A Comparison of Methadone, Oxycodone, and Hydrocodone Related Deaths in Northeast Ohio*

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Abstract

Increases in methadone and oxycodone related deaths have been recently documented in the United States. In response to these reports, the authors investigated cases over a six-year period in which postmortem toxicological analyses revealed the presence of methadone, hydrocodone, and oxycodone. The study was designed to determine whether regional methadone-associated mortality in Cuyahoga County reflected national trends and more specifically, to distinguish methadone mortality from other commonly used opioid analgesics. All records of decedents that were found to be positive for methadone, hydrocodone, and/or oxycodone in 1998-2003 were reviewed. The cause and manner of death and demographic information was compiled. The cases were divided into lethal intoxications and cases where a positive result was determined to be an incidental finding. Lethal intoxications as a result of only methadone, hydrocodone, or oxycodone were separated from polydrug intoxications. Throughout the study, an increase was observed in the number of positive cases. In contrast to recent national data, although the number of methadone-positive cases increased from 4 in 1998 to 18 in 2003, this did not result in an increase in methadone overdoses [1 death in 1998 (25%) to 4 deaths in 2003 (22%)]. Although the pharmacokinetic profiles differ, methadone, hydrocodone, and oxycodone lethal intoxications equally comprised 28-29% of cases in which these drugs were detected. There was an overlap in the range of blood concentrations observed for the drug-related death groups and the incidental finding groups. However, mean and median concentrations in oxycodone and hydrocodone related deaths were more than two times greater than those in non-drug-related deaths.

Introduction

Abuse of prescription drugs has exceeded all illicit drugs except marijuana in the U.S., according to the U.N. affiliated International Narcotics Control Board (1). According to the 2005 National Survey on Drug Use and Health (NSDUH), an estimated 6.4 million Americans used prescription drugs for non-medical purposes in the past month, and 4.7 million of these used prescription pain relievers (2). The most prevalent source of prescription drugs for non-medical users was “from a friend or relative for free.” As indicated by the U.S. Drug Abuse Warning Network (DAWN), there were approximately one-half-million emergency department (ED) visits involving non-medical use of pharmaceuticals in 2004, including an estimated 158,281 (31.9%) ED visits involving opiates/opioids. The most frequently reported opioids were hydrocodone products (26.8% of opiates/opioids), oxycodone products (23.1%), and methadone (20.1%) (3). Additionally, DAWN reported opiate-related drug misuse deaths in six states for the year 2003 (4). The states of Maine, New Hampshire, Vermont, Maryland, Utah, and New Mexico participated. Methadone-related mortality was greater than oxycodone or hydrocodone mortality in all but the state of Vermont, where oxycodone associated mortality was greatest.

Oxycodone is a semi-synthetic opioid derived from thebaine, a constituent of opium. Oxycodone is approximately equipotent to morphine when administered subcutaneously; however, the drug possesses a higher oral/parenteral efficacy ratio (5). Oxycodone®, the controlled release formulation, is indicated for the treatment of moderate to severe pain and has received increased attention in recent years. Rural areas have experienced the greatest abuse of oxycodone as a substitute for heroin, and thus the drug is referred to as “hillbilly heroin”. Illicit use by persons seeking feelings of euphoria, relaxation, and sedation often involves crushing the time-release formulation to render the entire dose immediately available for absorption. Acute intoxication with oxycodone can produce severe respiratory depression; skeletal muscle flaccidity; cold, clammy skin; reduction of blood pressure and heart rate; coma; respiratory arrest; and death. Oxycodone is a Schedule II drug under the federal Controlled Substance Act of 1970.

