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Circumstances and toxicology of sudden or unnatural deaths involving alprazolam

Shane Darke[a,*], Michelle Torok[a], Johan Duflou[b,c,d,e]

[a] National Drug and Alcohol Research Centre, University of New South Wales, Australia
[b] Department of Forensic Medicine, Sydney Local Health District, Australia
[c] Sydney Medical School, University of Sydney, NSW, Australia
[d] School of Medical Sciences, University of New South Wales, Australia
[e] Department of Pathology, University of Sydney, NSW, Australia

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ABSTRACT

Background: There has been a great deal of clinical concern regarding alprazolam abuse. This paper reported on alprazolam positive cases of sudden or unnatural deaths presenting to the New South Wales Department of Forensic Medicine (DOFM), 1/1/1997–31/12/2012.
Methods: Case series.
Results: 412 cases were identified. There was a large increase in the annual number of cases, from 3 in 1997 to 86 in 2012. By 2012, 4.5% of all DOFM case presentations involved alprazolam. The mean age was 41.3 years and 66.5% were male. Circumstances of death were: accidental drug toxicity (57.0%), deliberate drug toxicity (10.4%), suicide by means other than drug overdose (12.6%), disease (10.0%), accident (5.1%), homicide (2.4%). The major factor driving the increase in cases was accidental drug toxicity involving alprazolam, rising from 0 in 1997 to 58 in 2012. A history of drug/alcohol problems was noted in 80.4%, and 56.6% were injecting drug users. The median alprazolam concentration was 0.08 mg/L (range 0.005–2.10 mg/L), with 37.4% of cases having concentrations of ≥0.1 mg/L. In 94.9% of cases, drugs other than alprazolam and its metabolites were present, including all accidental overdoses. The most commonly detected drugs were opioids (64.6%), others were benzodiazepines (44.4%) and alcohol (34.5%). A third (31.8%) of cases were HCV positive.
Conclusions: Cases involving alprazolam increased markedly, driven mostly by toxicity deaths amongst people with known drug and alcohol problems. Caution in prescribing alprazolam would appear appropriate, particularly to those with known drug dependence.

1. Introduction

Alprazolam is a rapid onset, high potency triazolobenzodiazepine with an average half-life of 11 h, widely used in the treatment of anxiety and panic disorders (Baselt, 2011; Márquez et al., 2011; Verster and Volkerts, 2004). The toxicity of alprazolam is considered to be greater than that of other commonly used benzodiazepines, such as diazepam, and is exacerbated by concomitant central nervous system (CNS) depressant use (Isbister et al., 2004; Jones and Holgrem, 2013; Lee et al., 2012).

There has been a great deal of concern in recent times regarding alprazolam, relating to increased prescribing rates, abuse, and drug-related mortality. Significant increases in the number of emergency room presentations and fatal toxicity cases involving alprazolam have been reported, most commonly in combination with other drugs (Jones and Holgrem, 2013; Maxwell, 2011; Rintoul et al., 2013; Shah et al., 2012; Wolf et al., 2005; Wunsch et al., 2009). Much of the increase in toxicity cases involving alprazolam appears due to its widespread use by injecting drug users (IDU), among whom benzodiazepines (and rapid onset benzodiazepines in particular) have long been popular (Darke et al., 2010; Forrester, 2006; Horyniak et al., 2012; Lee et al., 2012; Shah et al., 2012). It is worthy of note that while widely popular amongst IDU, benzodiazepines are not prescribed for the long-term management of drug problems such opioid dependence (NSW Health, 2006).

Few large scale case series have reported on the circumstances, toxicology and disease profile of alprazolam-related death (Jenkins et al., 1997; Jones and Holgrem, 2013; Shah et al., 2012; Wolf et al., 2005). As noted recently by Jones and Holgrem (2013), the forensic toxicology of alprazolam-related death is not well documented.

* Corresponding author at: National Drug and Alcohol Research Centre, University of New South Wales, NSW 2052, Australia. Tel.: +61 02 9385 0333; fax: +61 02 9385 0222.
E-mail address: s.darke@unsw.edu.au (S. Darke).

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Therapeutic, toxic and fatal ranges vary widely and overlap, although concentrations greater than 0.10 mg/L are generally considered toxic (Baselt, 2011; Jones and Holgrem, 2013; Shah et al., 2012). Moreover, blood concentrations of toxicity cases involving alprazolam have been shown to overlap with non-toxicity deaths, as well as with those of impaired drivers (Jones and Holgrem, 2013; Wolf et al., 2005). Concomitant drug use is almost universally reported, most notably CNS depressants such as diazepam, opioids and alcohol, and psychostimulants such as cocaine and methamphetamine (Jones and Holgrem, 2013; Maxwell, 2011; Shah et al., 2012; Wolf et al., 2005). The role of alprazolam in such polydrug deaths is unclear. In cases involving opioids and/or alcohol alprazolam, as a respiratory depressant itself, is likely to further contribute to the respiratory depression that these drugs engender (Baselt, 2011). While the depressant effects of each drug individually may not be toxic, their combined effects may produce substantial respiratory depression. Indeed, it was recently reported that alprazolam concentrations were significantly lower in toxicity cases involving other drugs than those involving alprazolam alone (Maxwell, 2011; Shah et al., 2012). To our knowledge, only one study has reported on the disease profile, or possible role of disease, in cases of alprazolam-related death (Shah et al., 2012). The authors reported noting a significantly greater degree of cardiovascular disease than seen in drug-related deaths not involving alprazolam.

