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CASE REPORT

Multi-Factorial Causes of Torsade De Pointes in a Hospitalised Surgical Patient

*Prashanth Panduranga,[1] Mohammed Al-Mukhaini,[1] Mamatha P. Rajarao[2]

الأسباب المتعددة لالتواء تخطيط القلب حول النقطة في مريض جراحي داخل المستشفى

برشانث باندورانجا، محمد المخيني، مامثا راجاراو

الملخص: رجل في ال55 من العمر معروف بإدمان الكحول ومصاب بفيروس نقص المناعة البشرية تم إدخاله إلى جناح الجراحة بعد تصريف خراج العجان. تم اكتشاف وجود بطء في الجيب القلبي، مجمعات البطين المبكرة وانخفاض ضغط الدم الخفيف. النتائج المخبرية بينت وجود نقص خفيف ببوتاسيوم الدم. المريض كان مضطرب بشكل متقطع وتم تشخيصه بمتلازمة سحب الكحول. بعد الجراحة حصل المريض عن طريق الحقن الوريدي علي البيبراسيلين/تازوباكتام والمترانيدزول بالإظافة الى جرعة صغيرة من الدوبامين. أظهر تحليل جهاز مراقبة هولتر 24 ساعة (ECG) على فاصل QT مطول مع حالتين لإلتواء تخطيط القلب حول النقطة ذاتية الإنتهاء. تم علاج متلازمة سحب الكحول، تصحيح نقص بوتاسيم الدم وسحب الدوبامين والمضادات الحيوية. لم يكن هناك تكرار لإضطراب النظم القلبي. هذه الحالة سلطت الضوء على أهمية تجنب الأدوية التي تسبب إطالة فاصل QT في المرضى المدخلين للمستشفيات إذ إنه غالبا ما يكون المرضى لديهم عوامل خطر متعددة لاضطراب النظم المحرض.

مفتاح الكلمات: التواء تخطيط القلب حول النقطة، فاصل QT ، إطالة QT ، أدوية إطالة QT، متلازمة سحب الكحول، بفيروس نقص المناعة البشرية، عمان.

ABSTRACT: A 55-year-old chronic alcoholic male known to be positive for human immunodeficiency virus (HIV) was admitted to a surgical ward following perianal abscess drainage. He was noted to have sinus bradycardia, ventricular premature complexes, and mild hypotension. His laboratory investigations revealed mild hypokalaemia. He was intermittently agitated and alcohol withdrawal syndrome (AWS) was diagnosed. Postoperatively, he received intravenous piperacillin/tazobactam and metronidazole infusions along with a small dose of dopamine. Analysis of a 24-hour Holter monitor (ECG) showed a prolonged QT interval with two episodes of self-terminating torsade de pointes. His AWS was treated, hypokalaemia was corrected, and dopamine, along with antibiotics, was withdrawn. There was no recurrence of arrhythmias. This case highlights the importance of avoiding QT-prolonging drugs in hospitalised patients, since hospitalised patients often have multiple risk factors for a proarrhythmic response.

Keywords: Torsade de pointes; QT interval; QT prolongation; QT-prolonging drugs; Alcohol withdrawal syndrome; Human immunodeficiency virus; Case report; Oman.

Drug-induced QT prolongation and torsade de pointes (TdP) with cardiac arrest is a rare but potentially fatal event in hospital settings.[1] We present a patient with TdP in whom the aetiology was multifactorial.

Case Report

A 55-year-old non-diabetic, non-hypertensive male was admitted to the surgical ward at the Royal Hospital, Muscat, Oman, following perianal abscess drainage surgery. He was referred to a cardiologist for sinus bradycardia, ventricular premature complexes (VPCs), and mild hypotension, which were not present pre-operatively. He was not on any regular medications but was receiving regular doses of piperacillin/tazobactam and metronidazole infusions as antibiotics along with a dopamine infusion of 5 µg/kg/minute post-operatively. No cardiovascular symptoms were described. His past medical history had included chronic alcoholism and human immunodeficiency virus (HIV) positivity but he was without any history of substance abuse. An examination

