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SIBUTRAMINE-ASSOCIATED PSYCHOTIC SYMPTOMS AND ZOLPIDEM-INDUCED COMPLEX BEHAVIOURS: IMPLICATIONS FOR PATIENT SAFETY

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SUMMARY

Background: *Sibutramine is a weight loss agent recently withdrawn from the European market due to cardiovascular risk concerns. It was used for long–term obesity treatment. Zolpidem is a short acting hypnotic agent commonly used in the treatment of insomnia. A number of case reports describing psychotic reaction to sibutramine were reported in the literature.*

Case report: *We present a case of a 61–year–old Caucasian woman who developed two psychotic episodes related to sibutramine treatment. The second psychotic episode was complicated with complex behaviours after zolpidem use due to insomnia. Sibutramine and zolpidem discontinuation resulted in rapid resolution of psychotic symptoms.*

Conclusions: *This case suggests a possibility of incidence of psychotic symptoms and complex behaviour disturbances in patients prescribed sibutramine or other monoaminergic reuptake inhibitors.*

Key words: *sibutramine – zolpidem - adverse drug reaction*

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INTRODUCTION

Sibutramine is an appetite suppressant with a central serotonin, norepinephrine and dopamine reuptake inhibition mode of action. It was originally developed for the treatment of depression (Sharma & Henderson 2008) but failed to show significant antidepressant efficacy. It was approved for a long term use in the management of obesity in 1997. However, due to the increased cardiovascular risk, sibutramine was withdrawn from use within the European Union and in the United States (EMA 2010). A number of case reports suggested psychotic reaction as an adverse effect of sibutramine (Tafliński & Chojnacka 2000, Lee et al. 2008, Müller et al. 2010, Dogangun et al. 2008).

Zolpidem is a short acting non-benzodiazepine hypnotic drug. It is commonly used for short-term treatment of insomnia. It selectively acts on the GABA-A receptor complex binding preferentially to its alpha-1 subunit. Zolpidem differs from typical benzodiazepines in that it does not have any anxiolytic, anticonvulsive or muscle–relaxant properties. It is commonly used for short-term treatment of insomnia. Few cases of consciousness and complex behaviour disturbances after zolpidem use have been reported so far (Najjar 2007, Yun & Ji 2010, Hoque & Chesson 2009).

The incidental use of both drugs could be an example of time-related incidence of adverse drug reactions (ADRs) associated with both drugs or each drug might induce an adverse reaction independently. We present a case of a patient who developed ADRs differing in symptomatology due to the use of sibutramine and subsequently zolpidem.

CASE REPORT

A 61-year-old Caucasian woman experienced two psychotic episodes with auditory hallucinations accompanied by delusions after long–term use of sibutramine. She had a negative history of psychiatric treatment, neurologic disturbances or substance abuse. Psychotic symptoms developed after 3 months of successful and well-tolerated obesity treatment with sibutramine 15mg/day. At that time she started experiencing auditory hallucinations and subsequently, developed persecutory delusions and depressed mood. After 3 weeks she underwent psychiatric consultation and sibutramine was discontinued. She received risperidone 1 mg/day and fluvoxamine 50mg/day. All symptoms resolved over the course of 1 week.

In a short time the patient started taking sibutramine again and after 7 months of sibutramine treatment (15mg/day) she again developed psychotic episode. The psychiatrist recommended sibutramine discontinuation and prescribed risperidone 1mg/day. On the next day the auditory hallucinations were still present and she suffered from insomnia. Zolpidem 10 mg/day was recommended. During the next two nights after taking zolpidem she developed complex behaviours with amnesia. The patient was disorientated in time and place and preoccupied with undirected, chaotic motor activity. Next day she did not remember her night behaviour. As the auditory hallucinations were still present on fourth day, the patient was referred to the psychiatric inpatient ward.

On admission she presented auditory hallucinations and denied delusions with clear consciousness. Mode-

rate anxiety, lower mood and sleep disturbances were still present. The patient was prescribed the anti-psychotic agent perazine up to 400mg/day. Due to rapid resolution of psychotic symptoms perazine was tapered off in a week time. The results of laboratory tests, brain CT, ECG, and EEG revealed no abnormalities. The patient was discharged from the ward and across the follow-up period of two years remained symptom-free.

DISCUSSION

Sibutramine exhibits both serotonin and norepinephrine reuptake inhibition properties as well as a significant dopamine re-uptake inhibition. It has structural similarities to amphetamines. There are few reports of psychotic reaction as ADRs to sibutramine (Tafliński & Chojnacka 2000, Lee et al. 2008, Müller et al. 2010, Dogangun et al. 2008). Zolpidem is a short acting hypnotic agent used for treatment of insomnia. It was suggested that zolpidem usage is associated with higher risk of complex behaviours with amnesia due to its affinity to α1-subunit of GABA-A receptor (Najjar 2007, Yun & Ji 2010, Hoque & Chesson 2009, Cubała et al. 2008, Dolder & Nelson 2008).

