J Forensic Sci, Mar. 2004, Vol. 49, No. 2
Paper ID JFS2003221
Available online at: www.astm.org

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.*

Methadone-Related Deaths in Palm Beach County*

ABSTRACT: The authors reviewed cases investigated by the Palm Beach Medical Examiner's Office in which postmortem toxicologic studies indicated the presence of methadone over the period from 1998 to 2002, to examine the role of the drug in these deaths. There were 139 methadone-positive cases, including 75 in which the death was attributed to combined drug toxicity and 23 to methadone toxicity alone. Methadone was most frequently used in conjunction with other prescription or illicit drugs, most commonly benzodiazepines and/or cocaine. There was considerable overlap in the postmortem blood methadone concentrations among the groups. Concentrations ranged from 0.114 mg/L–1.939 mg/L (mean .0559 mg/L) in cases where death was attributed to methadone toxicity; 0.050 mg/L–1.903 mg/L (mean 0.411 mg/L) in cases of combined drug toxicity; 0.069 mg/L–0.644 mg/L (mean 0.224 mg/L) in deaths attributed to other drugs; 0.062 mg/L–1.090 mg/L (mean 0.344 mg/L) among deaths attributed to natural causes and 0.072 mg/L–2.7 mg/L (mean 0.605 mg/L) among deaths due to trauma. The concentrations of methadone detected indicate that it may not be possible to establish a lethal methadone range because some deaths occurred at methadone concentrations below previously reported lethal ranges, and because of the presence of other drugs. Determining the cause of death in methadone-positive cases necessitates correlation with autopsy results and investigative findings.

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

Methadone is a long acting orally active opioid agonist used therapeutically to treat opiate addiction and in the management of chronic pain. The initial use of methadone as a maintenance drug in the treatment of heroin addiction was followed by reports of death attributed to methadone itself, both in the induction phase of methadone treatment and due to the diversion of methadone to the non-treatment population (1–4). Methadone has more recently been used for the management of chronic pain, and has been prescribed with increasing frequency following reports of deaths associated with other analgesics, particularly oxycodone (5). Methadone has since become widely available for those for whom it is prescribed as well as for others, and an increase in fatal methadone overdoses has been reported (6–9).

Several investigators have commented on the difficulties inherent in the interpretation of postmortem methadone concentrations (2,10). Fatal concentrations may vary widely depending on an individual's level of tolerance (2,11). There has been an overlap of reported drug concentrations in cases in which the cause of death was attributed to methadone toxicity and those in which methadone was considered to be an incidental finding. Similar overlap in drug concentrations has been reported in cases of deaths attributed to methadone toxicity and concentrations found in individuals on methadone maintenance programs (12,13). Other drugs are often present in cases in which methadone is thought to play a role in the cause of death (9,10,12,14). Karch and Stephens (12) found a high incidence of the presence of cocaine in cases in which methadone was detected, and Mikolaenko and colleagues (10) have recently reported an increase of deaths resulting from co-intoxication with methadone and a benzodiazepine.

Recent media accounts of an increase in the number of deaths attributed to methadone toxicity in Palm Beach County have raised public concern over the illicit use of the drug. We undertook the current study to further elucidate the role of methadone as a cause of death, reviewing cases investigated by the Palm Beach County, Florida, Medical Examiner's Office over the five-year period from 1998 to 2002.

Materials and Methods

Case Reviews

The files of the Palm Beach County, Florida, Medical Examiner's Office from January, 1998 to December, 2002 were searched for cases in which methadone was detected in postmortem toxicologic specimens. 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, or in four cases, by the Dade County Medical Examiner Toxicology Division.

The investigative reports as well as the reports of the postmortem examinations and postmortem toxicologic studies were reviewed. Demographic data collected included the decedents' age, race, and sex. The autopsy reports were reviewed for cause and manner of death and for the presence of trauma or pre-existing natural disease. Information pertaining to the circumstances of death and the decedents' known prescription records were obtained from the investigators' reports.

Analytical Methods

As part of routine toxicology analysis, comprehensive urine drug screens were performed by immunoassay, thin-layer

[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, NY.
[3] Wuesthoff Reference Laboratories, Melbourne, FL.
* Presented in part at the February 2003 Annual Meeting of the American Academy of Forensic Sciences, Chicago, IL.
Received 28 June 2003; and in revised form 5 Sept. and 4 Oct. 2003; accepted 4 Oct. 2003; published 4 Feb. 2004.

chromatography and high performance liquid chromatography. Comprehensive blood drug screens were analyzed qualitatively by microtiter plate enzyme immunoassay (MPEIA), fluorescent polarization immunoassay and full scan gas chromatography-mass spectrometry (GC-MS). If methadone was identified by the drug screen, quantitation of the analyte was performed by GC-MS.

