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Forensic Aspects of Zolpidem Use

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Review Article

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Abstract

Zolpidem is one of the most commonly prescribed hypnotic drugs for short-term treatment of insomnia. Zolpidem use or abuse was associated with an increased risk of driving accidents, inducing of suicide attempts and death. Its use or abuse associate with hallucinations and bizarre behaviors. Zolpidem induces anterograde amnesia, confusion and sedation and abused as a tool in drug-facilitated crimes. From this view, its analysis and interpretation in forensic cases has been important. In this article, we reviewed the some forensic aspects of zolpidem use or abuse.

Keywords: Zolpidem; Abuse; Forensic Toxicology; Z-drugs

Abbreviations: LOD: Limit of detection; LOQ: Limit of quantification; UPLC/MS/MS: Ultra-performance liquid chromatography–tandem mass spectrometry; SPE-LC/MS: Solid-phase extraction-Liquid chromatography-mass spectrometry; HPLC-FL: High-performance liquid chromatography- fluorescence detection

Introduction

Zolpidem (Ambien®) is an imidazopyridine quick onset, short-acting non-benzodiazepine hypnotic drug which binds with a high affinity to the α1 subunit of the gamma amino butyric acid A (GABA-A) receptor [1]. Zolpidem along with zopiclone (a cyclopyrrolone) and zaleplon (a pyrazolopyrimidine) were developed as Z-drugs. These drugs have become as a choice medication for treatment of anxiety and sleeping disorders [2].

Zolpidem was introduced for therapeutic use in Europe and in the United States since 1986 and 1993, respectively [3]. It is commonly used for short-term therapy (up to 4 weeks) of sleep-onset insomnia. Its recommended dose is 10 mg in male adults, and 5 mg in women, elderly or patients with liver failure. Also, zolpidem is used as a sedative drug before surgery and a drug for the treatment of blepharospasm [3].

Bioavailability of zolpidem approximately 70% after oral ingestion. It is rapidly absorbed, within 20 to 40 minutes. Its plasma protein binding is 92.5% and the mean half-life is 2.6 hours (range: 1.4–4.5 hours). It has a low volume of distribution (0.5–0.7 L/kg) [3,4].

Zolpidem is extensively metabolized and has a significant first-pass effect. Its biotransformation is mediated by cytochromes P450 (CYP), mainly CYP3A4 isozyme. Zolpidem metabolites are pharmacologically inactive and are mainly excreted through renal and fecal elimination. The primary metabolites are a result of oxidation of each of the three methyl groups and the imidazopyridine ring of zolpidem. Less than 1% of parent molecule of the drug is detected unchanged in urine [3,4].

The most common reported side effects of zolpidem are including: nausea, loss of appetite, abdominal pain, dizziness, sedation, lethargy, malaise, agitation, headache, anterograde amnesia, hallucination, lightheadedness, vision problems,

lack of coordination, sleepwalking, speech difficulties, nightmares and sensitivity to light [3,10].

Although, zolpidem appears to be well-tolerated in patients and initially considered as a safer drug compared to benzodiazepines because of lower susceptibility for abuse, addiction and tolerance [4,5], however, over the last few years, increasing of evidences have been reported about zolpidem misuse, abuse, dependence and withdrawal at therapeutic and supratherapeutic doses [6-9].

Some adverse reactions of zolpidem have significant features in forensic caseworks. For example, zolpidem induces sedation and amnesia (including anterograde amnesia in dose-related manner) shortly after administration in individuals [3]. Zolpidem effect to induce and maintain sleep/unconsciousness, and amnesic are commonly seen in medications used in drug facilitated sexual assault [3]. Also, zolpidem- associated hallucinations have been reported as a rare side effect. However, the exact mechanism of hallucinations is unknown; it may be associate to serotonin reuptake inhibition [3,6]. This side effect may rise the risk of violence, self-harm and aggression behaviors in individuals. Concurrent use of zolpidem with central nervous system (CNS) depressants including ethanol, benzodiazepines and phenothiazines is especially threatening as these drugs can act synergistic and enhancing respiratory failure, and increasing the risk of death [3].

From this view, the aim of this article was to review of some special considerations of zolpidem use/abuse in forensic cases.

