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PAPER

TOXICOLOGY

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Toxicology and Characteristics of Fatal Oxycodone Toxicity Cases in New South Wales, Australia 1999–2008*

ABSTRACT: All cases of fatal oxycodone toxicity presenting to the New South Wales Department of Forensic Medicine over the period January 1, 1999, to December 31, 2008, were retrieved. A total of 70 cases were identified. The mean age was 48.9 years, 58.6% were men, 21.4% were suicides, and in 30% oxycodone had not been prescribed to the decedent. Injecting drug users constituted 27.1% of cases, and oxycodone tablets were injected immediately prior to death by 21.4%. The mean blood oxycodone concentration was 0.40 mg/L (range 0.06–53.00 mg/L). In all cases, psychoactive substances other than oxycodone were also detected, most frequently hypnosedatives (68.6%), other opioids (54.3%), antidepressants (41.4%), and alcohol (32.9%). Preexisting systemic disease was common: cardiovascular (64.2%), pulmonary (49.3%), hepatic (66.7%), and renal (43.9%).

KEYWORDS: forensic science, oxycodone, toxicity, toxicology, opioids

Oxycodone is an opioid analgesic typically prescribed for moderate to severe chronic pain (1). In recent years, there has been considerable concern in the United States (U.S.) about the abuse of oxycodone, with substantial increases in sales, and deaths attributed to the drug (1–9). In Australia, an increase in oxycodone use by illicit drug users has also been noted since the sustained reduction in heroin availability that occurred after 2000 (10,11). In 2008, a quarter of the national sample of injecting drug users (IDU) recruited for the Illicit Drug Reporting System reported recent oxycodone use, almost all by injection (12).

In sharp contrast to the extensive work conducted on the characteristics and toxicology of fatal toxicity cases involving opioids such as heroin and methadone (13–16), little comparable research has been done on oxycodone cases (17–21). The sole Australian study (18) was conducted in the early 1990s, prior to the sustained reduction in heroin availability. The current study aimed to determine the demographic characteristics, toxicology, and major autopsy findings of oxycodone toxicity cases presenting to the New South Wales (NSW) Department of Forensic Medicine (DOFM) over the 10-year period January 1, 1999, to December 31, 2008.

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Methods

Case Identification

All cases autopsied at the DOFM between January 1, 1999, and December 31, 2008, were identified in which the cause of death was attributed to oxycodone toxicity or the acute physical sequelae of such toxicity (e.g., hypoxic brain damage). 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 centre 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. Information was recorded on all major pathology noted in autopsy reports, including coronary, pulmonary, hepatic, and renal pathology. Quantitative toxicological analysis is performed in all non-natural deaths. Cause of death is determined by the forensic pathologist on the basis of circumstances of death, the comprehensive autopsy findings, and the toxicological analyses. The role of oxycodone toxicity was determined with reference to known toxic concentrations (22). Suicide was determined by the authors during the file audit on the basis of 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 veins) and were conducted by the Division

of Analytical Laboratories (DAL), NSW Department of Health. Blood toxicological data were reported for oxycodone, morphine (the primary metabolite of heroin), alcohol, methadone, cannabis (Δ-THC), methamphetamine (either methamphetamine or amphetamine), cocaine (determined by the presence of cocaine itself and/or the presence of benzoylecgonine), 3,4methylenedioxymethamphetamine (MDMA), benzodiazepines, antidepressants, and antipsychotic medications. All presented toxicological analyses were of whole blood. All bloods were screened by immunoassay and either by gas chromatography or by high-pressure liquid chromatography.

Statistical Analyses

Where distributions were highly skewed, medians and inter-quartile ranges were reported, otherwise means were presented. For bivariate comparisons, *t*-tests or odds ratios (OR) with 95% confidence interval (CI) were reported. For analysis of nondichotomous categorical variables, chi-square analyses were conducted. All analyses were conducted using SPSS for Windows (release 17.0) (23).

Results

Case Characteristics

A total of 70 cases were identified, 58.6% of which were men and a fifth due to suicide (Table 1). In 58 cases, diagnoses of multiple drug toxicity (including oxycodone) were made, and in 12 cases, oxycodone toxicity was diagnosed. A minority were married/de facto, and a small proportion employed. The majority were either retired or on a disability pension/benefit. Approximately a quarter were known IDU, and oxycodone tablets were injected immediately prior to death by a fifth. IDU were significantly younger than other cases (36.5 vs. 56.6 years, $t_{68} < 0.001$). In nearly a third of cases, oxycodone was not prescribed to the decedent, including 84.3% of IDU and 31.6% of other cases (OR 11.65, CI 3.42–39.72).

There were a number of significant gender differences. Women were older than men ($t_{68} = 4.3$, $p < 0.001$), and more likely to be married/defacto (OR 3.36, CI 1.16–9.71). They were less likely to be an IDU (OR 0.10, CI 0.03–0.50) or to have injected oxycodone prior to death (OR 0.16, CI 0.03–0.76).