Specimens were collected in tubes containing sodium fluoride. Peripheral whole blood specimens were used for quantitation in the majority of cases. Standards and deuterated internal standards were obtained from Cerilliant (formerly Radian Analytical Products, Austin, Texas). Two mL of whole blood was mixed with 50 μL of methadone-d3 internal standard and 4 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. Three mL of a 100 mM phosphate buffer was added and the pH was adjusted to 6 with phosphate buffer or 100 mM HCl. Samples were extracted by solid phase extraction (Clean Screen-United Technologies, Inc.) and an extraction procedure, as written by UCT, was conducted (15). One μL of sample was injected for analysis. GC-MS was performed with an Agilent Technologies (Palo Alto, CA) 5973 MSD, coupled to an 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 6890 GC was operated in the splitless mode. The injection port temperature was 180°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 5973 MSD was operated in the selected ion monitoring mode (SIM). The following ions were monitored: methadone target ion 294, qualifier ion 223, methadone-d3 target ion 297, qualifier ion 226. Methadone was identified by retention time and relative abundance of the two ions monitored as compared with 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. Standards were extracted and calibration curves were derived on all runs. Methadone was quantitated by comparing the ration of integrated ion peak area with that of deuterated methadone. Limit of detection, limit of quantitation, and limit of linearity were 50, 50, and 4000 ng/mL. Precision of assay as measured by percent CV was 3.1% at 180 ng/mL, 5% at 300 ng/mL, and 2.9% at 889 ng/mL.

Results

One hundred and thirty nine cases were identified in which methadone was detected in postmortem toxicologic studies: 2 cases were found in 1998, 3 in 1999, 10 in 2000, 37 in 2001, and 87 in 2002. Fourteen of these cases were omitted from analysis because no quantification of the methadone was performed, including 8 in which methadone was only detected in the urine, leaving 125 cases for analysis.

The cases included 98 males and 27 females. Ages ranged from 16 to 72 years (mean 38.6 years). All decedents were white except for one black male. Twenty-eight individuals were known to have been prescribed methadone for chronic pain.

The methadone-positive cases included 23 in which the cause of death was attributed to methadone toxicity, and 75 in which methadone was identified as contributing to combined drug toxicity. Methadone was considered to be an incidental finding in 7 cases in which death was attributed to another drug. The remaining cases included 11 deaths attributed to natural causes and 9 deaths due to trauma. The manner of death was classified as accidental in 105 cases, homicide in 1 (gunshot wound), suicide in 7 (2 combined drug toxicity, 1 heroin toxicity, 2 blunt force injuries, 1 sharp force injury, 1 gunshot wound), natural in 11 and undetermined in 2 (1 combined drug toxicity, 1 gunshot wound). In all of the non-accidental cases the decedents were found dead. There were no instances in which resuscitation or hospitalization resulted in an interval of time that would have affected the postmortem methadone concentration.

TABLE 1—*Postmortem methadone concentrations.*

Cause of Death	Blood Concentration (mg/L)	
	Range	Mean
Methadone toxicity	0.114–1.939	0.559
Combined drug toxicity	0.050–1.903	0.411
Other drugs	0.069–0.644	0.224
Natural causes	0.062–1.090	0.344
Trauma	0.072–2.7	0.605

The postmortem blood methadone concentrations in the deaths attributed to methadone toxicity alone ranged from 0.114 mg/L to 1.939 mg/L (mean 0.559 mg/L) (Table 1). In four of the cases, methadone was the only drug identified. The methadone concentrations in these cases were 0.114 mg/L, .0218 mg/L, 0.316 mg/L and 1.939 mg/L. Cannabinoids were identified in the blood in five cases. Benzoylecgonine and a therapeutic concentration of alprazolam were present in a case in which the methadone concentration was 0.440 mg/L. In one of these MDA and a therapeutic concentration of a benzodiazepine were also present. Ethanol was present in three cases, with blood ethanol concentrations of 0.024 g/dL, 0.029 g/dL and 0.120 g/dL. 6-monoacetylmorphine was detected in the urine in one of these cases. One individual with a blood methadone concentration of 0.75 mg/L also had a sertaline concentration of 0.79 mg/L, in addition to subtherapeutic concentrations of doxepin and oxycodone. In the remaining cases classified as death due to methadone toxicity, therapeutic concentrations of other prescription drugs were also present.

