# QT PROLONGATION AND VENTRICULAR ARRHYTHMIA IN METHADONE USER PRESENTING WITH SEVERE HYPOKALEMIA

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**Abstract:** Introduction: Severe hypokalemia is a serious, life-threatening condition that can lead to muscle weakness, paralysis, fatigue and different types of cardiac rhythm disturbances including QT prolongation and furthermore lethal arrhythmias. On the other hand, prolongation of the QT interval can be exacerbated in methadone users who receive high doses of the drug. Methadone is a drug that is mostly used as a replacement therapy for opiates, and it is known that it can interfere in the cardiac action potential cycle.
Case report: We present a case of 39y/old male who visited our clinic brought by an ambulance due to palpitations, fatigue and muscle weakness in the arms and legs. The patients' symptoms aggravated in the past 2 weeks when he lost the ability to do the everyday activities and finally to walk, because of extreme weakness of the extremities. On the day of the admission, he experienced a syncope for the first time in his life. His initial ECG revealed sinus rhythm with prolonged QT interval and polymorphic ventricular extrasystoles, which evolved in nonsustained ventricular tachycardia. His initial laboratory finding showed severe hypokalemia, and his previous medical history revealed use of methadone replacement therapy for approximately 20 years. The patient was closely monitored in the intensive care unit, and potassium replacement therapy was immediately initiated by the use of intravenous potassium infusion. Toxicologist and nephrologist were also included in the treatment in order to reduce the methadone dose and to exclude a secondary cause of severe hypokalemia. The patient's condition improved after 9 days, when the potassium level was in normal range and the rhythm disturbances completely resolved.
Conclusion: This case highlights the importance of timely recognition of severe electrolytic abnormalities that can lead to dangerous arrhythmias. Careful replacement with 24h monitoring and frequent laboratory analysis is required until the potassium level reaches the target range and until the heart rhythm stabilizes.
This case also reveals the importance of the significance of the follow up of every drug addict that receives methadone replacement therapy on a primary level, in order to exclude QT prolongation. In these cases, the dose of methadone should be reduced or replaced with another medication, in order to prevent potentially lethal arrhythmias.
**Keywords:** Hypokalemia, QT prolongation, methadone, arrhythmia

## 1. INTRODUCTION

Hypokalemia is a condition defined by a low potassium level in the blood (less than 3.5 mEq/L). Probably around 1% of the population in the world have a serum level of potassium less than 3.5 mEq/L without having any explained reason for it. The causes of hypokalemia can be mostly due to poor intake, increased excretion and increased potassium intracellular shift into the cells. A level of less than 2.5 mEq/L is defined as severe hypokalemia which is a serious, life-threatening condition (1). Among the most dangerous consequences of profound hypokalemia is the prolongation of the qt interval on a standard electrocardiogram, which can lead to heart rhythm disturbances including dangerous ventricular arrhythmias. A few studies have shown that QT prolongation can be worsened and can lead to a serious cardiovascular complications in cases associated with high dose methadone use, coadministration of CYP3A4 inhibitors, liver failure, a precipitating structural heart disease and the use of other medications which can prolong the QT interval (2,3). Methadone is a drug that is used mostly as an analgesic for

treating moderate to severe pain in patients with different diseases, but it is also used as a replacement therapy for illegal opiates used in the past few decades. Methadone has its own pathophysiological pathway of interfering in the cardiac action potential cycle, leading to a QT prolongation which increases the risk of lethal arrhytmias and a few studies have shown a dose dependence relation between the methadone and the QTc interval (3). When associated with an electrolytic imbalance, it can be even more dangerous and a prompt recognition and preventive and therapeutic measures are needed urgently to stop these consequences from happening.

