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Zolpidem-Induced Psychosis

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Zolpidem is reported to be a safe and effective hypnotic agent for the short-term treatment of insomnia. There are several case reports of zolpidem causing psychotic reactions in patients with no history of psychosis. We report two additional cases in which zolpidem was implicated in psychotic reactions characterized by auditory and visual hallucinations as well as delusional thinking. Both patients' symptoms resolved with the discontinuation of zolpidem use. It appears that our cases share several features in common with the other reported cases. All were female, there appeared to be some dose dependency involved, and the adverse event resolved fairly quickly upon zolpidem discontinuation. Zolpidem should be used at the lowest effective dose for the least amount of time as necessary. Female patients may possibly require smaller doses. In patients manifesting new-onset or unexplained psychotic symptoms, zolpidem use should be considered in the differential diagnosis.

KEY WORDS: Zolpidem; psychosis; hypnotic; adverse reaction.

INTRODUCTION

Zolpidem (Ambien) is a potent hypnotic agent of the imidazopyridine class with minor anxiolytic, myorelaxant, and anticonvulsant properties (1). A nonbenzodiazepine, zolpidem has been available in Europe since 1987 and was introduced into the United States in April of 1992. As with most newly introduced psychotropic medications, reports are accumulating describing adverse reactions in patients. Significantly, there have been five reports to date describing psychotic reactions (2–4), sensory distortions (5), and sleepwalking (6) associated with zolpidem use. Current product literature describes confusion as a "frequent" side effect (1/100), hallucinations and emotional lability as "infrequent" (1/100–1/1000), and abnormal thinking as "rare" (Ambien package insert; Searle, 1995).

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We report two additional cases of apparent zolpidem-induced psychotic reactions in patients with no previous history of psychotic symptoms.

CASE REPORTS

Case 1. A 30-year-old, white female outpatient with a 7-year history of bulimia nervosa and 2-year history of major depression had been treated with paroxetine, 20 mg/day for 6 months, with some remission of symptoms. There was no history of psychosis or substance abuse. Additionally, chronic complaints of insomnia had led to treatment with trazodone, 50 mg at bedtime as needed. The patient reported that this medication was only marginally effective and left her feeling "hungover" in the morning. Consequently, zolpidem, 10 mg at bedtime, was prescribed on a "prn" basis. For the first 11 doses, the patient broke the tablets in half and used only 5 mg, with good results. However, she eventually decided to increase the dose to 10 mg for a "good night's rest." Approximately 20 min after taking the first 10-mg dose, the patient began to experience visual hallucinations of shadows and moving plants,

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and she pointed to unseen objects on the floor. Further, she expressed feelings that there were many people in the room watching her, when in fact, only the patient and her husband were present. The patient became terrified and tearful. This episode lasted approximately 10 min after which the patient fell asleep. The following morning the patient had only vague memories of the incident. Zolpidem was discontinued and there have been no further episodes.

Case 2. A 36-year-old white female was admitted to our inpatient unit with a 12-year history of anorexia nervosa in remission, possible major depressive episode, and obsessive-compulsive traits. There was no history of psychosis or substance abuse. Medications on admission included fluoxetine, 40 mg daily; conjugated estrogen, 0.625 mg daily; medroxyprogesterone, 5 mg daily on days 16 through 25 of the month, and zolpidem, 20 mg at bedtime.

The patient, employed as a nurse, was admitted after reporting new onset of hearing "background noise," auditory hallucinations, paranoia, and feelings of losing control. Psychosocial stressors included increasing difficulties at work and marital discord. On the day of admission, the patient appeared disorganized and confused and reported auditory hallucinations. Mental status examination revealed a tearful, distressed patient with psychomotor agitation, speech latency, and possible thought blocking, paranoid delusions, and auditory hallucinations. Mood was depressed. Physical exam and laboratory findings were unremarkable. Urine drug screen was negative. The patient had begun treatment for middle-of-the-night awakening with zolpidem approximately 2 months prior to admission. The dose was initially 10 mg at bedtime but had been gradually increased to 20 mg at bedtime prior to admission because of lack of response. She had been using fluoxetine, 40 mg daily, for over 6 months.