The 7 deaths attributed to other drugs included 2 attributed to heroin, 2 cocaine, 1 morphine, 1 hydrocodone and 1 alprazolam. The blood methadone concentrations in these cases ranged from 0.069 mg/L to 0.644 mg/L (mean 0.224 mg/L).

The 21 cases in which death was attributed to non-drug related causes included 11 attributed to natural causes and 9 to trauma. The causes of death in the 12 cases attributed to natural causes included atherosclerotic cardiovascular disease (5), hypertensive cardiovascular disease (2), cardiac hypertrophy (1), intracerebral hemorrhage (1), pneumonia (1) and mesothelioma (1). The postmortem blood methadone concentrations among these cases ranged from 0.062 mg/L to 1.090 mg/L (mean 0.344 mg/L). Methadone concentrations in cases where deaths were clearly due to trauma ranged from 0.072 mg/L to 2.7 mg/L (mean 0.605 mg/L).

Methadone concentrations in the 75 cases in which death was attributed to combined drug toxicity ranged from 0.050 mg/L to 1.903 mg/L (mean 0.411 mg/L). Benzodiazepine and cocaine were the most common co-intoxicants in these cases. Benzodiazepine alone was detected in 22 cases, cocaine and/or its metabolites alone in 19 cases, and both a benzodiazepine and cocaine in 24 cases. Methadone concentrations ranged from 0.067 mg/L to 1.165 mg/L (mean 0.427 mg/L) in the cases where only a benzodiazepine was identified and from 0.070 mg/L to 1.189 mg/L (mean 0.349 mg/L) in the cases where only cocaine and/or its metabolites were identified. Methadone concentrations in the cases where both cocaine and a benzodiazepine were present ranged from 0.134 mg/L to 1.243 mg/L (mean 0.416 mg/L). Morphine was listed as a contributing drug in 8 cases, with 6-monoacetylmorphine identified in the urine in 4 of

these. Hydrocodone and oxycodone were each identified in 9 cases. Ethanol was detected in 6 of the cases of combined drug toxicity with the blood alcohol concentrations ranging from 0.048 g/dL to 0.183 g/dL (mean 0.135 g/dL).

Discussion

The introduction of methadone as a maintenance drug in addiction treatment was followed by recognition of risks associated with the drug, including deaths occurring in the induction phase and deaths among the non-treatment population (1,2,9). The advantages of methadone in the management of chronic pain include its long half-life resulting in prolonged blood concentrations, and high oral bioavailability (10). Deaths from methadone are due to central nervous system and respiratory depression, with nonspecific findings at autopsy (14).

Previous investigators have observed an increase in the number of deaths related to methadone toxicity in recent years (2,4,6–8,16). Several studies have commented on the predominance of white males among methadone-related deaths (14,17), in contrast to other studies, which have indicated a predominance of African American decedents (18–20).

We have reviewed deaths in which methadone was detected in postmortem toxicologic studies in Palm Beach County over the 5 year period from 1998 to 2002. In contrast to the recent study of Gagajewski and Apple (16) in which 34.7% of the methadone-positive deaths studied were among individuals on methadone maintenance programs, none of the decedents in the study were known to be on maintenance programs. Our findings indicated a dramatic increase in methadone-related deaths over the time period studied, from 2 deaths in 1998 to 87 in 2002. It is likely that the increase in methadone-related deaths seen in our county may be due to an increased availability of the drug in the population due to physicians prescribing the drug more frequently in light of the recognition of the hazards of other analgesics, such as oxycodone, the abuse of which has also received considerable media attention. We also found a predominance of white decedents. The majority of decedents were in the 35 to 50 year age range with a mean age at death of 38.6 years, in contrast to the study of Perret et al. (9) in which the decedents were predominantly younger males, probably due to the older population of south Florida.

Many previous studies have emphasized the frequency of the presence of other drugs in methadone-related deaths (9,11,16,21). Barrett and colleagues (14) reviewed 91 deaths in which methadone was detected in toxicologic studies. These investigators found that 85% of their cases had other drugs present with 34 deaths attributed to polydrug toxicity. Their findings indicated that the use of multiple drugs was the leading cause of death among their methadone-positive cases. Perret and co-workers (9) found the presence of other drugs in 35 of 36 of their methadone-positive lethal drug intoxications. Karch and Stevens (12), in a review of 38 cases of methadone-positive deaths, reported the presence of cocaine or benzoylecgonine in 42% of their cases. In a recent review of methadone-positive deaths in Jefferson County, Alabama, Mikolaenko and co-workers (10) found an increase in deaths resulting from co-intoxication with methadone and benzodiazepines. In their series of 101 cases in which methadone was detected in postmortem blood, benzodiazepines were the most frequently encountered co-intoxicants. These investigators found higher concentrations of methadone in cases where a benzodiazepine was present, as compared to cases where death was related to methadone alone. They postulated that higher concentrations of methadone may occur in acute intoxications with methadone and a benzodiazepine because benzodiazepines compete with methadone for methadone receptors, and that higher concentrations of methadone could occur in chronic abuse situations because benzodiazepines inhibit hepatic enzymes that metabolize methadone.

