SOFT-DFC Snapshot – Zolpidem

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SOFT-DFC Snapshots are short reports of critical information about the more common drugs associated with drug-facilitated crimes (DFCs). They are not complete literature reviews about the drug or drug class. One key aspect is their focus on the ability to detect a drug after a single-dose administration, as is often the situation in DFC investigations. As such, these summaries also point out instances in which available data is limited in the hopes that this will encourage further research studies. Finally, SOFT-DFC Snapshots point to the use of these drugs in actual DFC cases, as cited in the medical and open literature.

Zolpidem is an imidazopyridine derivative primarily prescribed as a sedative medication for the short-term treatment of insomnia. It has been available in the United States since 1993 and has been suspected or confirmed in numerous DFC investigations worldwide. A 2005 paper declared zolpidem as one of the most frequently used drugs to facilitate sexual assault in Paris and surrounding suburbs.[1] Likewise, a 2015 review of 555 DFSA cases analyzed at the National Forensic Service (NFS) in South Korea between 2006 and 2012 found zolpidem in nearly 6% of the cases.[2] In contrast, a recent US study found zolpidem in just 0.6% of 1000 cases analyzed over 15 months from March 2015 to June 2016.[3]

Drug Class:[4] Miscellaneous (Sedative-Hypnotic)

Generic Name: Zolpidem

Brand Name(s): Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist

Dosage Forms: Oral tablet (5 or 10 mg); oral tablet, extended release (6.25 or 12.5 mg); sublingual tablets (1.75, 3.5, 5 and 10 mg); oral spray (5 mg per metered spray).[5]

FDA Approval: Zolpidem is an imidazopyridine derivative with pharmacological effects due to binding to the $GABA_A$ receptor. This leads to the enhancement of GABAergic inhibition of neurotransmission in the central nervous system, resulting in the CNS depressants effects such as dizziness and drowsiness. It is approved for the treatment of insomnia. Other common side effects include memory loss, anxiety, and abnormal thoughts/behaviors. Complex sleep behaviors (e.g., sleepwalking, sleep-driving, and engaging in other activities while not fully awake) have been reported while using zolpidem.[6] Combining zolpidem with other CNS depressants (e.g., alcohol, benzodiazepines, opiates, sedative antihistamines, tricyclic antidepressants) results in an increased risk of CNS depression, including an adverse effect on psychomotor performance.[7]

Metabolism/Elimination: Hepatic metabolism occurs predominantly through CYP3A4 and to a lesser extent by CYP1A2 and CYP2D6, producing two primary, inactive urinary metabolites: zolpidem phenyl-4-carboxylic acid (metabolite I)

and zolpidem 6-carboxylic acid (metabolite II).[8] Metabolite I represents about 33-50% of the parent drug, while metabolite II accounts for about 6-10%.[9,10] The average elimination half-life of zolpidem ranges between 2 to 3.5 hrs.[5,7,11,12] It is noted that this may be extended for females, so lower doses are recommended to avoid prolonged impairment.[13,14] Extended elimination half-lives may also be observed in the elderly, where the half-lives may be about 32% longer with some formulation types.[7,15]

Single Dose Studies:

Urine:

The SOFT DFC Committee[4] and the AAFS Standards Board[16] have established the importance of testing urine samples from alleged victims of drug-facilitated crimes for zolpidem's primary urinary metabolite, zolpidem phenyl-4-carboxylic acid (metabolite I), at a decision point concentration of 10 ng/mL or lower. Urine is easily collected, straightforward to analyze, and provides a longer window of detection of zolpidem ingestion compared to blood.

There are limited single-dose studies of zolpidem with measurements made in urine specimens over time. In one study, three volunteers were administered a 10-mg oral dose of zolpidem and then provided urine specimens every 12 hrs. afterward up to 144 hrs.[17] With the author's LC-MS/MS method and a reported detection limit of 0.01 ng/mL, they were able to detect the single exposure of the parent drug zolpidem for up to 60 hr. in urine, with the largest concentrations (5-25 ng/mL) appearing in the first 12 hr. specimen after administration. The authors did not look for zolpidem metabolites in this study.

A 2012 study involved four Chinese subjects administered a single 10-mg oral dose of zolpidem.[18] The highest urinary concentrations for zolpidem (about 250 ng/mL) occurred at 4 hrs. post-administration. Likewise, the highest concentration of zolpidem metabolite II was 200 ng/mL at the 4-hr. collection. However, zolpidem metabolite I did not reach its maximum concentration (550 ng/mL) until 8 hrs. after ingestion.

