

CASE REPORT

NON-BENZODIAZEPINE HYPNOTIC DEPENDENCE: A CASE REPORT

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Abstract

Objective: This case report highlights the abuse and dependence potential of Zolpidem and the risk of life-threatening withdrawal symptoms upon abrupt discontinuation. **Method:** We report a case of Zolpidem dependence which presented with withdrawal symptoms upon abrupt discontinuation. **Results:** A 32 year old male, who had abused non-benzodiazepine Zolpidem for 6 years presented to the accident and emergency unit with generalized seizures upon stopping Zolpidem ‘cold turkey’. He required admission to the neurology high dependency unit for stabilization of the seizures and was later managed by the addiction team where a tapering dose of benzodiazepine was prescribed. **Conclusion:** This case demonstrates that non-benzodiazepine agents can cause tolerance and dependence, and thus produce withdrawal symptoms upon discontinuation. *ASEAN Journal of Psychiatry, Vol.11(1): Jan – June 2010: XX XX.*

Keywords: Zolpidem, abuse, dependence, addiction, withdrawal, intoxication

Introduction

Insomnia affects millions of individuals [1]. The prevalence of insomnia is reported to vary between 5-50 % depending on definition (i.e. insomnia symptoms, with or without daytime consequences, dissatisfaction with sleep, and insomnia syndrome) [2]. People who have trouble sleeping often complain of tiredness, mood disturbances and even intellectual disturbances and often seek medication to overcome their problem. Occasionally, these

medications were consumed beyond their intended use [3, 4].

The medications used to treat sleep medication include benzodiazepine group and non-benzodiazepine group. The benzodiazepines commonly used to treat sleep disorders are lorazepam, clonazepam and diazepam, whereas the non-benzodiazepine group include Zolpidem and zopiclone [1]. In the last decade, the use of benzodiazepine as treatment for insomnia has come into disrepute as concerns were

raised regarding its abuse potential. The benzodiazepines were implicated for their abuse ability, resulting in the invention of non benzodiazepine hypnotics which were claimed to have no dependence properties. Hence non-benzodiazepines such as short-acting imidazopyridine hypnotics, e.g., Zolpidem which was touted to have low or minimal abuse or dependence potential were recommended for treatment of insomnia [3, 4].

Zolpidem is a rapid onset short-acting hypnotic with half-life of 1-2 hours. It has similar effects to benzodiazepines such as anxiolytic, sedative, anti-convulsant and myorelaxing effects [1]. It produces a more physiological sleep pattern (reduction in sleep latency and in number of awakenings, and an increase in total hours of sleep) with less next day amnesia. Zolpidem is a prescription item and the recommended dose is 5-10 mg per day [3, 5].

Zolpidem was initially considered by physicians as almost devoid of abuse and dependence potential. Several recent publications, however, have suggested that this drug carry a significant risk of abuse [3, 6]. Although Zolpidem dependence has been reported in the literature in the United Kingdom, Italy and India, to our knowledge there has not been any reported case of Zolpidem dependence in Malaysia [7-9]. This article reports a case of Zolpidem dependence which presented as generalized seizures upon abrupt discontinuation.

Case Report

A 32 year old male presented to the accident and emergency unit with seizures. He developed generalized tonic clonic jerky movements with uprolling of the eyeballs and drooling of the saliva. He was previously well and had no fever or headache, nausea or vomiting or blurring of

vision. He did not have history of epilepsy or other medical illnesses such as hypertension or diabetes. He also did not have any history of psychiatric illness or substance abuse. Physical examination revealed no abnormalities. Blood investigations (full blood picture, renal profile and liver function test) were normal. CT scan of the brain was normal.

On further questioning, he revealed taking sleeping pills for the past 6 years. It all started at college where he initially started taking zopiclone for insomnia. However he changed to Zolpidem 3 years ago as he had faced difficulty in obtaining zopiclone in Malaysia. At the beginning, he took 10 to 20 mg Zolpidem per day but for the last 1 year he had increasing difficulty in sleep and consumed Zolpidem up to 90mg per night. He had attempted to abstain from Zolpidem but the attempts failed as he developed anxiety, agitation, became easily irritable, had poor concentration at work and developed rebound insomnia. He also reported increased in appetite and had gained 10kg in 2 years. There was no history of sleepwalking or being involved in any accidents before. On the day before the admission, he attempted to stop this dependence and go cold turkey. He stopped taking Zolpidem in the morning, but by mid-evening he became restless, anxious and had poor concentration. The seizures developed in the next morning.

