

Torsades de Pointes During Methadone Treatment

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Methadone is a synthetic opioid that has been used successfully to treat heroin addiction and chronic pain. It is usually well tolerated and has few side effects. Recently, an association with torsade de pointes has been reported. We present 4 cases of torsade de pointes during methadone treatment.

Key words: *Methadone. Torsade de pointes. Long QT syndrome.*

Torsade de pointes durante el tratamiento con metadona

La metadona es un opiáceo sintético que, con frecuencia, se utiliza para el tratamiento de la adicción a la heroína y el dolor crónico. En general es bien tolerada y tiene escasos efectos secundarios, aunque recientemente han surgido dudas respecto de su seguridad. Presentamos 4 casos de *torsade de pointes* en posible relación con tratamiento con metadona.

Palabras clave: *Metadona. Torsade de pointes. QT largo.*

INTRODUCTION

QT interval prolongation is a predisposing factor for the onset of potentially fatal ventricular arrhythmias. It is known to be associated with several drugs, such as antiarrhythmic agents, antibiotics and antihistamines, and has also been related to electrolytic and metabolic alterations.¹⁻³ Methadone is a synthetic opioid that is frequently used to treat heroin addiction and chronic pain. Although there are concerns about its safety, it is generally well tolerated and has few side effects.⁴ However, it has recently been reported that treatment with high doses of methadone may be associated with ventricular arrhythmia.^{5,6} We present 4 patients with QT interval prolongation and torsade de pointes (TdP) during methadone maintenance treatment.

CASE STUDIES

Four patients (3 men, 1 woman) with no known history of heart disease were seen in the emergency room for syncopal episodes (Table). All were under long-term methadone therapy, although only 1 was receiving >200 mg/day. Three of these patients were infected with human immunodeficiency virus (HIV), but only 1 was on antiretroviral therapy.

The electrocardiographic recordings and monitoring showed sinus rhythm, prolonged corrected QT interval, and runs of self-limiting TdP polymorphic ventricular tachycardia (Figure 1), which degenerated to ventricular fibrillation in 2 cases, requiring electrical cardioversion.

The biochemical parameters showed low serum potassium concentrations in 2 cases, whereas calcium and magnesium levels were normal in all patients. In addition, various toxic substances were detected in urine.

The echocardiogram showed severe biventricular dysfunction in 1 of the patients; ventricular function was normal in all others. After methadone was discontinued and magnesium sulfate, isoproterenol perfusion, and potassium supplements were started, polymorphic ventricular tachycardia disappeared within 7 hours of admission. After 2-3 days, methadone treat-

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TABLE. Clinical, Electrocardiographic, and Analytical Characteristics of the Patients*

	Sex	Age	HIV	Antiretroviral Treatment	Methadone Dose	Other Drugs	ECG	QTc, ms	Potassium	Magnesium	LV Function
Case 1	Male	42	No	No	110 mg/day	BZD	Polymorphic VT	640	2.9	2.2	Normal
Case 2	Male	29	Yes	Yes	>200 mg/day	Antiepileptics	Polymorphic VT	612	3.7	2.3	Reduced
Case 3	Male	38	Yes	No	200 mg/day	Cannabis, BZD	VF TdP	600	2.8	2.2	Normal
Case 4	Female	37	Yes	No	100 mg/day	Cocaine, opiates	VF TDP	658	3.3	2.4	Normal

*BZD indicates benzodiazepines; ECG, electrocardiogram; HIV, human immunodeficiency virus; LV, left ventricle; QTc, corrected QT interval; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

ment was resumed at the usual doses, with the QT_c interval progressively returning to normal in 3 cases; the fourth patient requested voluntary withdrawal before the study was completed.

