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Barbara C. Wolf,[1] *M.D.; Wendy A. Lavezzi,*[2] *M.D.; Linda M. Sullivan,*[3] *B.S.; and Lisa M. Flannagan,*[1] *M.D.*

One Hundred Seventy Two Deaths Involving the Use of Oxycodone in Palm Beach County

ABSTRACT: Oxycodone is a potent semi-synthetic narcotic prescribed for the management of pain. Previous investigators have reported that the abuse of oxycodone is most frequently seen in conjunction with the abuse of other drugs, although fatalities have been reported with oxycodone alone. We undertook a retrospective review of cases investigated by the Palm Beach County Medical Examiner's Office in which postmortem toxicologic studies indicated the presence of oxycodone. A total of 172 consecutive cases were studied, including 18 in which death was attributed to oxycodone toxicity, 117 to combined drug toxicity, 23 to trauma, 9 to natural causes and 5 to another drug or drugs. The postmortem blood concentrations of oxycodone overlapped among the groups. The mean blood oxycodone concentration among the cases of oxycodone toxicity was 0.69 mg/L, combined drug toxicity 0.72 mg/L and trauma 0.62 mg/L. Concentrations were lower in cases of deaths attributed to natural causes and to another drug or drugs (mean each 0.087 mg/L). Benzodiazepines, detected in 96 cases, were the most common co-intoxicants in the cases of combined drug toxicity, followed by cocaine, which was found in 41. The most frequently encountered benzodiazepine was alprazolam. This study confirms that deaths in which oxycodone is a factor are most commonly cases of combined drug toxicity. The high incidence of alprazolam as a co-intoxicant has not been previously recognized.

KEYWORDS: forensic science, oxycodone, death, drug concentrations, toxicology

Oxycodone is semi-synthetic opioid analgesic, which is used therapeutically in the management of moderate to severe pain. It is available in both immediate release forms, such as Percodan, and controlled release forms i.e., OxyContin (1). The drug is well absorbed, with a bioavailability of 60% to 87% (1). Oxycodone is metabolized to oxymorphone, an active narcotic analgesic, and to noroxycodone, which is relatively inactive (2).

Recent investigators have reported a rise in the abuse of oxycodone, in particular OxyContin (3–5). OxyContin has a high level of absorption when chewed because the controlled release mechanism is bypassed. Some abusers achieve this effect by crushing the tablets, dissolving them in water, and then either snorting or injecting the drug (4). An increase in deaths involving oxycodone has also been reported (6). Although deaths have been attributed to oxycodone alone (6–8), the majority of deaths attributable to oxycodone are cases of combined drug toxicity (7,9,10). Reported drug combinations have included alcohol, cocaine, other narcotics, benzodiazepines, marijuana, and anti-depressants (7,9).

We have noticed an increase in deaths attributable to oxycodone, alone or in combination, both in individuals prescribed the drug and in the non-treatment population, in Palm Beach County, Florida. Recent media accounts have called attention to the rise in oxycodone abuse. We undertook the current study to further elucidate the pattern of oxycodone abuse among oxycodone-positive decedents in cases investigated by the Medical Examiner's Office.

[1] Office of the Medical Examiner, Palm Beach County, West Palm Beach, FL.
[2] Department of Pathology and Laboratory Medicine, Albany Medical Center Hospital, Albany New York.
[3] Wuesthoff Reference Laboratories, Melbourne, FL.
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Materials and Methods

Case Reviews

One hundred seventy-two consecutive cases in which oxycodone was detected in postmortem blood specimens were retrieved from the files of the Palm Beach County, Florida, Medical Examiner's Office between January, 2000 and October, 2003. The cases had all been investigated initially by a forensic investigator from the Medical Examiner's Office, and a complete autopsy was performed by the Office. Toxicologic studies were performed by the Wuesthoff Reference Laboratory, Melbourne, Florida, or in occasional cases, by the Dade County Medical Examiner Toxicology Division.

The investigative reports as well as the reports of the postmortem examination and postmortem toxicologic studies were reviewed. Demographic data collected included the decedents' ages, race and sex. The autopsy reports were reviewed for cause and manner of death and for the presence of trauma or preexisting natural disease. Information pertaining to the circumstances of death was obtained from the investigators' reports.

