

Letter to the editor:

A CASE OF SUICIDE ATTEMPT WITH ZOLPIDEM - WILL ZOLPIDEM SHOW UP ON STANDARD URINE TOXICOLOGY SCREENING?

N. Willner^{1*}, E. Schiff²

¹ Dr. Nadav Willner, MD, Resident, Department of Internal Medicine B, Bnai-Zion hospital, Technion, Haifa, Israel

² Dr. Elad Schiff, MD, Chair, Department of Internal Medicine B, Bnai-Zion Hospital, Haifa, Israel; Department for Complementary/Integrative Medicine, Law and Ethics, International Center for Health, Law and Ethics, University of Haifa, Haifa, Israel

* corresponding author: Dr. Nadav Willner; e-mail: nadav.willner@gmail.com, phone number: +972-54-3249856

Dear Editor,

We describe a case of deep stupor after a suicide attempt with Zolpidem (Stillnox). A 64 year old patient was admitted unconscious to the emergency room. According to the medical document brought by his family, the patient was recently diagnosed with APLA syndrome, had 2 previous CVAs, the last one, having been located in the occipital lobe, resulted in cortical blindness. His wife described short-term memory deterioration, loss of appetite and a depressed mood over the last few months. A week before his current admission the patient was hospitalized in the neurology ward suffering from confusion and memory loss; had a brain CT and EEG done, and his Depalept dosage was increased. Chronically, he had been treated with Depalept, Venlafaxine (Viepax), Zolpidem (Stillnox), Prednison, Plaquenil (Hydroxychloroquine), Mirtazapine (Miro), Thioradazine (Ridazine), Atenolol (Normiten), Aspirin and Warfarin. The ambulance crew reported finding the patient unconscious in his bedroom with empty packages of unknown drugs scattered around him.

On admission to the ER, the patient showed hemodynamic and respiratory stability; vital signs were normal, level of consciousness was defined as a stupor or a coma (GCS – 6). Physical examination was normal, neurological examination revealed pain positioning bilaterally, pupils responsive to light, general hypotonus and a positive Babinski sign in the right leg. Nuchal rigidity was not observed. Complete blood test, full chemistry including electrolytes, blood gases and valporic acid levels were all non-remarkable. Gastric lavage revealed no drugs or any other offending substances. Chest X-ray and ECG were normal. The patient showed no response to Naloxon administration. During the night the patient remained in a stupor most of the time, but reacted to Flumazenil administration with short lucid intervals.

The first urine toxicology screening, sent for the patient approximately 3 h after estimated time of ingestion of the drug, was found negative for any offending substances including benzodiazepines. The second test, performed in the morning, approximately 20 h after estimated time of ingestion, showed a positive weak result for PCP (phencyclidine). By that time the patient had fully recovered and was able to confess to his suicide attempt by ingestion of around 40 pills of 5 mg Zolpidem (Stillnox). The patient explained in detail the reasons for his actions and asked for psychiatric assistance. During the next few days the

patient developed severe aspiration pneumonia, probably as a complication of his low level of consciousness upon admission. Chronic treatment with Zolpidem was stopped, and the patient was discharged from the hospital for continuing ambulatory follow up.

Zolpidem is an effective non-benzodiazepine hypnotic sedative for the short-term treatment of insomnia. It works quickly, usually within 15 minutes, and has a short half-life of two to three hours. The pharmacological activity of Zolpidem results from selective binding to the central benzodiazepine receptors of the omega 1 subtype (Salvà and Costa, 1995), which are the α 1-containing GABA_A receptors, found primarily in the brain. Its limited agonistic activity at α 2 and α 3 subunits makes Zolpidem a potent sedative and hypnotic agent with minimal anxiolytic efficacy (Gunja, 2013). Most common adverse effects include headache, gastrointestinal upset and dizziness, all possibly worse in elderly patients; therefore, a dosage reduction is recommended in this group (Drover et al., 2000).

In a review of 344 cases of intentional acute Zolpidem overdoses published in 1994, intoxication could be attributed unequivocally to Zolpidem in only 105 cases, with the majority of patients demonstrating drowsiness, and only very few coma or respiratory failure (Garnier et al., 1994). Very few cases of coma from Zolpidem overdose are reported in medical literature; most of them describe a short lasting, flumazenil responsive coma, and in all of them supportive measures led to complete recovery (Hamad and Sharma, 2001; Kuzniar et al., 2010). In our case, the clinical picture and history raised the suspicion of drug overdose, but none was detected using standard ER tools.

