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A Community-Based Evaluation of Sudden Death Associated with Therapeutic Levels of Methadone

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Abstract

BACKGROUND—Published case reports have associated the therapeutic use of methadone with the occasional occurrence of sudden cardiac death. Because of the established utility of this drug and with the eventual goal of enhancing safety of use, we performed a community-based study to evaluate this association.

METHODS—During a 4-year period, we prospectively evaluated all patients who consecutively had sudden cardiac death and underwent investigation by the medical examiner in the metropolitan area of Portland, Ore. Case subjects of interest were those with a therapeutic blood level of methadone (<1 mg/L), and case comparison subjects were those with no methadone identified. Patients with recreational drug use or any drug overdose were excluded from either group. Detailed autopsies were conducted, including the detection and quantification of all substances in the blood.

RESULTS—A total of 22 sudden cardiac death cases with therapeutic levels of methadone (mean 0.48 ± 0.22 mg/L; range 0.1–0.9 mg/L) were identified (mean age 37.0 ± 10 years, 68% were male) and compared with 106 consecutive sudden cardiac death cases without evidence of methadone (mean age 42 ± 13 years, 69% were male). The most common indication for methadone use was pain control (n = 12, 55%). Among cases receiving methadone therapy, sudden death-associated cardiac abnormalities were identified in only 23% (n = 5), with no clear cause of sudden cardiac death in the remaining 77% (n = 17). Among cases with no methadone, sudden death-associated cardiac abnormalities were identified in 60% (n = 64, $P = .002$).

CONCLUSION—The significantly lower prevalence of cardiac disease in the case group implicates methadone, even at therapeutic levels, as a likely cause of sudden death. These findings point toward an association between methadone and occurrence of sudden death in the community. Clinical safeguards and further prospective studies specifically designed to enhance safety of methadone use are warranted.

Keywords

Acquired long QT syndrome; Autopsy; Cardiac arrest; Population

The use of methadone, a synthetic opiate, is increasing steadily.[1,2] In addition to treatment of opioid withdrawal, methadone is of significant utility as a long-acting analgesic, particularly for neuropathic pain syndromes that accompany malignancy.[3,4] The drug has a long half-life, rapid mucosal absorption, and availability in oral, parenteral, and suppository forms, but the major contributing factor to increasing use is its low cost, making it an economical alternative

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to more expensive opiates.[5] Several case reports, as well as series of cases, have described the occurrence of a potentially fatal arrhythmia, torsade de pointes, with the use of methadone. This phenomenon has been attributed to cardiac potassium ion channel blockade by the drug, resulting in prolongation of cardiac repolarization and a prolonged QT-interval on the electrocardiogram.[5–14] Given the current widespread use of methadone in the community, a community-based study would be useful to confirm this association, with the eventual goal of finding methods of enhancing safety of drug administration.

Sudden and unexpected death in the absence of structural cardiac abnormalities known to be associated with sudden cardiac death can point toward fatal cardiac arrhythmia as the cause.[15,16] Given the potential for increased fatal arrhythmia risk with methadone, we hypothesized that methadone, even at therapeutic levels, might cause sudden cardiac death in some patients. In a prospective, community-based study, we compared 2 groups of patients who had sudden cardiac death: those using methadone at therapeutic levels at the time of sudden cardiac death and those not using methadone. A high prevalence of cardiac disease in the methadone group would decrease the chances of methadone as a potential cause of sudden cardiac death. Conversely, a low prevalence of sudden death-causing cardiac disease would implicate methadone as a likely cause of sudden cardiac death.

METHODS

All aspects of this investigation were approved by the Institutional Review Board of Oregon Health and Science University, as well as the other health systems serving this population.[15]

Population Studied

We studied all residents of the greater metropolitan area of Portland, Ore (population approximately 1 million) who had sudden cardiac death between 2002 and 2006, and underwent detailed evaluation by the Medical Examiner.

Definition of Sudden Cardiac Death

As published in detail elsewhere,[15,17] sudden cardiac death was defined as sudden unexpected death either within 1 hour of witnessed onset of symptoms or within 24 hours of having been observed alive and symptom free (if unwitnessed). For the determination of sudden cardiac death, an adjudication committee of 3 physicians made independent assessments of circumstances of death and all available medical records. In the event of disagreement, the majority opinion was used. Patients were excluded if death was not unexpected (eg, terminal cancer) or if noncardiac causes of sudden death were identified (eg, trauma, drug overdose, pulmonary embolism).

