

CASE REPORT

Remission of catatonia after intravenous propofol infusion for unrelated reasons

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Abstract

In the aftermath of a cerebrovascular accident, a 66-year-old male patient with a recurrent depressive disorder displayed prolonged stupor, mutism, negativism, immobility, catalepsia and posturing. The abrupt improvement of his symptoms directly after administering oral lorazepam confirmed the diagnosis of catatonia. Subsequent titration of lorazepam reduced the catatonic symptoms, but did not completely resolve them. Propofol infusion given for an unrelated reason led to an abrupt, remarkable and complete remission of the catatonic symptoms. This article contains a case report, description of the possible pathophysiological explanation for the beneficial effect of propofol on catatonia and a review of literature.

Background

Catatonia is a neuropsychiatric syndrome with motoric, psychic, behavioural and autonomic symptoms. It mostly occurs among persons with a psychotic or mood disorder. The DSM-V states that the diagnosis of catatonia requires three of the following symptoms: motoric immobility, excessive motor activity, extreme negativism or mutism, peculiarities of voluntary movement, and echolalia or echopraxia (*table 1*).^[1,2]

Catatonic symptoms can be caused by neurological and psychiatric disorders, intoxications, or withdrawal from alcohol or drugs.^[3,4] Catatonia is unexpectedly common, being found in 10% of psychiatric inpatients, more often in patients with mood disorders than in patients with schizophrenia.^[3] Yet it is often not recognised, even by psychiatrists. Van der Heijden et al. found that 18% of admitted psychiatric patients met the diagnostic criteria while psychiatrists diagnosed only 2% of patients with catatonia correctly.^[5] Untreated catatonia can result in complications such as contractures, decubitus, thrombosis, dehydration, malnutrition and pneumonia.^[6] In case of malignant catatonia, the patient develops

Table 1. Symptoms of catatonia (DSM-5, American Psychiatric Association 2013)

Symptom	Description
Stupor	No psychomotor activity; not actively relating to environment
Catalepsia	Passive induction of a posture held against gravity
Waxy flexibility	Slight and even resistance to positioning by examiner
Mutism	No, or very little, verbal response (not applicable if there is an established aphasia)
Negativism	Opposing or not responding to instructions or external stimuli
Posturing	Spontaneous and active maintenance of posture against gravity
Mannerisms	Odd caricatures of normal actions
Stereotypes	Repetitive, abnormally frequent, non-goal directed movements
Agitation	Not influenced by external stimuli
Grimacing	Odd and inappropriate facial expressions, irrespective of situation
Echolalia	Mimicking another's speech
Echopraxia	Mimicking another's movements

an acute onset of excitement, fever, autonomic instability and delirium which results in high mortality (10-20%).^[7,8] Consequently, unrecognised or untreated catatonia can cause further physical decline and even become lethal.

The first-choice treatment for catatonia is oral administration of lorazepam. Up to 85% of catatonic patients respond to lorazepam, usually within hours.^[8] This response is considered pathognomonic for catatonia. Propofol is a common intravenous sedative in critical care practice. It affects the inhibitory GABA-A receptors, as

benzodiazepines do, albeit at different sites.^[9] There is no consensus on the dosage of lorazepam. Treatment is titrated, usually starting with 1 or 2 mg of lorazepam every four to twelve hours. Titration balances gradual resolution of the catatonic symptoms against the sedative effect of lorazepam.^[10]

When symptoms persist for ten days or longer, catatonia is considered to be chronic, and chronic catatonia is notoriously unresponsive to lorazepam.^[4,11] The vast majority of patients with chronic catatonia, 59% to 100%, respond to electroconvulsive therapy (ECT). However, some patients cannot tolerate ECT due to its side effects.^[12]

The Bush-Francis Catatonia Rating Scale (BFCRS) can be used to identify and quantify catatonia. A BFCRS score of four or more has a sensitivity of 91% and a specificity of 91% for the diagnosis of catatonia.^[13] Research on a cohort of 136 ICU patients using the BFCRS showed that patients had delirium, catatonia, both or neither in 43%, 3%, 31% and 24%, respectively.^[14]

The case we report here suggests that high-dose propofol infusion may be a potent second-line treatment for catatonia after lorazepam titration.

