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Methadone-Related Deaths in Hennepin County, Minnesota: 1992–2002

ABSTRACT: Methadone maintenance therapy (MMT) is the only currently established medical therapy for heroin addiction. However, MMT still remains controversial. In Hennepin County, Minnesota, methadone is one of the top ten drugs reported in medical examiner investigated deaths and one of the most commonly diverted pharmaceuticals. This report reviews the role of methadone in medical examiner deaths over a 10-year period, 1992–2002. We compare cause and manner of death (accidental, natural, suicide) and methadone blood concentrations for decedents who were members of MMT programs with illicit users and those prescribed methadone for chronic pain. Findings reveal that 65% of decedents with measurable blood methadone concentrations were not participating in MMT programs. A total of 96 cases were identified, with the majority white (90.5%) and male (76.8%). MMTP program members were the minority (34.7%) of the methadone positive deaths and 39% were illicit users. Fifteen percent were chronic pain patients with almost half of this group dying from overdose. Methadone concentrations of drug caused/related deaths (0.18–3.99 mg/L) overlapped with those of deaths not attributable to methadone (0.18–3.03 mg/L) with no definable lethal level. Interpretation of methadone blood concentrations must be done in the context of the clinical history for determining cause of death, and may be confounded by postmortem redistribution.

KEYWORDS: forensic science, methadone, blood concentration, methadone maintenance treatment, pharmacokinetics

Methadone maintenance therapy (MMT) evolved in America in the 1960s with the report of Nyswander and Dole's clinical trial (1). In their group of 22 patients, they found that methadone maintenance combined with psychological and social services could effectively rehabilitate heroin abusers. Previous trials had been problematic due to inadequate maintenance drugs (1). For example, morphine is a short-acting drug requiring multiple daily doses and parenteral self-administration, with demonstrated fluctuating concentrations throughout the day (1). In addition, patients required progressive increases in dose as tolerance developed (2). Methadone has the advantages of long half-life, high oral bioavailability, and stabilization at one dose with chronic administration (1). Thus, MMT has become an established medical therapy for heroin addiction.

In 1988, the concept of MMT was revisited through the advancement of the metabolic theory of addiction as a physiological imbalance caused by chronic opiate abuse with the use of methadone analogous to insulin (2). Only through the chronic occupation of narcotic receptors would an individual achieve neuroendocrine homeostasis and end drug craving. Equilibrium between tissue-bound and serum methadone concentrations provides a constant, stable occupation of receptors and achieves a pharmacologic blockade against illicit heroin high and its pharmacologic activity (2). Counter-arguments of methadone therapy for opiate abusers includes the chronicity of lifetime treatment, ineffectual prevention of illicit drug use, marked heterogeneity of programs and availability of ancillary services (3). Dole noted that only a minority of patients would eventually wean off methadone (2). Further philosophical issues confound MMT, as some programs treat opiate dependence as an apparent character flaw and distribute methadone in a reward/punishment manner. If no illicit drug use is detected, the patient will receive his methadone maintenance dose; otherwise it is held until the drug screen is clean (2). Similarly, it has been observed that some treatment staff do not fully support long-term methadone therapy in favor of abstinence, and attempt to wean patients off methadone within one to two years (4). These and other programs have been found to use a low-dose regimen, less than the consensus panel recommended 60 mg/day for all patients (2). Surveys of methadone centers in the early 1990s revealed the average dose to be less than 50 mg/day (4). Centers that serve primarily African Americans were found to correlate with lower dose regimens. A survey of centers in the year 2000 revealed 35% of patients still receiving less that 60 mg/day (4). This is especially concerning in light of recent studies that have shown 80–100 mg/day to be more effective (5).

The pharmacokinetics of methadone varies significantly among patients and within individuals (6–10). This is due to intrinsic differences in metabolism of methadone and changes in pharmacokinetic parameters with changes in physiologic state (7). External factors include interactions with other drugs, which may induce microsomal metabolism (6). The mean oral bioavailability of methadone is 81–95% (range 36–106%) with a mean half-life of 31 h (range 13–58 h) (6,8). In new initiates where blood concentrations are unpredictable until steady state, it is important to understand inter-individual pharmacokinetic variability. In compliant patients, increases of serum concentrations up to 7-fold have occurred with no change in dose (9). The major metabolite of methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) peaks before the parent drug due to first-pass metabolism in the liver. EDDP peaks at mean 149 min (range 57–404 min) while methadone peaks at 220 min (range 106–408 min) (8). Further, different rates of metabolism for methadone and EDDP have been shown among patients, demonstrating the need for indi-

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vidualizing pharmacokinetics (8). In addition, some patients develop metabolic tolerance with the onset of withdrawal symptoms and require an increase in medication dose over their current maintenance dose (6). Tennant's investigation into illicit drug use among methadone patients found that some of those patients experienced significant opioid withdrawal symptoms (10). He found that even with monitored dosing some patients had no detectable blood methadone prior to their morning dose. For the above reasons, clinician response to client symptoms of withdrawal or intoxication, instead of measuring blood concentrations, may be more effective (2).