Driving Under the Influence (DUI)

DUI is a growing public safety problem. Evaluation of driving impairment due to drugs can be challenging for forensic practitioners as many factors need to be considered as the person's physiological condition, drug use history, the type and dose of drug(s) and drug–drug interaction [11].

Zolpidem use or misuse evaluated for potential interference with cognitive, behavioral and driving skills. Zolpidem impaired coordinative and cognitive skills more quickly than other agents [3].

The effect of zolpidem were studied by Jones and Holmgren [12]. They determined the concentrations of zolpidem and zopiclone in peripheral blood samples from living subjects (impaired drivers) and in femoral blood from deceased persons collected over a 10-year period (2001–2010). Zolpidem median concentration (0.30 mg/L) was found in intoxication deaths (N = 357) compared with 0.13 mg/L for other causes of death (N = 397) or 0.19 mg/L in impaired drivers (N = 837) ($p < 0.001$). The median concentrations of zolpidem in blood decreased among in co-ingested cases and increased for poisoning fatal cases. The most frequent co-ingested substances were ethanol in fatal cases and diazepam in the drivers [12].

In another study, Favretto et al. analyzed a total of 4066 blood samples collected from drivers involved in road traffic accidents in the Padova region of Italy for the presence of alcohol, drugs of abuse and pharmaceutical agents with sedative-hypnotic effects. From these samples, 175 blood samples were positive for sedative-hypnotic drugs above 1 ng/mL. Zolpidem was detected in 28% of samples. They concluded that sedative-hypnotics including zolpidem are pharmaceutical substances commonly detected in drivers involved in traffic accidents, frequently in concentrations associated with DUI [13].

Booth et al. evaluated the association between current use of zolpidem-containing medications and motor vehicle collisions (MVCs) among 2000 very old drivers aged ≥70 years residing in north-central Alabama, USA with current zolpidem use. They concluded that the current zolpidem users, specifically women and individuals aged ≥80 years, had higher MVC rates than nonusers [14]. Also, previously described that zolpidem has an additive effect of alcohol in the driving impairing effects. The performance skills tested including divided attention, memory and data processing rate indicated an additive impairment effect with alcohol and zolpidem [15].

Kwon and Han reviewed the drug abuse in recently reported cases of driving under the influence of drugs (DUID) in Asia, USA, and Europe. They showed that ketamine, morphine, methamphetamine and khat were frequently reported in Asia. Amphetamine, benzodiazepines and Z-drugs including zolpidem and cannabinoids were mainly reported in USA, and synthetic cannabinoids, opiates, and cocaine were reported in Europe [16].

Yang et al. by a case-crossover design using a randomly sampled cohort from the Taiwan National Health Insurance database on 12,929 individuals were identified as having been hospitalized between 1998 and 2004 due to an motor vehicle accidents demonstrated that the use of zolpidem one day before driving might be associated with an increased risk of motor vehicle accidents [17].

Drug-Facilitated Sexual Assault (DFSA)

The increase of drug-facilitated crimes (sexual assault, robbery, kidnapping, homicide) are considered as a serious general public security problem. Drugs involved can be pharmaceuticals including benzodiazepines (diazepam,

flunitrazepam, lorazepam, etc.), z-drugs (zolpidem, zopiclone, zaleplon), sedatives (neuroleptics, some antihistamine H1-blockers) or anaesthetics (γ-hydroxybutyrate, ketamine), muscle relaxants (Baclofen, carisoprodol) , drugs of abuse, such as cannabis, ecstasy or lysergic acid diethylamide (LSD), or mainly ethanol [18]. DFSA is considered a sub-category of drug-facilitated crimes. DFSA is defined as the incidence in which a person (male or female), is subjected to sexual activity while they are incapacitated or unconscious because of the ingestion of ethanol or any other intoxicating substance, resulting in the inability to resist or consent to such acts [19].

Zolpidem consider as a promote of sexual assault, because of its rapid onset of action, effectiveness to induce and maintain sleep/unconsciousness, and antrograde amnesia are all attributes commonly seen in drugs used in DFSA [3,20].

Carfora et al. reported a 56-year-old female tourist claimed to have been sexually assaulted by five men after having had a drug-spiked alcoholic beverage. After seven months, hair strands were also sampled to perform the segmental hair analysis. Gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–tandem mass spectrometry (LC-MS/MS) techniques were applied for the qualitative and quantitative analyses. Zolpidem (concentration range: 0.70- 1.06 pg/mg), flunitrazepam and oxazepam were detected in the hair segments corresponding to the time frame of the alleged rape [21].

