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Methadone-induced Torsade de pointes tachycardias

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Summary

Methadone is a synthetic opioid frequently used in drug maintenance programs for heroin addicts. It prolongs the QT-interval and is mainly metabolized by the isoenzyme CYP3A4 of the hepatic cytochrome-P450-system, which is used by numerous other QT-prolonging agents. Its most severe side effect is the development of life-threatening Torsade de pointes ventricular tachycardia in the setting of a prolonged QT-interval. Since drug addicts are prone to concomitant medical conditions requiring additional medication as well as to continued abuse of cocaine, they are at higher risk for developing this major complication of methadone therapy. Before subjecting patients on methadone to other drugs, the QT-interval should be determined and it should be ascertained whether the new agent has the property to prolong the QT-interval or is metabolised by the cytochrome-P450 system.

Key words: methadone; QT-prolongation; Torsade de pointes tachycardia

Magnitude of the problem

The synthetic opioid methadone has been used for substitution in patients with heroin addiction as well as for pain control for more than 30 years [1, 2]. In Switzerland, approximately 18 000 patients receive regular methadone maintenance treatment. These patients tend to have a high comorbidity and many receive additional virostatic or antibiotic drug treatment. Furthermore, some of these patients continue uncontrolled cocaine abuse. Particularly with the use of high doses of methadone, cases of drug-induced, potentially life threatening Torsade de pointes ventricular tachycardia (TdP-VT) have been reported [3, 4].

Our institutions are referral hospitals for a population of 1 to 1.5 million inhabitants. Over a period of one year, we observed five cases of nearly fatal TdP-VT in young intravenous drug abusers treated chronically with methadone. This corresponds to 0.3% of the 1.800 persons enrolled in the methadone maintenance programs in the regions of Basel and St. Gallen. Three patients required defibrillation of their TdP-VT. The main duration of participation in the methadone treatment program was 3.4 ± 0.9 years, the mean methadone dose 268 ± 190 mg/d, and the QTc at presentation 562 ± 77 ms. Of note, all patients had other contributing factors at the time of their arrhythmia (table 1). Four had QT-prolonging antibiotic agents initiated shortly before the event, two had consumed cocaine and one suffered from severe hypokalaemia after binge drinking. After correction of the respective contributing factors, the QT-intervals normalised and the symptoms disappeared in all patients.

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Table 1

Circumstances under which TdP-VT occurred in five patients in the methadone maintenance program.

Patient	Methadone dose (mg/d)	TdP-VT sustained/ non-sustained	QTc	Documented ECG with normal QT	QT prolonging drugs	Predisposing factors
#1 male/37 yo	140	Sustained	457	Yes	Ciprofloxacin	
#2 female/ 34 yo	60	Non-sustained	633	Yes	None	Hypokalaemia Binge Drinking Cocaine
#3 male/36 yo	200	Sustained	660	Yes	Ciprofloxaxin	
#4 male/41 yo	600	Non-sustained	556	Yes	Fluoxetine	Phenytoine Alcohol withdrawal
#5 male/44 yo	340	Sustained	502	Yes	Clarithromycin	Dilated cardiomyopathy

Factors triggering torsade de pointes ventricular tachycardia

The underlying mechanism for the development of TdP-VT is the prolongation of the QT-interval, which can be caused by methadone as well as numerous other drugs and medical conditions. Furthermore, the prolongation of the QT-interval is dose-dependent, which is important since patients receiving methadone as part of a methadone maintenance program tend to have relatively high doses of 60–120 mg/day.

Krantz and co-workers reported 17 cases of TdP-VT in patients receiving high-doses of methadone [3]. They demonstrated that the arrhythmia mostly occurred either after administration of other QT-prolonging agents or in the setting of hypokalaemia. A great number of drug classes can prolong the QT-interval [5]. Amongst those are numerous antibiotic and antiviral agents that are frequently employed in the population taking methadone. Cocaine, which often is used by these patients, has also been shown to prolong the QT-interval [6]. An updated list of drugs and agents that can cause TdP-VT can be found at www.qtdrugs.org [7].

Figures 1–3 show typical examples of methadone-induced QT-prolongation in the presence of contributing factors. The ECG in figure 1 was taken from a 34-year-old female drug addict who was admitted with nausea, vomiting, fatigue and dizzy spells for numerous days. She was chronically substituted with 60 mg of methadone daily and admitted to frequent use of cocaine. Upon admission, she collapsed and the ECG showed an episode of non-sustained TdP-VT. At this point, the serum potassium concentration was only 2.0 mmol/L and potassium and magnesium as well as fluids were supplemented intravenously. The 12-lead ECG showed a prominent U-wave and a markedly prolonged QT(U)c-interval of 633 ms (fig. 1). After rehydration and elevation of the potassium level, the tachycardia ceased and the QTc interval normalised.