Case

A 66-year-old male patient with a medical history of autism spectrum disorder, alcohol abuse and recurrent depressions suffered an ischaemic cerebrovascular accident (CVA). The aftermath of the CVA was characterised by a residual right-sided hemiparesis. It also caused recurrence of depressive symptoms, for which he was transferred to a clinical psychiatric department. Due to supportive care and treatment with antidepressants (paroxetine 20 mg, mirtazapine 15 mg and lithium carbonate 400 mg) his depressive symptoms diminished. He was open to conversation and participated in group activities. For further rehabilitation he was transferred to a nursing home. There, his psychiatric condition deteriorated. He gradually stopped making contact with the staff and residents, and showed loss of decorum (he was unkempt and walked around the premises in his underwear). He subsequently became mute and restricted his communication to repelling gestures. Eventually he became bedridden, often posturing with a raised leg or head. Only after persistent stimulation was he able to perform simple tasks that staff requested of him in the course of daily care.

Catatonia was suspected and a challenge of 1 mg of lorazepam twice a day resulted in a rapid improvement of symptoms. Sometime later, the patient fell while going to the toilet at night. Although it was debatable whether the fall could be attributed to lorazepam, the morning dose was reduced to 0.5 mg, after which symptoms of mutism and negativism recurred.

Shortly thereafter he inhaled a piece of meat at dinner. Heimlich manoeuvre was unsuccessful and he was rushed to the emergency department where he was intubated and his airways were cleared by

bronchoscopy. He was transferred to the ICU and was infused with 150 mg propofol per hour to prevent self-extubation; the dose was slowly tapered to 80 mg per hour. His Richmond Agitation Sedation Scale (RASS) was RASS-5 (unarousable) and slowly increased to RASS-2 (light sedation). After 14 hours the patient was extubated; he did not receive lorazepam during this period. After extubation the patient developed swelling of the airway and was reintubated. After two days the airway swelling had decreased sufficiently to justify extubation.

Upon awakening, he displayed a surprising and complete remission of his catatonic and depressive symptoms. He himself was amazed by his regained lust for life. Also his family were baffled by his recovery. After having refrained from activities for months, he was again listening to music, watched television and enjoyed discussions. Both the patient and his family described his recovery as a 'complete reset' after months of listlessness.

Outcome and follow-up

Sadly, within days after re-admission to the nursing home his catatonic state recurred, and his physical condition deteriorated. Again he became bedridden and his oral intake was greatly reduced. He was transferred to a clinical psychiatry department where his catatonic symptoms were treated with a total dose of 8 mg of lorazepam daily, unfortunately without a significant effect. He received a nasogastric tube for feeding because he stopped eating and drinking. He also developed pneumonia, for which he was treated with antibiotics. Because treatment with oral lorazepam failed, he was transferred to a psychiatric ward in a hospital to receive bilateral ECT. Sessions of ECT were given three times a week, with etomidate sedation and succinylcholine for muscle relaxation. The patient was treated with 8 mg of lorazepam daily together with his ECTs and gradually his catatonic symptoms improved. He regained the ability to mobilise with assistance, to communicate and eat normally. After two weeks of ECT treatment, the session frequency was reduced to twice a week.

After four weeks of treatment, abnormalities on his electrocardiogram were noticed, and an angioplasty proved to be necessary. ECT had to stop temporarily, after which his catatonic symptoms partially returned. Soon after the angioplasty, bilateral ECT was resumed twice a week. Pharmacologically a switch from paroxetine to nortriptyline was made. After a few weeks his catatonic symptoms diminished again, but he still spent most of his time in bed, made little eye contact and communicated by monosyllabic speech. His ECT protocol was adapted, replacing etomidate with propofol. Gradually he became a bit more active in mobility as well as in his communication. He repeatedly stated that he no longer felt depressed.

