

Torsade de Pointes Associated with Very-High-Dose Methadone

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Background: Methadone is an effective treatment for opioid dependency and chronic pain. A methadone derivative, levacetylmethadol, was withdrawn from the European market after being associated with torsade de pointes. To date, no association between methadone and this arrhythmia has been described.

Objective: To evaluate a series of methadone-treated patients experiencing torsade de pointes.

Design: Retrospective case series.

Setting: Methadone maintenance treatment programs in the United States and a pain management center in Canada.

Patients: 17 methadone-treated patients who developed torsade de pointes.

Measurements: Chart review for concomitant arrhythmia risk factors and quantification of corrected QT interval (QTc).

Results: The mean daily methadone dose was 397 ± 283 mg, and the mean QTc interval was 615 ± 77 msec. Fourteen patients had a predisposing risk factor for arrhythmia. A cardiac defibrillator or pacemaker was placed in 14 patients; all 17 patients survived.

Conclusions: This series raises concern that very-high-dose methadone may be associated with torsade de pointes. Given the likely expansion of methadone treatment into primary care, further investigation of these findings is warranted.

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Methadone, a synthetic opioid, has been successfully used for more than 35 years to treat heroin addiction; as a component of methadone maintenance treatment, it is prescribed daily to approximately 180 000 Americans (1). Methadone is also an effective and inexpensive therapy for chronic pain (2). In heroin-abusing patients, high-dose methadone (>60 mg/d) has shown greater efficacy in reducing illicit drug use than has lower-dose therapy (20 mg/d) (3). A national survey recently confirmed that higher doses of methadone are now being used: From 1988 to 1995, the average dose increased from 45 to 59 mg/d (4).

Currently, the U.S. Food and Drug Administration is no longer involved in direct oversight of methadone maintenance treatment, and the Center for Substance Abuse Treatment has recommended expanding access to treatment by shifting opioid-dependent patients to primary care, office-based practice (5). Levacetylmethadol, a derivative of methadone, is the only other approved therapy for opioid-dependent patients in the United States. Recently, the European Agency for the Evaluation of Medicinal Products withdrew levacetylmethadol from the market after noting an association with seven cases of torsade de pointes, a potentially fatal ventricular arrhythmia (6). In the United States, five such cases have been reported to the manufacturer of levacetylmethadol, and one case report has been published (7). To date, no such association has been described with methadone. We report 17 cases of torsade de pointes in patients receiving very high doses of methadone.

METHODS

Patients and Setting

Cases were observed in two clinical settings from 1996 to 2001. Nine cases were reported from methadone maintenance treatment programs for opioid addiction in the United States, and 8 cases were reported from a chronic

pain clinic in Alberta, Canada. The connection between cases was made solely as a result of communication between two physicians after 6 cases of torsade de pointes in methadone-treated patients from Denver, Colorado, aroused concern.

We did not formally attempt to identify patients by review of databases or medical records or by active case solicitation. We excluded 3 patients: 1 patient receiving methadone maintenance treatment who experienced torsade de pointes (excluded because of previous diagnosis of congenital long-QT syndrome) and 2 patients treated with methadone for chronic pain who died suddenly (excluded because of inadequate documentation of arrhythmia). We ascertained patient survival data through communication with primary care providers.

Definitions

All cases required the presence of a prolonged QT segment, with a corrected QT interval (QTc interval) of at least 500 msec in the setting of polymorphic ventricular tachycardia (8). We used Bazett's formula to determine the QTc interval: $QTc \text{ interval} = QT \text{ interval (in msec)} \div \sqrt{\text{preceding R-R interval (in sec)}}$ (9). All patients were assessed by echocardiography or angiography, or both, for the presence of structural heart disease, defined as left or right ventricular systolic dysfunction. Serum electrolyte levels measured at the time of presentation were reviewed. Hypokalemia was defined as a serum potassium level less than 3.5 mmol/L (3.5 mEq/L). Medications, alcohol, or illicit substances that may have contributed to this arrhythmia were tabulated for all patients. Medications were considered to be potential contributing factors if review of manufacturer labeling or a literature search revealed a clinical or experimental association with QT prolongation or torsade de pointes. In addition, drugs that may have inhibited the metabolism of

Context

Several drugs, including antiarrhythmic agents, antihistamines, and tricyclic antidepressants, can cause acquired long-QT syndrome (torsades de pointes).

