Solifenacin linked QT interval prolongation and Torsades de Pointes.

by

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Solifenacin is an M3- muscarinic receptor antagonist that is effective in the treatment of overactive bladder (OAB), reducing episodes of urgency and incontinence and decreasing micturition frequency (Luo et al., 2012). It can be used alone or in combination with other agents. For example, fixed dose combinations with tamsulosin appear to be well tolerated and effective in men with lower urinary tract symptoms (Drake et al., 2015).

The CredibleMeds® database (https://www.crediblemeds.org/) provides information on drugs linked to QT interval prolongation and *Torsades de Pointes* (TdP) arrhythmia. It categorises drugs associated with these ECG alterations according to strength of evidence of causality (for a review see Schwartz and Woosley, 2016). In September 2016, solifenacin was recategorised on CredibleMeds® as having a 'possible risk of TdP', which means that the drug is associated with QT interval prolongation but lacks evidence for TdP when taken as recommended. The recent Symphony study in patients ≥18 years found small increases in mean QTcF interval (Fridericia's correction) following 12 weeks of 2.5, 5 or 10 mg day^{-1} solifenacin (Abrams et al., 2015). In the MILAI study, 2.4% of patients at end of treatment with 2.5 or 5 mg day^{-1} had QTcF intervals exceeding 450 ms, whilst 1.4% had QTcF lengthening between 30 and 60 ms (Yamaguchi et al., 2015). In December 2016 we reviewed the case report evidence for QT_c prolongation with solifenacin (PubMed search: "solifenacin AND (QTc OR torsad*)" and found 3 reports of TdP with normal solifenacin use, the features of which are considered below.

The first case involved an 81-year-old-woman (Asajima et al., 2008). Her past medical history included hypertension, receipt of a pacemaker for sick sinus syndrome and amlodipine, and she had recently received cefazolin and subsequently teicoplanin for methicillin-resistant *Staph aureus*. Neither drug is independently associated with QT prolongation or TdP; her QT interval was normal prior to the prescription of solifenacin (QT 400 ms/QTc 360 ms). However, after two weeks of taking 5 mg day^{-1} solifenacin, she developed an isolated syncopal episode from which she regained full consciousness spontaneously. Electrocardiogram (ECG) measurement showed marked QT prolongation (QT 600 ms/ QTc 581 ms). Nine days later this progressed to recurrent episodes of syncope and concomitant TdP, which required resuscitation. Risk factors which predispose an individual to aLQTS include female sex and bradycardia; however, her pacemaker rate was increased from 60 beats min^{-1} to 90 beats min^{-1} to abbreviate the QT interval (QT 500

ms/QTc 408 ms) following solifenacin withdrawal. Electrocardiographic abnormalities resolved within days of solifenacin discontinuation. Aside from age, there were no other obvious risk factors including the cumulative effect from co-administration of other QT prolonging agents, impaired liver function, hypokalemia or hypomagnesemia. Interestingly, intravenous magnesium sulphate which is considered a first-line treatment for drug-induced TdP was not effective.

The second case in 2012 concerned an 81-year old man who also presented with a syncopal episode and QT prolongation (QT 680 ms/QTc 660 ms) (Yoshida et al., 2014). It was recognised that the patient was suffering from hypoglycaemia, possibly caused by the class 1a antiarrhythmic cibenzoline (given to protect against atrial fibrillation), which was discontinued on admission. However, after two days of hospitalisation he developed recurrent episodes of syncope and TdP requiring resuscitation. Infusion of magnesium sulphate was followed by temporary transcutaneous pacing which alleviated episodes of TdP by shortening QT interval. Following resuscitation, on day 3 solifenacin (10 mg day^{-1}) was discontinued and 5 days after the initial episode, QTc interval had reduced to 458 ms. There is conflicting evidence as to whether or not cibenzoline itself prolongs QTc (Kushner et al., 1984, Rothbart and Saksena, 1986, Miyamoto et al., 2000). Three other risk factors additional to age in this case can be highlighted, however; on admission the patient was hypoglycaemic (1.1 mmol/L), borderline bradycardic (57 bpm), and during the 5 day period he was also borderline hypokalaemic (3.1- 3.6 mEq/ml).