Methadone is a synthetic opioid agonist that belongs to a class of compounds referred to as diphenylpropylamine derivatives. Methadone has been used for over 40 years in the treatment of heroin addiction. Like oxycodone, methadone is also...
Material and Methods

The authors performed a computer database search of 21,460 deaths in Cuyahoga County, Ohio, from January 1, 1998 to December 31, 2003. The records of decedents positive for methadone, hydrocodone, or oxycodone were retrieved. Demographic information including age, gender, race, and location of residence was collected. The cause and manner of death was compiled and the cases divided into lethal intoxications and those cases where a positive result was determined to be an incidental finding. The authors restricted the lethal intoxication category to those cases in which opioid intoxication was explicitly reported as the cause of death. Lethal intoxications that resulted from only methadone, hydrocodone, or oxycodone were separated from polydrug intoxications. Polydrug intoxications for each of the opioids were compared to identify common drug combinations.

Toxicological results were tabulated for each type of drug based upon the laboratory testing regimen. The postmortem toxicological testing protocol included general screening techniques followed by confirmatory analyses. Screening techniques were as follows: colorimetry for acetaminophen and salicylates; volatiles by headspace gas chromatography with flame-ionization detection (GC-FID); drugs of abuse screening in urine by an enzyme multiplied immunoassay technique (EMIT®); liquid–liquid basic drug extraction and gas chromatography with nitrogen-phosphorus detection (GC–NPD); and liquid–liquid acidic/neutral drug extraction followed by GC–FID. GC–mass spectrometry with electron impact ionization (GC–MS) was the principal confirmatory technique utilized.

Methadone and oxycodone were qualitatively detected at or above 0.05 mg/L in urine with a liquid–liquid basic extraction and GC–NPD. Methadone and oxycodone blood concentrations were quantitated with a second basic liquid/liquid extraction and GC–NPD, utilizing an acidic back extraction to clean up the extract, with a limit of quantitation (LOQ) and low reporting limit (LRL) of 0.05 mg/L. For quantitation, a single-point calibrator at 1 mg/L was assayed with positive quality control samples at 0.5 and 1.5 mg/L. Promazine was the internal standard (I.S.) utilized. During 1998–1999, oxycodone was quantitated utilizing the method outlined here for hydrocodone. Hydrocodone was occasionally detected using the basic drug assay but was also detected by urine EMIT opiate class screening with a 0.30 mg/L cutoff (target drug = morphine). Blood was screened for the opiate class when urine was unavailable with a modified matrix solid-phase extraction and subsequent EMIT screen at a 0.02 mg/L morphine target cutoff. In house data demonstrated that hydrocodone would produce a positive result with this modified assay at concentrations ≥ 0.025 mg/L (8).

The presence of methadone and oxycodone was confirmed qualitatively utilizing GC–MS in SCAN mode and mass spectral comparison with a library or calibrator assayed in the same run. Suspected hydrocodone positive specimens were quantitated and confirmed following solid-phase extraction and N-methyl-N-trifluoroacetamide (MSTFA) derivatization utilizing GC–MS–EI selected ion monitoring (SIM) mode analysis with multipoint calibration (0.01–0.4 mg/L), a positive quality control sample (0.16 mg/L), and a LRL of 0.01 mg/L.

Results

A review of the data from 21,460 cases demonstrated 267 males and 147 females positive for one or more of the three opioids (N = 414). The majority of opioid-positive decedents were white (N = 323), 91 were black, and no other races were represented. Decedent ages ranged from 2 to 101 years. Caucasian males between the ages of 34 and 51 years (mean = 42.5) were the demographic group predominantly positive for each of the three opioids. Decedents in which methadone was detected were found to live equally within Cleveland city limits and the suburbs compared with more decedents living in the suburbs in the hydrocodone and oxycodone cases. Table I provides a summary of the demographic data for each group.

Figure 1 illustrates the number of positive cases for each year of the study for each drug. In the years 1998–2003, a total of 55 decedents were positive for methadone. The least number of cases occurred in 1999 with the largest number identified in the last year of the study. For the 200 cases positive for hydrocodone, a steep increase was observed between 1998 and 2000, followed by a plateau in the number of cases. A similar
pattern was also observed for the 190 oxycodone-positive cases. More than one drug of interest was detected in 31 decedents, resulting in a total of 445 positive results. The data demonstrated that the number of methadone cases increased by 450% over the study period compared with increases of 409% and 314% for oxycodone and hydrocodone, respectively.