The ECG is in figures 2 and 3 illustrate the dose-dependency of the QT-prolonging effect of methadone. The increase of the methadone dose from 120 mg per day to 200 mg per day for pain control for the treatment of pelvine osteomeylitis resulted in prolongation of the QTc interval and increase of the U-wave in a 36-year-old male drug addict. (fig. 2). Antibiotic therapy was started using cefepime and ciprofloxacin. During the same night, the patient developed a sustained TdP-VT that required defibrillation (fig. 3). After reduction of the methadone dose to 120 mg the QT-interval normalised.

Underlying mechanism

Methadone as well as its derivate levacetylmethadol prolong the QT-interval by inhibition of the rapid component of the delayed rectifier potassium ion current I_{Kr} [8, 9]. These in vitro findings are corroborated by an ECG study that demonstrated an 8% increase of the QTc interval after initiation of methadone [10]. By virtue of its pronounced negative chronotropic effects [10],

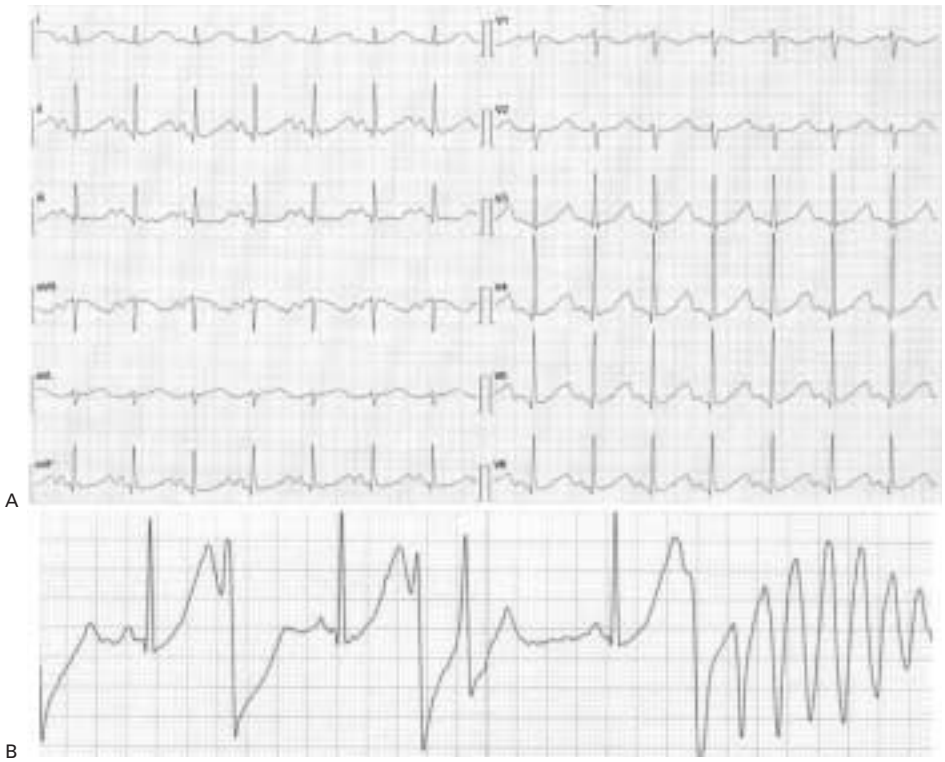
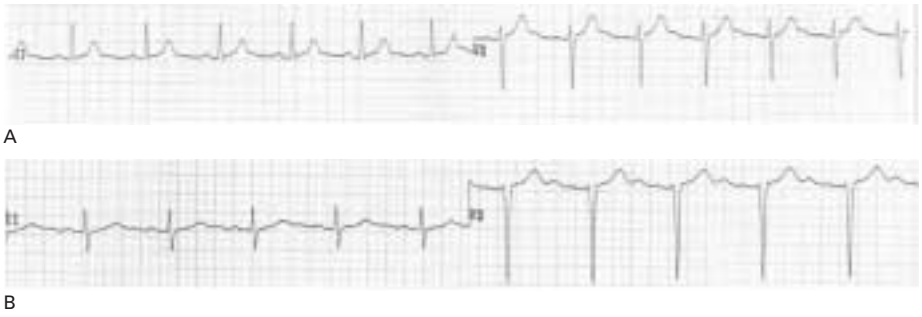


Figure 1

Methadone-induced QT-prolongation in the setting of severe hypokalaemia and after cocaine use,
A Surface ECG displaying marked QT-U fusion (QT(U)c 663 ms; 25 mm/sec),
B rhythm strip showing initiation of sustained TdP-VT (25 mm/sec).