Analytic Methods

As part of routine toxicology analysis, comprehensive urine drug screens were performed by immunoassay, thin-layer chromatography, and high performance liquid chromatography. Comprehensive blood drug screens were analyzed qualitatively by microtiter plate enzyme immunoassay (MPEIA), fluorescent polarization immunoassay, full scan gas chromatography-mass spectrometry (GC-MS). If an opiate was identified by the drug screen, quantitation of free and total opiates (codeine, morphine, hydrocodone, hydromorphone, 6-MAM and oxycodone) were performed by GC-MS.

Specimens were collected in red-top vials with measured sodium fluoride. Peripheral whole blood specimens were used for

quantitation when available. The samples were assayed in a batch, along with standards and controls. Standards and deuterated internal standards were obtained from Cerilliant (Austin, Texas). After enzyme hydrolysis with B-glucuronidase (total fraction only), 2 mL of whole blood was mixed with 50 μL of oxycodone-d6 internal standard and four mL of distilled water, vortexed for 30 s and allowed to sit for 10 min. Samples were centrifuged for 10 min at 2500 rpm, after which supernatant was removed. The oxime derivatives of hydrocodone and hydromorphone were formed by the addition of 50 μL of 10% hydroxylamine hydrochloride (HOX), capped, vortex mixed and incubated at 50°C for 30 min. The oxime introduces an additional region for silylation that produces different retention times and spectra for these compounds (11). The pH was adjusted with phosphate buffer (pH 6.0), and centrifuged for 10 min at 2500 rpm. Supernatant was transferred to tubes containing 1 mL of pH6 phosphate buffer. The addition of 300 μL of 1.0 N NaOH was added to samples for a final pH of 8.0. Samples were centrifuged and supernatant was transferred. Samples were extracted by solid phase extraction (Clean Screen-United Technologies, Inc). The opiate SPE procedure, as written by UCT, was conducted as described (12). Eluate was evaporated to dryness under nitrogen at less than 40°C. Fifty μL of acetonitrile was added and vortex mixed. One hundred μL MSTFA was added to tube, over-laid with nitrogen, capped, and vortex mixed. The samples were incubated at 70°C for 30 min. Samples were cooled, vortex mixed and transferred to a GC-MS vial. One μL of sample was injected for analysis.

GC-MS was performed with an Agilent Technologies (Palo Alto, CA) 5972 MSD, coupled to a HP-1 (15 m × 0.25-mm i.d., 0.25-μm film thickness) capillary column with a helium flow rate of approximately 0.9 mL/min. Chemstation software was utilized and the 5890 GC was operated in the splitless mode. The injection port temperature was 250°C, and the transfer line temperature was 290°C. The oven temperature was initially held at 120°C for 1 min and then increased by 20°C/min to a final temperature of 280°C and held for 2 min. The 5972MSD was operated in the selected ion-monitoring mode (SIM). The following ions were monitored: oxycodone target ion 474, qualifier ions 459, 385, oxycodone-d6 target ion 480, qualifier ion 465. Oxycodone was identified by retention time and relative abundance of the two ions monitored as compared to values obtained from standards analyzed on the same run. Ion ratios were derived by dividing the area of the qualifier ion by the area of the target/quant ion with an acceptance criterion of ±20%. Standards were extracted and calibration curves were derived on all runs. Oxycodone was quantitatively determined by comparing the ratio of integrated ion peak area with that of deuterated oxycodone. Range of linearity for oxycodone was 25–4000 ng/mL. Limit of detection and limit of quantitation was 25 ng/mL. Precision of assay as measured by percent CV was 2.6–4.9.

Results

There were 172 cases identified in which oxycodone was detected in postmortem blood specimens. The cases included 133 males and 39 females. Ages ranged from 17 to 91 years (mean 41.0 years). All of the decedents were white, except for two black females.

The oxycodone-positive cases included 18 in which the cause of death was attributed to oxycodone toxicity and 117 in which death was attributed to combined drug toxicity. The most common scenario involved an individual with a history of drug abuse who was found dead. Oxycodone was considered to be an incidental finding in 23 cases of death due to trauma, 9 attributed to natural causes and 5 deaths attributed to another drug or drugs.