Figure 2 illustrates the number of cases in which the cause of death was determined to be drug intoxication. In 1998 one methadone positive case was determined to be a drug-related death. By 2003, this number had risen to four cases. For oxycodone in 1998, three cases were determined to be oxycodone related deaths. The number of cases increased in 2000 to 13, and this number was maintained within 1-2 cases through the last year of the study. The number of hydrocodone intoxications increased by more than 200% from 1999 to 2000. Succeeding years maintained the rise observed in 2000. Gender, age, and race for methadone, oxycodone, or hydrocodone related deaths did not appear to differ from those cases of incidental findings. The oldest and youngest individuals in the study occurred in the oxycodone group. A 101-year-old white female died in the suburbs of acute bronchopneumonia following a fracture, with an oxycodone level of 0.27 mg/L. Conversely, a 2-year-old black female died in Cleveland of oxycodone intoxication with a blood concentration of 1.36 mg/L (9).

Table II summarizes opioid blood concentrations for drug-related and non-drug-related deaths. For methadone it is apparent that there is an overlap in the range of concentrations measured for the two groups. In addition, the mean concentrations are similar with large SDs. In the incidental group, methadone was detected in urine only for three cases, and no quantitation determined in the blood for one case. In this category, there were five cases with blood methadone concentrations > 1 mg/L [1.08, 1.17 (femoral 0.89), 1.45, 1.67 (femoral 0.41), and 4.26 mg/L]. The cause and manner of death in these cases were acute intoxication with paroxetine, accident; rupture of spleen due to splenomegaly due to fungal endocarditis, accident; bronchopneumonia, accident; ASCVD with organizing occlusive thrombosis, natural; and massive pulmonary embolism, natural, respectively. Similar blood concentrations were observed in four cases in the intoxication group (1.17, 1.19, 1.30, and 1.31 mg/L).

There were 135 cases for which the presence of oxycodone was considered an incidental finding. For 50 of these cases oxycodone was detected in urine, bile, or CSF only. In the remaining 85 cases, the oxycodone concentration ranged from 0.02 to 2.0 mg/L. Table II illustrates the mean ± SD and median for these findings. In this group there were 8 cases with oxycodone concentrations > 1.0 mg/L. The cause of death in these cases included natural deaths due to cancer, ASCVD, cardiomyopathy, diabetic ketoacidosis, and an accidental death due to blunt impact injury. There were 55 oxycodone related deaths. Urine-only positive results were obtained for five cases. The range of blood oxycodone concentrations in the remaining 50 cases was 0.01–36.54 mg/L. Table II illustrates the mean ± SD and median for these findings. If these parameters are calculated without the high result of 36.54 mg/L, the mean ± SD, median results are 1.15 ± 2.45 (N = 49), 0.55 mg/L, respectively. There were 15 (27% of oxycodone intoxication) cases with oxycodone concentrations > 1.0 mg/L (1.08–36.54 mg/L), including 6 cases > 2 mg/L with 2 cases with concentrations > 10 mg/L. Although the standard deviation for the intoxication group data was higher than for the incidental group, the mean and median oxycodone blood concentrations were more than two times greater for the intoxication deaths compared with deaths in which the presence of oxycodone was considered an incidental finding.

There were 200 cases positive for hydrocodone during the study period. The presence of hydrocodone was considered an incidental finding in 144 deaths. In
these cases, the blood concentration ranged from 0.01 to 2.56 mg/L (N = 115). The blood was negative in 29 cases; 20 cases in this group had blood hydrocodone concentrations > 0.200 mg/L. In these cases, the cause of death included hypertensive cardiovascular disease, arteriosclerosis [natural]; acute bronchopneumonia [accident]; hanging, asphyxification by carbon monoxide [suicide]; and strangulation with blunt impacts [homicide]. Two of these cases had concentrations > 1.00 mg/L [Case 1: putrefied specimens, coronary sclerotic heart disease with myocardial fibrosis; Case 2: no autopsy, atherosclerotic heart disease]. If these 2 cases are removed from the calculations the mean, SD, and median values are decreased to 0.09, 0.11, and 0.049 mg/L, respectively.

