of initial evaluation and at various intervals following the intervention.

Treatment

Given that lorazepam was already being administered regularly in a common dosage, the dose was gradually increased over time. The patient's clinical condition, vital signs, and BFCRS scores were closely monitored. Due to the slow pace of improvement, the lorazepam dosage was gradually titrated up to 130 mg per day (see Graph 1). This decision was made in consultation with several psychiatrists and a hospital pharmacist. The dosage was increased over 8 days, from 7.5 mg to 100 mg per day, with daily BFCRS assessments (see Graph 1). After three weeks, the dosage was further increased to 130 mg per day. By day twenty-one of admission, the BFCRS score had decreased to 3 points, reflecting stupor, mutism, and withdrawal. According to the Clinical Global Impression Improvement (CGI-I) scale [7], the patient scored a two, indicating a significant reduction in symptoms.

Graph 1



The orange line depicts the progression of the Bush-Francis Catatonia Rating Scale (BFCRS) over time, in relation to the lorazepam titration, as shown by the blue line.

During the titration process, vital signs (heart rate, blood pressure, oxygen saturation, and respiratory rate) were measured three times daily. Common adverse effects [8] associated with high doses of lorazepam (especially sedation and respiratory depression) were closely monitored closely. Over the first two weeks, the patient's blood pressure fluctuated between 110/90 mmHg and 65/50 mmHg. These hypotensive episodes were brief, and no clinical signs of hypotension were observed. This was attributed to autonomic dysregulation secondary to the catatonia. Although it could also be caused by the clozapine, due to its potent alpha 1 receptor blocking abilities [9]. His heart rate remained stable at 100-110 bpm, which is attributable to the clozapine. Remarkably, respiratory rate and oxygen saturation remained stable within normal values. Lorazepam blood levels were measured multiple times, with values of 701 µg/L and 905 µg/L at 100 mg and 130 mg per day, respectively. Weekly measurements of leucocytes, electrolytes, kidney function, and liver chemistry during the titration phase revealed no significant abnormalities (see Table 2).

Table 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Normal values
Leucocytes	4,9	3,5	4,2	4,8	4,3	4,3	5,0	4,0-10 10^9/l
ALAT	30	50	42	29	26	26	-	0-45U/l
ASAT	[a]	43	23	20	20	20	-	0-20U/l
Amylase	210	116	104	-	-	-	-	0-107 U/l
CRP	4	12	6	4	-	-	-	0-5mg/l
Creatinine	-	73	68	71	-	-	-	50-110umol/l
eGFR	-	120	124	-	129	-	-	>60ml/min
Clozapine[b]	-	587	886	505	664	-	-	350-700Ug/l
Norclozapine[b]	-	163	238	145	190	-	-	
Lorazepam	-			701[c]	815 [c]	889[d]	905[e]	50-250Ug/l

[a] Analysis failed

[b] The administration of clozapine was 400 mg.

[c] The administration of lorazepam was 100 mg.

[d] The administration of lorazepam was 120 mg.

[e] The administration of lorazepam was 130 mg.

- No analysis was performed.

Clozapine was titrated to 400 mg per day, with blood levels measuring 886 µg/L for clozapine and 238 µg/L for norclozapine.

Outcome

During the first three weeks of admission, the patient displayed self-neglect, poor adherence to instructions, and minimal social interaction, spending the majority of his time alone in his room. However, after the lorazepam dose was increased to 100 mg per day, a significant clinical improvement was observed. The patient's withdrawal symptoms decreased, self-care showed some improvement, and he became more compliant with instructions. Despite this progress, persistent negative symptoms such as social withdrawal, blunted affect, and avolition remained, along with disorganized thoughts and residual catatonia. No positive symptoms were noted. As of the time of writing this manuscript, the BFCRS score remained stable at 2 points.

