

Methadone Induced Torsades de Pointes

Alan Lucerna, DO
Combined Internal Medicine/Emergency Medicine
UMDNJ-SOM
lucernal@umdnj.edu

Case Report

A 45 YO female presented to the ER via EMS due to multiple episodes of loss of consciousness followed by “twitching”. The events lasted between 10-20 seconds. The patient woke up spontaneously each time with no post-ictal phases. The patient’s boyfriend, who witnessed these events, stated that the patient was in a chair watching television when these episodes occurred. There was no recent history of trauma or illness. The patient has no history of seizures or brain injuries.

The patient’s past medical history included chronic obstructive pulmonary disease, hyperlipidemia, fibromyalgia, diabetes mellitus, Reynaud’s disease, herniated cervical and lumbar discs, and obstructive sleep apnea. Her past surgical history included lung biopsies, appendectomy, bilateral carpal tunnel release, arthroscopic knee surgery, and laser eye surgery. She admitted to smoking two packs of cigarettes per day. She denied any illicit drug use or alcohol. The patient was on disability due to her chronic back pain. Her family history was notable for a father who died from CAD in his 60’s and a mother who died from lung cancer. Her medications consist of: potassium, oxycodone, soma, methadone, singular, albuterol inhaler as needed, lasix, glucophage, lipitor, and xanax. The patient claims allergies to morphine, penicillin, and avelox. She has not traveled recently.

On examination in the emergency room, the patient complained of shortness of breath but denied chest pain. Her vital signs were as follows: 122/66, 49, 16, 97.0 oral, 85-89% on room air, and 98% on non-rebreather. The bedside blood glucose finger stick was noted to be 258. The patient was mildly lethargic but her physical exam was otherwise unremarkable.

Strategies and Evidence

A comprehensive laboratory and imaging studies was ordered for the patient. The chest X-Ray showed mild vascular congestion. Initial electrocardiogram was remarkable for multiple premature ventricular complexes and a QTc of 678 (see Figure 1). Shortly after blood work was drawn, the patient suffered another loss of

