CLINICAL CASE

METHADONE OVERDOSE-INDUCED TORSADE DE POINTES IN A HIV-POSITIVE PATIENT – A RARE CASE REPORT

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ABSTRACT

Methadone belongs to the opioid class, being a synthetic compound that can be used as a replacement drug in heroin addicted patients. Patients on methadone can present with prolonged QT interval but progression to torsade de pointes (TdP) is highly uncommon. The aim of this report is to describe methadone-induced torsade de pointes in a HIV-positive patient. A 28-year old male taking methadone as substitution therapy was brought in the emergency department after purposely overdosing. On admission his hemodynamical and respiratory parameters were stable. Toxicology samples showed a urinary methadone level of 501 µg/l and a plasma level of 247 µg/l. Intensive care support was started. Soon after admission the EKG trace recorded short bigeminism aspect followed by torsade de pointes. The patient spontaneously converted to sinus rhythm with no need for resuscitation maneuvers. He maintained polymorphic arrhythmic tracing that resolved with lidocaine 1% administration. Dynamical determinations showed a gradual decrease in plasmatic and urinary methadone levels, while QT interval became normal. Even though TdP is not commonly met in methadone users, this adverse event should not be overlooked since it has fatal potential. Regular cardiological evaluation and exclusion of additional risk factors are mandatory.

KEYWORDS: *methadone, prolonged QT interval, torsade de pointe, arrythmia, cardiac toxicity*

INTRODUCTION

Methadone is on opioid of synthetic origin that acts as a long acting µ-receptor agonist with pharmacologic properties qualitatively similar to those of morphine. The first time the compound was created was during World War II in Germany and approved as an analgesic 10 years later by the US Food and Drug Administration (FDA) [1].

Methadone is a widely and safely used drug for handling of opioid addiction but also in

patients with all-cause chronic pain. However, overdoses have commonly been reported [2].

The long-term intake of methadone as a substitution therapy to opiate-dependent patients has been performed since 1965 when Dole and Nyswander used this synthetic drug for the first time in the United States to treat drug addiction [3]. The fundamentals for the use of methadone as substitution therapy for heroin addicts are based on the fact that there is a cross-dependence and -tolerance between different opiates [4].

The spreading use of methadone brought about an increased prevalence of methadone-induced cardiotoxic events (MIC) which in turn appears to be responsible for cases of sudden death2. In addition to methadone's adverse effects on the heart, which include QT interval prolongation, torsade de pointe (TdP), other effects may also be encountered, such as changes in QT aspect, abnormal U-waves, Takotsubo syndrome, Brugada-like syndrome or coronary heart disease [5].

TdP has been associated with several classes of recreational and therapeutic drugs which act primarily on the central nervous system (CNS) with additional effects on the heart and vessels, contributing to an increased morbi-mortality rate [6].

Studies have shown that methadone can disturb heart function parameters in multiple ways. One of the most frequently met mechanisms is blocking a gene named human cardiac ether à go-go-related gene (hERG) which is responsible for encoding Ikr, a potassium ion channel rectifier with delayed action. Methadone potently inhibits hERG channel [7] and its blockade leads to prolongation of the terminal portion of the cardiac action potential causing delayed repolarization. This mechanism is represented by corrected QT (QTc) interval prolongation on the EKG recording potentially leading to TdP which is a rare but life-threatening form of ventricular dysrhythmia [2].

The QT interval is the time that the ventricles require for depolarization and repolarization, starting at the QRS complex until the end of T wave. Since the QT interval depends on the heart rate, the corrected QT interval is necessary using the Bazett formula ($QTC = QT / \sqrt{RR}$). A prolonged QTc is defined as more than 450 msec for males and 470 msec for female adult patients [8].

QTc interval prolongation is a risk factor for developing polymorphic ventricular tachycardia or TdP. Despite the fact that QTc prolongation is known to occur in patients on methadone maintenance therapy, it usually has no significant impact except in cases where QTc interval is prolonged with a value over 500 msec thus heavily increasing patients' risk of developing TdP. Thus, reaching this prolonged QT interval is risky and indicates stopping methadone treatment [9].

Methadone can be responsible for QT prolongation and TdP via other mechanisms, namely inducing negative chronotropic effects through antagonization of calcium channels, showing a similarity to verapamil, and by an anti-cholinesterase effect. The consequent bradycardia makes patients prone to developing potentially fatal TdP [10].

Due to its multiple effects of QT prolongation, increased QT dispersion and negative chronotropy, methadone poses a significant risk for the development of TdP. Other associated risk factors are electrolyte abnormalities such as low levels of potassium, magnesium or calcium, female gender, drug interactions and HIV infection [11], [12].

