JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, September 2012, Vol. 57, No. 5
doi: 10.1111/j.1556-4029.2012.02117.x
Available online at: onlinelibrary.wiley.com

PAPER

TOXICOLOGY

Shane Darke,[1] *Ph.D.; Mark Deady,*[1] *B.Psych. (Hons); and Johan Duflou,*[2,3,4] *M.Med.Path. (Forens)*

Toxicology and Characteristics of Deaths Involving Zolpidem in New South Wales, Australia 2001–2010*

ABSTRACT: All cases presenting to the New South Wales Department of Forensic Medicine between January 1, 2001 and September 31, 2010 in which zolpidem was detected, were retrieved. A total of 91 cases were identified. The mean age was 49.4 years, 65.9% were male, and 61.5% were suicides. Zolpidem was a factor contributing to death in 35 (37.3%) cases, of which 31 (34.1%) involved zolpidem toxicity. The median blood zolpidem concentration was 0.20 mg/L (range 0.05–3.50 mg/L), with no significant gender difference. Drug toxicity cases involving zolpidem had significantly higher median blood zolpidem concentrations than other cases (0.50 vs. 0.10 mg/L). In 83.5% of cases, psychoactive substances other than zolpidem were detected, most commonly antidepressants (46.2%), benzodiazepines (35.2%), opioids (26.4%), and alcohol (39.6%). In summary, zolpidem was a factor contributing to death in a large proportion of cases, predominately involving drug toxicity and suicide.

KEYWORDS: forensic science, zolpidem, hypnotics, suicide, toxicity, toxicology

Zolpidem is a quick onset, short-acting nonbenzodiazepine hypnotic, used for the treatment of insomnia (1,2). While believed to be a safer alternative to benzodiazepines for the treatment of insomnia, having lower risks for both toxicity and dependence (3,4), numerous instances of adverse events after administration have been reported. These include bizarre dissociative behaviors such as sleep driving, anterograde amnesia, hallucinations (including self-harm command hallucinations), and suicide (4–11). Despite its lower risk of toxicity, cases of accidental and deliberate zolpidem poisoning have been reported (12–17). In most cases of toxicity reported in the literature, multiple substances have been detected, most commonly central nervous system (CNS) depressants (12–17).

The current study aimed to determine the demographic characteristics, the involvement of zolpidem in the cause of death, circumstances of death, and toxicology of cases presenting to the Department of Forensic Medicine (DOFM), Sydney, over the period January 1, 2001–September 31, 2010 in which zolpidem was detected during routine quantitative toxicological investigations.

Methods

Case Identification

All cases autopsied at the DOFM between January 1, 2001 and September 31, 2010 in which zolpidem was detected in blood, liver, or urine were identified. Autopsy reports and police summaries of all such cases were retrieved from the database of the DOFM. Permission to inspect the files had been received from the Sydney South West Area Health Service human research ethics committee. The DOFM is located in central Sydney, and is the primary forensic pathology center in NSW, conducting approximately 3000 autopsies a year. All cases were reviewed by the authors.

In NSW, a case must be reported to the Coroner where a person dies a violent or unnatural death, or a person dies suddenly and the cause is unknown. All such cases, including all those presented here, undergo a standardized forensic autopsy, with examination of all major organs, including microscopy. Information was collected on age (years), body length (m), and weight (kg), and body mass index (BMI) calculated. Quantitative toxicological analysis is performed in all nonnatural deaths. Cause of death is determined by the forensic pathologist based on the circumstances of death, the comprehensive autopsy findings, and the toxicological analyses. The role of zolpidem toxicity was determined with reference to known toxic concentrations (1). Cases were classified as suicide based on a determination by the Coroner. In those cases where the Coroner made an open or no finding in relation to suicide, the authors classified cases as suicide based on the presence of suicide notes, verbal statements of intent given to witnesses, police reports, and witness statements.

