Methadone-associated QT prolongation and torsades de pointes

Sir,

I would like to add to the subject of Dubrey and Grocott-Mason's article (vol 68(1), 2007, p. 50). Methadone, the most commonly prescribed substitute medication for treatment of opioid dependence, can cause QT prolongation and even torsades de pointes (Peles et al, 2007) – very rarely with even fatal consequences. Important risk factors for methadone-associated torsades de pointes in opioid-dependent patients include high dose of methadone (generally above 120 mg daily), simultaneous use of drugs that increase serum levels of methadone, co-existing cardiac abnormalities, hepatic dysfunction and HIV (Justo et al, 2006).

Clinicians who prescribe methadone need to be aware of its propensity to induce QT prolongation and even torsades de pointes – especially in those on high doses or those with other risk factors for QT prolongation. Careful clinical monitoring and cardiac evaluation before and after stabilization on methadone is recommended in these patients. It is also worth noting that buprenorphine, a newer treatment for opioid dependence, does not have this associated risk of QT prolongation or torsades de pointes.

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Justo D, Gal-Oz A, Paran Y, Goldin Y, Zeltser D (2006) Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction* **101**: 1333–8

Peles E, Bodner G, Kreek MJ, Rados V, Adelson M (2007) Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment patients-a cross-sectional study. *Addiction* **102:** 289–300

Sir,

Dubrey and Grocott-Mason's patient was undertreated for her atrial fibrillation. She was given 625 µg of digoxin/7 days and 137.5 mg of metoprolol/7 days, i.e. 29.2 µg digoxin/day and 19.6 mg metoprolol/day. These are subtherapeutic doses for ventricular control in atrial fibrillation. Full digitalisation may be achieved either within 24 hours by giving two doses of 500 µg or slow digitalisation over a week by administering a maintenance dose of 125 µg from the start.

More interestingly, they attempted chemical cardioversion on day 8 with sotalol 40 mg/day for 3 days. This dose of sotalol has only a placebo effect and is almost devoid of any antiarrhythmic effect. Although a cumulative dose of 120 mg is mentioned, it is extremely unlikely that this dose of sotalol or larger doses will have a cumulative effect, as its half life is 6–8 hours. This woman had spontaneous reversal to sinus bradycardia indicating the possibility of an underlying tachy-bradyarrhythmia.

The prolonged QT interval in the first strip was spurious. The giant negative wave in the first strip was a combination of T and U wave leading to TU wave with pseudo-prolongation of QT interval. The actual U wave is superimposed on the descending limb of the T wave with some distortion. In such cases it is difficult to define the end of the T wave causing miscalculation of the QT interval. Most cases of presumed prolongation of QT interval are really QU intervals.

Even if we accept the giant wave as pure T wave, there is no consistent prolongation of QTc using different formulas. Although with Bazett's formula with most limitations (Bazett, 1920) the patient's heart rate with corrected QT interval was prolonged, with the more accurate formulae from Fridericia (1920) and Rautaharju et al (1990) her QTc was within normal range.

It was clearly shown in the second strip of the electrocardiogram that the QT interval of this patient was normal at 440 ms. There was a clear distinction between the T and U wave, hence the bout of ventricular tachycardia which followed the R on T phenomena was not torsades de pointes which has a totally different mechanism. It is caused by abnormal repolarization causing differences in the refractoriness of the myocytes.

The after depolarization can be propagated to the neighbouring cells via differences in the refractory periods, leading to re-entrant ventricular arrhythmias. This is believed to be the result of reopening of L-type calcium channels during the plateau phase of cardiac action potential.

Ventricular tachycardias with normal QT have different mechanisms and different treatments from torsades de pointes.

Lastly, whenever you suspect prolong QT interval you should always measure rectal temperature and test thyroid function (especially when the electrolytes are normal) as both hypothermia and hypothyroidism can cause prolonged QT.

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Bazett HC (1920) An analysis of the time-relation of electrocardiograms. *Heart* **7**: 353–70

Fridericia LS (1920) The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. *Acta Med Scand* **53**: 469–86

Rautaharju PM, Warren JW, Calhoun HP (1990) Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. *J Electrocardiol* **23 (suppl)**: 111–17

Sir,

In response to the criticism that our dose-age regime was sub-therapeutic; we have not tried to achieve therapeutic plasma levels but rather to control a ventricular response with these drugs. This was achieved with the low dosage stated in our case. Hence no escalation of dose was necessary in this very elderly woman.

With regard to the use of sotalol at a cumulative dose of only 120 mg, we would accept this is a low dose but this patient was again very sensitive to the beta blockade effect of this medication before any anticipated class III actions.

We do not understand the comments regarding the 'repolarization' wave being a combination of the T and the U wave. We were well aware of this, clearly labelled it as such in *Figure 1* (Q-TU interval) and referred to an R on 'TU' in *Figure 2*. If one accepts that it is almost impossible to distinguish between the T and the U waves, how is it then possible to propose that the QT interval is not prolonged (by whatever formula you decide to choose)?

The whole point of this case was to illustrate the extreme sensitivity of the elderly to very low dosages of drugs that can potentially extend the QT interval and have, in this case, caused a bizarre appearance to the T and U waves.

Lastly the patient was not hypothermic or hypothyroid.

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