

## Methadone induced torsades de pointes and ventricular fibrillation: A case review

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### Case Report

#### Abstract

**BACKGROUND:** Methadone is a synthetic opioid, which has been successfully used in treating heroin addiction and chronic pain syndrome in palliative care for more than 30 years. This drug is a potent blocker of the delayed rectifier potassium ion channel, which may result in corrected QT (QTc) interval prolongation and increased risk of torsades de pointes (TdP) in susceptible individuals.

**CASE REPORT:** We describe here a case of methadone-induced TdP that deteriorated into ventricular fibrillation, which was resolved after treatment with IV magnesium, potassium, and Lidocaine. Our purpose in this case review was to highlight the risk of cardiac arrhythmias, in particular QTc interval prolongation leading to TdP in a heroin-dependent patient receiving methadone substitution therapy, and then to present a perspective on treatment and prevention strategies of methadone induced prolonged QTc.

**CONCLUSION:** Methadone-induced TdP is a potentially fatal complication of methadone therapy. As the popularity of methadone use grows, clinicians will encounter more cases of methadone induced TdP, especially in our region, Iran. Hence, a thorough patient history and electrocardiogram monitoring are essential for patients treated with this agent, and alterations in treatment options may be necessary.

**Keywords:** Torsades de Pointes, Methadone, Ventricular Fibrillation, Prolonged Corrected QT

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#### Introduction

Methadone is an established and effective pharmacological agent to treat heroin dependent patients and chronic pain syndromes worldwide.<sup>1</sup> Although methadone has proven efficacy in reducing the use of nonprescription opioids and in alleviating pain, it has the potential for serious adverse effects. Methadone delays cardiac repolarization by blocking the rapid component of potassium ion current (I<sub>Kr</sub>) potassium channels, encoded by hERG or KCNH2 gene and hence it is independently associated with a prolonged corrected QT (QTc) interval and progression to torsades de pointes (TdP).<sup>2,3</sup> QTc prolongation is common in patients with Methadone maintenance therapy, but it does not lead to any significant consequences unless the QTc interval becomes

profoundly prolonged (500 ms), exposing patients to developing TdP.<sup>4</sup> TdP is an abnormal cardiac rhythm displaying a regular and wide polymorphic QRS complex tachycardia that twists around the isoelectric baseline.<sup>5</sup> Here is a review on a case presented by TdP and ventricular fibrillation following methadone use.

#### Case Report

A 65-year-old man presented to the emergency department complaining of feeling unwell, chest pain during exercise, nausea and vomiting for a few days ago. He had recurrent episodes of apnea, palpitation and dizziness since the night before. A review of his past medical history revealed that he was a previous intravenous heroin user who was attending a community methadone substitution

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program. He was prescribed syrup methadone 240 mg daily. He was not known to have cardiac, respiratory, hepatic or neurological disease. Physical examination was remarkable for normal mental status, blood pressure of 140/90 mmHg, pulse of 50 beats/min in sinus rhythm, O<sub>2</sub> saturation: 90%, no cardiac murmurs, and no signs of heart failure. Laboratory studies included potassium of 2 mmol/l and magnesium of 1.4 mmol/l, white blood cell: 12,000/mm<sup>3</sup>, hemoglobin: 15 g/dl, platelet: 222,000/mm<sup>3</sup>, blood sugar: 122 mg/dl. We thought his hypokalemia was due to prolonged vomiting. His electrocardiogram (ECG) demonstrated sinus bradycardia and a QTc of 550 ms (Figure 1).

The patient was admitted to the cardiology service for ECG monitoring. Shortly thereafter, the patient experienced an episode of TdP and ventricular fibrillation (Figure 2).

Cardiopulmonary resuscitation, defibrillation and Lidocaine administration resulted in a successful return of spontaneous circulation. Lidocaine was an antiarrhythmic agent of choice because it does not prolong QTc anymore in contrast to other antiarrhythmic agents.