Toxicological Analyses

All presented toxicological analyses were of peripheral blood (femoral or subclavian vessels), liver samples, or of urine, and were conducted by the Division of Analytical Laboratories, NSW Department of Health. Toxicological data were reported for zolpidem, morphine, methadone, buprenorphine, oxycodone, alcohol, cannabis (Δ-THC), methamphetamine (either methamphetamine or amphetamine), cocaine (determined by the presence of cocaine

[1]National Drug and Alcohol Research Centre, University of New South Wales, NSW, Sydney, Australia.
[2]Department of Forensic Medicine, Western Sydney Local Health District, Sydney, Australia.
[3]School of Medical Sciences, University of New South Wales, Sydney, Australia.
[4]Sydney Medical School, University of Sydney, NSW, Sydney, Australia.
*Funded by the Australian Government Department of Health and Ageing.

Received 28 Feb. 2011; and in revised form 17 May 2011; accepted 3 July 2011.

itself and/or the presence of benzoylecgonine), 3,4 methylenedioxymethamphetamine (MDMA), benzodiazepines, antidepressants, and antipsychotic medications. All samples were screened by immunoassay and either by gas chromatography or high-performance liquid chromatography. Zolpidem was measured quantitatively in blood and urine by liquid chromatography with photo-diode array detection or gas chromatography with nitrogen phosphorus detection and confirmed by gas chromatography-mass spectrometry, with a screening detection of 0.05 mg/L.

Statistical Analyses

Where distributions were highly skewed, medians and inter-quartile ranges (IQR) were reported, otherwise means were presented. For bivariate comparisons, *t*-tests or odds ratios with 95% confidence interval were reported. For analysis of nondichotomous categorical variables, chi-square analyses were conducted. Spearman rank order correlations were used to correlate skewed distributions. All analyses were conducted using PASW, release 18.0 (18).

Results

Case Characteristics

A total of 91 cases were identified, 65.9% of which were male (Table 1). In four cases, zolpidem was present only in urine. In further five cases, zolpidem was detected in the liver, with sample decomposition preventing analysis of blood. The mean age was 49.4 years (SD 15.8, range 20–93 years), with female cases being significantly older ($t_{89} = 2.26$, $p < 0.05$). A minority were married/de facto, and a third were known to have been employed. The direct causes of death were drug toxicity ($n = 41$), disease ($n = 20$), hanging/asphyxia ($n = 19$), drowning ($n = 8$), traumatic injury ($n = 6$), gassing ($n = 2$), and electrocution ($n = 1$). In two cases, cause of death could not be determined. Zolpidem was noted as a direct, or contributing, factor to death in 35 cases (37.3%), on which 31 (34.1%) involved zolpidem toxicity. Bizarre, dissociative behaviors that resulted in death were noted in two cases, both of which involved falls from heights. In one case, the person was reported to be dissociated, and was observed dancing on a window ledge prior to the fall, while the other abruptly jumped out of a window during an argument.

Approximately 60% of cases were classified as suicides, with no difference from other cases in either gender ($p = 0.91$) or age ($p = 0.19$). The most common suicide method was drug toxicity, followed by hanging. In 31 of the 56 suicides (55%), zolpidem was noted as contributing to the death.

Toxicology

Blood zolpidem concentrations were available for 86 cases. The median concentration was 0.20 mg/L (IQR 0.54, range 0.05–3.50 mg/L) (mean = 0.47 mg/L), with no significant association with gender ($p = 0.09$), age ($p = 0.30$), or BMI ($p = 0.67$) (Table 2). The distribution of zolpidem blood concentrations was skewed (skewness = 2.5, kurtosis = 6.7), with 15.1% of cases having concentrations of 1.0 mg/L or greater (Fig. 1).

In 76/91 (83.5%) of cases, psychoactive substances other than zolpidem were detected. The most prevalent substances were CNS depressants: antidepressants, alcohol, benzodiazepines, and opioids. The mean blood alcohol concentration among alcohol positive cases was 0.08 g/100 mL (range 0.01–0.21 g/100 mL). Antipsychotics, cannabis, and psychostimulants were only present in small proportions.