An adverse reaction to the 20-mg zolpidem dose was initially suspected, so the dose was decreased to 10 mg at bedtime. However, the patient refused both fluoxetine and zolpidem, believing them to be implicated in her current difficulties. She was persuaded to take haloperidol, 2 mg at bedtime, and to resume fluoxetine, 40 mg daily. The patient was much improved the following day and was discharged 1 day later, appearing more organized, with greater speech fluency, brighter affect, and no auditory hallucinations. No further psychotic symptoms have appeared since the discontinuation of zolpidem and the subsequent discontinuation of haloperidol 1 day after discharge.

DISCUSSION

Zolpidem is reported to be a safe and effective short-acting hypnotic agent. However, our two cases bring the total number of psychotic reactions or sensory distortions reported with zolpidem to seven. Both of our patients were receiving concomitant selective serotonin reuptake inhibitors (SSRIs), paroxetine, and fluoxetine, respectively. Recently, a case report by Katz (4) suggested that paroxetine and zolpidem may interact to produce hallucinations and delirium. However, examination of that case indicates that the reaction took place following the first dose of zolpidem added to an existing paroxetine regimen. Thus, it cannot be assumed that a drug interaction accounted for the adverse event. However, Katz raised the possibility of competitive protein binding between paroxetine and zolpidem, leading to increased concentrations of zolpidem, which may have resulted in the adverse reaction. It was also suggested that paroxetine-induced inhibition of cytochrome P450 IID6 was unlikely to elevate concentrations of zolpidem, as the manufacturer had indicated that zolpidem was not metabolized in this manner. Indeed, a recent *in vitro* study using human hepatocytes indicates that the metabolism of zolpidem is mediated principally through cytochrome P450 3A4 (7).

A review of the reported cases of zolpidem-induced psychosis and sensory distortions reveals several common features. Interestingly, all cases are female. Consistent with this finding, pharmacokinetic data indicate that young women have approximately 45% higher zolpidem plasma concentrations compared to men receiving the same dose, and elderly women may have 63% higher concentrations (1). It is possible that higher plasma concentrations are associated with the adverse reaction. Additionally, all reported cases including ours occurred at doses of 10 mg or higher, which further suggests a dose-dependent effect. One of our patients had been taking 20 mg nightly, which is twice the manufacturer's recommended dose. Reactions generally appear 20–30 min after dosing and most resolve within minutes to hours. Some patients remembered

the episodes, while others had no recollection. In some of the reported cases patients were receiving concomitant medications such as SSRIs, which could theoretically interact with zolpidem, while others received zolpidem only (2,3). It cannot be ruled out that other potential mechanisms such as sensitization with neurotransmitter changes secondary to the SSRI played a role in the adverse event.

Zolpidem should be used at the lowest effective dose for as short a duration as necessary. While the manufacturer recommends a starting dose of 10 mg in nonelderly patients, we have found that a 5-mg dose can be effective for treating insomnia in nonagitated, young, healthy adults. It is possible that female patients may require smaller doses than males. Finally, in patients with new-onset or unexplained psychotic symptoms, recent zolpidem use should be considered in the differential diagnosis.

REFERENCES

1. Salva P, Costa J: Clinical pharmacokinetics and pharmacokinetics of zolpidem. Clin Pharmacokinet 1995; 29:142–153
2. Ansseau M, Pichot W, Hansenne M, Gonzales-Moreno A: Psychotic reactions to zolpidem. Lancet 1992; 339:809
3. Iruela LM, Ibanez-Rojo V, Baca, E: Zolpidem-induced macropsia in anorexic woman. Lancet 1993; 342:443
4. Katz, SE: Possible paroxetine-zolpidem interaction. Am J Psychiatry 1995; 152:1689
5. Pies RW: Dose-related sensory distortions with zolpidem. J Clin Psychiatry 1995; 56:35–36
6. Mendelson WB: Sleepwalking with zolpidem. J Clin Psychopharmacol 1994; 14:150
7. Pichard L, Gillet G, Bonfils C, Domergue J, Thenot JP, Maurel P: Oxidative metabolism of zolpidem by human liver cytochrome P450S. Drug Metab Dispos 1995; 23:1253–1262