TABLE 1—*Postmortem oxycodone blood concentrations.*

Cause of death	Range (mg/L)	Mean (mg/L)
Oxycodone toxicity	0.21–4.71	0.69
Combined drug toxicity	0.025–17.50	0.72
Trauma	0.025–1.99	0.62
Natural	0.025–0.19	0.087
Other drug(s)	0.025–0.17	0.087

Those deaths in which oxycodone was the only drug detected in toxic concentrations were ruled as oxycodone toxicity and included 11 males and 7 females. Ages ranged from 17 to 64 years (mean 40.0 years). The manner of death was classified as accidental in 15 cases and suicide in 3 cases. The ruling on the manner of death was based on a combination of postmortem toxicologic studies and investigative information. A case was classified as a suicide only if there was clear-cut information indicating that the individual intended to die. The postmortem blood oxycodone concentrations in the cases of oxycodone toxicity ranged from 0.21 mg/L to 4.71 mg/L (mean 0.69 mg/L) (Table 1). Oxycodone was the only drug detected in postmortem toxicologic studies in 8 of these cases, with the oxycodone concentrations ranging from 0.21 mg/L to 1.22 mg/L (mean 0.55 mg/L).

The cases of death attributed to combined drug toxicity included 89 males and 28 females. Ages ranged from 17 to 91 years (mean 39.3 years). These deaths included 100 accidental deaths and 16 suicides. The manner of death was classified as undetermined in 1 case. Oxycodone concentrations ranged from 0.025 mg/L to 17.50 mg/L (mean 0.72 mg/L).

Benzodiazepines were the most common co-intoxicants in the cases of combined drug toxicity. A benzodiazepine or benzodiazepines were detected in 96 cases, including alprazolam in 46 cases and diazepam and/or nordiazepam in 37. Oxycodone blood concentrations in cases in which alprazolam was present ranged from 0.025 mg/L to 2.9 mg/L (mean 0.552 mg/L). In 25 cases, both cocaine and/or its metabolites and a benzodiazepine were detected. Cocaine and/or its metabolites alone were found in 16 cases. Heroin, identified by the presence of morphine and 6-monoacetylmorphine, was found in 3 cases, including 2 in which cocaine was also present. Morphine was identified in 11 cases, hydrocodone in 17 and methadone in 22 cases. Ethanol in a concentration of >0.08 G/dL was present in 22 cases.

The 23 cases of death due to trauma included 21 males and 2 females. Ages ranged from 18 to 84 years (mean 47.6 years). Oxycodone concentrations ranged from 0.025 mg/L to 1.99 mg/L (mean 0.62 mg/L). The cases included 8 classified as accidents, 7 suicides, 6 homicides and 2 in which the manner of death was undetermined.

The cases in which death was attributed to natural causes included 8 males and 1 female. Ages ranged from 22 to 69 years (mean 52.3 years). Oxycodone concentrations ranged from 0.025 mg/L to 0.19 mg/L (mean .087 mg/L).

The 5 deaths attributed to the toxicity of another drug in which oxycodone was considered to be an incidental finding included 4 males and 1 female. Ages ranged from 25 to 78 years (mean 46.8 years). Oxycodone concentrations ranged from 0.025 mg/L to

0.17 mg/L (mean 0.087 mg/L). Four cases were classified as accidental deaths and 1 as suicide.

Discussion

Oxycodone is a potent narcotic analgesic, which is popularly prescribed for the management of pain. The increased therapeutic use of oxycodone, particularly OxyContin, the sustained release form of the drug, has been followed by an increase in deaths attributable to oxycodone, both in the treatment and non-treatment populations (8). We reviewed 172 cases in which oxycodone was detected in postmortem toxicologic studies. The oxycodone-positive deaths in our series included 133 males and 39 females. The mean age was 41.0 years, and there is a striking predominance of white individuals. These demographics are similar to those reported by previous investigators (4,7).