Although urine and blood samples have been conventionally used for testing of drugs in DFSA, these matrices have limited application because they have a relatively short detection period and can be used only in case of recent drug exposure. Therefore, it is necessary to use an alternative biological sample to obtain the evidence of drug misuse in DFSA [22]. Due to important role of segmental hair analysis for determining of trace levels of involved drugs in DFSA, there are some sophisticated methods have been developed for forensic toxicology analysis. For example, Kim et al. developed a LC–MS/MS method for determining picogram-level of zolpidem and its main metabolites [zolpidem phenyl-4-carboxylic acid (ZPCA) and zolpidem 6-carboxylic acid (ZCA)] in hair using a zirconia-based hybrid solid–phase extraction technique [22]. The lower limit of quantification of zolpidem, ZPCA, and ZCA were 1.0, 0.5, and 1.0 pg/ mg, respectively [23].

Acute Poisoning and Postmortem Toxicology

There are few data available to evaluate the lethal potential of zolpidem. Although the literature is replete with reports of numerous intoxications, zolpidem alone is rarely the cause of death. A review of the literature suggests that most cases of fatal intoxications involve zolpidem in combination with alcohol and/or other drugs [3].

In a retrospective analysis of 344 patients of acute zolpidem poisoning in a French poison control center, the fatality rate was 6% and could not be directly related to zolpidem alone. The zolpidem ingested doses ranged between 10-1400 mg, with half of the cases ingesting alcohol and/or other psychotropic drugs.

Signs of poisoning (drowsiness, confusion, incoherent speech, gait disturbances) were observed in approximately one-third of the patients. Only five cases of coma or respiratory depression were reported for doses of 140-400 mg. Therapy for intoxication was mainly supportive and symptomatic. Symptoms of intoxication resolved rapidly, and for the most part patients went home without sequelae [24].

Recently, Tardelli et al. conducted a study for trend analysis of overdose deaths involving non-BZD hypnotic/sedatives(including zolpidem) in the USA (from 2000-2018) using data from the National Center for Health Statistics. Finally, they concluded that deaths due to non-benzodiazepine hypnotics and gabapentinoids increased significantly over the last two decades [25].

Recently, Hasegawa et al. reported the first fatal case of intravenous self-administered zolpidem in a male.

The decedent was found on floor of his room, with a tourniquet band and new injection marks on his right forearm. Nearby the body, a medical disposal syringe containing small volume solution dissolving crushed zolpidem tablets was found. The concentration of zolpidem and its phenyl-4-carboxylic acid metabolite in various specimens analyzed by LC-MS/MS were generally extreme higher than those of reported fatal cases, supporting that the victim had died of intravenous zolpidem injection. The concentrations of zolpidem in femoral vein blood and right and left heart blood specimens in this case were 9.55, 28.5 and 46.9 μg/mL, respectively [26].

Yamaguchi et al. studied quantification of zolpidem and its metabolites in postmortem urine samples using LC-MS/MS. These metabolites including two carboxylic acids (zolpidem phenyl-4-carboxylic acid [M1] and 6-carboxylic acid [M2]) and four hydroxyzolpidems (4-(hydroxymethyl) phenyl zolpidem [M3], 6-hydroxymethyl zolpidem [M4], 7-hydroxyzolpidem [7OH] and 8-hydroxyzolpidem [8OH]). The concentration of M1 was highest in all cases and M2 and total M4 concentrations were relatively high. Most of M4 and 8OH metabolites were excreted as conjugated form whereas mostly of 7OH was excreted in its free form [27].

Recently, Øiestad et al. studied the concentrations of benzodiazepines (including clonazepam, 7-aminoclonazepam, flunitrazepam, 7-aminoflunitrazepam, nitrazepam, 7-aminonitrazepam, diazepam, nordiazepam, oxazepam, alprazolam, midazolam) and z-hypnotics (zopiclone and zolpidem) in alternative matrices to assess whether these concentrations are comparable to concentrations in peripheral blood. They showed that the measured concentrations in vitreous humor were generally much lower than those of peripheral blood (PB) for all compounds except zopiclone. Concentrations of the parent nitrobenzodiazepines in muscles were higher than those in PB, but for the other compounds, concentrations in muscle showed good correspondence with PB [28].

