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CASE REPORT

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Multifactorial QT interval prolongation

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Abstract

Acquired long QT interval has been widely reported to be a consequence of drug therapy and electrolyte disturbances. We describe two cases of multifactorial acquired QT interval prolongation and torsades de pointes. In the first case, the drugs venlafaxine, amiodarone and domperidone may have contributed to QT interval prolongation in a patient with hypokalemia and hypomagnesaemia. In the second case, QT interval prolongation occurred in a patient taking quetiapine and citalopram, and whose use of hydrocholorothiazide and history of chronic alcohol abuse likely contributed by rendering the patient hypokalemic. These cases highlight the potential risks associated with polypharmacy and demonstrate that though torsades de pointes is an uncommon arrhythmia, the combination of multiple factors known to prolong QT interval may precipitate this life-threatening arrhythmia. (Cardiol J 2010; 17, 2: 184–188)

Key words: acquired long QT interval

Introduction

Long QT (LQT) interval is an electrocardiography (ECG) manifestation of delayed repolarization of the heart that can precipitate life-threatening arrhythmias, such as torsades de pointes (TdP). Acquired LQT is most commonly a consequence of drug therapy or electrolyte disturbances. Several studies have shown a role for polytherapy in causing prolonged QT intervals, especially when therapy includes both an antipsychotic and an additional antidepressant [1, 2]. Furthermore, electrolyte disturbances, especially hypokalemia, have been shown to increase the risk of developing cardiac arrhythmias and of prolonging the QT interval [3].

We describe two cases of QT interval prolongation and TdP occurring as a result of polypharmacy with drugs known to prolong QT interval and in the setting of electrolyte disturbances caused by diuretics and/or a history of chronic alcohol abuse. These cases highlight the potential risks associated with polypharmacy and reveal the multifactorial nature of QT interval prolongation that may allow TdP to manifest itself.

Case 1

A 64 year-old obese, Caucasian woman with a medical history of stable angina, type 2 diabetes mellitus, hypertension, stroke, atrial fibrillation (AF), hypothyroidism and mechanical mitral valve from rheumatic valvular disease, presented to the Emergency Department (ED) after a motor vehicle accident. She described experiencing a non-prodromal syncopal episode prior to the accident and reported having had three similar episodes in the last five years. Her home medications are listed in Table 1. Notably, she recalls having previously been on citalopram 40 mg but was switched to venlafaxine within the last six months. Her baseline labora-

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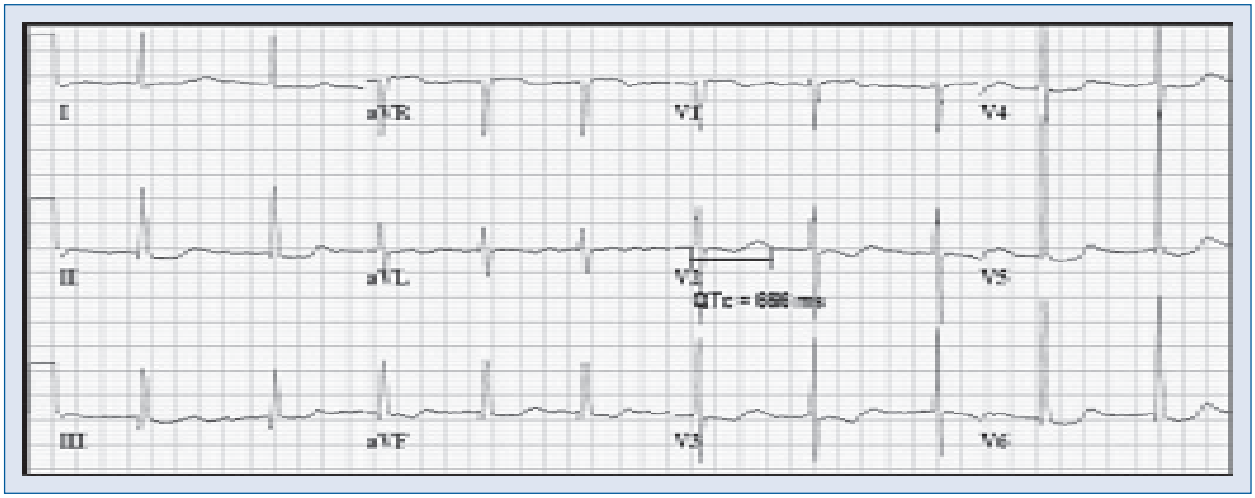