Potassium and magnesium were administered intravenously to correct hypokalemia and hypomagnesemia. Due to the recurrent episode of TdP temporary pacemaker was inserted, and it was set at rate of 100-120 beats/min to prevent bradycardia. Temporary pace maker (TPM) was removed after 48 h. Methadone was discontinued and substituted with buprenorphine. Over the following 7 days, QTc interval progressively returned to normal limits. Discharge serum potassium and magnesium were 4.5 mmol/l and 2.5 mg/dl respectively. The patient was discharged with buprenorphine and a follow-up at the cardiology clinic, 2 weeks and 1 month later revealed no further cardiac symptoms with a normal ECG. He did not have any electrolyte abnormality at follow-up.

## Discussion

Opiate substitution therapy with methadone has been introduced as a pharmacological treatment option for heroin-dependent individuals. The recommended dose for methadone maintenance therapy is about 60-100 mg/day. High dose methadone has been reported to prolong the QTc interval.<sup>6</sup>

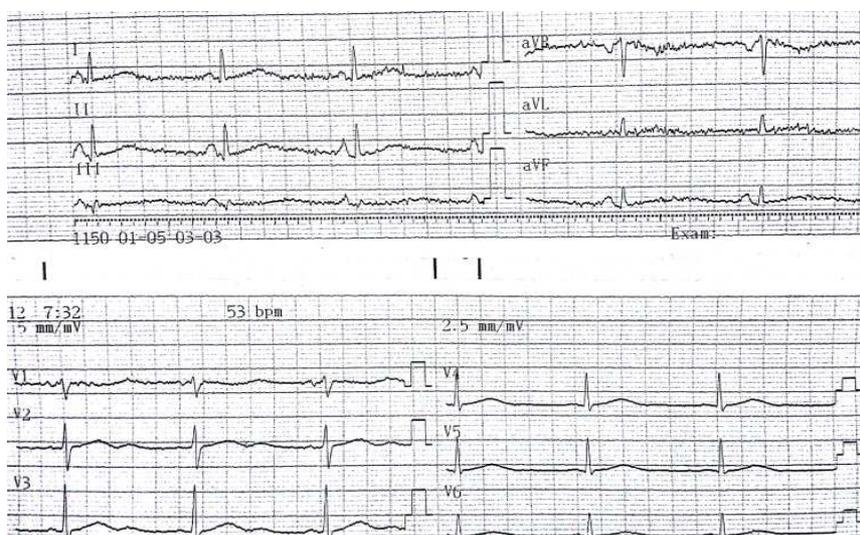


Figure 1. Long corrected QT interval

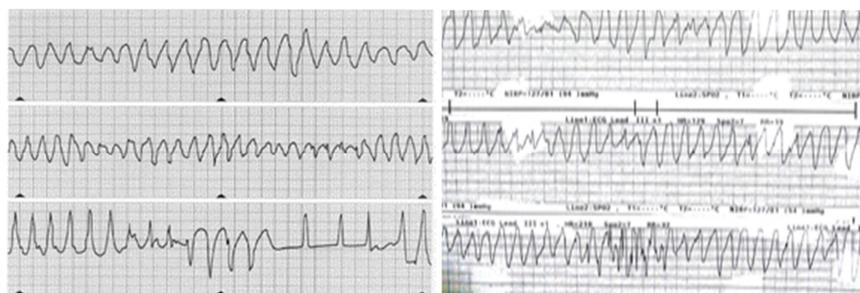


Figure 2. Torsades de pointes

The QT interval is measured from the beginning of the QRS complex to the end of the T wave. The QT interval varies with heart rate and is often corrected for this (QTc). Formula for QT correction that is insensitive to heart rate is:  $QTc = QT + 1.75 (\text{heart rate} - 60)$ .<sup>7</sup> A QTc interval of 500 ms or longer can confer an increased risk of TdP. QTc > 500 ms has been reported in 1.3-16% of methadone-treated patients in various cohorts and is rarely associated with methadone doses < 100 mg/day. Although most sudden cardiac arrests on methadone maintenance therapy have been reported at high doses, life-threatening arrhythmias have been described at dosages as low as 29 mg/day.<sup>8,9</sup>