A

B

Figure 2

Dose-dependent QT-prolongation by methadone (leads II and V2)
A ECG on 120 mg of methadone (QTc 420 ms, QT[U]c 610 ms, 25 mm/sec),
B ECG on 200 mg of methadone (QTc 430 ms, QT[U]c 660 ms, 25 mm/sec).

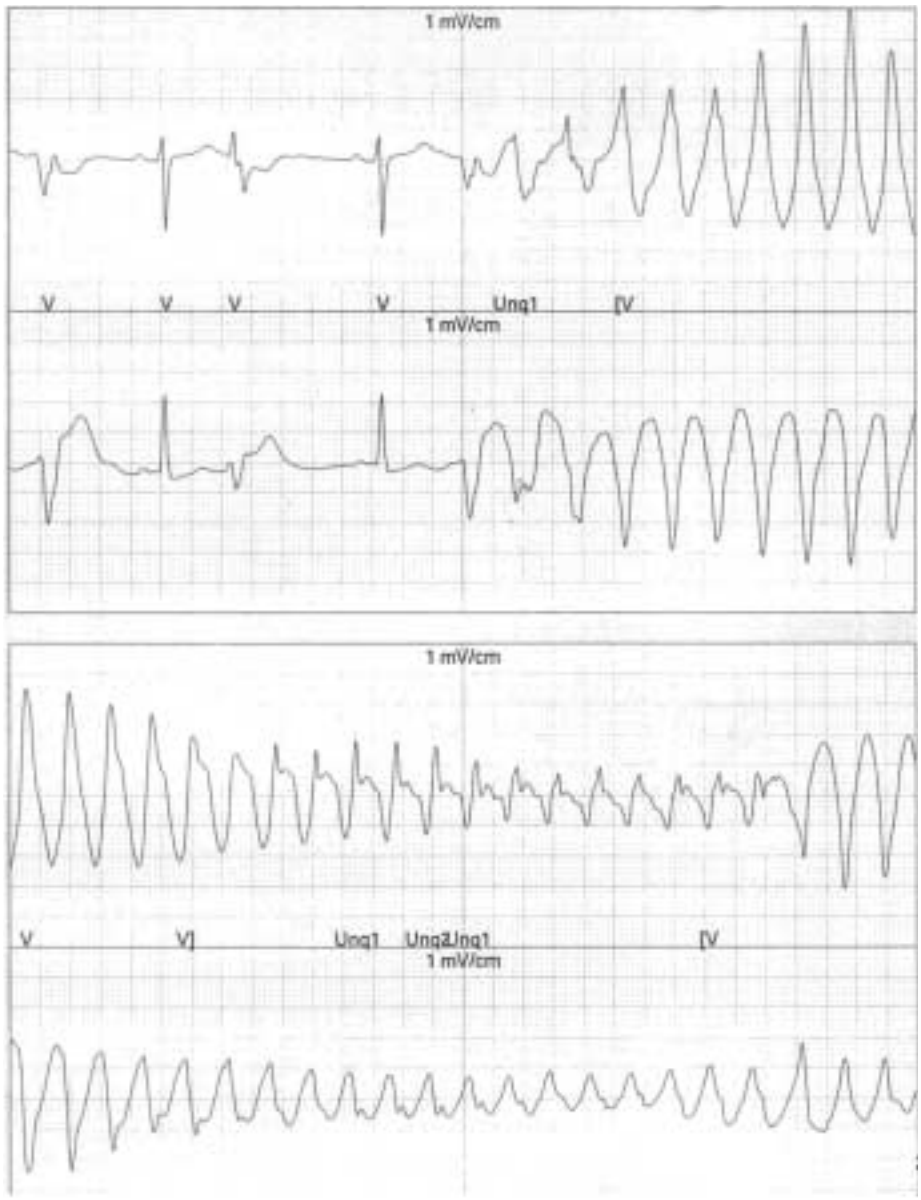


Figure 3

Rhythm strip showing sustained TdP-VT (25 mm/sec) after increase of methadone to 200 mg/day and addition of ciprofloxacin.

methadone facilitates the occurrence of bradycardia-dependent TdP-VT [11].