Oxycodone abuse most commonly occurs in conjunction with the abuse of other drugs (7,9,10). Limited data is available in the literature on postmortem blood oxycodone concentrations in cases of deaths involving the drug. Because of the frequent presence of other drugs in postmortem toxicologic analysis, it may be difficult to determine the actual role of oxycodone in theses cases. Baselt (2) reviewed 6 deaths involving oxycodone, 3 of which involved at least 1 other depressant drug. Postmortem oxycodone levels in these cases ranged from 0.4 mg/L to 14.0 mg/L. Spiller (8) reported 24 deaths attributable to oxycodone alone, with no other drugs detected in postmortem analysis. The postmortem blood oxycodone concentrations in those cases ranged from 0.12 mg/L to 8.0 mg/L (mean 1.23 mg/L), with 13 cases having oxycodone concentrations less than or equal to 0.5 mg/L. Drummer and colleagues (6) studied 9 deaths involving oxycodone. Other drugs were detected in all of the cases investigated, although in 3 cases no other drug was found in a toxic concentration. Blood oxycodone concentrations in those cases ranged from 0.6 to 1.4 mg/L (mean 0.90 mg/L).

The postmortem oxycodone blood concentrations in the 18 cases of oxycodone toxicity in our study ranged from 0.21 mg/L to 4.71 mg/L (mean 0.69 mg/L). In 8 of these cases, oxycodone was the only drug detected, with concentrations ranging from 0.21 mg/L to 1.22 mg/L (mean 0.55 mg/L). These ranges overlapped those seen in the 117 cases where death was attributed to combined drug toxicity, where oxycodone concentrations ranged from 0.025 mg/L to 17.50 mg/L (mean 0.72 mg/L). Our findings are in contrast to those of Cone and co-workers (13). These investigators studied 919 cases of oxycodone-related deaths and found a lower mean blood oxycodone concentration in cases with multiple contributory drugs than in cases in which oxycodone was the only drug involved. The postmortem oxycodone blood concentrations seen in our oxycodone-related deaths also overlapped those seen in cases of death due to trauma, where oxycodone was considered to be an incidental finding and where oxycodone blood concentrations ranged from 0.025 mg/L to 1.99 mg/L (mean 0.62 mg/L). Because of this overlap, it may not be possible to conclusively establish toxic and lethal concentrations of oxycodone. It may also be difficult to determine the actual role of oxycodone in cases of combined drug toxicity.

A number of previous studies have reported that oxycodone abuse generally occurs in conjunction with the use of other drugs (1,7–9). Abusers of oxycodone may not be aware of the potential deleterious effects of combining the drug with other commonly detected drugs in cases of polypharmacy abuse. These drugs have included both other depressant drugs, such as benzodiazepines, which would potentiate the respiratory depressant effects of opioids (7,14–16), and psychostimulants, such as cocaine (9). We also found that the majority of deaths involving oxycodone were cases of combined drug toxicity. Benzodiazepines were the most common co-intoxicants in our cases of combined drug toxicity, detected in 96 cases, with alprazolam the most frequent benzodiazepine found. The high rate of alprazolam co-intoxication found in our series has not been previously reported. Cocaine was the second most common co-intoxicant. We have previously reported that benzodiazepines and cocaine were the most common co-intoxicants in cases where methadone was believed to play a causal role in death (17).

Dalpe-Scott and co-workers (18) have reported that oxycodone may exhibit postmortem redistribution. There was no appreciable difference in the means and ranges of postmortem blood concentrations of oxycodone in peripheral blood versus central blood in our cases.

In conclusion, oxycodone abuse in Palm Beach County, Florida is most frequently encountered in the setting of multiple drug co-intoxication. There is significant overlap in blood oxycodone concentrations between cases in which death is attributed to oxycodone toxicity, combined drug toxicity, and those in which oxycodone is considered to be an incidental finding. The paucity of data in the literature establishing toxic levels of oxycodone makes it difficult to determine its role in cases in which the drug is detected. This difficulty is compounded in the majority of cases in which the concentrations of other drugs detected also need to be taken into consideration.

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Additional information and reprint requests:
Barbara C. Wolf, M.D.
Deputy Medical Examiner
Office of the Medical Examiner
Palm Beach County
3126 Gun Club Road
West Palm Beach, FL, 33406