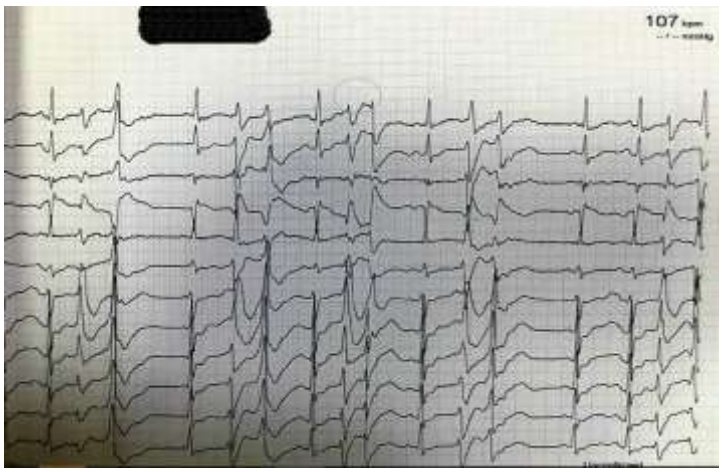
**2. CASE REPORT**

In this case report we report a 39 years old patient who presented in the emergency department by an ambulance with palpitations, fatigue and general weakness, especially dominating in the arms and legs without the ability to do the regular everyday physical activity. He denied other symptoms including vomiting and diarrhea and the use of loop /thiazide diuretics. The symptoms developed 2 weeks prior to admission, but significantly worsened within the last 2 days. The patient who used to be physically active young adult revealed that he lost the ability to walk in the past few days due to extreme muscle weakness. The further aggravation happened when these symptoms affected the upper part of his body and he couldn't use his arms and became completely dependent of the help of his family even for basic daily needs. The patient consulted his primary care physician who checked his blood count and advised to seek for specialist help if the condition does not improve in the next few days. On the day of the admission the patient experienced a syncope for the first time in his life and at this point the patient's family called the emergency service.

His past included medical history included hypertension, hepatitis C (treated with Ombitasvir/Paratparevir/Ritonavir + Dasabuvir for 6 months, therapy was finished 6 months prior the event) and methadone replacement therapy for the last 20 years because of intravenous drug addiction (70mg methadone per day).

On the admission his physical examination was unremarkable except the neurological examination which revealed diminished muscle power in both upper and lower limbs and the presence of irregular heart rate. His vitals were within normal ranges (except his blood pressure which was high – 190/90mmHg, HR~100, RR ~ 16, O2 97%) The initial electrocardiogram revealed sinus rhythm, heart rate 107 bpm, with a prolonged QT interval (680 msec) and a pair of polymorphic ventricular extrasystoles and shortly after that an ECG with non-sustained ventricular tachycardia.

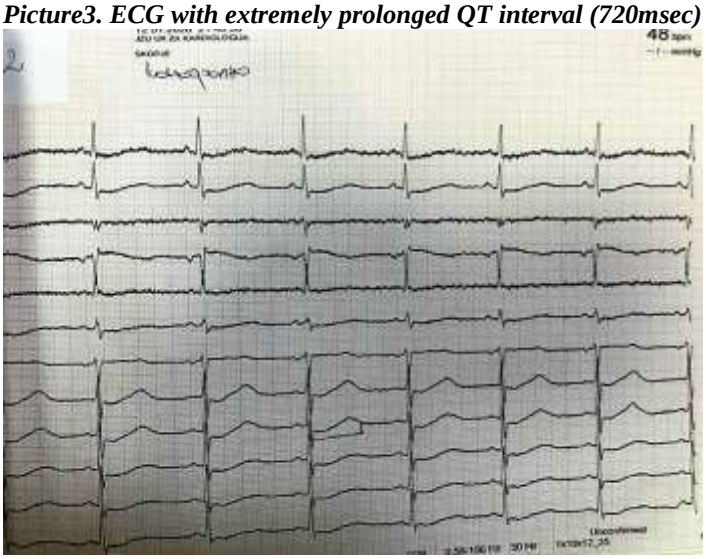
***Picture 1. Initial ECG recording – sinus rhythm, HR-107/min, prolonged QT interval(680msec) and polymorphic ventricular extrasystoles***




***Picture 2. Non-sustained VT***

After the short check-up and examination at the emergency department, the patient was admitted at the intensive cardiovascular care unit. The first line treatment included antihypertensive therapy with ACE inhibitor and b-blocker) but shortly after, further prolongation of the QT interval was noticed (720 msec), with drop of the heart rate of 48bpm.