Cases of drug toxicity that included zolpidem had significantly higher median blood zolpidem concentrations than other cases (0.50 vs. non 0.10 mg/L, $U = 1245$, $p < 0.001$) (means 0.78 and

TABLE 1—*Characteristics of cases in which zolpidem was detected, 2001–2010.*

	Male ($n = 60$)	Female ($n = 31$)	All ($n = 91$)
Age (mean years)	46.6	54.5	49.4
Marital status (%)			
Single	35.0	25.8	31.9
Married/De facto	36.7	38.7	37.4
Separated/divorced	8.3	6.5	7.7
Widow/er	1.7	12.9	5.5
Unknown	18.3	16.1	17.6
Employment status (%)			
Unemployed	18.3	22.6	19.8
Employed	41.7	22.6	35.2
Disability pension/sickness benefits	1.7	–	1.1
Student	3.3	3.2	3.3
Retired	6.7	29.0	14.3
Unknown	28.3	22.6	26.4
Suicide (%)	60.0	64.5	61.5
Hanging/asphyxia	16.7	9.7	14.3
Toxicity (gas/substance)	25.0	29.0	26.4
Toxicity and asphyxia	3.3	6.5	4.4
Toxicity and drowning	1.7	6.5	3.3
Fall from height	3.3	0	2.2
Electrocution	1.7	0	1.1
Drowning	5.0	9.7	6.6
Sharp object injury	1.7	0	1.1
Gunshot	1.7	3.2	2.2
BMI (mean)	27.9	26.7	27.5

TABLE 2—*Toxicology of cases in which zolpidem was detected, 2001–2010.*

	Male ($n = 60$)	Female ($n = 31$)	All ($n = 91$)
Zolpidem (median mg/L)*	0.20	0.30	0.20
Benzodiazapines (%)	31.7	41.9	35.2
Diazepam	18.3	29.0	22.0
Temazepam	6.7	19.4	11.0
Alprazolam	6.7	12.9	8.8
Oxazepam	5.0	12.9	7.7
Flunitrazepam	1.7	0.0	1.1
Any blood opioid (%)	20.0	38.7	26.4
Buprenorphine	0	0	0
Codeine	11.7	25.8	16.5
Methadone	1.7	3.2	2.2
Morphine	3.3	9.7	5.5
Oxycodone	5.0	6.5	5.5
Other opioid	3.3	3.2	3.3
Alcohol (%)	45.0	29.0	39.6
Psychostimulants (%)	3.3	–	2.2
MDMA	3.3	0.0	2.2
Cocaine	0.0	0.0	0.0
Methamphetamine	0.0	0.0	0.0
Cannabis (%)	1.7	3.2	2.2
Antidepressants (%)	40.0	58.1	46.2
SSRI	28.4	25.8	27.5
SNRI	10.0	9.7	9.9
Tricyclics	1.7	16.1	5.5
Tetracyclics	1.7	9.7	3.3
MAOI	1.7	3.2	1.1
Antipsychotics (%)	5.0	9.7	6.6
Chlorpromazine	0.0	6.5	2.2
Olanzapine	5.0	3.2	4.4

*$n = 86$ (five cases liver zolpidem only).