DISCUSSION

Methadone has been widely used for the treatment of heroine addiction and chronic pain for more than 3 decades. It is generally well-tolerated, has few adverse reactions, and until recently its cardiac effects were unknown. In fact, in 2001 the U.S. Food and Drug Administration discontinued drug surveillance of methadone therapy, considering it safe, and recommended that heroine dependence treatment with this drug be expanded and made more flexible.⁵ Although some experts do not include methadone treatment as a cause of QT interval prolongation¹ and others only consider this possibility to be improbable,⁴ several cases of polymorphic tachycardia have recently been reported in association with high-dose methadone treatment.^{6,7}

Experimental studies have found that methadone can affect numerous cardiac function parameters through various mechanisms. The stimulation of opiate receptors has a negative chronotropic effect, a phenomenon known to be a predisposing factor for TdP. In addition, in vitro methadone inhibits the rectifying current of the 3 potassium I channels (HERG) or I_{Kr} current, prolonging the action potential of the cardiac cells and consequently, the QT interval.⁸ The latter is

the same mechanism that explains the acquired QT interval prolongation caused by administration of other drugs.^{1,4} Consistent with these results, later clinical studies have shown that initiation of methadone treatment in patients addicted to heroine is followed by significant QT interval prolongation.⁹

Among HIV-infected patients receiving antiretroviral therapy and high doses of methadone Gil et al⁷ reported 4 cases of QT interval prolongation with TdP in 3 of them. Antiretroviral therapy, in particular, protease inhibitors such as nelfinavir, can cause important pharmacological interactions with methadone by inducing or inhibiting the CYP3A4 isoenzyme of cytochrome P450, through which it is metabolized. Concomitant administration of nelfinavir and methadone can result in important changes in plasma concentrations of the latter, possibly leading to the onset of withdrawal symptoms or to intoxication.

As occurred with most patients in earlier studies,^{6,7} our patients presented some associated risk factors related to QT interval prolongation, for instance, hypokalemia, intake of drugs that affect the duration of the QT interval, and/or the presence of structural heart disease. The first and third patients had hypokalemia and were also taking benzodiazepines at high doses. The second was taking methadone doses well above those recommended, with inconstant values due to interaction with the antiretroviral therapy and self-medication. In addition, he presented severe ventricular dysfunction and was being treated with gabapentin, as occurred with one third of the patients

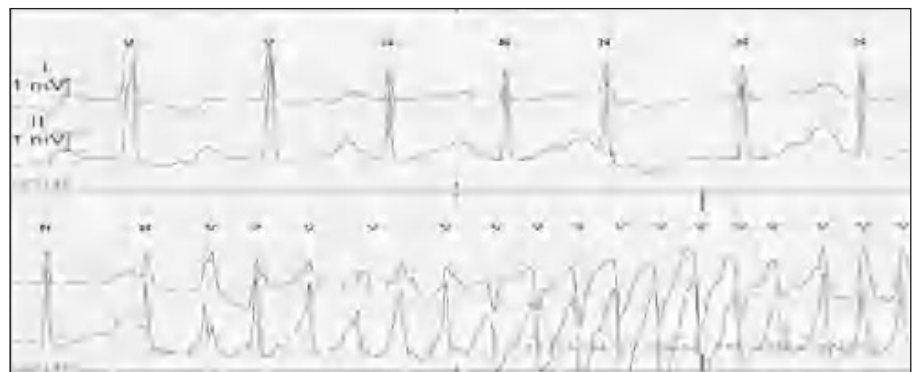


Figure. QT_c interval prolongation and an episode of polymorphic ventricular tachycardia are observed.

in the study conducted by Krantz et al.⁶ Methadone treatment was continued in all our cases, and suppression of the triggering factors was what led to normalization of the QT interval and disappearance of arrhythmia.

In conclusion, methadone should be included among the drugs that can produce QT interval prolongation and TdP. The risk-benefit ratio of this treatment should also be assessed before combining it with other drugs that prolong repolarization or interfere with their metabolism. In this case, the QT_c interval duration should be monitored before and after combined treatment, as well as when high doses of methadone are prescribed, and treatment should be discontinued in case of that induce prolongations of QT_c interval duration >500 ms.^{1,4}

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