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Zolpidem and Possible Side Effects on Brain Circulation: A Case Report and Review of Literature

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ABSTRACT

The brain is one of the most sensitive organs to hypoxia and the most vulnerable to ischemia and vascular events. Zolpidem, as a GABA-A receptor agonist, has an inhibiting effect on the central nervous system. In this study, the possible side effects of zolpidem on brain perfusion were reported in a patient with zolpidem addiction. Moreover, the correlated literature has been reviewed. The patient was a 33-year-old man who was referred with a complaint of cognitive impairment, gait disturbance, confusion, and seizure. The patient reported taking the daily dose of 270 mg of zolpidem. He developed acute dystonia, rigidity, and bradykinesia during treatment with haloperidol in the psychiatric ward. Brain MRI and EEG were requested due to the prolongation of cognitive impairment and parkinsonism symptoms. The Neurologist utilized Brain MRA to determine the source of microvascular lesions found in the brain MRI. Unexpectedly, a reduction in Anterior Cerebral Artery (ACA) perfusion was detected after a comprehensive evaluation by Brain MRA. In addition, impairment of several cognitive domains was observed in the follow-up visit. Zolpidem could reduce cerebral perfusion in various vascular territories. It seems that in patients who take zolpidem with higher than therapeutic doses, vascular complications and a decreased cerebral perfusion have occurred, resulting in more neurological complications, including cognitive disorders and vascular events. A holistic investigation of the patient with zolpidem abuse and neurological symptoms would be recommended to determine the probable vascular complication of zolpidem.

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Introduction

The brain is the most sensitive organ to hypoxia and hypotension. The hippocampus and cerebellum in the brain are most at risk for ischemia and vascular events (1, 2). Zolpidem influences the central nervous system by facilitating the function of GABAergic neurons (2). Zolpidem, as an agonist of GABA- A receptors, acting on the chloride channel, induces an inhibitory effect on central nervous system function (3).

However, zolpidem has some advantages over other sedatives and hypnotics, such as reduced drowsiness, forgetfulness, and psychomotor retardation. Nevertheless, taking zolpidem in a higher than therapeutic dosage may lead to side effects such as dizziness, imbalance, hypotension, and behavioral complications, including restlessness and depression (4).

Various studies show that zolpidem can improve brain perfusion in people with brain injuries (5, 6). Claus et al., showed that zolpidem could increase cerebral blood flow in primates due to the interaction between ω1 and ω2, which may be due to the involvement of omega receptors in the brain circulation, but its mechanism of action in

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humans is unclear (5-7). Zolpidem is the agonist of ω1 and to a lesser extent ω2 (8). Receptors ω1 and 2ω react with GABA binding sites and induce chloride influx by GABA-independent reactions (9). GABA increases the permeability of post-synaptic membranes to potassium. Therefore, it increases the threshold potential and acts as an inhibitory neurotransmitter (10).

This article reported the possible side effects of zolpidem on brain perfusion and cognition in a hospitalized patient with a history of zolpidem abuse.

Patient description

A 33-year-old man was referred to Roozbeh Psychiatric Hospital with a complaint of cognitive impairment, balance disorder, and seizure. The patient's insomnia symptoms have been treated with zolpidem for many years before admission. The Zolpidem dosage has been increased two years before admission up to 30 mg per day. During the two years before the visit and after increasing the dose of zolpidem, he had three probable attacks of seizures.

About one year before the visit, he was referred to a psychiatrist due to insomnia and feeling of sadness and was treated with Quetiapine, citalopram, and olanzapine. About four months before the visit, the patient had taken 40 mg of methadone intending to commit suicide and was transferred to the hospital with a loss of consciousness.

Regarding the history of psychiatric disorders in his family, his mother mentioned a history of aggression, and his brother mentioned a history of depression.

The patient was admitted to the psychiatric hospital to manage benzodiazepine (BZD) abuse and was treated with chlordiazepoxide and haloperidol. Chlordiazepoxide was gradually tapered. During admission, a neurological consultation was requested due to dystonia and rigidity probably caused by haloperidol and failure to resolve despite treatment.