Hennepin County, Minnesota's population of over 1 million is served by six regional methadone clinics serving over 1200 opiate addicts, with more on waiting lists (11). Methadone is one of the top ten drugs reported in medical examiner cases (12). Methadone is also one of the most commonly diverted pharmaceuticals in Hennepin County as patients may sell their methadone dose. The population of methadone users includes MMT members, chronic pain sufferers, and illicit users. The purpose of this report was to perform a retrospective review of methadone-associated deaths over ten years in Hennepin County in order to clarify the role of methadone in deaths where methadone was detected in blood, urine or liver tissue.

Methods

The Hennepin County Medical Examiner's office (HCMEO) database for the years 1992–2002 was searched for cases in which the decedent's urine, blood, and/or liver tested positive for methadone. The case reports were reviewed by one author. Demographics, cause and manner of death, circumstances of death, and toxicology results were collected for analysis. MMT members were compared with illicit users and prescription users. Qualitative screening for methadone in blood, urine, or liver tissue was performed by either immunoassay or by liquid chromatography. HCMEO uses the thoracic inferior vena cava (IVC) as the source of blood for screening and quantitation.

Methadone was quantitated after solid phase extraction from whole blood by gas chromatography mass spectrometry (GCMS) on a Hewlett-Packard 5972 mass selective detector following chromatography on a 5890 gas chromatograph equipped with a 30 m DB-5 capillary column (Agilent Technologies, Palo Alto, CA). A Unix-based Target Thru-Put operating software computer system was used for data compilation. Standards and deuterated internal standards were obtained from Radian Corp (Austin, TX). For example, one mL of whole blood (appropriate standards, controls, and case) was mixed with 50 μL methadone-d3 internal standard and 4 mL of water was added to this solution and vortexed for 5 min. After sitting for 5 min, it was spun at 3000 rpm for 10 min to remove the supernatant. Two mL of 100 mM phosphate buffer was added, followed by pH adjustment to 6. This specimen was then transferred onto a preconditioned solid phase extraction column (Bond Elut, Varian, Harbor City, CA). Following treatments with water, 100 mM acetic acid, and methanol, the column is eluted with methylchloride, isopropanol, and ammonium hydroxide. The elution was evaporated at 30 to 40°C with nitrogen, reconstituted with 0.1 mL ethyl acetate, and transferred for analysis into the autosampler for injection on the GCMS. The MS was operated in the select ion monitoring mode (SIM), and the following ions were scanned: methadone quantitating ion 294, qualifier ion 223; methadone-d3 quantitating ion 297; qualifier ion 226. Standard curves were derived for each analysis. Area ratios for unknowns were used to calculate the corresponding analyte concentration. Quantitation of methadone was based upon ratios of integrated ion areas to the corresponding deuterated internal standard. Ion ratios were calculated by dividing the area of the qualifier ion by the area of the quantitative ion. Analytes were identified based upon comparison of retention time and ion ratios with the corresponding values of calibration standards assayed in the same run. Limit of detection, limit of quantitation and limit of linearity were 50, 50, and 2000 μg/L. The assay's precision (%CV) at 100 μg/L was 3.5%.

The mean and range of methadone concentrations were compared amongst the subpopulations and with respect to the cause and manner of death. Statistically significant differences in groups were determined by two tail student t tests and ANOVA with $p < 0.05$ demonstrating significance.