Discussion

During his admission to the nursing home the patient was evaluated for delirium. Although he did show symptoms such as altered awareness, a hypokinetic state and change of behaviour, catatonia

was suspected to be the cause. He also showed an abrupt recovery of symptoms after administration of lorazepam, which is pathognomic for catatonia.^[8] Catatonia and delirium show overlapping symptoms; however, antipsychotic drugs which are used as treatment for delirium can worsen catatonia, and benzodiazepines are the first-choice treatment for catatonia and can worsen delirium.^[15]

There is a wide range of potential aetiologies for catatonia such as infections, inflammation, structural pathologies of the brain and systemic toxic metabolic states. Up to 45% of patients with catatonia have a psychiatric medical history, 36% have a central neurological problem, 58% show symptoms of an affective disorder and often patients have a history of substance abuse. Major depressive disorder was the most frequently reported clinical feature (33.7%).^[16] Our case describes a patient who suffered from recurrent depression in the aftermath of a stroke and a history of alcohol abuse. All are possible causes for his catatonic deterioration.

Neuroimaging in patients with catatonia has shown various cases with signs of acute post-hypoxic damage in the frontal and parietal cortex, the encephalon and the hippocampus.^[17] Catatonia is caused by an imbalance in neurotransmitters due to dopamine and GABA hypoactivity and glutamate hyperactivity. Glutamate is also a regulator of catecholamine release and up-regulation of this neurotransmitter can therefore further disrupt the balance.^[18]

Three circuits in the brain are thought to be dysregulated in catatonia, resulting in behaviour with akinesia or hyperkinesia. The first system regulates the inhibition and excitation of movements, the second circuit regulates the motor dynamics and timing, and the third circuit regulates motor organisation and speed. These three circuits are interconnected and tightly regulated by the supplementary motor area (SMA). Hyperactivity in the SMA can result in inhibition of areas of the brain and simultaneously excitation of others, resulting in hypokinetic or hyperkinetic behaviour.^[15]

The right parietal and lateral orbitofrontal pathways are important for the motor and affective symptoms of catatonia. They are inhibited by GABA-A receptors. Insufficient inhibition results in a hyperexcited state which in turn produces behavioural anomalies such as copying of behaviour of other persons.^[19]

Benzodiazepines enhance the effect of GABA on GABA-A receptors, bolstering inhibition. ECT is thought to increase the number of GABA-A receptors and potentiates them, enhancing the effect of lorazepam.^[4,12] These mechanisms presumably explain the suppression of catatonia by benzodiazepines and ECT.

Propofol is commonly used for induction of anaesthesia as well as continuous infusion for sedation of patients on the ICU. It enhances the effect of GABA on GABA-A receptors, bolstering inhibition of the central nervous system. Propofol also inhibits

the excitatory NMDA receptor and the excitatory postsynaptic effects of glutamate. Propofol enhances the inhibitory effect of benzodiazepines on GABA-A receptors but cannot be blocked by a benzodiazepine receptor antagonist, suggesting benzodiazepines and propofol bind to different subunits.^[9]

The nature of supportive ICU care allows much deeper and longer sedation than would be feasible on the psychiatric ward, where the dosing of lorazepam is limited by concerns for respiratory depression and sedation. As a result, far more potent GABA-A enhancement was achieved. We hypothesise that the dose effect may explain the remarkable abrupt improvement after prolonged high-dose propofol with an instant unprecedented recovery from the catatonia resulting from the effect of more potent GABA modulation. This may well be more significant than the application of propofol rather than benzodiazepines.

This hypothesis can explain incomplete resolution of symptoms after initial treatment with lorazepam. In the same way, it can explain the later partial resolution under the various other treatments: lorazepam, etomidate sedation during ECT and propofol sedation during ECT. Procedural sedation such as that used during ECT is far less deep and more brief than deep sedation on the ICU. In these cases the interruption of the regimen due to complications may also have contributed to the less pronounced result.