TABLE 1—*Characteristics of oxycodone toxicity cases, 1999–2008.*

	Male ($n = 41$)	Female ($n = 29$)	All ($n = 70$)
Age	42.5	58.0	48.9
Suicide (%)	12.2	34.5	21.4
Marital status (%)			
Single/Separated/Widowed	80.5	55.2	70.0
Married/Defacto	19.5	44.8	30.0
Employment status (%)			
Unemployed	43.9	20.7	34.3
Disability pension/Sickness benefits	34.1	17.2	27.1
Retired	9.8	48.3	25.7
Employed	12.2	13.8	12.9
Injecting drug user (%)	41.5	6.9	27.1
Route of administration (%)			
Oral	68.3	93.1	78.6
Injected	31.7	6.9	21.4
Oxycodone treatment status (%)			
Not prescribed to person	39.0	17.2	30.0
Prescribed (chronic pain)	61.0	82.8	70.0
BMI	28.0	28.7	28.2

BMI, body mass index.

Cases of suicide were more likely to be women (OR 3.78, CI 1.13–12.66) and significantly older (58.7 vs. 46.3 years, $t_{68} = 2.7$, $p < 0.01$). A third (32.7%) of non-IDU were suicide cases compared to 6.7% of IDU ($p = 0.07$). Of the 14 non-IDU suicides, 12 were chronic pain patients.

Toxicology

The mean blood oxycodone concentration was 0.40 mg/L (range 0.06–53.00 mg/L), with no gender difference (Table 2). These are supratherapeutic levels of oxycodone (22). In all cases, psychoactive substances other than oxycodone were detected. The most prevalent substances were hypnosedatives (most commonly diazepam), other opioids (codeine and morphine), antidepressants (tricyclics), and alcohol. The median blood alcohol concentration among alcohol positive cases was 0.12 g/100 mL (range 0.01–0.40 g/100 mL). Antipsychotics were present in approximately a fifth of cases. Cannabis and psychostimulants were present in small proportions.

Systemic Disease

Preexisting systemic disease was present among substantial proportions of cases: cardiovascular (64.2%), pulmonary (49.3%), hepatic (66.7%), and renal (43.9%) (Table 3). There were no differences between men and women in the presence of cardiovascular disease (61.0% vs. 69.2%, $p = 0.49$), pulmonary disease (41.5% vs. 61.5%, $p = 0.1$), or hepatic disease (70.7% vs. 60.0%, $p = 0.37$), but women were more likely to have renal disease (68.0% vs.

TABLE 2—*Toxicology of oxycodone toxicity cases, 1999–2008.*

	Male ($n = 41$)	Female ($n = 29$)	All ($n = 70$)
Oxycodone median	0.40 mg/L (range 0.06–2.40)	0.55 mg/L (range 0.10–53.00)	0.40 mg/L (range 0.06–53.00)
Other opioids (%)	48.8	62.2	54.3
Codeine	17.1	44.4	27.1
Morphine	17.1	24.1	20.0
Tramadol	7.3	10.3	8.6
Propoxyphene	2.4	13.8	7.1
Meperidine	2.4	0.0	1.4
Alcohol (%)	31.7	34.5	32.9
Psychostimulants (%)	12.2	0.0	7.1
Methamphetamine	9.8	0.0	5.7
Cocaine	4.9	0.0	2.9
MDMA	0.0	0.0	0.0
Cannabis (%)	2.4	3.4	2.9
Hypnosedatives (%)	68.3	69.0	68.6
Diazepam	46.3	41.4	44.3
Oxazepam	19.5	10.3	15.7
Temazepam	7.3	13.8	10.0
Alprazolam	12.2	6.9	10.0
Clonazepam	7.3	3.4	5.7
Zolpidem	4.9	6.9	5.7
Nitrazepam	2.4	6.9	4.3
Flunitrazepam	0.0	3.4	1.4
Antidepressants (%)	31.7	51.2	41.4
Tricyclics	17.1	24.1	20.0
SSRI	12.5	17.2	14.3
SNRI	2.4	6.8	4.3
Tetracyclics	0	3.4	1.4
MAOI	0.0	3.4	1.4
Antipsychotics (%)	19.5	17.2	18.6
Olanzapine	14.6	10.3	12.9
Quetiapine	0.0	6.9	2.9
Amisulpride	2.4	0.0	1.4
Lithium	2.4	0.0	1.4

TABLE 3—*Major organ pathology of of oxycodone toxicity cases, 1999–2008.*

	Male (n = 41)	Female (n = 26)	All (n = 67)
Cardiac (%)			
Coronary artery atherosclerosis (Mod-Severe)	32.2	42.3	37.3
Fibrosis			
Myocardial fibrosis	17.1	23.1	19.4
Interstitial fibrosis	12.2	19.2	14.9
Perivascular fibrosis	9.8	17.2	13.4
Ventricular hypertrophy	12.2	19.0	14.9
Cardiomegaly	14.6	7.7	11.9
Pulmonary (%)			
Bronchopneumonia	19.5	23.1	20.9
Emphysema	14.6	19.2	16.4
Fibrosis	4.9	23.1	11.9
Asthma	4.9	0.0	3.0
Bronchitis	2.4	3.8	3.0
Hepatic (%)			
Steatosis	56.1	44.0	51.5
Lymphocytic infiltrate	31.7	16.0	25.8
Hepatomegaly	7.3	20.0	12.1
Fibrosis	7.3	8.0	7.6
Cirrhosis	4.9	4.0	4.5
Renal (%)			
Nephrosclerosis	17.1	56.0	31.8
Fibrosis	12.2	20.0	15.2
Cysts	2.4	12.0	6.1
Nephritis	2.4	4.0	3.0