Results

Ninety-six Medical Examiner cases were identified in which the decedents tested positive for methadone. The majority of the decedents were white, 90.5%, and male, 76.8%. The mean age was 44.9 y, range 28–86 y. Table 1 describes the blood methadone concentrations observed by group in all deaths. Overall the difference between the blood methadone concentrations of the MMT program member group (mean 1.17 mg/L) and non-member group (mean 0.65 mg/L) was statistically significant ($p < 0.003$). 34.7% of decedents were enrolled in MMT programs at the time of death. 36.3% of these deaths were drug caused or drug related. Three (25%) of these decedents were MMT program members for less than one week, and their deaths were attributed to methadone toxicity. Two of these decedents had blood concentrations of 0.64 mg/L, with the third at 0.19 mg/L. The latter was classified as drug related. All deaths classified as drug-related were attributed to positional asphyxia associated with drug and/or alcohol use. The remainder were listed as polydrug toxicity, except one case, which was classified as doxepin toxicity; with a liver doxepin and metabolite total concentration of 57 mg/kg and a blood methadone concentration of 0.58 mg/L and blood benzoylecgonine (BZE) concentration of 0.59 mg/L. Methadone concentrations in the drug caused/related deaths ranged from 0.18–3.99 mg/L (mean 1.31 mg/L). Benzodiazepines were present in 67% of these deaths at or below therapeutic concentrations. None of the drug deaths (except the above mentioned doxepin death) had another drug present at a concentration considered in the toxic or lethal range. The incidence of other recreational drugs is as follows: BZE, $n = 5$; opioids, $n = 5$; ethanol, $n = 6$. Deaths of MMT program members not attributed to drugs had methadone concentrations ranging from 0.18–3.03 mg/L (mean 1.16 mg/L). 15.7% of the decedents studied were prescribed methadone for chronic pain with 46.6% dying from overdose. The remainder of this group died of natural causes. Methadone concentrations in the chronic pain group ranged from 0.05 to 3.99 mg/L (mean 0.87 mg/L). The mean blood concentration of the overdose deaths was twice that of those dying of natural causes (1.0 mg/L vs. 0.52 mg/L). Only one overdose case had an associated drug that may have contributed to toxicity; with blood concentrations of codeine at 2.25 mg/L and methadone at 1.55 mg/L. There were three incidents each of ethanol and benzodiazepines, one of BZE, and one methamphetamine. Only one of the chronic pain overdose deaths was classified as suicide with the others deemed accidental. All the other suicidal overdoses in this study were in the illicit user group. The remaining two suicides in the study were MMTP members who died via gunshot wound (methadone concentration 1.18 mg/L) and ligature hanging (2.42 mg/L).

The remainder of the decedents, 39%, were classified as illicit users. Blood methadone concentrations in this group ranged from 0.08 mg/L to 1.86 mg/L, mean 0.61 mg/L. The incidence of other drugs is as follows: opioids, $n = 100$; cocaine/BZE, $n = 9$; benzo-

TABLE 1—*Methadone positive deaths in Hennepin County, Minnesota, 1992–2002*.*

Manner of Death	Subgroup	Blood Concentration (mg/L) Range	Mean
Accidental (overdose)	MMTP members ($n = 13$)	0.18–3.99	1.14
	Non-members ($n = 18$)	0.14–1.86	0.77
	Prescription ($n = 2$)	0.38; 0.27	
	Illicit users ($n = 16$)	0.14–1.86	0.82
Accidental (other)	MMTP members ($n = 5$)	0.26–3.03	1.16
	Non-members ($n = 2$)		
	Prescription ($n = 0$)	na	
	Illicit users ($n = 2$)	0.15; 1.55	
Natural	MMTP members ($n = 11$)	0.18–2.2	1.1
	Non-members ($n = 16$)	0.16–0.93	0.48
	Prescription ($n = 9$)	0.26–0.93	0.52
	Illicit users ($n = 7$)	0.16–0.77	0.42
Suicide (overdose)	MMTP members ($n = 0$)	na	na
	Non-members ($n = 6$)	0.27–1.15	0.53
	Prescription ($n = 1$)	1.0	
	Illicit users ($n = 5$)	0.27–1.15	0.64
Suicide (other)	MMTP members ($n = 2$)	1.18; 2.42	
	Non-members ($n = 0$)	na	

* Cases without blood concentrations available and undetermined and homicidal deaths excluded; na = not applicable; MMTP = methadone maintenance treatment program; non-members = chronic pain (prescription) and illicit methadone users.

diazepines, $n = 3$; and ethanol, $n = 11$. Overall the incidence of recreational drug use (including ethanol) was not significantly different between the two groups ($p = 0.2$). With rare exception, the decedents were typically found at the scene with no clear reference for time of death. Over 90% of cases had an estimated interval from death to autopsy of ≥24 h.

Discussion

This paper is the first to compare the subpopulations of methadone users by cause and manner of death and to contrast blood methadone concentrations between the groups. In addition, other drug use incidence was noted for each group. There was a mean of 9.6 deaths per year in Hennepin County which tested positive for methadone. Other national and international studies conducted in the late 1980s through the 1990s showed rates of 6 (Sheffield, UK); 9 (Geneva, Switzerland); and 18 (Harris County, Texas) methadone positive deaths per year (13–15). The former regions have populations approximately half, and the latter has roughly twice that of Hennepin County. The methadone blood concentrations for MMT program members at 1.14 mg/L averaged nearly twice that of non-members, 0.61 mg/L, and chronic pain patients, 0.87 mg/L. Methadone concentrations in decedents dying from overdoses overlapped with those succumbing to natural disease or external events, e.g., motor vehicle collision or homicide. Members of MMT programs made up a minority (34.7%) of the total deaths with approximately 10% of these decedents being members for less than one week. The incidence of recreational/illicit drug use, in addition to methadone, was lowest for the MMT program members than the other two groups.