***Picture3. ECG with extremely prolonged QT interval (720msec)***



The rhythm disturbances were present during the first 72hours of his stay, with an episode of ventricular tachycardia that spontaneously terminated after a few minutes without any pharmacological or electrical intervention.
The laboratory findings came in and showed severely decreased potassium level at 1.7mmol/L. Other laboratory findings including blood count, magnesium levels, renal function, hepatic function, thyroid function and urinalysis were in normal range. Bedside echocardiography showed structurally normal heart.
Because of the profound hypokalemia, replenishment was initiated promptly using intravenous potassium. This approach required close follow-up in the ICU with continuous ECG monitoring, and serial potassium levels checks, because higher dosages may increase the risk of cardiac complications. The replacement was obtained via central venous line with a starting dose of 20mmol/hour during the first two hours, and afterwards with a maintaining dose of 10mmol/hour, with repetitive serum potassium level check multiple times during the first day and in the following days. Day by day the level of potassium was increasing and the ventricular extrasystoles were reduced. Additionally, the QT interval became shorter at each day this electrolyte level improved.

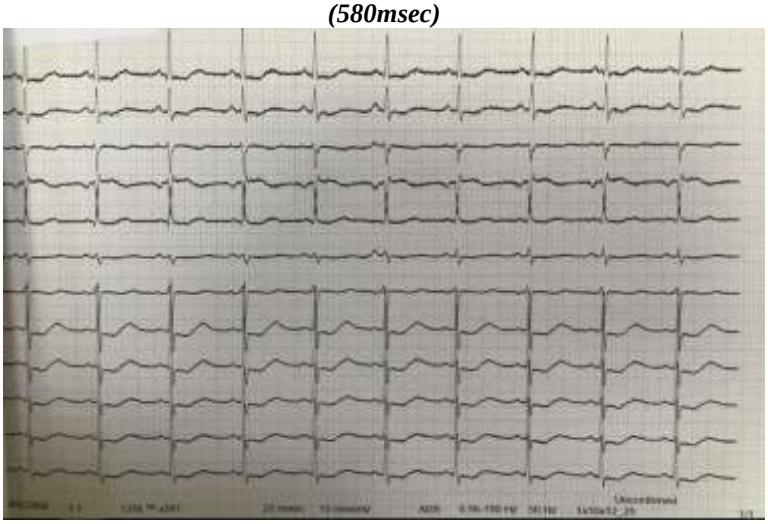
***Table 1. Potassium levels by date***

| Date | 12/01 | 13/01 | 14/01 | 15/01 | 17.01 | 21.01 |
|---|---|---|---|---|---|---|
| Potassium level (mmol/l) | 1.7 | 1.9 | 2.1 | 2.3 | 3.3 | 4.8 |