Study Design

We used a case– case analysis to compare sudden cardiac death cases with therapeutic levels of methadone with sudden cardiac death cases with no methadone detected on toxicology screen. Similar to case-control methodology, case– case studies allow restricted but refined comparisons of diseased individuals with and without an exposure, serotype, or genotype of interest.[18] In the present study, this design facilitated the evaluation of factors associated with sudden cardiac death in the presence of therapeutic methadone levels compared with factors associated with sudden cardiac death in the absence of methadone.

CLINICAL SIGNIFICANCE

- The findings of this study point toward an association between methadone at therapeutic levels and sudden death in a community-based setting.

- It is possible that these deaths resulted from fatal cardiac arrhythmias or respiratory depression, both of which are known side effects of methadone.
- Because a sizeable population benefits from this drug, a large prospective evaluation of methadone therapy is warranted.
- Judicious use of methadone may require additional safeguards, such as prior electrocardiogram and assessment of the potential for respiratory suppression.

Ascertainment of Cases with Methadone

We prospectively identified all consecutive sudden cardiac death cases investigated by the medical examiner in whom therapeutic levels of methadone were identified through a toxicology screen of the blood (methadone <1 mg/L). We excluded patients with any evidence of non-methadone recreational drug use or any drug overdose (including methadone overdose that was defined as ≥1 mg/L).

Ascertainment of Cases without Methadone

Case comparison subjects were all consecutive cases of sudden cardiac death investigated in detail by the Medical Examiner during the same time period, but without evidence of methadone use on toxicologic examination of the blood. Subjects with use of any recreational drug, or overdose of any therapeutic agent, were also excluded from this group.

Postmortem Examination

For all subjects, an autopsy was conducted, and detailed information, including results of cardiac pathologic examination and toxicology screen, were obtained. Detailed criteria for cardiac pathologic diagnosis have been published.[16] Left ventricular hypertrophy was defined as a heart weight/body weight ratio greater than the 95% upper limits of normal. Mild and moderate left ventricular hypertrophy were defined as a heart weight/body weight ratio within 25% and 50% of upper limits of normal, respectively. Significant coronary artery disease was defined as luminal narrowing of 50% or more in 1 or more major coronary arteries. Both severe left ventricular hypertrophy and significant coronary disease are among the cardiac conditions most commonly associated with sudden cardiac death.[16]

Analysis

To identify causes of sudden cardiac death, a detailed analysis of complete postmortem findings and available medical records was performed for both case groups. Comparisons of identified causes were conducted between the 2 groups using Pearson's chi-square tests and Fisher exact tests when appropriate.

RESULTS

Description of Cases with Methadone

A total of 72 consecutive patients were identified who had sudden cardiac death and evidence of methadone on toxicologic screen. Of these, 43 had evidence of methadone overdose (n = 11) or evidence of recreational drug use/overdose (n = 32) and were therefore excluded from the case group. The remaining 29 subjects had sudden cardiac death and evidence of therapeutic levels of methadone in the blood, but only 22 of these underwent detailed autopsy (in 7 the autopsy was limited to an external examination). Accordingly, the case group consisted of these 22 subjects (mean age 37.0 ± 10 years, 68% were male), all of whom had therapeutic levels of methadone (0.48 ± 0.22 mg/L; range 0.1–0.9 mg/L). Indications for methadone use were pain

control in 55% (n = 12), opioid withdrawal in 14% (n = 3), recreational use in 14% (n = 3), and a reason for use not established in 18% (n = 4).

Description of Cases without Methadone

A total of 111 subjects with sudden cardiac death were consecutively investigated by the Medical Examiner and did not have evidence of methadone or a recreational drug or any drug overdose on the toxicologic screen. Because 5 subjects did not undergo complete autopsy (autopsy was limited to an external examination), the remaining 106 met criteria for inclusion in the case group without methadone (mean age 42 ± 13 years, 69% were male).

Case–Case Comparisons for Cause of Sudden Cardiac Death

Among cases with methadone, a cardiac abnormality that could have caused sudden cardiac death was identified in 23% (n = 5, Table 1). All of these 5 patients had significant coronary artery disease. In the remaining 77% (n = 17), a significant cardiac abnormality that could have caused sudden cardiac death was not identified. Patients either had structurally normal hearts (n = 13) or mild abnormalities, such as mild left ventricular hypertrophy (n = 3) and mild myocardial fibrosis (n = 1). A proportion of cases (45%, n = 10) were taking other drugs with therapeutic levels that included antidepressants, anxiolytics, psychotropic drugs, drugs for pain, and antihistamines (Table 1).