One confounding factor in interpretation of blood drug concentrations is the possibility of postmortem redistribution. Two representative studies show evidence of this phenomenon with methadone. Prouty and Anderson (16) report five cases with heart blood: femoral blood ratios of 0.8–1.4. Levine, et al. (17) also found discrepant heart and alternate site [subclavian, inferior vena cava, femoral, pericardial] variation with only 26% of cases showing concentrations within 20%. As in the Prouty-Anderson study no consistency in the direction of change at each site was seen. The fact that HCMEO consistently samples from the IVC supports comparison of methadone concentrations among the decedents. However, postmortem redistribution is recognized as one possible limitation of our study.

Other studies of methadone deaths were found from European countries, with most national studies dating back to the 1970s (18,19). The most recent study, performed in Texas in 1991 by Barrett et al. (13), demonstrated methadone deaths with a similar population of methadone users as in the current study, with a white male majority. Studies from Washington, D.C., Chicago, and New York had predominately black populations (3,18,19). Barrett et al. (13) also found a substantial number of decedents (22%) dying of methadone or polydrug toxicity within one week of starting a MMT program. In contrast to our findings, only 9% of the Hennepin County MMT program member deaths were due to trauma, compared with 43% of their population. Deaths due to natural causes and apparent accidental overdose each accounted for 36% of MMT program member deaths.

In our study there was no clear association between methadone concentration and toxicity. Threshold toxic blood concentrations for methadone in the literature range from 0.1–1.0 mg/L (13,20). One difficulty in evaluating such deaths is the lack of dosing information to medical examiner investigators. The drug dose history and pattern of prior use or current illicit use was therefore unknown. Relatively low postmortem methadone blood concentrations could be explained by opiate naïve users and the lack or loss of tolerance, due to low purity heroin or recent prison releases who lost tolerance while abstinent. This problem was identified in the deaths of the three decedents who were MMTP members for less than one week. Their death was caused or related to methadone toxicity. A higher risk of methadone toxicity in MMTP initiates has been previously observed (14,21). Drummer describes 10 cases in which the decedents died of methadone toxicity with a mean of three days in MMTP (21). The starting dose ranged from 20 to 70 mg/day, with a mean blood concentration of 0.7 mg/L (15). In Clark's study of methadone related deaths, 7 of the 18 total deaths were MMTP members for only 12 hours to four days (14). The combination of pharmacokinetic variability during initiation of

methadone therapy (8,9) combined with the subjective assessment of tolerance by providers likely contributes to this phenomenon.

Another possible explanation for the wide range of blood methadone concentrations could be prolonged survival time after administration of a toxic dose. Milroy's study of 111 deaths found evidence of bronchopneumonia in 45%, with the speculation of respiratory depression followed by aspiration leading to death (20). Therefore, low methadone concentrations could be accounted for by prolonged peri-mortem interval with continued metabolism of methadone, decreasing the parent drug concentration. Methadone toxicity was listed as the main cause of death in only four of our cases. However, some polydrug overdose cases had toxic concentrations of methadone with relatively little contribution from other drugs present in non-toxic concentrations. One goal of this study was to further delineate a lethal methadone level. None was identified. Interpretation of drug toxicity cannot be made using numbers alone. Generally, our lab considers methadone concentrations greater than 1.0 mg/L consistent with toxicity. However, drug use history and circumstances of death *must* be taken into consideration. The most illustrative example is the accidental death in a fire of an 86-year-old male MMT member who had a blood methadone concentration of 3.03mg/L. His carbon monoxide saturation was 79% suggesting methadone had no role in his death, yet, in other situations, a concentration that high would comfortably be indicative of causing death.

In March 2001, the administrative oversight of MMT programs shifted from the FDA to SAMHSA with significant changes to improve the quality and increase availability of MMT. The changes provide for increased medical supervision and individualized therapy with private physician office-based treatment. These physicians must be affiliated with an opioid treatment program. Major modifications include methadone dispensed in higher dosages and in solid form, while currently only liquid is permitted. In addition, up to a 31-day supply of methadone can be provided, while under the FDA the maximum was 6 days. All programs and clinicians will have to undergo an accreditation procedure for certification (22). Comparison of deaths associated with methadone use after implementation of the new federal regulations will provide more insight into the utility of MMT.

Conclusions

The majority (65.6%) of decedents over a ten-year period in Hennepin County with positive methadone concentrations were not members of MMT programs. We found no definitive lethal methadone blood concentration. There was significant overlap of values between accidental and suicidal overdoses with those dying of natural causes. Also present were the confounding factors of varied opiate tolerance, presence of other drugs, unknown dosing regimens, and potential for postmortem redistribution. Thus, interpretation of blood methadone concentrations must be weighed along with the clinical circumstances surrounding death.

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