The current study aimed to provide new data on trends, characteristics and clinical presentation sudden or unnatural death involving alprazolam across a 15-year period. We examined all cases presenting to the New South Wales Department of Forensic Medicine (DOFM) between 1997 and 2012 in which the alprazolam was detected in standard toxicological tests conducted as part of the medico-legal process. The DOFM is located in central Sydney, and is the primary forensic pathology centre in New South Wales (NSW), conducting between 2000 and 2500 autopsies per year. Specifically the study aimed to:

(1) Determine the characteristics, circumstances and causes of death of sudden or unnatural deaths involving alprazolam; and (2) Determine the toxicology of sudden or unnatural deaths involving alprazolam.

2. Methods

2.1. Case identification

Autopsy reports and police summaries of all cases in which blood alprazolam was detected and who underwent autopsy at the DOFM between 1 January, 1997 and 31 December, 2012 were retrieved. Permission to inspect the files was received from the Sydney Local Health District human research ethics committee. All cases were reviewed by the authors.

In NSW a case must be reported to the Coroner in a range of circumstances, including principally where a person dies a violent or unnatural death or where the cause of death is not known. Information was collected on age (years), marital status, employment, drug use histories, body length (m) and weight (kg), and body mass index (BMI) calculated. Circumstances of death, and case histories, were obtained from accompanying police reports to the coroner. Suicide was determined by the presence of suicide notes, verbal intent, police reports and witness statements. The majority of cases, including all suspected overdose cases, undergo a standardised forensic autopsy, with examination of all major organs and quantitative toxicological analysis. Cause of death is determined by the forensic pathologist on the basis of circumstances of death, the autopsy findings and the toxicological analyses. The forensic pathologist may report on: (i) the direct cause of death, (ii) the antecedent cause that lead to the direct cause, and (iii) other significant conditions associated with the death. Circumstances of death, and case histories, were obtained from accompanying police reports to the Coroner.

All autopsy blood samples were taken peripherally (femoral or subclavian vessels). Toxicological data were reported for alprazolam, other benzodiazepiness, alcohol, cannabis (determined by the presence of Δ-9-THC), opioids, psychostimulants, benzodiazepines, antidepressants and antipsychotic medications. Cocaethylene, an active metabolite of cocaine formed from the concomitant ingestion of cocaine and alcohol, was not tested for in routine screens. In cases where there was prolonged hospitalisation prior to death, antemortem toxicology taken at admission was reported, and drugs administered by hospital and medical staff excluded. All samples were screened by immunoassay and either by gas chromatography, high-performance liquid chromatography (HPLC) or liquid chromatography-quadrupole time of flight mass spectrometry (LC-QTOF-MS) for common drugs of abuse and select therapeutic substances. In 343 cases, full quantitation of alprazolam was available. In the remaining 69 cases, alprazolam was detected at a concentration <0.1 mg/L, with no further quantitation. All analyses were conducted by the toxicology laboratory of the NSW Forensic & Analytical Science Service (formerly the Division of Analytical Laboratories).

2.2. Statistical analyses

For normally distributed variables, means, standard deviations (SD) and ranges were presented, otherwise medians and ranges were presented. All analyses were conducted using IBM SPSS Statistics v. 20.0 (SPSS, 2011).

3. Results

3.1. Cases and circumstances of death

A total of 412 cases were identified. There was a large increase in annual cases, from 3 in 1997 to 86 in 2012 (Table 1). Cases increased sharply from 2009, and 81.6% of all cases occurred between 2009 and 2012. Overall, 1.3% of all case presentations to the DOFM across the study period involved alprazolam, rising from 0.1% in 1997 to 4.5% by 2012. There were no significant variance in cases by day of the week ($p = .92$), or month ($p = .17$).

Table 1
Cases involving alprazolam by circumstances of death, 1997–2012.

Year	Accidental drug overdose	Deliberate overdose	Violent suicide	Accident	Disease	Homicide	Cause unascertained	All cases	Proportion of cases presenting to DOFM[a]
1997	0	1	2	0	0	0	0	3	0.1%
1998	1	1	0	0	0	0	0	2	0.1%
1999	0	1	2	0	0	0	0	3	0.1%
2000	4	3	3	0	0	0	0	10	0.5%
2001	1	0	1	1	1	0	1	5	0.2%
2002	1	0	3	0	1	0	0	5	0.2%
2003	4	3	1	1	2	0	0	11	0.5%
2004	4	1	1	0	1	0	0	7	0.3%
2005	6	2	1	2	1	0	0	12	0.6%
2006	9	1	2	2	3	0	0	17	0.9%
2007	14	3	3	2	1	0	1	24	1.2%
2008	14	2	2	1	2	1	0	22	1.2%
2009	28	4	8	5	10	1	1	57	2.3%
2010	47	8	11	2	4	1	3	76	3.6%
2011	44	7	5	3	8	4	1	72	3.7%
2012	58	6	7	2	7	3	3	86	4.5%
Total	235	43	52	21	41	10	10	412	1.3%

[a] Department of Forensic Medicine.