Departments of [1]Cardiology, [2]Emergency Medicine, Royal Hospital, Muscat, Oman
**Corresponding Author e mail: prashanthp_69@yahoo.co.in*

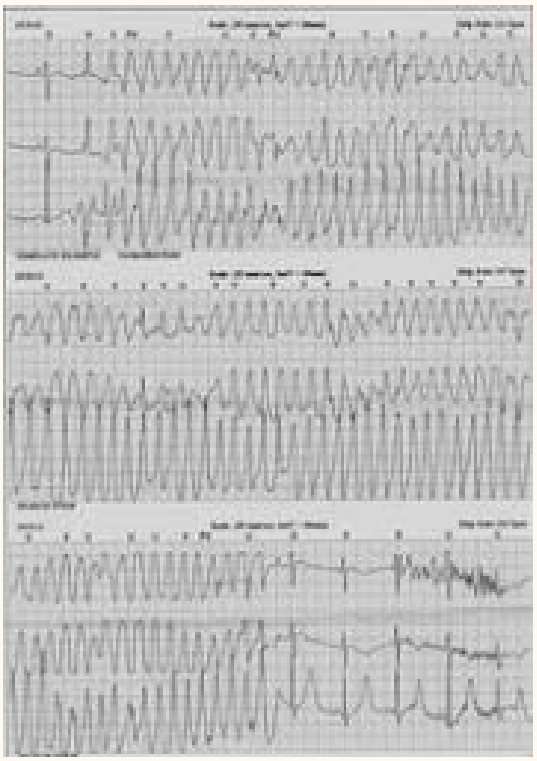

Figure 1: Electrocardiogram rhythm strips from a 24-hour ECG (Holter monitor) showing self-terminating non-sustained torsade de pointes in a patient with alcohol withdrawal syndrome and human immunodeficiency virus infection receiving dopamine and QT-prolonging antibiotics.

demonstrated anxiety, agitation, tremors, and excessive sweating, but no cardiovascular issues or other abnormalities. There were no episodes of seizure, hallucination, or *delirium tremens*. His serum potassium level was 2.9 mmol/L. Other routine blood tests, including amylase, troponin T, calcium, sodium, and magnesium were normal. His baseline electrocardiogram (ECG) showed a sinus rhythm of 60 beats/minute, and narrow normal QRS complexes with few uniform VPCs, and a normal corrected QT interval (QTc).

A diagnosis of alcohol withdrawal syndrome (AWS) was made and treated with oral diazepam. He was also given intravenous (IV) fluids with potassium supplementation. His transthoracic echocardiography was normal. A 24-hour ambulatory Holter monitor ECG showed an intermittently prolonged QTc interval (QTc, Bazett's correction = 470 ms) along with two episodes of self-terminating non-sustained torsade de pointe (TdP) ventricular tachycardia [Figure 1]. The first episode lasted 6 seconds and the second episode lasted 11 seconds. There were no ST-segment changes noted. The nursing staff on the ward were unaware of these arrhythmias. His dopamine and antibiotics were withdrawn. The patient's symptoms settled within 72 hours and the rest of his stay was uneventful. His discharge serum potassium level was 4.9 mmol/L with no VPCs or TdP on telemetry monitoring. The patient also had a normal QTc interval.

Discussion

The role of alcohol in causing heart failure (alcoholic cardiomyopathy) and supraventricular arrhythmias, especially atrial fibrillation (holiday heart syndrome) is well-known.[2] TdP is a form of polymorphic ventricular tachycardia associated with a prolonged QT interval (either congenital or acquired). QT prolongation is known to occur in AWS.[3,4] Otero-Anton *et al.* documented a prolonged QTc interval in 46% of patients studied and Cuculi *et al.* in 63% of patients who had AWS, with two patients developing TdP, but without any pre-treatment with QT-prolonging drugs.[3,4] However, our patient was treated with piperacillin/tazobactam and metronidazole, which have recently been discovered to cause TdP.[5] Cuculi *et al*. opined that QT prolongation may be due to autonomous system disturbances in AWS.[3] This was demonstrated in recent experimental studies involving rats.[6,7] Abrupt termination of the chronic ethanol intake in rats increased heart rate variability and QT interval dispersion, suggesting impaired homogeneity of myocardial repolarisation and a shift of the cardiac sympathovagal balance toward sympathetic predominance and reduced vagal tone.