CASE PRESENTATION

We report the case of a 28-year-old male patient with a history of cocaine abuse which was discontinued more than two years ago and successfully entered a national program of methadone substitution therapy. In addition, he suffered from HIV infection, but no antiretroviral drugs were initiated because of patient's reluctancy to treatment. To present, no progression to AIDS was noted by patient's attending physician.

Apart from a daily methadone dose of 125mg, patient had no other recorded prehospital medication, and he was not known to have any cardiac, hepatic or neurological conditions. No history of seizures was included in his previous medical files.

The patient presented at the emergency department after self-overdose, administering an unknown drug dose. Upon admission, he exhibited a mediocre state, he was conscious but slightly somnolent and partially cooperative with the medical staff. He had a blood pressure of

140/80 mmHg, pulse of 88 beats per minute and his O2 saturation was 97%. Patient was stable both hemodynamically and respiratory and showed present diuresis.

Laboratory studies were performed but results were unremarkable with normal potassium, magnesium and calcium levels, normal cardiac enzymes, blood sugar and cell blood count.

Given the overdose drug intake, toxicology blood and urine samples were drawn and revealed a urinary methadone level of 501 µg/L, significantly higher than the laboratory reference value of 300 µg/L and a plasma level of 247 µg/L (300 µg/L).

Intensive support therapy was established which included volemic repletion, electrolyte rebalancing and oxygen therapy. Treatment with diuretics, vitamin supplements, and thromboprophylaxis were added.

Shortly after hospital admission the EKG recording revealed short bigeminism tracing followed by rapid installation of torsade de pointes (Figure 1).

No prior EKG trace was available in order to assess patient's baseline QTc interval or during methadone treatment.

Despite being unconscious during the episode, resuscitation maneuvers were no longer initiated since the patient spontaneously converted to sinus rhythm, maintaining further polymorphic arrhythmic events (Figure 2). Lidocaine 1% (1 mg/kg) was administered with no further repeated episodes of TdP. Magnesium sulphate 2 g was immediately initiated in continuous perfusion.

Patient had subsequent favorable evolution, with no cardiac arrythmias while ulterior sequenced determinations showed a progressive decline in plasmatic and urinary methadone levels, with QT interval normalization.

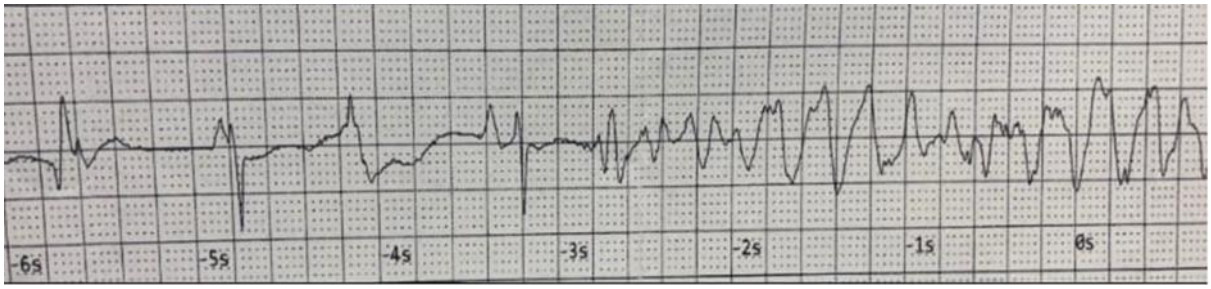

Figure 1 – Sinus rhythm trace with multiple ventricular extrasystoles, exhibiting short-long-short phenomenon with dispersion of ventricular repolarization and degeneration into TdP