Discussion

We present a case in which an exceptionally high dose of lorazepam was used in the treatment of catatonia. Lorazepam is generally accepted as a first-line treatment of catatonia. The primary reason lorazepam is the first-choice

treatment is the extensive experience in using it to treat catatonia, more so than with other benzodiazepines and due to its rapid onset of action [5]. The onset of effect of lorazepam varies depending on the method of administration: 1 to 3 minutes when given intravenously, 15 to 20 minutes intramuscularly, and up to 2 hours when administered orally [10]. Most studies typically employ doses ranging from 1 to 4 mg per day, with some recommending a maximum dose of up to 30 mg per day [4,11,12]. It is also recommended to increase the lorazepam dose until catatonic signs are relieved sufficiently [13]. It is unclear what the upper limit for safe and effective treatment is. In our case, lorazepam was safely titrated to a dose of 130 mg per day.

When treating aggression, in rare cases, high-dose therapy is required [14]. Since our clinic specializes in aggression there is experience with higher than recommended dosing schedules in a safe and effective manner. Furthermore, it is standard practice to internally consult with fellow psychiatrists and external specialized hospital pharmacists when considering off-label medication use or dosages outside of clinical guidelines. In doing so, we place strong emphasis on the effectiveness, proportionality, and safety for the patient.

In this case, the patient responded positively without any significant side effects. Initially, the dose was increased to 100 mg, and at that point, the BFCRS score was 3. When clinical improvement plateaued and no side effects were observed, the decision was made to increase the dose gradually to 130 mg per day. Subsequently, the BFCRS dropped to 2 points. Although, the clinical picture showed improvement following the dose increase to 120 mg. The increase from 120 mg to 130 mg did not result in any notable clinical changes. Although the clinical picture improved, this was not reflected in the BFCRS. We hypothesize that the BFCRS may not have been able to capture minimal changes at lower scores. The persistence of negative symptoms, such as social withdrawal, blunted affect, and avolition, could also be attributed to the underlying schizophrenia. Additionally, the patient's cognitive function has declined over time, likely due to recurring psychotic and catatonic episodes, as well as substance abuse. Although this cognitive decline does not fully explain his current mental state.

The reason some patients with catatonia require higher dosages of lorazepam remains unclear. It has been postulated that catatonic patients who tolerate high doses of benzodiazepines may have a disruption in the GABA pathway [12]. We also suggest that the chronic nature of the condition may contribute to such disruption. This idea is supported by a study in which traditional dosages were less effective in chronic cases of catatonia [15,16]. In addition, the relationship between blood levels of lorazepam, receptor occupancy, and clinical outcomes is not well understood. In our patient, lorazepam blood levels were significantly higher than assumed toxic thresholds without the appearance of any toxic clinical effects. Especially sedation and respiratory depression. Further research is needed to explore these mechanisms in more detail.

Guidelines recommend ECT [4] when patients fail to respond or show insufficient response to medication. In this case, the patient continued to respond to lorazepam, and ECT was not available at our institution. While practical considerations should not be the sole basis for treatment decisions, it was more feasible to continue pharmacological therapy in this case. Moreover, the patient is continuing to improve, was able to eat and drink adequately, and his check-ups were not concerning.

Conclusion

To our knowledge, this is the first international published case report detailing the use of extremely high doses of lorazepam in the treatment of catatonia. Our findings suggest that lorazepam can be administered safely at extremely high doses, provided that patients are closely monitored for potential side effects. Particularly central nervous system and respiratory depression, which can lead to hypotension, ataxia, confusion, coma, excessive sedation, muscle weakness, and even death. In patient populations where ECT is not feasible or unavailable, we advocate for considering higher doses of benzodiazepines than currently recommended by guidelines when a patient is not fully responding to typical dosages. We also encourage further research into the mechanisms of action, effectiveness, safety, long-term consequences, and appropriate tapering strategies for benzodiazepine treatment in catatonia. As others have called for [17], we emphasize the need for high-quality studies to refine and improve treatment protocols

Declarations

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Written informed consent was obtained from the patient.

Author Contributions

-*Groen, H.J.:* writing original draft, project administration, conceptualization, data curation, visualization

-*Looman, N.M.G.:* supervision, visualization, writing - review and editing

-*Lettinga, J.R:* supervision and writing - review and editing

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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