Blood/Plasma/Serum:

Blood, plasma, and serum specimens allow for more meaningful quantitative assessments of positive findings; however, zolpidem and its metabolites may no longer be detectable if these specimens are collected more than 8-12 hrs. after the alleged ingestion of a single dose.

Peak plasma concentrations in healthy adults following oral administration of 5 or 10 mg conventional zolpidem tablets averaged

59 (range: 29-113) and 121 (range: 58-272) ng/mL, respectively, at a mean time (T_{max}) of 1.6 hours for both.[5]

In another study, single oral 12.5 mg extended-release zolpidem tablets found an average peak plasma concentration of 134 ng/mL occurring at a T_{max} of 1.5 hours.[19]
3.5 mg sublingual zolpidem tablets administered to fasting young adults resulted in a peak plasma concentration of 57 ng/mL at a T_{max} of 0.9 hours.[11] Others have reported that the T_{max} ranges between 30-180 minutes, with a median time of 82 minutes for some sublingual formulations.[5]

Zolpidem oral spray is quickly absorbed from the oral mucosa and GI tract resulting in a T_{max} that is under 1 hour.[5]

Hair:

Hair allows for the longest window of detection for zolpidem. Still, it comes with the disadvantage of being more difficult to analyze, the requirement of methods about 1,000-1,000,000 times more sensitive than what is needed for analyzing blood or urine, and the general inability to differentiate ingestions from one week to the next.

Shima et al. developed a sensitive LC-MS/MS procedure (LOD: 50 fg/2-cm of a single hair) to analyze single hairs collected from a volunteer after ingestion of a single 10-mg dose of zolpidem.[20] 14 of the 15 hairs collected 67 days after ingestion had detectable amounts of zolpidem in the first 2-cm of the single hairs estimated to average 43 pg (range: 27-63 pg).

Another study used an LC-MS/MS method to analyze hair specimens from three volunteers collected 3-5 weeks after ingestion of a single 10 mg dose of zolpidem.[17] Zolpidem was detected in the hair specimens at concentrations ranging from 2 to 10 pg/mg.

Remarkably higher concentrations were reported in another study.[21] Hair collected from 20 Chinese volunteers one month after administration of a single 10-mg dose of zolpidem found zolpidem concentrations ranging between 135-555 pg/mg in the first 2-cm segments of hair.

DFC Cases:

A 2004 publication reported a young, hospitalized female who was offered a coffee by a male nurse and subsequently went unconscious. As she regained consciousness, she realized she was being sexually assaulted; however, she did not report this to the police until 6 days later. A hair specimen was collected 15 days after the alleged offense and was found to contain unprescribed zolpidem in the first 2 cm segment.[17]

One of the most high-profile cases involved an American NFL star – Darren Sharper – who was accused of raping numerous women from 2011 to 2014 in different states while either drugged or unconscious.[22,23] Zolpidem was one of the drugs that Sharper was accused of and later admitted to, surreptitiously administering to his victims.[22,24] Two co-conspirators in the Louisiana crimes also pleaded guilty to using zolpidem in those rapes.[25]

A 2012 study reported a girl drinking a soft drink offered by a young man at a party.[18] After consuming the drink, she became unconscious. Approximately 16 hours later, she woke up and realized she had been sexually assaulted. After reporting the assault to the police, she had blood and urine collected at the hospital (approximately 20 hours after the assault). Zolpidem metabolite I was found at 10 ng/mL in the victim's blood specimen, but zolpidem and zolpidem metabolite II were not detected. Zolpidem and both metabolites were identified in the urine specimen.

In 2014, a Houston businessman admitted using zolpidem to drug a female employee while traveling together on a business trip. While unconscious, he took photographs of her nude body and attempted to commit a drug-facilitated sexual assault.[26]

In 2016, a 56-year-old female claimed to have been sexually assaulted by a group of five men (employees of the hotel where she was staying) after consuming an alcoholic drink offered by one of them. Three urine specimens were collected at 38, 44, and 45 hours after the assault, and a hair sample was collected seven months later. Although the urine specimens were tested following SOFT recommendations, no drugs were detected. However, zolpidem and two other CNS depressant drugs (flunitrazepam and oxazepam) were detected in the hair sample. The reported zolpidem concentration ranged between 0.7 to 1.1 pg/mg in different hair segments.[27]

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