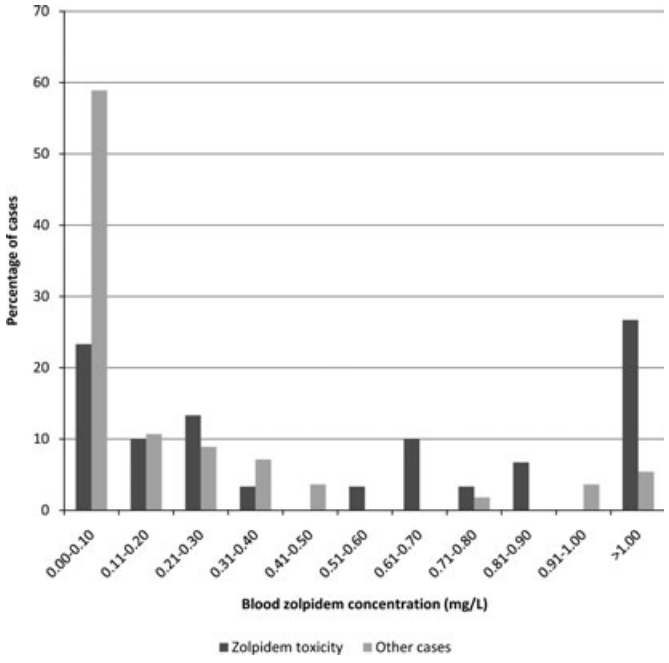

FIG. 1—*Blood zolpidem concentrations by zolpidem toxicity status, 2001–2010.*

0.30 mg/L respectively). Of the 31 cases of zolpidem toxicity, 28 had drugs other than zolpidem also present, most commonly benzodiazepines (15/31), opioids (15/31), antidepressants (15/31), and alcohol (11/31). Of these cases, 21 were suicides.

Discussion

Several major findings emerged from this case series. First, zolpidem was deemed a factor contributing to death in a third of cases in which it was detected. The majority of cases in which zolpidem contributed to death were cases of drug toxicity. Blood zolpidem concentrations in such cases were five times higher than other cases. Indeed, a quarter of such cases had zolpidem concentrations that exceed 1.0 mg/L, far in excess of therapeutic concentrations, as has been reported in other case series (1,12–17). Doses far in excess of those prescribed, both in suicide and accidental overdose, appeared common.

As has been seen previously with zolpidem toxicity (12–17), other psychoactive substances were present in the majority of cases, most commonly other CNS depressants. Such patterns of polydrug toxicity are commonly seen among illicit drug users, and substantially contribute to drug-related death (19). Polydrug toxicity is clearly a clinical problem for users of depressant drugs *per se*. Alcohol is illustrative, as it is contraindicated when medicated with zolpidem. Despite this, approximately 40% of cases had consumed alcohol prior to death, with a median concentration of 0.08 g/100 mL.

Over half of cases in this series were suicides, including two-thirds of toxicity cases. Associations with self-harm and suicide have been noted previously for other sedatives and hypnotic drugs, such as diazepam (20–22), as well as isolated case reports related to zolpidem (7,8). While care should be taken in imputing causality, the high proportion of suicides in cases where zolpidem was deemed to be a contributor to death suggests that a high degree of caution is warranted in prescribing zolpidem, particularly for those known to have mood disorders, as is the case for all sedative or toxic drugs. The findings also suggest that standardized screening for zolpidem, and potentially other "Z-drugs" in fatalities presenting for medico-legal death investigation, is warranted.

As noted earlier, there have been concerns about reports of atypical, dissociative behaviors occurring among patients after consuming zolpidem (4–11). Evidence for such sequelae of zolpidem ingestion was seen here. In two of the deaths in this series, both of which involved falls from heights, such behaviors were noted. One was an abrupt leap from a window during an argument, which was deemed to be an impulsive suicide, while the other involved bizarre and atypical behaviors on a high story window ledge. In neither case, was there a history of severe psychopathology. Both cases involved multiple substances. In addition to their zolpidem consumption, both cases had high blood alcohol concentrations (>0.10 g/100 mL), and one case also had MDMA detected. The dissociative behaviors thus occurred in the context of polydrug use that was typical of this case series.

We must put these findings in an epidemiological perspective. In 2008, in Australia, the rate of zolpidem prescription was 0.91 defined daily doses per 1000 of the population. With this in mind, the number of cases presented in this study is relatively small compared with population dosage. The reader should not have the impression that there is an epidemic of zolpidem-related cases. This case series, however, has demonstrated that cases in which zolpidem directly contributes to death do occur, most commonly presenting as multiple drug toxicity. It should be noted, however, that data on accident and emergency presentations involving zolpidem were not available.