Figure 1. Case 1: electrocardiogram at admission. QTc: 666 ms.

tory investigations at the time of presentation to the ED revealed a serum potassium level of 2.9 mmol/L, serum magnesium of 0.62 mmol/L, as well as a normal CBC, glucose, urea, creatinine, corrected calcium, TSH and two sets of cardiac enzymes. An initial ECG (Fig. 1) demonstrated AF with a ventricular response rate of 65 bpm, and a 'scooped' ST-segment with a corrected QT interval (QTc) of 666 ms. The patient was stable, having suffered no serious injuries from the accident, and was thus admitted under the orthopaedics service to a ward bed with telemetry monitoring.

That night, the patient experienced two short episodes of wide complex tachycardia. She felt dizzy with the first, and lost consciousness with the latter. A bolus of 150 mg of amiodarone was administered, followed by intravenous infusion. A 12-lead ECG (Fig. 2) revealed a classic short-long-short sequence followed by an 'R on T' phenomenon initiating self-terminating, asymptomatic TdP. The patient was transferred to the Coronary Care Unit where rapid correction of hypokalemia and hypomagnesaemia was initiated and all medications known to be associated with QT interval prolongation were discontinued. A temporary transvenous pacemaker was inserted with the aim of increasing the heart rate (HR) to 120 bpm. Over the subsequent twenty-four hours, the patient's QTc normalized and she was discharged home with no recurrent episodes of TdP.

Table 1. List of medications prior to admission.

Case 1	Case 2
Irbesartan 150 mg BID	Quetiapine 50 mg TID and 200 mg QHS
Digoxin 0.25 mg OD	Citalopram 60 mg OD
Furosemide 40 mg OD	Hydrochlorotiazide 25 mg OD
Metalazone 2.5 mg OD	Clonazepam 1 mg TID
Metformin 1000 mg BID	Acamprosate 333 mg TID
Glyburide 5 mg BID	Atenolol 25 mg BID
Venlafaxine 112.5 mg OD	Ranitidine 150 mg OD
Levothyroxine 200 μg OD	Mirtazipine 30 mg QHS
Omeprazole 20 mg OD	Rosuvastatin 10 mg OD
Lipitor 10 mg OD	
Domperidone 10 mg TID	

Case 2

A 58 year-old woman with a history of chronic alcohol abuse presented to a peripheral hospital ED complaining of weakness, nausea, diaphoresis and malaise. She suffered no chest discomfort or lightheadedness. She reportedly had not consumed any alcohol in the previous three days. Her medical history was significant for congestive heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea, and hypertension. Her regular medications are listed in Table 1. Initial laboratory investigations revealed serum potassium of 2.5 mmol/L and serum magnesium of 0.75 mmol/L. A 12-lead ECG (Fig. 3A) showed a prolonged QTc of 720 ms. TdP was documented in an ECG strip that is not of sufficient quality to be published. A transfer to our tertiary care hospital was initiated. En-route, she experienced three episodes of ventricular fibrilla-