Among cases without methadone, a structural cardiac abnormality that could have caused sudden cardiac death was identified in 60% (n = 64, $P = .002$ vs cases with methadone) (Table 2). The majority of these patients had significant coronary artery disease (44%, n = 47), whereas other identified abnormalities were hypertrophic cardiomyopathy or severe left ventricular hypertrophy (11%, n = 12), cardiac structural anomalies (2%, n = 2), myocarditis (2%, n = 2), and dilated cardiomyopathy (1%, n = 1). A proportion of cases without methadone also had therapeutic levels of other drugs identified (Table 2), with no significant differences when compared with the cases with methadone group (29% vs 45%, $P = .14$). Alcohol was detected in the blood of 2 of the 22 patients with sudden cardiac death and methadone use versus 25 of the 106 patients with sudden cardiac death without methadone use (9% vs 24%, $P = .16$). The 2 patients with sudden cardiac death and methadone and alcohol detected on the toxicologic screen had 0.16 g/dL and 0.23 g/dL of ethanol. The mean level of ethanol in the 25 non-methadone sudden cardiac death group was 0.17 ± 0.14 g/dL.

DISCUSSION

Summary of Main Findings

In this community-based case– case study of sudden cardiac death with and without methadone use, 22 sudden cardiac death cases with therapeutic levels of methadone were compared with 106 consecutive sudden cardiac death cases without evidence of methadone on toxicologic screen. Among cases with methadone, a cardiac cause of sudden cardiac death was identified in only 23%, with no clear cause of sudden cardiac death in the remaining 77%. Among cases without methadone, however, an attributable cardiac cause of sudden cardiac death was identified in 60%. Therefore, the majority of non-methadone sudden cardiac death cases had identifiable cardiac causes of sudden cardiac death. The low prevalence of identifiable cardiac disease or structural abnormalities in the cases with therapeutic levels of methadone (<1 mg/L) strongly suggests a causative role for methadone in the pathogenesis of sudden cardiac death among this group.

In published case reports and case series of patients, concern has been expressed about 2 potentially lethal side effects of methadone, especially when used in high doses. The first side effect is the acquired long QT syndrome, that is, prolongation of cardiac ventricular

repolarization manifested as lengthening of the corrected QT interval on the 12-lead electrocardiogram, which can increase the risk of the occurrence of torsade de pointes.[9,19–21] The association between methadone and occurrence of torsade de pointes has been documented in multiple case reports, now comprising at least 28 patients.[6,7,11–14,22,23] Opioid agonists are among several classes of drugs that can prolong ventricular repolarization by blocking the action of cardiac human *ether-a-go-go*-related (HERG) potassium current (I_{HERG}).[24] However, among a range of opiates tested, methadone and LAAM had the most potent and rapid blockade of I_{HERG}.[25] Krantz et al.,[26] evaluating a series of 17 patients with torsade de pointes associated with methadone, found a positive correlation between daily methadone dose and QTc prolongation after adjusting for other QTc-prolonging variables. A subgroup of adults in the age range of this study are expected to have structurally normal hearts, indicating unexplained sudden death or relatively rare genetic syndromes such as long QT and Brugada syndromes.[16,27] However, the unexpectedly high proportion (77%) of otherwise unexplained sudden deaths in the methadone group points to a significant contribution of this drug toward the occurrence of sudden cardiac death among these patients. The cardiac conditions identified among the majority of cases without methadone, such as coronary artery disease, hypertrophic cardiomyopathy, and severe left ventricular hypertrophy, are established determinants of sudden cardiac death.[16]

We cannot rule out that some patients who met our criteria for sudden cardiac death may actually have died as the result of the potential suppression of breathing by methadone, especially during sleep. Teichtahl and colleagues[28] reported that stable patients enrolled in a methadone prevention program had more sleep architecture abnormalities than controls and a higher prevalence of central sleep apnea. They recommended that patients in methadone programs have awake and sleep respiration assessed to identify those potentially at risk. Either side effect is likely to be potentiated by specific drugs used concomitantly with methadone. In the present study, there were other medications that may have contributed to additional prolongation of the QTc interval, such as the antidepressants and psychotropic agents,[29] but these agents were identified to similar extents in both groups. Also, none of these drugs have been shown to increase mortality in the manner reported for methadone. Similarly, the use of methadone with alcohol or concomitant use prescription drugs with sedating effects, such as benzodiazepines, has the potential for a synergistic effect on suppression of breathing with subsequent respiratory failure.[30,31] Finally, because methadone has an elimination half-life of 24 to 36 hours and is mainly stored in the liver, drugs that compete for the cytochrome P450 mechanism could also potentiate the effects of methadone.[14]