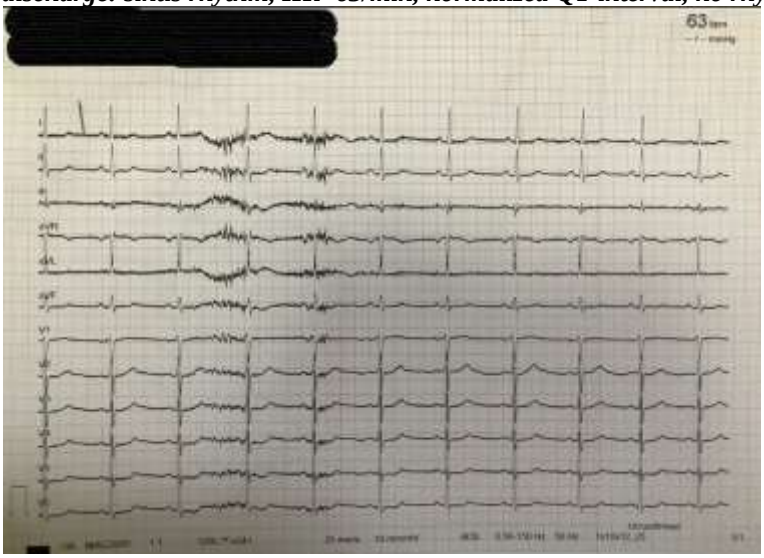
24 hours Holter rhythm monitoring was performed at the 5$^{th}$ day of his admission (before that he was in the intensive care unit with a 24h hour monitoring of all his vital signs and an ECG), and it showed prolonged QT interval without significant amount of extrasystoles , nor ventricular arrhythmias. At this point the serum level of potassium was increased almost double from the starting point at around 3.3mmol. Further diagnostic workup included urinary potassium excretion in 24h urine collection which excluded renal cause of hypokalemia, and blood gas analysis which were normal. An opinion from a toxicology specialist was obtained regarding the methadone treatment as a possible contributor for the long QT interval. It was suggested to reduce the dose from 70mg per day to 40mg. Urine toxicology analysis showed methadone and benzodiazepines present. Expert opinions were obtained from endocrinologist and nephrologist to exclude secondary cause for hypokalemia. Because of the normal potassium levels in the 24-hour urine sample, no further diagnostic workup was advised by the nephrologist. MRI of the abdomen with a focus on the suprarenal glands was performed and together with the aldosterone/renin ratio excluded Conn disease as the primary reason for the hypokalemia associated with a hypertension. Further treatment of the patient included vigorous potassium replacement and hypertension treatment with both ACE inhibitor and

aldosterone antagonist. The potassium level increased day by day and 9 days was a period needed to restore his normal blood level (4.8 mmol/L). At this point, no rhythm disturbances were obtained, his ECG recording was completely normal with QT interval in the normal range (400msec).

***Picture4. ECG at the 5th day of admission, after iv potassium substitution , the QT interval is still prolonged (580msec)***



***Picture5. ECG at discharge: sinus rhythm, HR~63/min, normalized QT interval, no rhythm disturbances***



His weakness also disappeared. He was discharged only with an antihypertensive therapy (including ACE inhibitor and aldosterone antagonist) with a recommendation for a checkup at his primary care physician one week after discharge, ans regular drug addiction specialist follow up.

**3.DISCUSSION**

When we admitted the patient in the intensive care unit, the idea was to prevent these pairs of ventricular extrasystoles into becoming a life-threatening arrhythmia, taking into account that he had a syncope the day prior the admission, and then to find out what causes them. After administrating beta blocker and having a clear look at the basic electrocardiogram we noticed a long QT interval. On a standard ECG we measured the QT interval from the beginning of the QRS complex to the end of the T wave. We use different types of formulas to estimate it. This time we used the Bazett formula, which estimated it at 680ms. The significance of the prolongation of the QT interval is because its prolongation can lead to a ventricular tachycardia, torsades de pointes and furthermore ventricular fibrillation which can escalate rapidly and cause cardiac arrest (1). Can this be the reason for the loss of consciousness in our patient? A syncope surely can be precipitated by a ventricular tachycardia but a very few

interesting cases have been described in the literature of a self-terminating ventricular fibrillation (4) Our patient was on a methadone replacement therapy for almost 20 years. Methadone is a drug that is quite known to interfere with the action potential of the heart by inhibiting the cardiac potassium channel hERG and can cause a prolonged QT interval (2). hERG, first identified in 1994, is located on chromosome 7 and codes for the potassium ion channel which intercedes repolarization of the cardiac action potential (5). A well-known additional reason can even worsen the prolongation of the QT interval such as concomitant hypokalemia, administration of drugs metabolized trough the CYP3A4 system, liver failure and a coronary artery disease (4,6,7). The patient told us that he finished his hepatitis C therapy including a combination of Ombitasvir/Paratparevir/Ritonavir + Dasabuvir 6 months ago. Ritonavir works as a CYP3A4 inhibitor. In combination with methadone, it increases the risk of QT prolongation and risk of sudden cardiac death. We couldn't find any articles about ritonavir causing a QT prolongation by itself, but Kimberley Hunt and his associates found an association of saquinavir/ritonavir therapy in HIV positive patients as a combination therapy that can interfere with the QT interval. (8) Since its half-life is approximately 3-5 hours, and taking into consideration the fact that he finished his hepatitis C therapy more than half a year ago, we can't prove the interference at the time of the hospitalization, but a close ECG monitoring is beneficial in a methadone therapy user on a standard hepatitis C therapy. The patient was on a therapy with 70mg of methadone. The methadone replacement therapy correlates positively with the QTc interval, a few case series have showed (9,10)

