

ZOLPIDEM DEPENDENCE AND WITHDRAWAL SEIZURE - Report of two cases

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SUMMARY

Zolpidem is a non-benzodiazepine property which binds selectively to the α_1 -GABA_A receptors, and has been widely prescribed to patients suffering from insomnia. We report two cases of zolpidem dependence with withdrawal seizure in the Asian population. The first case is a 43-year-old woman who took zolpidem up to the dosage of 200 to 400 mg per night. The second case is a 35-year-old woman who even began to take zolpidem every 15 to 30 minutes to get euphoric and relaxed, and she gradually increased the dosage to 400 to 500mg per day. After abrupt discontinuation of zolpidem, both cases immediately developed anxiety, global insomnia, restlessness, and tonic seizure. The purpose of this case report is to suggest that clinicians should pay close attention to the potential of zolpidem tolerance, abuse and dependence. The possibility of withdrawal seizure cannot be excluded especially at high doses.

Key words: zolpidem - dependence - withdrawal - seizure

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INTRODUCTION

Zolpidem, an imidazopyridine derivative agent, has been shown with rapid onset and ability to effectively prolong sleep duration (Langtry & Benfield 1990). Zolpidem displays a high affinity to α_1 -GABA_A receptor in in-vitro studies and minor anxiolytic, myo-relaxant and anti-convulsant effects (Visser et al. 2003). It was considered a safer hypnotic than benzodiazepines because of a lesser liability for abuse and dependence (Holm & Goa 2000).

Nevertheless, a growing body of cases reports of zolpidem abuse or dependence (Sakkas et al. 1999, Monti et al. 1996, Krueger et al. 2005), as well as epileptic-seizure related to zolpidem withdrawal (Aragona 2000, Cubala & Landowski 2007, Tripodianakis et al. 2003) have been discussed in Western countries (Victorri-Vigneau et al. 2007). For the Asian population, a case of zolpidem dependence has also been demonstrated (Huang et al. 2007); however, patients with zolpidem withdrawal seizure have not been reported yet. So far, there is no literature investigating ethnic variation for the liability of zolpidem dependence. Zolpidem has been widely prescribed in recent years for patients with insomnia in Taiwan by psychiatrists, other specialists and primary care physicians. Therefore its safety and dependence potential are of great concern.

CASE REPORTS

Here we report two cases of seizure clearly related to dependence and withdrawal of zolpidem after long-term use in high dosage in Taiwan.

Case 1.

A 43-year-old woman suffering from dysthymic disorder had been taking hypnotics for insomnia for more than 20 years. Two years ago she began to take zolpidem alone without mixing other kinds of hypnotics, and 50 to 60 mg of zolpidem used to be initially effective in treating her insomnia. Unfortunately, as tolerance and psychological dependence developed gradually, she had to go to several doctors to get prescriptions for 200-400 mg that she needed per night. At the end she had to discontinue zolpidem abruptly because she could not afford it anymore. Anxious mood, global insomnia and restlessness were noted since that evening. She suddenly showed facial spasm, mouth opening, tonic seizure, and loss of consciousness for about 5 minutes early next morning. Post-ictal confusion with clouded consciousness, psycho-motor retardation, regressed attitude and behavior, and disorientation to time persisted in the subsequent 5 days. Then similar tonic seizure attacks occurred twice on the seventh day after drug discontinuation. She was therefore brought to hospital and admitted to the neurology ward. EEG revealed intermittent, generalized, diffuse theta wave and diffused cortical dysfunction. After a series of laboratory tests and other examinations, no other etiologies than zolpidem withdrawal could be identified. Lorazepam 2mg and alprazolam 0.5 mg were prescribed to her. She had no further seizure attacks and her post-ictal confusion resolved gradually seven days after admission.

Case 2.

A 35-year-old woman suffering from major depressive disorder had been abusing hypnotics and oral analgesics prescribed by different doctors for more than 10 years. She began to take zolpidem one year ago with an initial dose of 10 to 20mg. She increased the dosage gradually up to 400 to 500mg per day and even began to take it every 15 to 30 minutes to get euphoric and relaxed. During the same period of time, no other substance use was reported except for some over-the-counter cold syrup for headache. One day she decided to discontinue zolpidem and rapidly developed withdrawal symptoms including insomnia, anxiety, palpitation, and dyspnea hours later. On the next day, she showed disturbance of consciousness, facial spasm, mouth opening, tongue protrusion and limb convulsions for about 3 minutes. She was brought to hospital for help. At the emergency department, EEG performed revealed spikes of epileptic discharge and grand mal seizure was diagnosed. She was hospitalized and clonazepam was prescribed to her. She then showed no further seizures attacks during admission.

DISCUSSION

A number of double-blind randomized studies demonstrated that sudden discontinuation of zolpidem treatment after 2 to 4 weeks was not associated with withdrawal symptoms, but the dosage in these controlled studies were within the normal recommended range (Holm & Goa 2000, Vartzopoulos et al. 2000) Literature review and our cases suggest that the withdrawal symptoms including insomnia, anxiety and epileptic attack were noted soon after abrupt discontinuation of zolpidem in the real world.