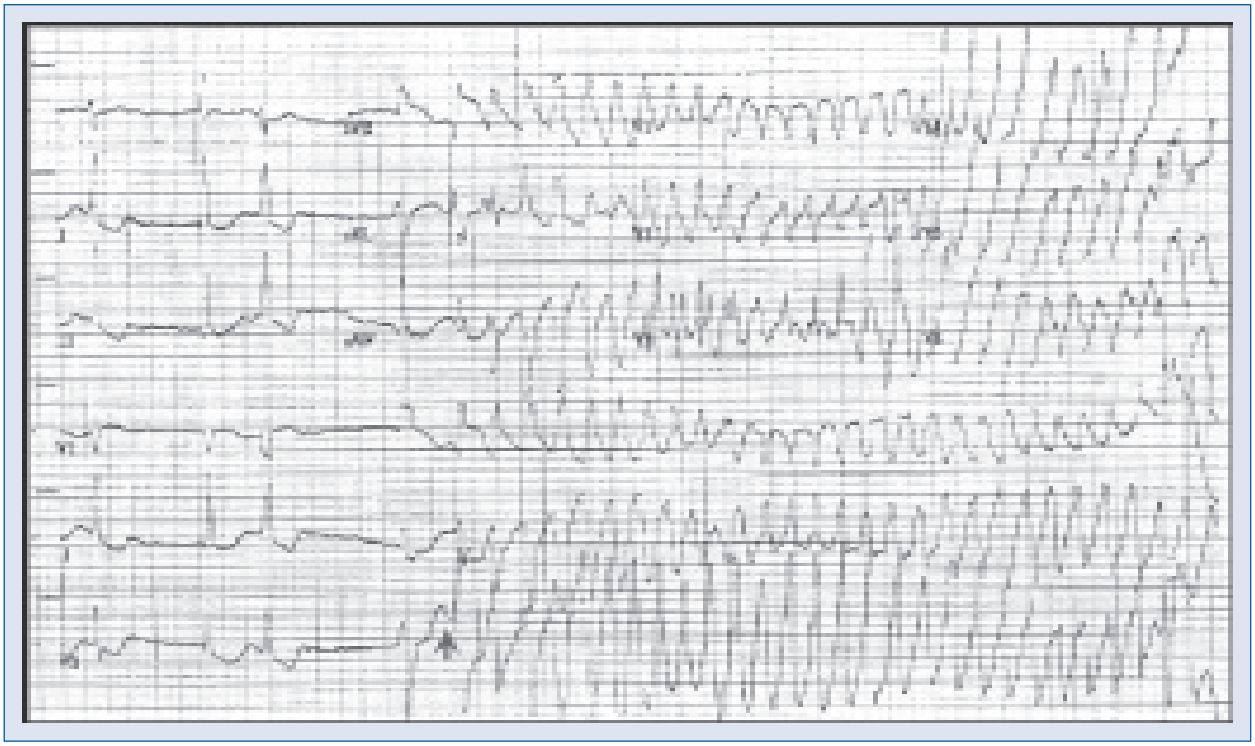

Figure 2. Electrocardiogram demonstrating a short-long-short sequence followed by an 'R on T' phenomenon (arrow) initiating torsades de pointes. Note long QT interval preceding the initiation of the arrhythmia.

tion requiring numerous defibrillations. On arrival, the patient was treated with intravenous magnesium sulphate and metoprolol, a temporary transvenous pacemaker to increase the HR to 120 bpm, and all medications known to be associated with a prolonged QT interval were discontinued. Subsequent ECGs demonstrated correction of the QTc interval and, ultimately, the patient was discharged home without recurrence of arrhythmias. At follow-up, her measured QTc was still in the normal range at 410 ms (Fig. 3B).

Discussion

These two cases illustrate the medical importance of multifactorial QT interval prolongation. Acquired LQT interval is most commonly a consequence of drug therapy or electrolyte disturbances. Also, some patients have a 'forme fruste' of congenital LQT syndrome, in which a mutation or polymorphism in one of the LQT syndrome genes is clinically unapparent until the patient is exposed to a particular drug [4].

The means by which drugs prolong the QT interval is typically linked to the blockade of rapidly activating delayed rectifier (repolarizing) potassium currents (I_{Kr}). This not only results in reduction of the repolarizing currents and consequent prolongation of the QT interval, but also the development of early afterdepolarizations and re-entry phenomena [5]. However, although an increase in the QT interval favours the occurrence of TdP, it seems as though this arrhythmia often requires potentiation by certain risk factors for TdP to become manifest. Notably, female gender has been identified as one of the most commonly involved risk factors, along with heart disease and hypokalemia in the setting of polypharmacy [6]. Additionally, co-administration of certain drugs known to affect metabolism, produce hypokalemia, or directly prolong QT interval may also potentiate this effect [7].