Contribution

This case series describes 17 patients who had torsades de pointes while taking very high doses of methadone for chronic pain or methadone maintenance. The average daily methadone dose was about 400 mg. Fourteen of the patients had known risk factors for arrhythmia, such as hypokalemia, or were taking other drugs that could prolong the QT interval.

Cautions

These data suggest, but do not prove, that very-high-dose methadone can cause torsades de pointes.

—The Editors

methadone were tabulated. Particular attention was given to screening for antihistamines, macrolide and fluoroquinolone antibiotics, imidazole antifungal agents, antimalarial agents, phenothiazines, and tricyclic antidepressants.

RESULTS

We documented 17 cases of torsade de pointes in methadone-treated patients. The Table summarizes the patients' clinical characteristics. The mean age (\pm SD) of the patients was 49 ± 9 years; 10 of the 17 patients were female. Each patient experienced overt syncope during arrhythmia documentation. The mean daily methadone dose

was 397 ± 283 mg. The mean QTc interval on presentation was 615 ± 77 msec; the mean heart rate was 64 ± 15 beats/min, and 10 patients were bradycardic (≤ 60 beats/min). Seven patients had hypokalemia, and 1 patient had hypomagnesemia on presentation. Nine patients were receiving a potentially QT-prolonging drug, and 1 patient was taking a medication known to inhibit the metabolism of methadone. Only 3 patients were found to have structural heart disease. Overall, 14 of 17 patients had at least one potential risk factor for arrhythmia. Of note, 5 patients being treated for chronic pain were receiving the anti-epileptic drug gabapentin. Six patients had had their methadone dose increased within 1 month before presentation with torsade de pointes, and 7 had been receiving methadone therapy for 3 or fewer months. An implantable cardiac defibrillator or pacemaker was placed in 14 patients; all 17 patients survived.

DISCUSSION

This series raises concern about a possible association between very-high-dose methadone and torsade de pointes. The clinical characteristics of patients in this series typify most cases of drug-induced torsade de pointes, which are characterized by a relative absence of structural heart disease, by associated hypokalemia, and by a female predominance (10, 11). A noteworthy finding was that 6 patients had had an increase in methadone dose in the month just before presentation. Although 2 patients who died suddenly were excluded from analysis, they had also begun receiving substantially higher methadone doses 48 hours before their death. A previous study (12) showed a similar

Table. Clinical Characteristics of the Patients

Patient	Sex	Age	Dose	Treatment Duration	Corrected QT Interval	Contributing Drugs	Potassium Level*	Structural Heart Disease
		y	mg/d	mo	msec		mmol/L	
1†	M	50	1000	>12	600	Olanzapine	4.1	No
2†	M	52	550	9	625	None	4.6	No
3	M	60	97	>12	560	None	4.3	No
4	F	51	90	4	585	Cocaine	(3.2)	Yes
5†	F	45	85	3	590	Alcohol	4.1	No
6	F	46	126	6	500	Alcohol, fluoxetine	(2.3)	No
7	M	38	300	>12	700	Fluoxetine, levacetylmethadol	4.0	No
8	M	51	110	>12	570	Nelfinavir	4.1	No
9	F	47	65	2	540	Olanzapine, alcohol	(3.0)	No
10	F	52	650	11	785	None	4.1†	Yes
11	F	43	600	6	765	Olanzapine	4.6	No
12†	F	41	660	<1	611	Fluoxetine	(3.3)	No
13	F	55	270	1	600	None	(3.2)	No
14	F	33	680	10	625	None	3.6	Yes
15†	M	52	540	1	650	Amitriptyline	(3.4)	No
16†	M	47	600	<1	635	None	4.2	No
17	F	75	330	3	522	None	(3.3)	No
Mean \pm SD		49 ± 9	397 ± 283		615 ± 77			

* Serum potassium levels below the reference range (<3.5) are noted in parentheses.