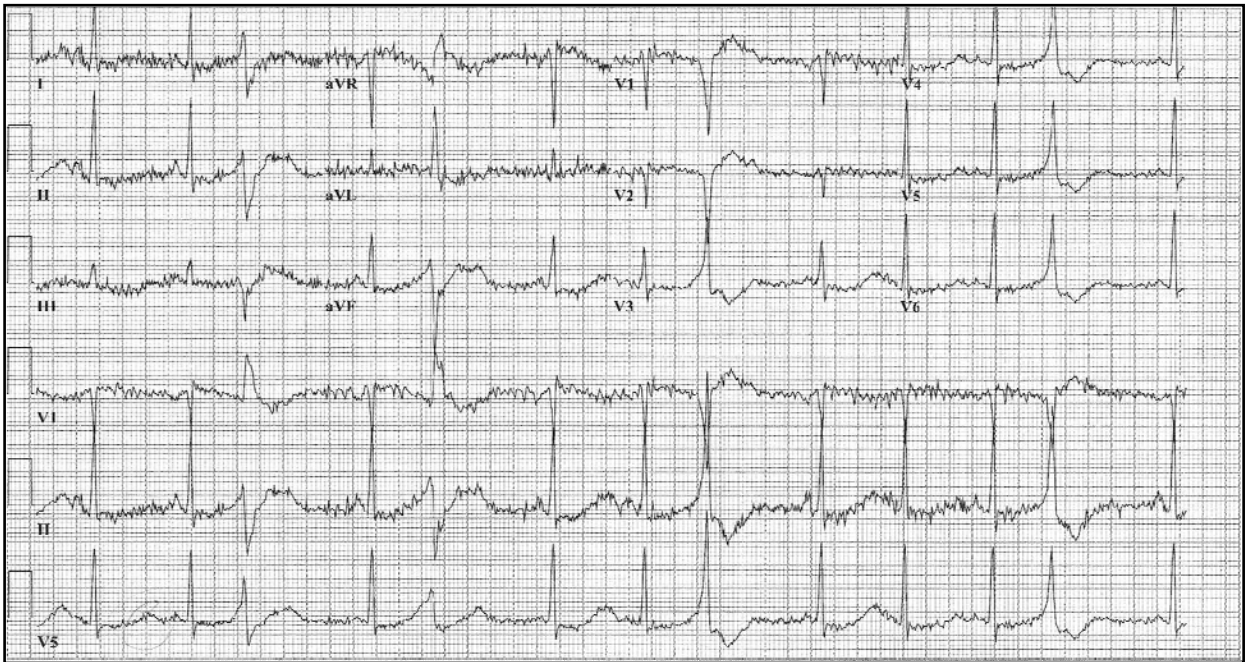


Figure 1. The patient's ECG showing an extremely prolonged QTc and multiple PVC's

consciousness. Telemetry strips revealed that the patient was experiencing polymorphic ventricular tachycardia consistent with torsades de pointes (TdP) (see Figure 2). The arrhythmia was self-terminating and the patient awoke without any intervention. The results of the laboratory tests were as follows: WBC, 19.8; Hgb, 15.8; platelet 252, 000; K+: 2.7; Glucose: 206; Cardiac enzymes: negative; UDS: + Benzodiazepines. The patient was immediately given intravenous potassium chloride. Magnesium sulfate 2 g intravenously was also given.

A careful inventory of the patient's medications showed that methadone was the only agent that can cause a QTc prolongation. The hypokalemia was attributed to lasix and was discontinued. After consulting with the on-call cardiologist, the patient was started on an amiodarone drip and she was admitted to the Intensive Care Unit (ICU). However, the patient further experienced ventricular ectopy with a self-terminating runs of TdP. The patient's telemetry tracings were carefully reviewed and it revealed that her events were preceded by episodes of bradycardia. Drug-induced TdP is typically a pause-dependent arrhythmia, usually occurring at slow heart rates. The amiodarone drip was discontinued. She was then started on isoproterenol to maintain a heart rate of 90 -100. With her heart rate maintained around 100 beats per minute and her electrolytes fully replaced, the Torsades de Pointes never recurred.