In summary, in a large proportion of cases in which zolpidem was detected, the drug was a factor contributing to death, and a large proportion of such cases were suicides. Multiple drug toxicity was the dominant cause of death, with CNS drugs other than zolpidem seen in nearly all such cases.

Acknowledgment

The authors wish to thank Vera Alderton for her assistance.

References

1. De Haas SL, Schoemaker RC, Van Gerven JMA, Hoever PA, Cohen F, Dingemanse J. Pharmacokinetics, pharmacodynamics and the pharmacokinetic/pharmacodynamic relationship of zolpidem in healthy subjects. J Psychopharmacol 2010;24:1619–29.
2. Baselt RC. Disposition of toxic drugs and chemicals in man, 8th edn. Foster City, CA: Biomedical Publishers, 2008.
3. Darcourt G, Pringuey D, Sallie D, Lavoisy J. The safety and tolerability of zolpidem update. J Psychopharmacol 1999;13:81–93.
4. Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehab 2009;88:410–8.
5. Hoque R, Chesson AL. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. J Clin Sleep Med 2009;5:471–6.
6. Inagaki T, Miyaoka T, Tsuji S, Inami Y, Nishida A, Horiguchi J. Adverse reactions to zolpidem: case reports and a review of the literature. Prim Care Companion J Clin Psychiatr 2010;12:e1–8.
7. Manfredi G, Kotzalidis GD, Lazanio S, Savoja V, Talamo A, Koukopoulos AE, et al. Command hallucinations with self-stabbing associated with zolpidem overdose. J Clin Psychiatr 2010;7:92–3.
8. Olsen LG. Hypnotic hazards: adverse effects of zolpidem and other z-class drugs. Aust Prescriber 2008;6:146–9.
9. Siddiqui F, Osuna E, Chokroverty S. Writing emails as part of sleepwalking after increase in zolpidem. Sleep Med 2009;10:262–4.
10. Tsai JH, Yang P, Chen CC, Chung W, Tang TC, Wang SY, et al. Zolpidem-induced amnesia and somnambulism: rare occurrences? Eur Neuropsychopharmacol 2009;19:74–6.

11. Weiss KJ, Del Busto E. Sleep-driving and pathological intoxication: saved by the FDA? Am J Forensic Psychiatr 2010;31:5–15.
12. 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.
13. Gock SB, Wong SH, Nuwayhid N, Venuti SE, Kelley PD, Teggatz JR, et al. Acute zolpidem overdose—report of two cases. J Anal Toxicol 1999;23:559–62.
14. 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.
15. Levine B, Wu SC, Smialek JE. Zolpidem distribution in postmortem cases. J Forensic Sci 1999;44:369–71.
16. Meeker JE, Som GM, Macapagal GM, Benson PA. Zolpidem tissue concentrations in a multiple drug related death involving Ambien. J Anal Toxicol 1995;19:531–4.
17. Tracqui A, Kintz P, Mangin P. A fatality involving two unusual compounds—zolpidem and acepromazine. Am J Forensic Med Path 1993;14:309–12.
18. SPSS Inc. PASW statistics, 18.0. Chicago, IL: SPSS Inc., 2009.
19. Darke S, Degenhardt L, Mattick R. Mortality amongst illicit drug users: epidemiology, causes and intervention. Cambridge, UK: Cambridge University Press, 2007.
20. Berman ME, Jones GD, McCloskey MS. The effects of diazepam on self-aggressive behavior. Psychopharmacology 2005;178:100–6.
21. Carlsten A, Waern M. Are sedatives and hypnotics associated with increased suicide risk of suicide in the elderly? BMC Geriatr 2009;9:20.
22. Neutal CI, Patten SB. Risk of suicide after benzodiazepine and/or antidepressant use. Ann Epidemiol 1997;7:568–74.

Additional information and reprint requests
Professor Shane Darke, Ph.D.
National Drug and Alcohol Research Centre
University of New South Wales
NSW 2052
Sydney
Australia
E-mail: s.darke@unsw.edu.au