Comprehensive laboratory tests were requested for the patient, and the results were summarized in Table 1. Reasonably, Brain MRI and EEG were requested by the Neurologist. Eventually, microvascular lesions in the brain MRI and a decrease in ACA artery perfusion in Brain MRA were detected. The patient was discharged with trazodone and psychotherapy sessions to prevent slipping. In the follow-up visit, he stated that he had started zolpidem abuse again two days after discharge due to insomnia. The patient was prescribed trazodone, gabapentin, and Quetiapine again with more regular follow-up visits. In the follow-up assessment and cognitive evaluation, cognitive decline in the domains of memory and attention were detected in the MOCA battery.

Table 1. Summary of the patient's results.

Laboratory test	Patients result	Normative data
T3	4.7 pmol/L	3.1 - 6.8 pmol/L
T4	18 pmol/L	12 - 22 pmol/L
TSH	2.3 µ units/mL	0.5 – 6.0 µ units/mL
CBC		
WBC	6.2 × 103/mm3	4.3-10.8 × 103/mm3
• Hb	14.2 gm/dL	13 – 18 gm/dL
• PLT	250,000/mL	150,000 – 350,000/mL
ANA	Negative	>1/40: positive
RF	Negative	Normal : less than 1:80
Anti-ds-DNA	Negative	Negative : < 10 IU/mL
B12	460 pg/ml	180 – 1000 pg/ml
Homocysteine	11 µmol/L	4-14 µmol/L
Folate	7 ng/ml	>4.0 ng/ml
Urine analysis	Normal	-
Urine-Toxicology: Morphine	Negative	-
Amphetamine Methamphetamine	Negative	-
	Negative	-

Literature review

Numerous complications have been associated with zolpidem abuse. In a review of the clinical trials, CNS-related adverse effects included lightheadedness or dizziness (5.2%), somnolence (5.2%), headache (3.0%), fatigue (2.4%), memory deficits (1.8%), nightmares (1.6%), confusion (1.6%), and depression (1.2%)(11) Adverse drug reaction categories could include, bizarre sleep-related behaviors, Parasomnias, Amnesia, Hallucination, and Suicidality (12).

However, taking zolpidem in high doses can lead to disorders such as meningitis, headache, imbalance, hypotension, and muscle cramps (8,13). In addition, in long-term use, hallucinations and delusions may occur. For instance, Manfredi G. et al. have been described, a 32-year-old man, who presented with feelings of agitation, insomnia, and depressed mood and had taken zolpidem 5 times a day (14). There is also a risk of mania in low-dose drug addiction. Sabe et al., have demonstrated that 89.4% of cases were euphoric, and 15.7% had drug-induced mania with delusions. Seventy-five percent of cases suffering from depression consumed zolpidem for more than 1 year, with significantly more increased daily doses than in non-depressed cases (15). Kinnan et al., have reported a 27-year-old man with mania due to zolpidem use with a history of schizoaffective disorder (16).

Discussion

Various studies have been performed on the effects of zolpidem on cerebral perfusion. Clauss et al., (2004) utilized the brain SPECT in four patients with the use of zolpidem at a dose of 10 mg and demonstrated increased cerebral blood flow in these patients (17). Sutton et al., concluded that zolpidem might play a role in the relative improvement of neural activity in parts of the brain that were irreversibly destroyed due to brain infarction (18). Clauss et al., Showed that Zolpidem could improve a wide range of brain damage by increasing cerebral perfusion based on evidence from the 99MTc HMPAO Brain SPECT (18). Bomalaski et al., have demonstrated that zolpidem could improve many types of neurological disorders, especially movement disorders, and increase consciousness after traumatic brain injury (13).

In contrast, some studies showed that zolpidem could reduce cerebral perfusion (19). Mattila et al., found that Zolpidem reduced perfusion in the visual cortex of the brain and has a role in reducing the level of consciousness in the patients (20). The results of another study conducted by Licata et al. showed a significant effect of zolpidem on reducing perfusion and blood oxygen levels in the visual cortex of the brain (21).

Conclusion

In conclusion, caution is warranted by physicians and healthcare professionals when prescribing zolpidem to ensure patients are adequately informed about potential neuropsychiatric adverse events. The latest FDA recommendations for lowering zolpidem doses should be adopted by all countries. Zolpidem prescriptions should be contraindicated for populations with identified risk factors. The vascular complications of zolpidem abuse should be considered in patients who use zolpidem in a higher dose than the standard therapeutic prescription. Also, the cognitive domains and comprehensive neuroimaging assessment would be emphasized in patients with a history of zolpidem abuse and unreasonable neurological symptoms.

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