The natural course of chronic catatonia is still largely unknown. Nakamura et al. describe a two-year follow-up of a patient with chronic catatonia due to a cerebrovascular accident and possible underlying depression. The catatonic symptoms of the patient first deteriorated after discharge and start of outpatient treatment. After treatment with benzodiazepines, he demonstrated psychiatric stability and during the following two years he gradually regained his mobility and required little assistance in his daily activities.^[20] It cannot be excluded that our patient's recovery was spontaneous. However, it cannot be excluded that other mechanisms contributed significantly to the patient's acute recovery. However, the abruptness of his recovery after deep propofol sedation does not match the gradual recovery Nakamura reports and the timing of this acute recovery further suggests a causal relationship with prolonged deep propofol sedation.

An extensive search of the literature could only identify two prior publications of such a beneficial effect of propofol on catatonia. The first case describes a patient with a psychiatric history and a history of leukaemia presenting with catatonic symptoms. She received deep propofol sedation after agonal breathing and respiratory failure, and was intubated for 12 hours. After extubation she showed resolution of the catatonic symptoms. She remained in a state of mild paranoia and shortly after discharge she was readmitted with fever and confusion. The cerebrospinal fluid tested positive for a viral encephalitis, which was possibly the underlying cause of her catatonia. She died shortly afterwards.^[21]

A second case describes a young woman whose catatonic symptoms resolved after procedural sedation with propofol for surgery. The attribution of remission of catatonia to propofol infusion can be questioned here as there is an alternative explanation. In this case, catatonia was attributed to an anti-NMDAR antibody-mediated paraneoplastic limbic encephalitis, secondary to an ovarian tumour which was concomitantly removed during surgery.^[22]

Literature regarding deep propofol sedation for catatonia is sparse. This may be explained by the fact that this treatment is only possible in the controlled ICU environment and that catatonia is seldom recognised in ICUs.^[14] It is, moreover, not the standard of care in patients with catatonia. This case and the two prior publications arguably create grounds for considering deep propofol sedation in selected serious and refractory cases of catatonia. Because these cases are so rare this hypothesis cannot be studied in large clinical trials, but it certainly warrants further medical research in select cases as a form of rescue therapy. We think that this case report is relevant to the intensivist because it offers a basis for evaluation of rescue therapy in patients with catatonia who do not respond to therapy with benzodiazepines and ECT.

In summary, catatonia is a distinct syndrome that, when left untreated, can result in serious and even lethal complications. It is often mistaken for delirium which is highly unfortunate as catatonic symptoms can be aggravated by the treatment given for delirium. Catatonia and delirium require different treatments.

Lorazepam is the standard treatment for catatonia but its applicability is restrained by its sedative effect. Second-line treatment generally consists of ECT.

This case is suggestive of a beneficial effect of administration of prolonged high-dose propofol in addition to lorazepam treatment in catatonic patients. The immediate and complete remission of catatonic symptoms in our case was so evident and remarkable that a causal relationship is more than likely.

Both propofol and lorazepam inhibit the central nervous system by interacting with GABA-A receptors. Their synergy may be explained by the fact that they interact with different parts of the receptor. In addition, propofol inhibits the excitatory effects of the NMDA receptors in the brain, which might further explain the positive effect of propofol on the catatonic symptoms in our case.

Learning points/take home messages

- Catatonia is a common syndrome on psychiatric wards and ICUs, but often unrecognised. It can cause severe, even lethal complications;
- First-choice treatment for catatonia is with lorazepam, followed by ECT in the second line;
- Lorazepam and propofol have similar but distinct inhibitive GABA-A receptor mediated effects on the central nervous system;
- Moreover propofol also binds to the NMDA receptor, possibly

further explaining the added effect of prolonged high-dose propofol;

- Prolonged propofol infusion might be valuable second-line treatment for catatonia;
- Research is warranted but it may prove challenging to collect series of patients;
- Prolonged deep propofol sedation may be considered in highly selected cases as off-label rescue therapy.

Disclosures

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