In the first case, QT prolongation was likely associated with amiodarone, domperidone and venlafaxine. Amiodarone is thought to generate ventricular arrhythmias by prolonging the duration of the ventricular action potential, thereby increasing refractoriness even at therapeutic concentrations [5]. However, the frequency of TdP generation with amiodarone administration is remarkably low. It is thought that the rarity of TdP with this drug, compared to other class III antiarrhythmic drugs, may be due to concurrent blockade of the L-type calcium

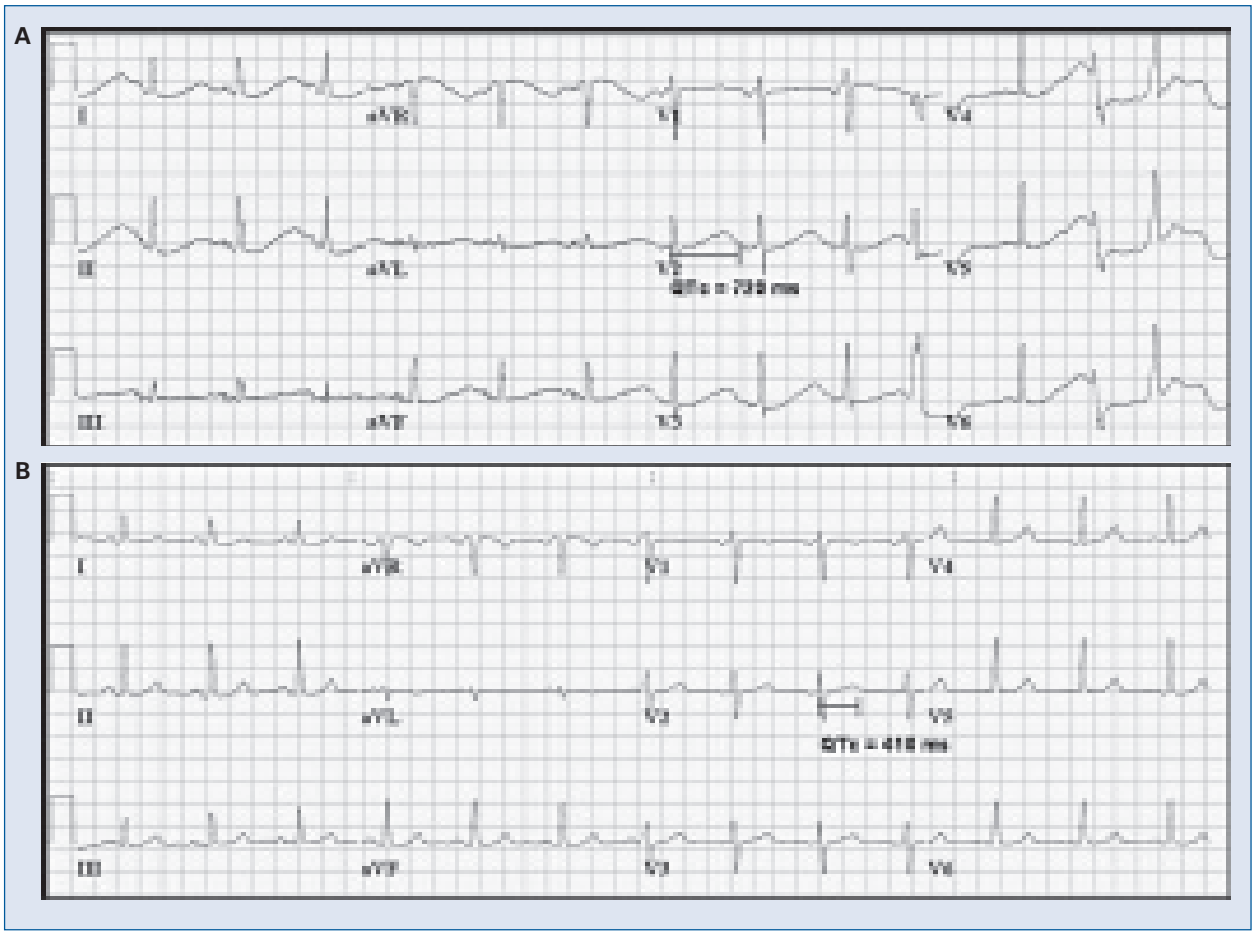

Figure 3. Case 2: electrocardiogram at admission **(A)** with QTc 720 ms and at discharge **(B)** with QTc 410 ms.

channels, lack of reverse use dependence, and less QT dispersion [8]. Oral domperidone, a prokinetic agent, has been suggested as a drug that may cause TdP [9]. However, though it has been shown to prolong the QT interval by about 14 ms in infants [10], a documented case of domperidone causing TdP has not been reported. Venlafaxine, a selective serotonine/norepinephrine reuptake inhibitor, was shown to cause QRS widening and ventricular tachycardia by blocking the fast inward sodium current (I_{Na}) in a concentration-dependent manner. Although a dose-dependent relationship between venlafaxine ingestion and prolonged QTc has also been demonstrated [11], to our knowledge, venlafaxine has not been reported as a cause of TdP. Each of the aforementioned drugs is known to individually prolong QT interval. So, the role of each drug in the presented cases remains speculative. It seems likely that the combination of these drugs in the setting of electrolyte disturbances ultimately led to the prolongation of the QT interval and TdP in the present case.

With regards to the second case, QT prolongation was probably associated with citalopram and quetiapine. A link between citalopram ingestion and ECG alterations has been well established. Several reports, including one by our group, indicate that these ECG changes include QTc prolongation [12], TdP [13], widening of the QRS complex and junctional rhythm with sinus arrest and/or atrioventricular dissociation [12]. Meanwhile, quetiapine, a new generation antipsychotic drug, was shown by Harrigan et al. [2] to prolong