Co-morbid conditions also play an important role in the occurrence of the QTc prolongation or TdP in methadone users. Some of these risk factors are: older Age, cardiac, liver, and renal abnormalities; concomitant use of cocaine and alcohol; ingestion of medications known to prolong the QTc; electrolyte imbalances (hypokalemia and hypomagnesaemia); human immunodeficiency virus infection; and female sex.<sup>10,11</sup> At least one of these risk factors was present in the majority of documented cases of ventricular arrhythmias in methadone maintenance patients.<sup>12</sup>

The pathophysiology of methadone-induced torsades can be explained via two mechanisms. It has been shown that methadone has a negative chronotropic effect due to its chemical similarity to verapamil.<sup>13</sup> It is thought that TdP is mediated through bradycardia since drug-induced arrhythmias generally tend to occur at slow heart rates and are pause - dependent. In addition, experimental studies have demonstrated that methadone inhibits the rapidly activating component of the delayed rectifier I<sub>kr</sub> encoded by the hERG or KCNH2 gene, resulting in the cardiac action potential prolongation by delaying repolarization.<sup>14</sup>

Management of methadone-treated patients with prolonged QTc interval without manifest ventricular arrhythmia requires careful consideration of risks and benefits of continuing methadone or altering therapy. In any case, more frequent monitoring, counseling about worrisome symptoms and elimination of contributing factors such as additional QTc-prolonging medications and electrolyte abnormalities are required.

Acute treatment of TdP depends on the patient's hemodynamic status. Defibrillation is indicated when torsades has degenerated into ventricular fibrillation. DC-cardioversion can be used when the

patient is haemodynamically compromised but may lead to recurrence of torsades. Lidocaine, mexiletine, or phenytoin can be tried. The correction of any predisposing factor (e.g. hypokalemia) and cessation of any predisposing medication is necessary. Magnesium is the first-line treatment of torsades; 2 g intravenously is followed if required by either a continuous infusion or a further bolus 5-15 min later. Potassium should be administered to achieve high normal levels (4.5-5.0 mmol/l). Temporary ventricular overdrive pacing can also be used in the short term. It prevents bradycardias and pauses and decreases the QTc interval due an increase in heart rate. Alternatively, acceleration of the basic heart rate using isoproterenol may be used. It should be used when the underlying rhythm is slow, the torsades is pause-dependent, and pacing is not able to be implemented. Long-term treatment in acquired long QT syndrome is generally not required.<sup>15</sup> Implants cardioverter-defibrillators (ICDs) have been suggested for patients with symptomatic ventricular arrhythmias who continue to take methadone. ICDs effectively prevent sudden death in these patients, but full risks and benefits of ICD in this patient population are not known.<sup>16</sup>

Although methadone has been reported to induce ventricular arrhythmias, the small risk of TdP should not deter physicians or psychiatrists from offering methadone as a treatment option to heroin-dependent individuals. The treatment of methadone induced TdP centers on prevention and risk stratification. A12-lead ECG should be obtained prior to starting methadone and should be repeated at regular intervals throughout the treatment.<sup>11</sup> Clinicians should carefully review the patient's current medications to look for other drugs that may prolong the QTc. The process should be repeated each time a new medication is added. Patients should be instructed to promptly report any episodes of palpitations or syncope, as well as conditions or therapies that can cause hypokalemia, such as gastroenteritis (diarrhea or vomiting) or the addition of diuretics to the patient's regimen.<sup>17</sup> In patients who experienced methadone induced arrhythmias, methadone should be stopped and an alternative safer medication such as buprenorphine, which is a partial opioid agonist should be considered.<sup>10</sup>

## Conclusion

Methadone induced TdP is a potentially fatal complication of methadone therapies. As the

popularity of methadone use grows, clinicians will encounter more cases of methadone induced TdP, especially in our region. Due to the unpredictable nature of QTc prolongation and TdP, clinicians should be alert of how to monitor these medications and to prevent potentially fatal arrhythmias. Periodic ECG monitoring of the QTc interval and discontinuation of offending medications in the setting of prolonged intervals is ideal. Electrolyte disturbances especially hypokalemia, should be promptly corrected. In the case of patients with severe opioid dependency requiring, very high doses of methadone, alternative agents such as buprenorphine, a mixed opioid antagonist/agonist, should be considered.

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### Conflict of Interests

Authors have no conflict of interests.

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