Benzodiazepines show non-selective affinity to all the GABA-A receptors, which include α_1 , α_2 , α_3 , α_4 , and α_5 subunits receptors. The α_1 receptors were considered selectively involved in sleeping mechanisms; α_2 receptors contribute to anxiolytic action; and α_5 receptors are associated with cognition and memory (McKernan et al. 2000). In the traditional view of pharmacological mechanism, zolpidem displays high affinity to α_1 -GABA_A receptors, and it was considered the key mechanism of zolpidem's pure hypnotic effect (Visser et al. 2003). Nevertheless, zolpidem shows physiologic and psychological reinforcing effects and abuse potential similar to those of benzodiazepines (Toner et al. 2000). Our report also suggests that zolpidem might exhibit similar pharmacologic effects to benzodiazepines and lose its selectivity on α_1 -GABA_A receptors, particularly at high doses and long-term use.

There are some assumptions about the variables associated with the adverse effects of zolpidem use. Gender is one of the susceptibility factors associated with adverse effects of zolpidem. Women had been found to have a significantly higher serum zolpidem concentration than men at equivalent dosage (Cubala et

al. 2008). In addition, zolpidem is metabolized by the hepatic enzyme cytochrome P450 3A4, and the degree to which its isoenzyme could be inhibited by concomitant psychotropic agents (Holm & Goa 2000). Hence, the protein binding affinity of zolpidem makes it higher in free form among patients with concomitant medication use and hepatic impairment (Cubala & Landowski 2007). This might have contributed to toxicity and increase the risk of withdrawal seizure attack. Ethnic differences have been demonstrated with the drug metabolizing enzymes, CYP2C9, 2C19, and 2D6 (Anthony & Berg 2002). However, it is still uncertain whether the ethnic differences exist in the properties of pharmacokinetics and pharmacodynamics, and pharmacogenetics for zolpidem.

CONCLUSIONS

Our cases suggested that the potential of zolpidem dependence and withdrawal seizure are also present in the Asian population. The female-gender, high dosage and long-term use of zolpidem might be risk factors for development of adverse effects. It warrants further investigation whether there is ethnic variation for the liability of zolpidem dependence. Nevertheless, worldwide clinicians should pay attention to the risk of withdrawal seizure related to this agent, especially at high doses.

REFERENCES

1. Anthony M & Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part ii. *J Womens Health Gend Based Med* 2002; 11: 617-629.
2. Aragona M. Abuse, dependence, and epileptic seizures after zolpidem withdrawal: Review and case report. *Clin Neuropharmacol* 2000; 23: 281-283.
3. Cubala WJ & Landowski J. Seizure following sudden zolpidem withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 539-540.
4. Cubala WJ, Landowski J & Wichowicz HM. Zolpidem abuse, dependence and withdrawal syndrome: Sex as susceptibility factor for adverse effects. *Br J Clin Pharmacol* 2008; 65: 444-445.
5. Holm KJ & Goa KL. Zolpidem: An update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; 59: 865-889.
6. Huang MC, Lin HY & Chen CH. Dependence on zolpidem. *Psychiatry Clin Neurosci* 2007; 61: 207-208.
7. Krueger TH, Kropp S & Huber TJ. High-dose zolpidem dependence in a patient with chronic facial pain. *Ann Pharmacother* 2005; 39: 773-774.
8. Langtry HD & Benfield P. Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; 40: 291-313.
9. McKernan RM, Rosahl TW, Reynolds DS, Sur C, Wafford KA, Atack JR, Farrar S, Myers J, Cook G, Ferris P, Garrett L, Bristow L, Marshall G, Macaulay A, Brown N, Howell O, Moore KW, Carling RW, Street LJ, Castro JL,

- Ragan CI, Dawson GR & Whiting PJ. Sedative but not anxiolytic properties of benzodiazepines are mediated by the gaba(a) receptor alpha1 subtype. *Nat Neurosci* 2000; 3: 587-592.
10. Monti JM, Monti D, Estevez F & Giusti M. Sleep in patients with chronic primary insomnia during long-term zolpidem administration and after its withdrawal. *Int Clin Psychopharmacol* 1996; 11: 255-263.
 11. Sakkas P, Psarros C, Masdrakis V, Liappas J & Christodoulou GN. Dependence on zolpidem: A case report. *Eur Psychiatry* 1999; 14: 358-359.
 12. Toner LC, Tsambiras BM, Catalano G, Catalano MC & Cooper DS. Central nervous system side effects associated with zolpidem treatment. *Clin Neuropharmacol* 2000; 23: 54-58.
 13. Tripodianakis J, Potagas C, Papageorgiou P, Lazaridou M & Matikas N. Zolpidem-related epileptic seizures: A case report. *Eur Psychiatry* 2003; 18: 140-141.
 14. Vartzopoulos D, Bozikas V, Phocas C, Karavatos A & Kaprinis G. Dependence on zolpidem in high dose. *Int Clin Psychopharmacol* 2000; 15: 181-182.
 15. Victorri-Vigneau C, Dailly E, Veyrac G & Jolliet P. Evidence of zolpidem abuse and dependence: Results of the french centre for evaluation and information on pharmacodependence (ceip) network survey. *Br J Clin Pharmacol* 2007; 64: 198-209.
 16. Visser SA, Wolters FL, van der Graaf PH, Peletier LA & Danhof M. Dose-dependent eeg effects of zolpidem provide evidence for gaba(a) receptor subtype selectivity in vivo. *J Pharmacol Exp Ther* 2003; 304: 1251-1257.

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