The toxicology specialist decided to reduce the maintaining dose to 40mg instead of switching it to buprenorphine although a few studies showed no correlation between the buprenorphine users and QTc prolongation (11,15). There were a lot of patients in this study taking benzodiazepines, which was also the case with our patient when we did the toxicology urine quantitative samples that were positive to both methadone and benzodiazepines, it was proved that benzodiazepines do not have effect on the QT interval. Laboratory findings showed another potential substrate for the risk of potential ventricular arrhythmias, which was the severe hypokalemia, a potassium level of 1.7 mmol/L. The potassium level explained the general weakness. Hypokalemia is well known for its potential to cause ventricular arrhythmias, especially when it is severe. A form of malnutrition caused hypokalemia was excluded given the fact the patient had a normal nutritive status. He had no diarrhea or vomiting that could explain the loss of potassium. This is why we consulted a nephrology specialist who suggested taking a 24-hour urine sample and measuring the level of potassium in it. A value of less than 20 mmol/24-hr urine specimen suggests appropriate renal conservation of $K^+$, while values above that indicate some degree of renal wasting. In our patient, the level was below 20mmol/24-hour urine, therefore renal cause of hypokalemia was excluded. The MRI of the abdomen with a focus on suprarenal glands which can be used as a diagnostic tool for the suspicion of Conn disease, showed no pathological findings.

Aldosterone renin ratio also showed normal values and together with the radiological findings excluded the suspicion for Conn. The patient was not using any potassium wasting diuretics and he was not taking other medications that can shift potassium into the cells and be the reason for hypokalemia. We knew that taking back the QT interval into a normal value won't go so fast having in mind the fact that the half-life of methadone can be from 8 to 59 hours and the severe hypokalemia will even make the therapeutic approach harder. (12,14) Furthermore, the methadone dose was only reduced, not fully excluded in order to prevent abstinence syndrome. We started parenteral administration of potassium chloride as previously explained, with close monitoring of the serum potassium level. Meanwhile we searched for a secondary reason causing this hypokalemia. The imperative of the therapy approach in patients presenting with a long QTc interval is to reduce the risk of sudden cardiac death caused by ventricular arrhythmias by correcting the possible corrective causes This is why we constantly administrated a potassium chloride intravenously until the serum potassium level reached the target level, the rhythm disturbances disappeared and the patients' symptoms diminished. In patients presenting with ventricular arrhythmias the minimum blood level should be at least 4.0mmol/L. (13) Another electrolyte that we have to have in mind is the magnesium level (16,17). In our case it was normal, so there was no need for a magnesium sulphate therapy. Ventricular arrhythmias can occur in any moment in this kind of patients, so when a hemodynamic instability occurs, an electrical cardioversion has to be available at any moment (1,18).

**4.CONCLUSION**

QT interval prolongation can lead to life threatening ventricular arrhythmias and that is why it is of a highest importance to obtain an ECG in every patient presenting with an episode of syncope before the time of the examination. An admission at the ICU is obligatory in order to monitor these kinds of patients and stabilize them hemodynamically while searching for the cause. Hypokalemia and methadone overdose can both prolong the QT interval (among other reversible and non-reversible causes). It is why every drug addict receiving methadone replacement therapy should have an ECG made at every appointment with the drug addiction specialist to measure if

there is a QT prolongation or not and reduce the dose of methadone or replace it with another medication which is safe and doesn't cause ECG abnormalities. Low potassium blood level can make this correction even harder, so it is essential to obtain electrolyte status and make a correction if needed.

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