The mechanism for most QT-prolonging drugs is inhibition of the KCNH2-encoded human ether-à-go-go related gene (hERG) potassium channel which mediates IKr (rapid component of the delayed rectifier potassium current), although some drugs mainly modify sodium channels.[8] Inhibition of this current results in prolongation of myocardial repolarisation/action potential duration along with a prolonged QT interval as well as changes in T-U wave morphology. There is a graded increase in the risk for TdP as the QTc increases. Specifically, each 10-millisecond (msec) increase in QTc leads to an approximate 5–7% increase in a patient's risk for developing TdP.[1] There is no threshold of QTc prolongation at which TdP is certain to occur. In this patient, TdP occurred at a mildly prolonged

QTc interval. However, small studies of drug-induced TdP have shown an increased risk when the threshold of QTc >500 msec is exceeded.[1] The onset of TdP is pause-dependent and is precipitated by either bradycardia, in which sudden long cycles may lead to arrhythmogenic early afterdepolarisations, or by premature beats that lead to short-long-short cycles.[1] Both these factors were seen in this patient. The trigger for TdP is a VPC that results from an early afterdepolarisation generated during the abnormally prolonged repolarisation phase of the affected myocardium.[1] Because of the extreme delay of repolarisation in certain regions of the myocardium, conduction of the VPC is blocked initially in some directions but not in others, which sets up re-entry that perpetuates TdP.

Although in the majority of cases prolonged myocardial repolarisation caused by drugs is clinically silent, when prescribed in the setting of other risk factors, it may lead to TdP as seen in this patient. In-hospital risk factors for TdP include female gender, advanced age, electrolyte derangements (hypokalaemia, hypomagnesaemia, hypocalcaemia), treatment with diuretics, underlying heart disease, rapid IV infusion, use of more than one QT-prolonging drug (including various antipsychotics, antidepressants, antibiotics, antiemetics, antihistaminics, inotropes, and class IA and III antiarrhythmics), hepatic and/or renal failure, pharmacokinetic/pharmacodynamic interactions, occult congenital long QT syndrome, genetic polymorphisms, and bradycardia.[1,8] This patient had five risk factors for TdP. These included acute AWS, HIV infection, bradycardia, hypokalaemia, and treatment with three QT-prolonging drugs (dopamine, piperacillin/tazobactam, and metronidazole). HIV infection has been shown to be an independent risk factor for QT prolongation. Kocheril *et al.* reported a prevalence of QT prolongation in 28% of hospitalised HIV patients.[9] In the recent HIV-infection and heart disease (HIV-HEART) study, the prevalence was 20%.[10] Yang *et al.* have demonstrated that the IKr-blocking properties of certain drugs is directly dependent on extracellular potassium.[11] They showed anincreasing drug block of the potassium current precipitated by hypokalaemia. This was an important mechanism to explain the link between hypokalaemia and TdP.[11] Analysing data from the United States Food and Drug Administration (USFDA) Adverse Event Reporting System, Poluzzi *et al.* reported additional drugs that can cause QT prolongation and TdP, which included piperacillin/tazobactam and metronidazole.[5] Management of TdP includes correction of any predisposing factors, such as hypokalaemia, and cessation of any predisposing medication. Acute treatment includes electrical (DC) cardioversion if haemodynamically compromised, defibrillation if TdP degenerates into ventricular fibrillation, IV magnesium (first-line therapy), and isoprenaline or temporary ventricular overdrive pacing to augment the heart rate.

Conclusion

In conclusion, this case highlights the importance of avoiding QT-prolonging drugs in hospitalised patients, since hospitalised patients often have multiple risk factors for a proarrhythmic response. In addition, this case reiterates the recent American Heart Association/American College of Cardiology Foundation (AHA/ACCF) scientific statement to raise awareness among acute care physicians, managing such patients in hospital units, about the multiple risk factors, ECG monitoring, and management of drug-induced long QT syndrome (LQTS).[1]

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