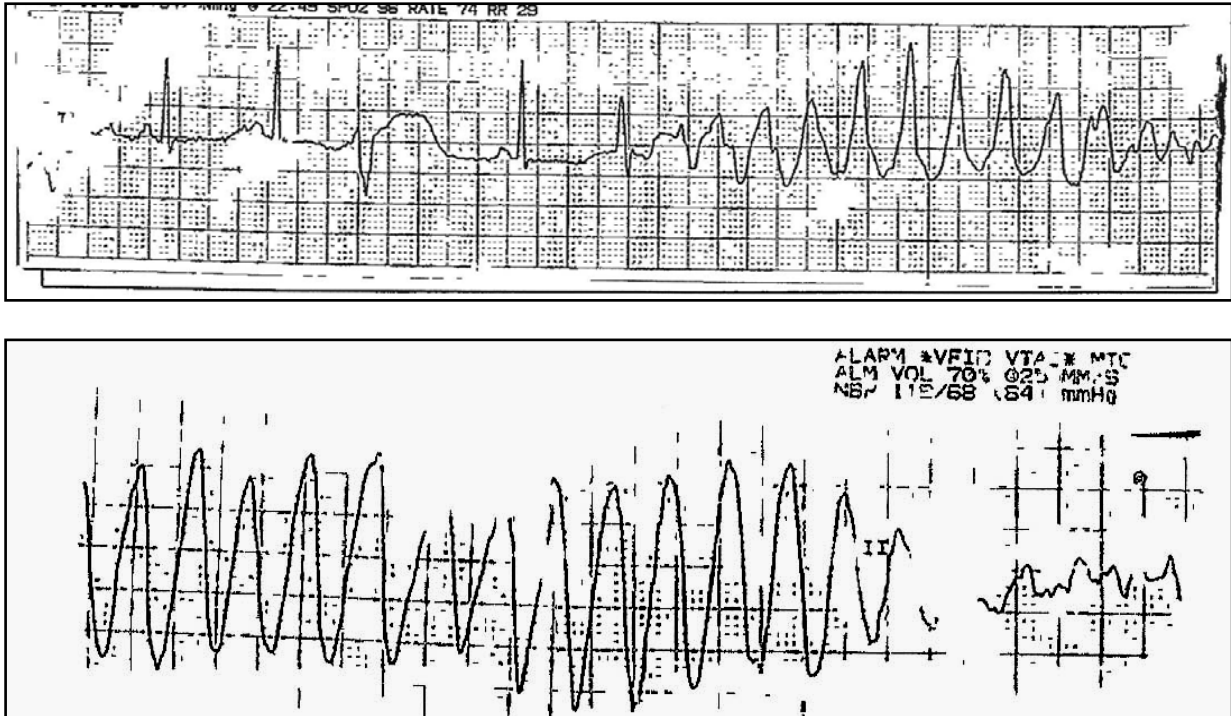


Figure 2. Polymorphic Ventricular tachycardia captured during the patient's episode of loss of consciousness

Reasons for Presentation

This case report highlights the potentially lethal risk of methadone therapy especially in the setting of hypokalemia. Methadone use is not uncommon and its clinical use is growing. Patients who are under this therapy can have significant co-morbidities (e.g. cardiac or liver disease), potentially putting them at even higher risk for TdP. This case also reminds us that drug inventories is an essential step towards preventing severe drug-drug interactions.

Discussion

Torsades de pointes (TdP) is an uncommon variant of ventricular tachycardia (VT). In the United States, about 300,000 sudden cardiac deaths occur per year. About 5% of these are attributed to torsades. In general, the underlying etiology and management of torsades is quite different than other ventricular arrhythmias such that early recognition of this entity is crucial [9].

Research into the underlying etiology of torsades has lead to the identification of a phase 3 delay of the action potential. This phase of the action potential is mediated by a potassium ion channel and encoded by the gene called hERG or Human Ether-a-Go-go Related Gene (see figure 3).

Described as “twisting of points”, torsades de pointes is a polymorphic VT in which the QRS complex changes from beat to beat and QRS vector varies from negative and positive around the isoelectric point [9]. TdP also requires that the QT interval be prolonged. Usually occurring in non-sustained bursts, the torsades may not be captured in the rhythm strip or ECG. A prolonged QTc may be the only clue to the preceding events.

Methadone is a synthetic opioid used by nearly 1 million Americans being treated for heroin addiction and chronic pain syndromes [1,3]. High dose methadone has been reported to prolong the QT interval. Recently, cases of Torsades de Pointes have been reported in the population taking this medication.

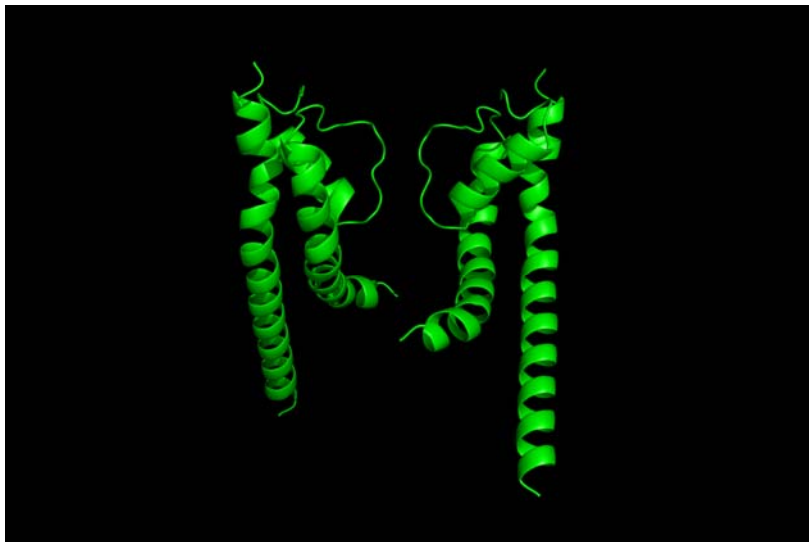


Figure 3. Picture of hERG gene from http://www.pcg.de/report_pictures/Schneider_herg.png

