The Methadone Menace

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In this issue of the *Journal*, Vallecillo and colleagues [1] reconfirm the important association of methadone therapy with QT prolongation and identify several clinical factors that contribute to the extent of QT prolongation and, presumably, to the risk of life-threatening ventricular arrhythmias.

Worldwide there are surely more than a million people taking methadone chronically in maintenance programs or for pain relief. Methadone’s relatively slow onset and long half-life, and its low cost make it an attractive option for both indications, but among the clinically available opioids, it is the most potent *I*_<sub>Kr</sub> blocker at usual plasma concentrations, and the most likely to induce potentially lethal torsades de pointes ventricular tachycardia. As the authors [1] point out, safer opioids are available. Perhaps the extensive prescribing of methadone should be questioned.

Since significant curbing of methadone use is not likely in the near future, clinical awareness of methadone’s proarrhythmic risk is currently the most effective means to prevent treatment-related sudden death. Vallecillo and coworkers [1] have made an important contribution by demonstrating the dose-relatedness of QT prolongation in an HIV-infected cohort, and by showing an additive effect of concomitant QT prolonging drugs concurrent hepatitis-C-induced cirrhosis in this group. The clinician should recognize the importance of reducing the dose of methadone as much as possible and avoiding concomitant use of other QT prolongers and should take special precautions, including ECG monitoring and, ideally, use of an alternative drug, in patients that require a higher methadone dose or have liver dysfunction.

Apparent shortening of QT in patients receiving antiretroviral drugs is a curious finding in this study, given their known QT‐prolonging effects. As the authors [1] suggest, this might be a result of treatment‐related improvement in the patient’s HIV status, but it may also be related to unknown study‐related biases, which makes clinical application of this observation questionable.

Review of electrocardiographic methods in this study may be helpful. The authors used the Bazett correction [2] to mitigate the effect of heart rate on QT duration (increased heart rate reduces the QT interval). The Bazett formula (*QTcB = QTVRR*) is known to overcorrect at higher heart rates. In other words, in patients with heart rates substantially greater than 60 beats per minute, a likely condition in HIV‐infected patients, *QTcB* exaggerates the duration of the corrected QT interval. Thus, if they had used the Fridericia [3] or other formulae that correct more accurately at higher heart rates, they would have observed lower QTc values. The reported incidence of QT prolongation may have been further exaggerated by the authors’ choice of an upper limit of normal of 450 msec for *QTcB* in both sexes. In a study that included about 80,000 subjects [4], the upper 2 percentile for *QTcB* was 454 msec in unselected males aged 40–49 years (the mean age in Vallecillo’s group[1] was 44.5 years, and 64% were men) and in women of the same age the cutoff was 465 msec. On the other hand, ECGs were performed at the predicted trough of methadone plasma concentration; peak QTc values were undoubtedly higher. Finally, the ECG measurement methodology used in this study was less exacting than that used in core ECG laboratories. Heart rate and QT were measured on unmagnified paper printouts rather than in a high‐resolution computer workstation. Despite these methodological issues,
which may bring into question the precision of the authors’ observations, there is little doubt that the reported risk factors for longer QTc in this population are reliable.

What should be done to mitigate the risk of drug-induced sudden death associated with methadone use [5, 6]? The first and easiest steps have been identified by Vallecillo and colleagues [1]. However, while knowledge of the problem and careful patient management will save some lives, these are weak answers in comparison to the obvious solution: stop prescribing methadone. The United States Food and Drug administration imposed Risk Evaluation and Mitigation Strategy requirements in 2012 and 2013 on the manufacturer (Roxane Laboratories, Columbus OH) of methadone tablets (Dolophine), and the drug’s label includes a boxed warning. While these requirements and labeling will improve knowledge of both prescribers and users of the risks of methadone, they may not substantially reduce widespread use and the resultant arrhythmic consequences of methadone. FDA and other regulatory agencies have prohibited use of many drugs that prolong the QT interval, at least some of which probably did not have the potential to do as much harm as methadone. Because there are safer, effective alternatives to methadone for both maintenance programs and pain relief, should methadone be withdrawn from the market?
References