The range of concentration in the blood of hydrocodone related deaths was 0.012-1.66 (N = 54). Twenty-three (43%) cases had concentrations > 0.200 mg/L (0.214-1.66 mg/L). Although the range in blood concentration was similar for both groups, the mean and median concentrations for hydrocodone related deaths were more than 2 and 3 times higher, respectively, than the same parameters in the incidental group.

The data for the drug-related deaths was evaluated for single and polydrug abuse. When considering the methadone deaths, only 3/16 or 19% of decedents died as a result of methadone intoxication alone. The blood methadone concentrations in these deaths were 0.31, 0.74, and 1.17 mg/L. The most common drug combinations were opioids, including 6-acetylmorphine, codeine, morphine, hydrocodone, hydrodromorphone, meperidine, tramadol, propoxyphene, and methadone, N = 22; benzodiazepines (N = 20); ethanol (N = 16); cocaine and metabolites (N = 20); antihistamines (N = 7); and muscle relaxants (N = 5). Hydrocodone-only intoxications accounted for 7 of the 56 (12.5%) hydrocodone related deaths. The blood concentrations in these cases ranged from 0.072 to 1.663 mg/L. In this group of opioid deaths, the most common drug combinations were also other opioids (N = 34, including 7 oxycodone cases), benzodiazepines (N = 27), antidepressants (N = 18), muscle relaxants (N = 13), ethanol (N = 12), acetaminophen (N = 10), and antihistamines (N = 9).

Table II. Blood Opioid Concentrations

<table>
<thead>
<tr>
<th>Blood Drug Concentration (mg/L)</th>
<th>Methadone</th>
<th>Oxycodeone</th>
<th>Hydrocodeone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>190</td>
<td>200</td>
</tr>
<tr>
<td>Drug-related N</td>
<td>16</td>
<td>55*</td>
<td>56*</td>
</tr>
<tr>
<td>Range</td>
<td>0.11-1.31</td>
<td>0.01-36.54</td>
<td>0.012-1.66</td>
</tr>
<tr>
<td>Mean</td>
<td>0.7</td>
<td>1.86</td>
<td>0.28</td>
</tr>
<tr>
<td>SD</td>
<td>0.397</td>
<td>5.56</td>
<td>0.341</td>
</tr>
<tr>
<td>Median</td>
<td>0.68</td>
<td>0.56</td>
<td>0.17</td>
</tr>
<tr>
<td>Non-drug-related N</td>
<td>35*</td>
<td>135*</td>
<td>144*</td>
</tr>
<tr>
<td>Range</td>
<td>0.10-4.26</td>
<td>0.02-2.0</td>
<td>0.01-2.56</td>
</tr>
<tr>
<td>Mean</td>
<td>0.64</td>
<td>0.4</td>
<td>0.11</td>
</tr>
<tr>
<td>SD</td>
<td>0.746</td>
<td>0.43</td>
<td>0.29</td>
</tr>
<tr>
<td>Median</td>
<td>0.42</td>
<td>0.26</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Five cases urine POS only.
† Two cases urine POS only.
‡ Three cases urine POS only.
§ Fifty other matrix POS.
&& Twenty-nine cases urine/vitreous POS only.