In the span more than 30 years (1969–2002), 43 cases of methadone-associated TdP and 16 cases of QTc prolongation have been reported to the U.S. Food and Drug Administration’s MedWatch program [12]. Other sources have cited 40 patients with methadone-associated TdP from 2002 to 2005 [11].

The occurrence of the QTc prolongation or TdP in methadone users is not due to the direct effect of methadone alone; co morbid conditions also play an important role. Among the known risk factors for methadone-induced TdP include: older age; cardiac, liver, and renal abnormalities; concomitant use of cocaine and alcohol; ingestion of medications known to prolong the QT; electrolyte imbalances (hypokalemia and hypomagnesaemia); HIV infection; and female sex [10, 11, 12]. Case reports have also indicated that affected patients affected are either on high doses or have had their doses recently increased [1]. The recommended range for

methadone maintenance is about 60–100 mg/day. The mean methadone dose in the reported cases was 410 mg/day (range, 29–1680 mg/day). Multiple studies however, have failed to show what dose of methadone causes clinically significant QTc prolongation or TdP [12].

The pathophysiology of methadone-induced torsades can be explained via two mechanisms. It has been shown that methadone has a negative chronotropic effects due to its chemical similarity to verapamil [14]. 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 (Figure 3). Additionally, experimental studies have demonstrated that methadone inhibits the rapidly activating component of the delayed rectifier potassium ion current (I_{kr}), resulting in the cardiac action potential prolongation by delaying repolarization [1,7].

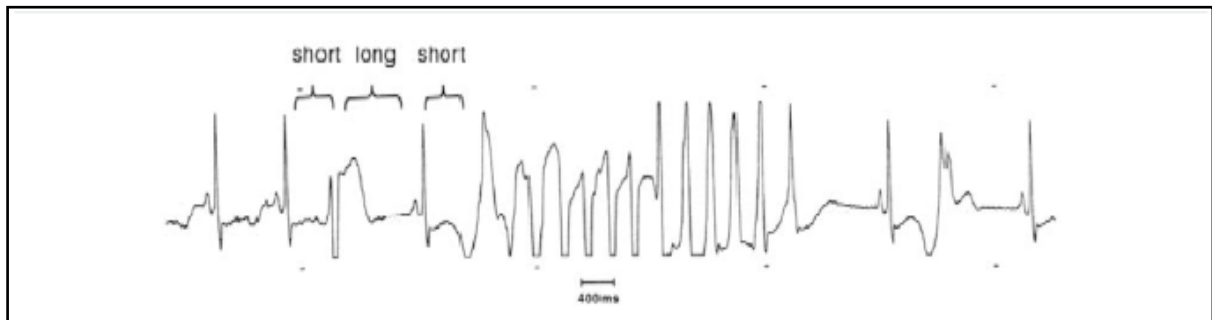


Figure 4. Triggered bursts of torsades precipitated by a short-long-short-sequence. From Gupta A et al Current concepts in the mechanisms and management of drug-induced QT prolongation and torsades de pointes

Based on electrocardiographic studies, an absolute increase of 8% in the QTc interval has been demonstrated after methadone initiation [1]. The threshold generally considered for increased risk of developing TdP is a QTc of 500 msec [4,5]. It is rare to develop TdP in a QTc with less than 500 ms in duration [4]. The risk of syncope or sudden death with a QTc >498 ms is about > 70%. Deaths that were previously attributed to methadone overdose may have been due to arrhythmias resulting to sudden death. Unfortunately, the prevalence of QTc prolongation and TdP in patients treated with methadone is unclear. This is either because patients are asymptomatic or because sudden death is the outcome [12].