† Patients who had an increase in methadone dose within 1 month of arrhythmia presentation.

‡ This patient had a low serum magnesium level—0.68 mmol/L (reference range, 0.70 to 1.00 mmol/L).

temporal association between malignant arrhythmia onset and an escalating dose of cisapride.

Another consideration in evaluating drug-induced torsade de pointes is the effect of metabolic inhibitors on serum drug concentration. Methadone is metabolized primarily via the hepatic cytochrome P450 isoenzyme CYP3A4 (13). In one case in our series, therapy with nelfinavir, a potent inhibitor of CYP3A4, was initiated just before the development of torsade de pointes. This type of drug–drug interaction leading to torsade de pointes is well documented for cisapride and the antihistamine terfenadine (12, 14).

Two potential pathophysiologic mechanisms might explain an association between methadone and torsade de pointes. One possibility is that synthetic opioids mediate this arrhythmia through bradycardia. Drug-induced torsade de pointes is generally a pause-dependent arrhythmia, usually occurring at slow heart rates (15, 16). Both methadone and its derivative levacetylmethadol have demonstrated negative chronotropic effects in vitro (17). The bradycardia seen in most patients in this series suggests that methadone may have facilitated torsade de pointes through these effects. Another possibility is that methadone may lead to this arrhythmia through prolongation of cardiac action potential duration by delaying repolarization. This mechanism underlies most cases of drug-induced QT prolongation and torsade de pointes, and it frequently occurs through inhibition of the rapidly activating component of the delayed rectifier potassium ion current (I_{kr}) (10). Experiments using the whole-cell patch-clamp technique have recently shown that methadone diminishes this current in vitro (18). An electrocardiographic study demonstrating an 8% absolute increase in the QTc interval after methadone initiation corroborates this in vitro mechanism (19).

Our report has many limitations. The sample size is small, and in the absence of a control group, we cannot make definitive statements about a true causal association. Moreover, we did not conduct genetic testing of individuals for congenital long-QT syndrome. Baseline electrocardiographic data were not available because, unlike with levacetylmethadol, the manufacturer of methadone does not require this screening before initiation of methadone therapy. In addition, because cases were discovered fortuitously, we cannot estimate the actual incidence of torsade de pointes in methadone-treated patients. Although patients are monitored closely in both methadone maintenance treatment programs and the chronic pain clinic, other cases may have been missed. An under-reporting bias might exist in the methadone maintenance treatment population, where it may be assumed that sudden death is the result of narcotic overdose.

In summary, the characteristics of patients in this series are consistent with most cases of drug-induced torsade de pointes, in which a confluence of factors is implicated in arrhythmia development. An association between methadone and torsade de pointes seems plausible in light of

cases observed with the chemically similar compound levacetylmethadol, as well as the in vitro and electrocardiographic evidence suggesting that methadone delays cardiac repolarization. However, our report should not be interpreted to suggest that high-dose methadone cannot be used safely. The mean methadone dose associated with arrhythmia in this series was substantially higher than doses typically encountered in clinical practice. For instance, the average methadone dose in Colorado's 1400 actively treated patients in 1999 was 68 mg/d, and although doses greater than 100 mg/d were prescribed for 22% of patients, fewer than 0.1% of patients received doses greater than 300 mg/d (Colorado Department of Human Services, Alcohol and Drug Abuse Division, May 1999). In contrast, the chronic pain clinic in this report tended to use substantially higher doses: In approximately 130 actively treated patients, the average dose was 300 mg/d. Nevertheless, physicians involved in methadone maintenance treatment and chronic pain management should be aware of a potential association between very-high-dose methadone and torsade de pointes, particularly in the setting of additional arrhythmia risk factors. Because methadone treatment will probably expand into the realm of the general internist, further studies appear to be warranted.

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