The patient was subsequently admitted to the neurology high dependency unit for observation for 2 days. He was given midazolam infusion 1mg/ml and intravenous phenytoin 100 mg 8 hourly. The seizures stopped and the intravenous medications were discontinued and changed to oral sodium valproate 200mg twice/daily. He was then referred to the addiction team. A review of his mental status revealed an anxious individual who was preoccupied

with his medication use. He was started on dose-tapering diazepam. He responded well; reported ability to sleep well, had no anxiety symptoms and did not develop any withdrawal symptoms. At 1 week follow up, he reported to be free from diazepam. An EEG done at outpatient clinic was normal.

Discussion

This case illustrates the problem of Zolpidem dependence in a man who consumed up to 90 mg of Zolpidem and presented with grand mal seizures upon discontinuing use. To our knowledge, thus far, the literature has not reported any such cases from Malaysia. Our patient developed withdrawal seizures about 24 hours after stopping the drug. Zolpidem withdrawal is probably the cause of the seizure as there was no other explanation of the seizure. He was well previously and did not have any history of seizure and blood investigations and CT Scan of the brain was normal.

Zolpidem, a non-benzodiazepine short-acting hypnotic is an imidazopyridine derivative and has selective affinity for the benzodiazepine receptor type-1 [1]. Initial reports said that it had lower potential for abuse than benzodiazepines [10]. However evidence from recent clinical and animal studies have showed that Zolpidem's potential for dependence should not be underestimated. Concerns have been raised regarding the routine use of Zolpidem as it may lead to dependence and abuse. The abuse potential of Zolpidem was noted to be similar to Triazolam, a benzodiazepine and animal studies had shown that the drug had higher reinforcing properties than benzodiazepine.

Contrary to initial reports, tolerance and dependence can develop with Zolpidem [1]. Thus discontinuation of the drug will induce withdrawal symptoms such as anxiety,

tremor, myoclonic jerks, disorientation, confusion and generalized seizures [8]. In this patient, he had stopped the medication abruptly and subsequently developed life-threatening generalized seizures. However compared to a similar case in Italy where the patient was on Zolpidem 600 mg, our patient was only taking 90 mg of Zolpidem. This case is thus an important reminder that the non-benzodiazepine group has abuse and dependence potential and that abrupt cessation (even at a dose of 90mg) as opposed to tapering may lead to withdrawal seizures.

In a review of cases of Zolpidem abuse and dependence it was found that majority of cases were reported in former drug and alcohol abusers and/or patients with psychiatric disorders. However our patient had no history of psychiatric illness and neither history of other substance abuse. The literature also reports more cases of Zolpidem dependence compared to zopiclone dependence. This may however be dependent on availability of the drug [11]. It was interesting however that Zolpidem dependence occurred in all ages and was not gender dependence [6, 12]. In extreme cases, doses of between 30-120 times the recommended dose have been reported. Our patient however was on 90 mg daily (about 9 times the recommended dose).

In this case report, we would also like to highlight the danger of stopping Zolpidem 'cold turkey'. Our patient developed life-threatening seizures which required further management in a high-dependency unit. Similar complications were also described in the literature upon sudden discontinuation of Zolpidem [13, 14]. Other complications reported include delirium, psychomotor agitation, flushing and anxiety [15]. To avoid such complications, people dependent on Zolpidem need to be prescribed a tapering dose of long acting benzodiazepine

[9]. One possible explanation for the withdrawal seizure is that at supratherapeutic doses, Zolpidem may act non-selectively on omega 2 receptors of GABAA just like benzodiazepines and result in withdrawal seizures [16].

This article thus highlights the abuse and dependence potential of Zolpidem and the danger of sudden cessation of Zolpidem. We would like to suggest that its usage should be monitored as per use of benzodiazepines. Although Zolpidem and its group of non-benzodiazepine have been touted to have minimal abuse liability, doctors need to be aware that it has dependence potential and be vigilant of its abuse ability.

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