Methadone-associated TdP often occurs with the addition of another QT-prolonging agent. Methadone is metabolized primarily via the isoenzyme CYP3A4

of the hepatic cytochrome P450 system [2,4]. Therefore, in addition to several drug classes affecting this pathway, liver disease can also influence the metabolism and clearance of methadone [10]. The drug-drug interactions cause a change in either the pharmacodynamics (via a combined effect) or pharmacokinetics (involving an alteration of breakdown). For example, voriconazole, an antifungal, is a potent inhibitor of the CYP3A4 enzyme. When taken together, the plasma concentration of methadone can increase by 65% [5]. Some of the known CYP3A4 inhibitors include antibiotics (e.g., fluoroquinolones and macrolides), antihistamines (terfenadine) and psychiatric drugs (e.g., haloperidol and chlorpromazine) [10]. Other agents that may synergistically increase the risk of TdP include: amiodarone, cisapride, clarithromycin, droperidol, erythromycin, pentamidine, pimozide, procainamide, quinidine, sotalol, thioridazine [12]. Several protease inhibitors used in the treatment of HIV can also prolong the QT interval. Websites like www.torsades.org or www.qtdrugs.org have an extensive list of medications that can affect the QTc.

Street drugs, like cocaine, are another cause of acquired long QT. Cocaine abuse is not uncommon in patients undergoing methadone maintenance programs. Cocaine lengthens the QT interval by blocking the delayed rectifier potassium channel and when taken with methadone, can progress to torsades. Routine drug screening is an invaluable tool that should be implemented in patients undergoing opiate substitution therapy with methadone.

HIV infection has also been reported to affect cardiac repolarization and may act as an independent risk factor for QT prolongation. One report showed a prevalence of a prolonged QT in 28.6% of hospitalized HIV patients [5]. The mechanism behind this is still unclear, though myocarditis or autonomic neuropathies may play a role [5,8].

The treatment of methadone induced TdP centers on prevention and risk stratification. A 12-lead ECG should be obtained prior to starting methadone and should be repeated at regular intervals throughout the treatment [12]. Clinicians should carefully inventory the patient's current medications to look for other drugs that may prolong the QT. The process should be repeated each time a new medication is added. Additionally, patients should be educated about over the counter medications that may prolong the QT or drugs that could interfere with methadone metabolism. Patients being treated for heroin addiction with cardiac, renal, and liver abnormalities may benefit from buprenorphine instead because it is not known to have an effect on the QT interval. 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 or the addition of diuretics to the patient's regimen [11]. Urine drug screens should be routinely obtained while on therapy to screen for the use of other street drugs, especially cocaine.

Acute treatment of torsades de pointes depends on the patient's hemodynamic status. Defibrillation is indicated when torsades develop into ventricular fibrillation. Once hemodynamic stability is achieved, prevention of subsequent recurrence is the next goal of treatment. Electrolyte replacement and cessation of any offending drugs should be undertaken. Magnesium sulfate is the first line medical therapy of torsades. Overdrive pacing and isoproterenol can also be used to prevent bradycardia and pause-dependent episodes of TdP [13]. Patients who for some reason cannot tolerate the alternatives methadone, should be fully educated about the risk of recurrence and the possibility of increased morbidity and mortality with continued methadone use. Automatic implantable defibrillators (AICD) have been described in the literature as potential life –saving treatment in these patients [12]. It should be emphasized however, that AICD placement is an invasive procedure that carries its own independent risk.

Conclusion

Methadone induced Torsades de Pointes is a potentially fatal complication of methadone therapy. As the popularity of methadone use grows, clinicians will encounter more cases of methadone induced TdP. Vigilance is vitally important to decreasing the risk of sudden cardiac death among people taking methadone. Possible drug-drug interactions should be routinely evaluated and electrolyte disturbances especially hypokalemia, should be promptly corrected.

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