There are some potential limitations of this study. There are some differences between the 2 case groups, mainly related to age (mean age 37 vs 42 years) and the likely prevalence of opioid addiction, that might have affected the analysis. The proportion of patients who were excluded from the analysis because the medical examiner performed a limited external examination was also different between the 2 groups. However, the age differences are small, and at this age range, the overall prevalence of coronary disease among patients with sudden cardiac death is still low.[16,32] In addition, the majority of patients in the methadone group (55%) were receiving methadone for pain control and not opioid addiction.

CONCLUSIONS

The findings of this study point toward an association between methadone at therapeutic levels and sudden death in a community-based setting. It is possible that these deaths resulted from fatal cardiac arrhythmias or respiratory depression, both of which are known side effects of methadone. Because a sizeable population benefits from this drug, a large prospective evaluation of methadone therapy is warranted. The judicious use of methadone might require

additional safeguards, such as a prior electrocardiogram and assessment of the potential for respiratory suppression.

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Table 1

Findings in the Case Group of 22 Patients with Sudden Cardiac Death and Therapeutic Levels of Methadone

Cardiac Findings	Extracardiac Findings	Methadone Level (mg/L)	Indication for Methadone Use	Other Medications on Toxicology Screen
Normal	Early cirrhosis	0.15	Pain	
Normal		0.2	Illicit use	Diphenhydramine
Normal	Pulmonary edema	0.22	Illicit use	
Normal	Peribronchiolar fibrosis	0.25	Pain	
Normal	Pulmonary edema	0.3	Opioid withdrawal	Diphenhydramine
Normal		0.3	Pain	Citalopram
Normal		0.5	Pain	
Normal		0.5	Could not be determined	
Normal		0.6	Opioid withdrawal	Sertraline
Normal		0.6	Pain	Citalopram
Normal	Focal pneumonia, early cirrhosis	0.6	Could not be determined	
Normal		0.7	Opioid withdrawal	
Normal		0.8	Pain	Venlafaxine, olanzapine, trazodone
Mild myocardial fibrosis	Endometritis	0.4	Pain	
Mild LVH		0.4	Pain	Promethazine, chlordiazepoxide, oxycodone
Mild LVH		0.6	Could not be determined	Citalopram
Mild LVH	Steatosis, early cirrhosis	0.8	Could not be determined	Citalopram
CAD, mild LVH		0.1	Pain	
CAD, mild LVH		0.6	Illicit use	
CAD	Cholelithiasis, fatty metamorphosis	0.4	Pain	Cyclobenzaprine, promethazine
CAD		0.6	Pain	
CAD		0.9	Pain	

LVH = left ventricular hypertrophy; CAD = coronary artery disease.

Table 2

Case–Case Comparison: Patients with Sudden Cardiac Death With and without Therapeutic Levels of Methadone on Toxicology Screen

	Cases with Methadone	Cases without Methadone	*P* value*
Cardiac disease or abnormalities	5 (23%)	64 (60%)	.002
CAD	5	47	
HCM/severe LVH	0	12	
Cardiac or coronary anomaly	0	2	
Myocarditis	0	2	
Dilated cardiomyopathy	0	1	
No cardiac abnormalities	17 (77%)	42 (40%)	
Normal heart	13	28	
Unexplained isolated fibrosis	1	5	
Mild-moderate LVH	3	8	
Mitral valve prolapse	0	1	
Any other medication on toxicology screen	10 (45%)	31 (29%)	.14
Psychotropic medications†	1	2	
Antidepressants	6	7	
Antiseizure	0	2	
Benzodiazepines	1	2	
Opioid analgesics (non-methadone)	1	11	
Other pain medications or muscle relaxants	1	4	
Antihistamines	4	7	
Ephedrine	0	3	

LVH = left ventricular hypertrophy; CAD = significant coronary artery disease; HCM = hypertrophic cardiomyopathy.

*Pearson chi-square test, any cardiac disease or abnormality versus none, and any other medication versus none.

†Individual medications add to more than the “any other medication” sum because some patients took more than 1 other medication (2 cases with and 7 cases without methadone had 2 other medications in blood; 1 case with methadone had 3 other medications in blood).