Discussion

During the period of this study, the number of postmortem cases positive for methadone increased. However, there was not a corresponding increase in methadone related deaths. These findings are in agreement with several other studies. In 2005, Lemos et al. (10) reported the results of 35 methadone-positive cases received in San Francisco in 2002. Similar to the current study, white males with a median age of 45 years predominated. The incidence of methadone was 4.4/100,000 compared with 5.0/100,000 in 1997-1998. A review of methadone-related overdose deaths in New Mexico between 1998 and 2002 demonstrated a decrease, averaging 1.6 per 100,000 (11). In this review, 22.4% of methadone-related deaths were due to methadone alone, compared with 19% in the current study. A decline or apparent stabilization of methadone related deaths
has also been reported overseas. Investigators in the United Kingdom (12) and Switzerland (13) suggested this was due to increased supervision of methadone use in these countries.

These findings are in contrast to other studies which have documented increases in methadone related deaths. Miller et al. (14) reported a decrease in cocaine related deaths and an increase in methadone deaths, from 1 to 6, in the Shreveport region of Louisiana in 2000–2002. A larger sample size was reported in the study of Distefano (15) from 7 in the period 1990–1992 to 140 during the years 2000–2002. A study in Maryland demonstrated an eightfold increase in methadone deaths in 1998–2004 (16). The state of North Carolina also reported increases in methadone deaths from 12 in 1997 to 80 in 2001 (17). Further, methadone-only deaths comprised 75% of the cases, compared with the current finding of 19%. These studies appear to demonstrate that the increase in methadone related deaths observed in the recent past is regional. Multiple factors may be contributing to these differences, including the availability of methadone, prescribing practices, availability of drug use history, and potentially, interpretation of the significance of the toxicological findings.

A similarity in the studies described and confirmed in the current study, is the most common drug combinations found in multiple drug intoxications which include methadone. In NE Ohio, other opioids, antidepressants, and benzodiazepines were typical drug combinations. In Alabama, benzodiazepines were the most frequently detected co-intoxicant (18). A review of the cases of the New York City Chief Medical Examiner for 2003 revealed that the presence of a tricyclic antidepressant and/or benzodiazepine in methadone positive cases was associated with an accidental overdose death more often than death from any other cause (19). The results of a study of methadone deaths in Kentucky between 2000 and 2004, showed antidepressants, benzodiazepines, and other opioids to be the most common drug combinations (20). This trend has also been observed in other countries. In Australia, two reports described the co-ingestion of benzodiazepines (21) and psychotropic drugs, especially ethanol and benzodiazepines (22). The risks associated with benzodiazepine co-ingestion include increasing upper airway obstruction (21), competition with methadone for receptors, and inhibition of hepatic metabolic enzymes (18). The study of Williamson et al. (22) found drug combinations accounted for 86% of the deaths, a finding similar to the current study in which polydrug intoxications were deemed responsible for 81% of the methadone related deaths.

In NE Ohio, blood methadone concentrations were similar for intoxication and incidental finding deaths. This has also been observed in other regions. For example, Wolf et al. (23) reported the following ranges of methadone concentrations in deaths due to methadone toxicity, combined drug toxicity, and other causes (disease/trauma), respectively (mg/L): 0.114–1.939, 0.050–1.903, and 0.062–2.70. Similar findings were reported in a study in Minnesota that examined deaths of individuals in methadone maintenance therapy programs, illicit users, and prescription use for chronic pain (24). Methadone concentrations in methadone related deaths ranged from 0.18 to 3.99 mg/L, overlapping with concentrations in deaths due to other causes (0.18–3.03 mg/L). Gordon et al. (25) evaluated methadone concentrations in three populations, namely, post-mortem cases and living impaired drivers and individuals enrolled in methadone treatment programs. In the latter group, blood concentrations of individuals receiving doses of 9–250 mg/day ranged from 0.013 to 0.85 mg/L, and concentrations in drivers ranged from 0.015 to 0.83 mg/L. The methadone concentration in the postmortem population was reported to be 0.05–7.4 mg/L (all positive cases). The authors concluded that the presence of co-administered drugs, enrollment in a treatment program, and length of time of drug use are factors to be considered when assessing the significance of a positive methadone result in a death investigation.