Suicide and Bizarre Behaviors

Epidemiological studies showed that an association with risk of suicide with zolpidem use. Khan et al. conducted a systematically reviewed and meta-analyzed the current evidence from studies reporting the risk of suicide with the zolpidem use. This meta-analysis was based on four studies with 344,753 participants, of which 42,279 were zolpidem users. A significantly increased risk of suicide or suicide attempt was found in zolpidem users compared to non-users [pooled relative risk was 1.88 (95% CI: 1.54 – 2.30)]. Also, an increased risk of suicidal death was observed in zolpidem users with a pooled relative risk of 1.82 (95% CI: 1.43 – 2.30) compared to non-users. They concluded that zolpidem use was related to an increased risk of suicide or suicide attempt and suicidal death [29].

Kim et al. demonstrated that zolpidem has become the greatest risk factor for the elderly Koreans in suicide attempts. From 12,104 patients who attempted suicide by ingesting drugs, the elderly (73.5%) ingested more sedatives and hypnotics than the non-elderly (53.9%); of these drugs, zolpidem ingestion was higher in the elderly than the non-elderly [30].

Some reports show the bizarre and high risk behaviors in zolpidem users that considered as a risk factor for morbidity and mortality. Reports of short-lasting psychological disturbances (including: perceptual distortions, visual illusions, hallucinations), often occurring 30-60 min after intake of the drug [4].

Parsa et al. reported a 27-year-old single male pharmacist had taken 100 mg of zolpidem and afterwards, went into an unknown status of narcolepsy, faint, seizure or transient coma. In this case, he declared that eating and drinking became more favorable than usual. He took 10 tablets of zolpidem 10 mg with a full glass of water. He heated up the meal on a gas oven and started to eat. He lost his consciousness while eating and in the morning after he found a remarkable amount of meal in his mouth [31].

Zolpidem-induced somnambulism and amnesic sleep-related behavioral problems has been reported as a high risk events in zolpidem users. In a study, of the total 255 zolpidem users, 13 (5.1%) reported incidence of somnambulism or amnesic sleep-related behavioral problems [32-38].

Analysis of Zolpidem in Biological Samples

Zolpidem has been analyzed in various biological samples (such as whole blood, serum, plasma, urine, saliva, hair and postmortem materials including stomach content, vitreous humor and tissues) using of different analytical methods including immunoassays (for screening in clinical laboratory) and chromatographic-based techniques both in forensic and clinical toxicology laboratories. Table 1 summarizes some of these methods have been used for zolpidem analysis in forensic and clinical toxicology settings (Table 1).

Method	Sample(s)	LOD (ng/mL)	LOQ (ng/mL)	Recovery (%)	Reference No.
UPLC/MS/MS	Urine Blood	0.05	0.1	70-98.3	33
SPE-LC/MS	Whole Blood, Oral fluid	0.2	1	79.9-104.1 (For Blood sample) 80.2- 103.8 (For oral fluid sample)	34
HPLC-FL	Plasma	0.2	1	90.44- 112.62	35
LC/MS/MS	Hair	0.005	0.001	62.5-96.6	36
LC/MS/MS	Hair	0.002	0.001	92.8	37
UPLC/MS/MS	Postmortem samples (Blood, Urine, Liver, Spleen, Brain, Muscle, Heart, Vitreous humor and Lung)	0.4	0.2	78-87	38

Table 1: Some analytical methods for analysis of zolpidem in biological samples in forensic and clinical toxicology.

Conclusion

Zolpidem is a short-acting nonbenzodiazepine hypnotic which it has the most widely prescribed as sleep aid, worldwide. Due to adverse effects of this drug on driving skills, sedative effects, inducing of suicide attempts and bizarre behaviors, it has a significant feature in forensic casework. Due to zolpidem induced- anterograde amnesia and unconsciousness are frequently used as date rape drugs. Hallucination-associate to zolpidem use may rise the risk of violence, and self-harm behaviors. Fatality has been reported during co-ingestion of zolpidem with CNS depressants. In conclusion, the investigation of zolpidem in postmortem samples has an important task in forensic toxicology laboratory.

Conflict of Interest Statement

The author declares that he has no conflicts of interest.

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