Manning et al. (22) reported a lethal methadone concentration ranging from 0.4 mg/L to 1.8 mg/L. In 22 of our cases, death was attributed to methadone toxicity alone, with 3 cases having no other drugs present and only one having a concentration of another drug above the therapeutic range. In 12 of these cases the postmortem methadone concentrations were below this range. These included cases where only methadone was present. In all cases thorough investigation of the circumstances of death indicated death due to a drug overdose, and the autopsy findings revealed no other cause of death. It is clear, therefore, that death can occur at methadone concentrations below the previously reported lethal ranges.

Our results support those of previous investigators who have indicated that other drugs are often present in cases where methadone is believed to play a causal role. Our review of 125 cases of methadone-positive deaths included 75 deaths attributed to combined drug toxicity. The most common scenario was the presence of both one or more benzodiazepines or benzodiazepines and cocaine. This combination was seen in 24 of the 75 cases (32%). One or more benzodiazepines were seen in 22 cases (29%) and cocaine and/or its metabolites in 19 cases (25%). However, in contrast to the findings of Mikolaenko et al. (10), we did not find high concentrations of methadone in cases of co-intoxication with benzodiazepines, as compared to cases of methadone toxicity alone. The mean methadone concentration among cases with co-intoxication with benzodiazepines was 0.427 mg/L, and that with the presence of both cocaine and benzodiazepines 0.416 mg/L. The mean methadone concentration among cases with deaths attributed to methadone toxicity alone was 0.559 mg/L.

Many previous investigators have commented upon the difficulty in establishing a lethal blood methadone concentration (2,9,12–14,16). The presence of other drugs complicates the interpretation of methadone dosage and concentrations. Drug interactions may affect methadone concentrations through several mechanisms, including decreasing methadone concentrations through the acceleration of methadone metabolism due to the induction of hepatic microsomal enzymes with chronic abuse or, alternatively, increasing methadone concentrations due to the inhibition of these enzymes, as has been reported with benzodiazepines (10). Additionally, other drugs may act synergistically with methadone in the production of respiratory depression. Fatal concentrations may also vary widely with an individual's level of tolerance and susceptibility. An opiate naïve individual would be expected to be susceptible to lower concentrations of methadone. Lack of tolerance is no doubt a factor in the deaths seen in the induction phase of methadone treatment for heroin addiction.

The interpretation of postmortem blood methadone concentrations may also be complicated by the phenomenon of postmortem redistribution. Several previous studies have indicated that there is a difference in blood concentrations between blood drawn from the heart and alternate site blood samples, with no consistency of the drug concentration being higher or lower between heart blood and alternate samples (23,24). In our cases peripheral blood was used for analysis whenever available.

Our results also indicate that considerable overlap exists in postmortem methadone concentrations among cases where death is attributed to methadone toxicity or to combined drug toxicity and death in which methadone is detected but is not considered to be a contributory factor. Although the mean methadone concentrations among the cases of methadone toxicity and combined drug toxicity

were greater than the means seen among the cases of deaths attributed to natural causes and to other drugs, because there was such overlap in the ranges among these groups the concentration in an individual case cannot be used to determine whether methadone was a causal factor in the death or an incidental finding. Indeed, the highest maximum and mean methadone concentrations occurred in the group of deaths attributed to trauma, with a maximum blood concentration of 2.7 mg/L and a mean blood concentration of 0.605 mg/L.

Differences among pathologists in the interpretation of postmortem blood methadone concentrations is indicated by the overlap between those cases where methadone was thought to play a role in the cause of death and those in which deaths were attributed to other drugs or natural causes and methadone was considered to be an incidental finding. Reliance on the currently published lethal ranges for methadone may explain this variability in the interpretation of the drug concentrations. It is clear that postmortem methadone concentrations in individuals where natural disease processes coexist require careful interpretation, because the concentrations in these cases overlap those where the deaths were considered to be methadone related.

Data pertaining to methadone metabolite concentrations were not available in this study. It would be important to know the ratio of methadone to its metabolite and further study is essential to determine whether the ratio would be useful in discriminating between the overlapping ranges of blood concentrations of the parent drug alone.