Zolpidem can be detected mainly in blood or urine, the latter being more useful in routine screening of drugs of abuse and toxicology. The detection window in urine for therapeutic doses is assumed to be around 24-48 h, and is likely to be increased with overdose ingestions or poisoning (Drover et al., 2000). The most reliable method of analysis is gas or liquid chromatography with the detection method of choice being mass spectrometry. These methods are expensive, require advanced technology, and are not in routine use in emergency departments. More commonly, emergency departments and clinics use the antibody-based tests (immunoassays). These simple diagnostic kits are very efficient in that they provide caregivers with a swift positive or negative result for a broad spectrum of drugs of abuse.

The toxic screening kit used in our institution is the Multi Drug kit manufactured by Innovacon™; its lower limits for benzodiazepines and PCP are 300 ng/ml and 25 ng/ml, respectively. Worldwide, there are very few immunoassay kits for specific detection of Zolpidem in urine, and their specificity based on the limited literature existing on this issue is 25 %-90 % (Reidy et al., 2011; Huynh et al., 2009). The reasonable explanation for such high false-positive detection rates is assay cross-reactivity with Zolpidem metabolites. Zolpidem's excretion profile is different in naïve patients compared to long-term users, and the metabolites of this drug seem to have different excretion profiles over time, sometimes causing higher concentrations of specific metabolites for a longer time after ingestion (Reidy et al., 2011).

Nevertheless, Zolpidem itself is not reported to have cross reactivity with standard drugs of abuse tested in toxicology screening, including PCP (Piergies et al., 1997). Specifically for PCP, there are 5 documented drugs in the medical literature with possible cross reactivity with PCP on the immunoassay-based toxicology screening kits: dextromethorphan, venlafaxine, meperidine, thioridazine, and mesoridazine (Krasowski et al., 2009; Sena et al., 2002). Therefore, it is prudent to conclude that in our case the positive PCP reading in the patient's urine is attributed to thioridazine which the patient was given on the first morning of hospitalization as part of his chronic treatment. It is important to note that the patient's chronic treatment with venlafaxine was stopped at the beginning of hospitalization and renewed only 3 days after admission, making it less likely to have been the false positive cause.

Considering the very common use of Zolpidem in the U.S (and worldwide) it should be considered as a possible etiology for stupor or coma in any patient exposed to this drug. Negative toxicology urine screening and positive clinical reaction to Flumazenil (and not to Naloxon) could serve as important clues/indicators for the diagnosis. Additionally, our case report is consistent with previous publications about Thioridazine as a possible cause for false positive results for PCP in immunoassay based toxic drug screening kits.

REFERENCES

- Drover D, Lemmens H, Naidu S, Cevallos W, Darwish M, Stanski D. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamics profiles of zaleplon and zolpidem. *Clin Ther* 2000;22:1443-61.
- Garnier R, Guerault E, Muzard D, Azoyan P, Chaumet-Riffaud AE, Efthymiou ML. Acute zolpidem poisoning - analysis of 344 cases. *J Toxicol Clin Toxicol* 1994;32:391-404.
- Gunja N. The clinical and forensic toxicology of Z-drugs. *J Med Toxicol* 2013;9:155-62.
- Hamad A, Sharma N. Acute zolpidem overdose leading to coma and respiratory failure. *Intensive Care Med* 2001;27:1239.
- Huynh K, Wang G, Moore C, Barhate R, Coulter C, Rodrigues W et al. Development of a homogeneous immunoassay for the detection of zolpidem in urine. *J Anal Toxicol* 2009;33:486-90.
- Krasowski MD, Pizon AF, Siam MG, Giannoutsos S, Iyer M, Ekins S. Using molecular similarity to highlight the challenges of routine immunoassay-based drug of abuse/toxicology screening in emergency medicine. *BMC Emerg Med* 2009;9:5.
- Kuzniar TJ, Balagani R, Radigan KA, Factor P, Mutlu GM. Coma with absent brainstem reflexes resulting from zolpidem overdose. *Am J Ther* 2010;17:e172-4.
- Piergies AA, Sainati S, Roth-Schechter B. Lack of cross reactivity of Ambien (zolpidem) with drugs in standard urine drug screen. *Arch Pathol Lab Med* 1997;121:392-4.
- Reidy L, Nolan B, Ramos AR, Walls HC, Steele BW. Zolpidem urine excretion profiles and cross-reactivity with ELISA(®) kits in subjects using Zolpidem or Ambien(®) CR as a prescription sleep aid. *J Anal Toxicol* 2011;35:294-301.
- Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. *Clin Pharmacokinet* 1995;29:142-53.
- Sena SF, Kazimi S, Wu AH. False-positive phencyclidine immunoassay results caused by venlafaxine and O-desmethylvenlafaxine. *Clin Chem* 2002;48:676-7.