In 2015, an 84-year-old male presented to hospital with episodes of syncope having taken solifenacin 10 mg day^{-1} for 15 days (Ozmen et al., 2015). During evaluation the patient lost consciousness and a sustained ventricular tachycardia was measured. Following resuscitation a prolonged QT_C interval of 548 ms was observed. Again magnesium sulphate was ineffective at preventing recurrence of the dangerous cardiac arrhythmia and a temporary pacemaker was implanted. Solifenacin was subsequently discontinued and 3 days later the QT interval was 420 ms and TdP did not recur. In this case, whilst the patient also received treatment with metformin for diabetes and atorvastatin for hyperlipidemia, there was no sign of coronary artery disease, serum potassium was normal, nor were there other obvious risk factors additional to solifenacin therapy and old age.

The majority of drugs that prolong the QT interval inhibit the *human Ether-à-go-go Related Gene* (hERG)-encoded potassium channel which mediates the rapid delayed rectifier current (I_{Kr}), and is integral to cardiac ventricular repolarisation (Hancox et al., 2008). Impaired repolarisation predisposes to development of early afterdepolarisations (EADs) and progression to drug-induced TdP. We were unable to find published evidence of hERG channel block by solifenacin; however, the drug has been reported to exhibit prolongation of the duration of Ca^{2+} transients and induce EAD-like signals in human induced pluripotent stem cell-derived cardiomyocytes (Zeng et al., 2016). This is suggestive of the capacity for a direct proarrhythmic effect.

Common features of the three case reports that we identified are age >80 years and responsiveness to pacing. There also appeared to be a lack of sensitivity of the arrhythmia to magnesium sulphate. Two of the three patients had normal serum potassium; borderline hypokalemia, bradycardia and hypoglycaemia were present in one case. In all three cases, QTc intervals normalized on withdrawal of solifenacin. Rechallenge with solifenacin was not attempted in any case. A QT interval nomogram has been proposed that allows estimation of the risk of developing TdP from QT interval – heart rate pairs; in this, values placed above the nomogram line are considered to be "at risk" (Chan et al., 2007; Waring et al., 2010). The measured QT intervals in solifenacin the first two case reports (600 ms and 680 ms) lie far above the nomogram line across the entire heart rate range, whilst values estimated from the QT_c interval of the third case (QT interval of 500 ms and 516 ms respectively for Bazett's and Fridericia's corrections) also lie above the nomogram line. Thus, QT nomogram predicted risk for these three cases would have been consistent with the documented arrhythmias in each case. We additionally interrogated publically available information from the European Medicines Agency (EMA) EudraVigilance database. Up to November 2016, 15 individual cases of TdP had been reported, 11 of which had recovered/resolved, 3 of which were resolving and for 1 of which the outcome was unknown. 13 of the 15 cases were between 65 and 85 years of age and 10 of 15 were female (European Medicines Agency, 2016). Heart rate and QT interval information for these cases were not obtained.

The fact that most TdP cases were amongst elderly patients is notable, though perhaps not surprising given the primary indications for solifenacin use. An increased risk of TdP in older patients may be linked to falls in serum testosterone and progesterone levels in men and women respectively (Tisdale, 2016). Cardiac ageing is also associated with ventricular fibrosis, which can facilitate development of re-entrant circuits (Biernacka and Frangogiannis, 2011). The contribution of such underlying factors to TdP development in the particular cases discussed here is not known. Considering all of the available information together, it seems prudent that elderly patients, especially those of >80 years, should be carefully evaluated before prescribing solifenacin and that the drug be avoided in patients with other known risk factors for TdP. Elderly females may be at particular risk.

Disclosures: None

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