In contrast to the multiplicity of reports of methadone related deaths, there have been few recent accounts describing deaths due to oxycodone and/or hydrocodone in the peer-reviewed forensic literature. With regard to oxycodone, the current study observed similar demographic findings to the methadone cases. White males predominated with a similar mean and median age. In addition, the number of intoxications as a proportion of deaths were similar (29%). In non-drug-related deaths, the concentration range, mean, and median were lower than those observed in oxycodone intoxications. Backer and Poklis (26) reported oxycodone blood concentrations in 70 postmortem cases. Cases were divided into oxycodone only (N = 4, 0.23–0.76 mg/L), mixed drug (N = 38, 0.06–1.6 mg/L), and natural (N = 28, 0.10–0.6 mg/L) deaths. The mean blood concentration in the current study for non-drug-related oxycodone deaths (0.40 mg/L) is similar to the mean concentration for the mixed-drug deaths (0.42 mg/L) reported by Backer and Poklis (26). In the latter study, the number of cases evaluated was lower than the present study (38 mixed drug, compared with 135 non drug related). Other drugs reported were benzodiazepines, carisoprodol, cocaine, other opioids, and antidepressants in decreasing order of prevalence (26). Wolf et al. (27) reported oxycodone concentrations in 172 deaths in Florida. In agreement with the present study, although they found overlapping concentrations between oxycodone related and non-oxycodone-related deaths, these investigators demonstrated a lower mean oxycodone blood concentration for the non-oxycodone-related deaths (N = 37) compared with intoxications (N = 135). The mean concentration determined in the non-oxycodone deaths was lower than the current study (0.087 mg/L compared with 0.4 mg/L). These authors also determined that benzodiazepines, notably alprazolam, and cocaine were the most common co-intoxicants. An evaluation of oxycodone in multiple drug deaths was reported by Cone et al. (28) in 2004. In reviewing 1014 fatalities, these authors found higher blood oxycodone concentrations in single drug deaths compared with levels in multi-drug deaths. These authors suggested that the findings supported the hypothesis that oxycodone is more toxic when combined with other centrally active drugs and that in cases of multiple drug deaths, the cause should not be limited to a single drug.

Spiller (29) reported blood concentrations of oxycodone and hydrocodone in postmortem specimens from 88 drug deaths. In 24 oxycodone-only deaths, the range in concentration was 0.12–8.0 mg/L, within the range observed in the current study. For the 17 hydrocodone-only deaths, the range
was 0.12–1.6 mg/L, also within the range observed in the current study. However, the mean and median hydrocodone results in the Spiller (29) study were higher than those observed in N.E. Ohio (0.53 and 0.40 mg/L, respectively). In support of the findings of Cone et al. (28) and other investigators, combined drug deaths, for example, oxycodone and hydrocodone, resulted in lower mean drug concentrations compared with single drug deaths. Common co-intoxicants included ethanol, other opioids and antidepressants. Unfortunately, Spiller (29) did not report hydrocodone concentrations in non-hydrocodone related deaths. No additional recent studies reporting postmortem hydrocodone concentrations were found. It should be noted that the presence of dihydrocodeine, an active metabolite of hydrocodone, may be contributing to the toxicity observed in hydrocodone deaths. Beause dihydrocodeine is unavailable in the U.S., unlike other countries (30), the majority of laboratories do not test for this compound, and therefore, its potential role remains unknown.

In summary, this study has reported drug concentrations in a large cohort of postmortem specimens. The work has demonstrated that national trends may obscure regional differences in drug use patterns. In evaluating the potential significance of a drug concentration in a death, many factors must be considered. Regarding methadone, oxycodone, and hydrocodone, other psychoactive drugs were found to be prevalent in these deaths, including other opioids, benzodiazepines, and antidepressants. Corkery et al. (31) have suggested that many deaths are preventable (with regard to methadone) if drug interactions and polydrug use are avoided and the pharmacokinetics of the drug (e.g., lipophilicity and rapid distribution into tissues resulting in low plasma levels, long half-lives, presence of active metabolites) and the individual’s tolerance level are considered.

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