29.3%, OR 5.13, CI 1.75–15.15). Older age was associated with higher risk of cardiovascular (OR 1.08, CI 1.03–1.13), pulmonary (OR 1.04, CI 1.01–1.07), and renal pathology (OR 1.08, CI 1.04–1.12), but not with hepatic pathology (p = 0.15).

Injecting drug users were more likely to have hepatic disease (88.9% vs. 58.3%, OR 5.71, CI 1.18–27.68) and non-IDU to have cardiovascular disease (71.4% vs. 44.4%, OR 3.13, CI 1.02–9.52), with no differences between IDU and others in pulmonary (33.3% vs. 55.1%, p = 0.11) or renal pathology (27.8% vs. 50.0%, p = 0.11). Of the 19 known IDU, 6 (31.6%) had refractile/polarizable material detected in their pulmonary vasculature. Two of these cases exhibited signs of pulmonary hypertension diagnosed, and one had evidence of a recent pulmonary infarct.

Discussion

The cases in this series fell into two broad groups: younger IDU aged on average in their 30s and chronic pain patients aged on average in their 50s. While IDU constituted a significant proportion of cases, the majority belonged to the latter group. In a third of cases, the oxycodone used prior to death was not prescribed to the individual. This did not, however, solely reflect the two major types of cases identified. While the overwhelming majority of IDU were not prescribed oxycodone, this was also true of a third of other cases.

One of the major findings to emerge was the prominent role of suicide. One in five cases was due to deliberate overdose, including a third of women. Such a high level of suicide has clinical implications for caution by medical practitioners in the prescribing of oxycodone. Suicide, however, occurred almost exclusively among older pain patients, with only one of 15 suicides being an IDU. Indeed, one in three non-IDU cases were deliberate overdoses, nearly all chronic pain patients. IDU cases, consistent with previous studies of opioid overdose among IDU (14–17), appeared overwhelmingly accidental. Clinically, it is the older, depressed pain patients who appear to be the high-risk group. In terms of clinical risk, it is notable that over 40% of cases had antidepressants detected, including half of women. In terms of prescribing, such a demographic profile carries a great risk of mortality. Similarly, in cases of fatal oxycodone toxicity from this demographic, suicide should be treated as a highly likely possibility.

The toxicology of cases was consistent with earlier studies of oxycodone, although it should be noted that testing of other tissues was not conducted (17–21). In *all* cases, substances other than oxycodone were also detected. Consistent with the toxicological patterns seen among opioid toxicity cases (13–21), the major concomitantly occurring substances were central nervous system depressants, specifically benzodiazepines, alcohol, and opioids other than oxycodone. The preponderance of benzodiazepines more closely parallels the toxicology of methadone or buprenorphine than of heroin, in which alcohol is typically the most frequent concomitant substance (13–16).

While a third of cases were IDU (n = 19) and there was a large proportion of nonprescribed use of oxycodone, there was no evidence of an "epidemic" of IDU oxycodone deaths as seen in the U.S., where such cases grew to exceed those due to heroin or cocaine (4,6,7). By way of comparison, a recent study reported that over the 10-year period 1998–2007, 1000 heroin overdose cases and 193 cases of methadone overdose presented to DOFM (14). This may reflect that oxycodone use, while common, is also sporadic among IDU, whereas use by IDU appears far more common in the U.S. (12). While the reasons for this cultural difference are unclear, it may reflect the widespread availability of cheap heroin in Australia, which is the drug of choice for illicit opioid users (12). It is the older, chronic pain patient who appeared to constitute the highest risk for oxycodone toxicity in this series.

There were significant levels of systemic disease. While IDU are well documented to have high levels of systemic disease (14), non-IDU cases in this series showed similarly high levels. Indeed, it was only hepatic pathology in which IDU exceed other cases, reflecting the high rates of hepatitis C among these populations (13,14). Non-IDU had higher levels of cardiovascular disease, a probable reflection of the older age of these cases. The presence of polarizable material in the pulmonary vasculature of a third of known IDU (a sequelae of injecting tablet form preparations) is of clinical import, as it is associated with the development of long-term pulmonary vascular pathology, particularly pulmonary hypertension. Indeed, two IDU cases had pulmonary hypertension and a further one had evidence of a recent pulmonary infarct.

In summary, two distinct populations of cases emerged: IDU and older pain patients. For both groups, polypharmacy was universal. While most cases were accidental, polydrug overdoses, deliberate overdose was prominent among older cases, and women in particular.

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