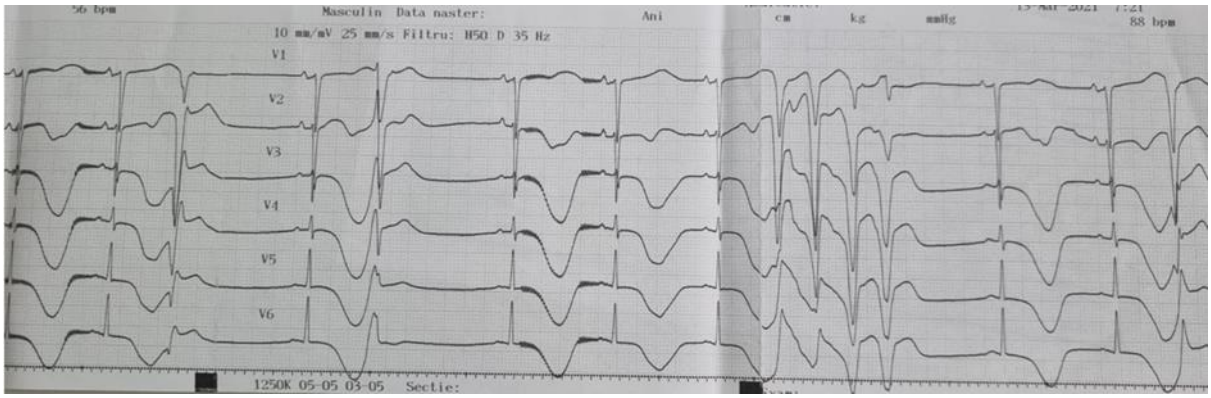

Figure 2 – Sinus rhythm with obvious prolonged QT interval, bradycardia and episodes of non-sustained ventricular tachycardia

DISCUSSIONS

Methadone is a preferred alternative to morphine in chronic pain management strategies and opioid-abusers' programs since it is a long-acting drug and less expensive. Side effects like constipation, nausea, vomiting are less encountered in methadone users as compared to morphine intake [9].

Patients with history of drug addiction currently on methadone substitution therapy are more prone to overdose this therapy, leading to acute opioid intoxication. The present case reports a patient with voluntary methadone overdose during a suicidal attempt.

Since methadone has an affinity to lipid-tissue binding, it can accumulate in adipose tissues and be responsible for increased toxicity. It is metabolized by the P450 cytochrome system in the liver, thus being prone to interact with other drugs with the same metabolization mechanism and leading to unstable drug serum levels [13].

Apart from potentially harmful respiratory and CNS events, methadone can also prolong the QT interval and cause life-threatening arrhythmias including TdP [14].

The presented case displays the risk of TdP installation in a HIV-positive patient on methadone maintenance therapy.

The cause of TdP in the above-presented patient is multifactorial. Apart from potential genetic predisposition which cannot be proven with certainty in the lack of previous cardiological evaluation or EKG recordings, the patient was a HIV seropositive patient. Almost a third of patients with active HIV infections have a prolonged QTc and the prevalence rate increases to around 45% in patients with advanced AIDS. The mechanisms behind this association is still under debate but it seems that contributory factors are represented by chronic HIV infection itself, specific HIV drugs like protease-inhibitors or opportunistic infections [15]. As stated, patient was not under HIV therapy and no infections were confirmed during hospitalization.

In patients with HIV, longer QT intervals can also be due to HIV-induced cardiomyopathy, autonomous neuropathies and multiple drugs for opportunistic infections (quinolones, trimethoprim/sulfamethoxazole, macrolides and others). Moreover, in concurrent methadone users, adjustment of dose might be necessary because of the effects on cytochrome P450 of antiretroviral drugs [16].

Consistent data on TdP secondary to methadone-induced QT prolongation has been published and this effect seems to be dose-dependent and if the QTc exceeds 500msec. Other additional risk factors are concomitant drugs that can alter QT or electrolyte imbalance like hypokalemia.

Other risk points to consider are female gender, older age, cardiac, liver or renal diseases, use of cocaine or alcohol [5].

Management of TdP is influenced by patient's hemodynamic state. If TdP progressed to ventricular fibrillation, defibrillation is recommended [17]. Lidocaine or phenytoin are available therapeutical options together with risk factor correction. In patients at high risk of repeating TdP events, implantable cardioverter-defibrillators (ICDs) might be effective [18].

The clinical case report highlights the importance of monitoring methadone users in order to correctly identify those at high risk of developing harmful arrythmias. Thus, when initiating a methadone maintaining therapy, physicians should order a baseline EKG recorder to assess QTc then monitor EKG aspect at least annually. Drug interactions should be checked at starting point or every time a new drug is recommended. Patients should be aware to notify if clinical changes occur like palpitations, dizziness or syncope together with electrolyte disturbances situations like diarrhea, vomiting.

CONCLUSIONS

Heroin-dependent patients benefit from methadone substitution therapy that helps social reintegration. Methadone use is responsible for QTc prolongation leading to further fatal dysrhythmias, depending on the dose and other additional risk factors, including HIV infection. Although TdP is not commonly encountered during methadone treatment, this adverse event should be taken into consideration given its potentially lethal effect. Periodic cardiological monitoring is strongly recommended together with the avoidance of any favoring factors that could lead to cardiac rhythm disturbances. In patients with history of methadone-toxicity, buprenorphine might be considered as an alternative [19].

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