the QT interval by 14.5 ± ± 5.0 ms. But until now, no cases of quetiapine-induced TdP have been reported. Nonetheless, the potential harm of polypsychotherapy has been demonstrated by one study [1] that showed that, compared to patients on monotherapy, polytherapy patients treated with an antipsychotic with an additional antidepressant and/or lithium had a significantly increased mean QT interval.

The hypokalemic status of both of our patients was likely induced by the use of diuretics. Notably, the relationship between hypokalemia and thiazide

diuretics [14] is dose-dependent, and the severity is accentuated with the combination of diuretics, especially in the presence of a potent diuretic such as metalozone [3]. The principle physiological changes that can lead to arrhythmias in the setting of hypokalemia are the increase in length and refractory period of the action potential, automaticity enhancement, and the decrease in myocardial conductivity. These effects can lead to prolongation of the QT-U interval, premature ventricular beats, ventricular tachycardia and fibrillation [3, 15].

Another potential cause of hypokalemia in the second case relates to the patient's chronic alcohol abuse. In fact, hypokalemia has commonly been reported as an electrolyte abnormality observed in chronic alcoholics, partly due to inappropriate kaliuresis as a result of co-existent hypomagnesaemia [16]. Moreover, acute alcohol withdrawal, as seen in this case, has been reported to provoke increased QT variability and repolarization lability, which may elevate the risk for serious cardiac arrhythmias [17].

Conclusions

These cases highlight the fact that though torsades de pointes is an uncommon arrhythmia, the combination of multiple factors known to prolong QT interval may allow this life-threatening arrhythmia to become manifest. While certain drugs directly cause prolongation of the QT interval, others cause electrolyte disturbances that indirectly affect QT duration. When these drugs are combined in a patient with certain risk factors for QT prolongation, the result can be disastrous. It is of the utmost importance that medical therapy be administered prudently in order to minimize potentially deadly risks.

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