Methadone is mainly metabolised by the isoenzyme CYP3A4 and to a lesser extent by the isoenzyme CYP2D6 of the hepatic cytochrome-P450-system. These pathways are also utilised by numerous antibiotics, virostatic agents, antihistamines, antimalaria agents, or antidepressants, which all will influence the metabolisation of methadone [5, 12, 13]. Furthermore, there is evidence that 10 to 15% of subjects who develop QT prolongation and TdP-VT after drug exposure have DNA variants of the coding regions of congenital long-QT disease genes [14].

In the study by Krantz, the mean dose of methadone at the time of TdP tachycardia was very high (397 ± 283 mg/day) and 12 of the 17 patients received either a contributing drug or had low potassium levels [3]. In contrast, in our patients TdP-VT occurred at a lower mean methadone dose of 268 ± 190 mg/day. All patients received either other QT-prolonging drugs (cocaine), drugs that increase the methadone level by virtue of inhibition of CYP3A4 (ciprofloxacine, cocaine), or had very low potassium levels.

Diagnosis and preventive measures

For proper diagnosis, the precise measurement of the QTc interval is critical. A group of experts recently proposed guidelines for the correct measurements of the QTc interval [15]. Frequently, there is uncertainty as to whether the U wave should be included in the measurement. U waves correspond to late repolarisation of M-cells in the mid-myocardium and have been mechanistically implicated in the initiation of arrhythmias [16, 17]. Therefore, according to expert consensus, U waves should be included in the QT measurement if they are large enough to merge with the T wave [15]. Interestingly, all our patients displayed large U waves at the time of occurrence of TdP-VT.

It has to be emphasized that patients in methadone maintenance programs tend to have additional medical problems and are prone to experience severe electrolyte dysbalances, to abuse the QT-interval prolonging drug cocaine, and to need additional medication. In order to avoid potentially life-threatening TdP-VT, it is prudent to take a 12-lead ECG and determine the QT-interval on methadone before and after subjecting these patients to changes in their drug regimen. Furthermore, it is advised to ascertain whether newly added agents have the property to prolong the QT-interval or are metabolised by the cytochrome P450 isoenzyme 3A4. Other predisposing factors, such as the presence of a congenital long-QT syndrome, frequent episodes of hypokalaemia, bradycardias, as well as the use of cocaine should be taken into account. Chronic treatment of TdP-VT in patients with acquired long-QT syndrome consists of avoidance of QT-prolonging drugs, hypokalemia, hypocalcemia, hypomagnesemia, as well as bradycardia. In certain cases, in particular, if an underlying congenital long QT-syndrome is suspected, high doses of beta-blockers, implantation of a pacemaker or even an implantable cardioverter defibrillator may be necessary [5].

Conclusion

Methadone-induced TdP-VT is not an uncommon event. It appears that the arrhythmias do not primarily occur after initiation of methadone therapy. The most common setting for the development of TdP-VT is the addition of other QT-prolonging agents, the presence of severe electrolyte dysbalances, or the concomitant use of cocaine in patients who are on chronic methadone maintenance therapy. Therefore, it is advisable to repeat a surface ECG and to determine the QTc-interval after every change in drug regimen in this population. Furthermore, it should be ascertained whether drugs added have the property to inhibit the cytochrome P3A4 enzymes or prolong the QT interval.

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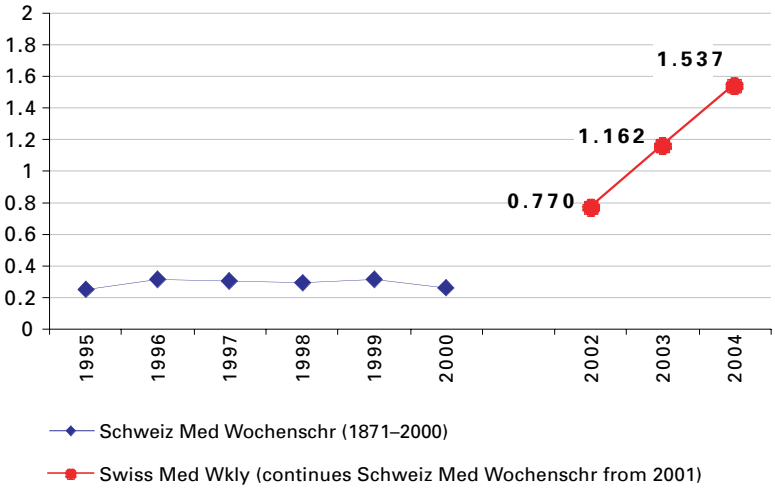

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