In conclusion, our results support those of previous investigators in indicating that it is not possible to establish a definitive lethal blood methadone range. The presence of other drugs in most cases makes it difficult to establish the role of methadone. However, methadone alone can be interpreted as being a cause of death, and death can occur at methadone concentrations below the previously reported lethal ranges. The determination of the cause and manner of death in methadone-positive cases necessitates correlation of the toxicologic findings with autopsy results and investigative findings. Our findings also support those of Gagajewski and Apple (16), who state that the interpretation of methadone blood concentrations must be weighed along with the clinical circumstances surrounding death.

References

1. Ali RL, Quigley AJ. Accidental drug toxicity associated with methadone maintenance treatment. MJA 1999;170:100–1. [PubMed]
2. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994, lives lost and saved. MJA 1999;170:104–9. [PubMed]
3. Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on methadone maintenance program. Am J Forensic Med Pathol 1992;13:346–50. [PubMed]
4. Segal RJ, Catherman RL. Methadone-a cause of death. J Forensic Sci 1974;19:64–70. [PubMed]
5. Drummer OH, Syrjanen ML, Phelan M, Cordner SM. A study of deaths involving oxycodone. J Forensic Sci 1994;39:1069–75. [PubMed]
6. Bently AJ, Busutill A. Deaths among drug users in south-east Scotland (1989–1994) Med Sci Law 1996;36:231–6. [PubMed]
7. Cairns A, Roberts IS, Benbow EW. Characteristics of fatal methadone overdose in Manchester 1985–1994 BMJ 1996;313:264–5. [PubMed]
8. Neeleman J, Farrell M. Fatal methadone and heroin overdose: time trends in England and Wales. J Epidemiol Comm Health 1997;51:435–7.
9. Perret G, Deglon J-J, Kreek MJ, Ho A, La Harpe R. Lethal methadone intoxications in Geneva, Switzerland from 1994 to 1998. Addiction 2000;95:1647–53. [PubMed]
10. Mikolaenko I, Robinson CA, Davis GG. A review of methadone deaths in Jefferson County, Alabama. Am J Forensic Med Pathol 2002; 299–304. [PubMed]
11. White JM, Irvine RJ. Mechanics of fatal opioid overdose. Addiction 1999;94:961–72. [PubMed]
12. Karch JB, Stephens BG. Toxicology and pathology of deaths related to methadone: retrospective review. West J Med 2000;172:11–6. [PubMed]
13. Milroy CM, Forrest ARW. Methadone deaths: a toxicological analysis. J Clin Pathol 2000;53:277–81.
14. Barrett DH, Luk AJ, Parrish RG, Jones TS. An investigation of medical examiner cases in which methadone was detected. Harris County, Texas 1987–1992. J Forensic Sci 1996;41:442–8.
15. United Chemical Technologies, Inc. Product application. Methadone by GC/MS. Bristol, PA: United Chemical Technologies, Inc.
16. Gagajewski A, Apple FS. Methadone-related deaths in Hennepin County, Minnesota: 1992–2002. J Forensic Sci 2003;48:668–71. [PubMed]
17. Worm K. Steentoft A, Kringsholm B. Methadone and drug addicts. Int J Leg Med 1993;106:119–23.
18. Cushman P. Ten years of methadone maintenance treatment; some clinical observations. Am J Drug Alcohol Abuse 1977;4:543–53. [PubMed]
19. Kirn TF. Medical news and perspectives: methadone maintenance treatment remains controversial even after 23 years of experience. JAMA 1988;260:2070–1,5.
20. Greene MH, Luke JL, DuPont RL. Opiate overdose deaths in the District of Columbia. part II-methadone related fatalities. J Forensic Sci 1974;19:575–84. [PubMed]
21. Stitzer ML, Griffiths RR, McLellan AT, Grabowski J, Hawthorne JW. Diazepam use among methadone maintenance patients; patterns and dosages. Drug Alcohol Dependence 1981;8:189–99.
22. Manning T, Bidanset JH, Cohen S, Lukash L. Evaluation of the Abuscreen for methadone. J Forensic Sci 1976;21:112–20. [PubMed]
23. Levine B, Wu SC, Dixon A, Smialek JE. Site dependence of postmortem blood methadone concentrations. Am J Forensic Med Pathol 1995;16: 97–100. [PubMed]
24. Prouty RW, Anderson WH. The forensic science implications of site and temporal inferences on postmortem blood-drug concentrations. J Forensic Sci 1990;35:243–70. [PubMed]

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