The patient experienced acute psychotic episodes after 3 and 7 months of sibutramine therapy. Drug discontinuation along with antipsychotic medication with risperidone and second time with perazine, a moderate-potency typical antipsychotic of the phenol-thiazine class. Its use is limited to Germany, Poland, the former Yugoslavia and the Netherlands (Leucht and Hartung 2006). Treatment with perazine resulted in complete remission of symptoms. The mechanism of sibutramine-associated hallucinations and delusions remains unknown. We hypothesize psychotic episodes were induced with sibutramine due to its serotonergic, norepinergic and also dopaminergic properties. Contradictory to initial findings focusing on serotonin and norepinephrine the mechanism of action of sibutramine animal studies indicate that sibutramine has at least as great an effect on brain extracellular dopamine levels as on brain serotonin. This effect appears to be dose related. Reuptake inhibition of neurotransmitters could have led to increased serotonin, norepinephrine and dopamine neurotransmission and consequently appearance of psychotic symptoms.

The incidence of complex behaviours with amnesia after taking zolpidem was probably related to the spectrum of zolpidem ADRs but also might have been associated with the concurrent use of sibutramine.

Complex behaviours with amnesia appeared twice after taking zolpidem - 36 hours and 58 hours after discontinuation of sibutramine. Acute withdrawal from sibutramine may have resulted in sleep deprivation manifested as a complaint of insomnia. It is well established that after sleep deprivation there is a period of rebound sleep often resulting in increased deep sleep (slow-wave sleep). Increased deep sleep has been reported to be associated with the occurrence of sleepwalking and similar disorders unrelated to sedative hypnotics (Dijk 2010). However, rebound sleep is not thought to be required for the occurrence of zolpidem related complex behaviours. Even in the absence of sleep deprivation complex behaviours may occur, especially in the first days after treatment with zolpidem is initiated. Thus, sibutramine and sibutramine associated insomnia was not a necessary requirement for the complex behaviours although it could have casual relationship to symptoms exacerbation.

A possible pharmacological interaction between these two compounds which may have led to the appearance or exacerbation of complex behaviours should also be discussed.

As zolpidem was administered first time 36 hours after discontinuation of sibutramine it is important to address sibutramine and its metabolites pharmacokinetics. Sibutramine exerts its pharmacological actions predominantly via secondary (M1) and primary (M2) amine metabolites that inhibit the reuptake of neurotransmitters with significantly lower potency than the parent compound sibutramine. The elimination half-life of each metabolite is about 14 to 19 with complete elimination of sibutramine and its metabolites after approximately 96 hours. This may correspond, although to lesser extent, to the prolonged pharmacodynamic action of metabolites of sibutramine. There is no obvious pharmacokinetic mechanism responsible for this interaction, as both sibutramine and zolpidem are mainly metabolized by CYP3A4 isoenzyme and none of them is a strong inducer of any CYP 450 izoenzymes. A pharmacodynamic interaction mechanism could be possible based on the fact that sibutramine and its metabolites (which were still present at the time of zolpidem administration) as well as zolpidem are highly protein bound and could interact through competitive binding. This could lead to an increase of zolpidem serum level and incidence of complex behaviours.

To our knowledge this is the first case of possible drug interaction of sibutramine and zolpidem. Similar pharmacodynamic interaction mechanism has been suggested in context of paroxetine (which is also highly protein bound) and zolpidem (Katz 1995).

Sibutramine withdrawal could also lead to periodic dopaminergic dysfunction which is also suggested as a mechanism of complex behaviours with amnesia. Additionally a number of risk factors for complex behaviours with amnesia occurred, e.g. female gender, mood disorder, psychoactive drug, eating disorder.

The temporal relationship between the incidence of psychotic symptoms and sibutramine treatment as well as the remission after drug discontinuation support a causal relationship of psychotic ADR as related to sibutramine. Also complex behaviours with amnesia appeared in ‘challenge-rechallenge’ mode with the use of zolpidem.

CONCLUSION

This case report demonstrates the potential risks of the pharmacological treatment with an antiobesity agent with monoaminergic proprieties and additional risk of polypharmacotherapy with a commonly used hypnotic. To our best knowledge there is no literature suggesting the risk of interaction between zolpidem and sibutramine. Prescribing hypnotics and other drugs affecting monoaminergic transmission together should be considered with caution.

Although sibutramine was withdrawn from market use in 2010 it is still present in some countries as a dietary supplement distributed on a black market. Thus, specific vigilance for sibutramine associated ADRs is still of prime importance particularly in association with z-drugs which are being commonly prescribed and misused.

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