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Individual patient assessment of methadone induced QT prolongation with digital holter recording

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Running Head: Methadone induced QT prolongation

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Abstract

A 27 year old male who had been on methadone therapy for six months was investigated with a 12-lead digital holter because of a prolonged QT on a standard 12-lead electrocardiogram (ECG). The patient had 24 hour holter recording on and off methadone therapy and multiple digitized 12-lead ECG data was captured for on-screen measurement of the QT interval. QT-HR pairs for each 24 hour period were plotted on the QT nomogram showing QT prolongation on methadone but not when it was ceased. This provides a highly accurate method for evaluating drug-induced QT prolongation.

Methadone has been associated with QT prolongation and torsades des pointes (TdP)(Pearson *et al.*, 2005) which has led to the development of guidelines for the screening of QT prolongation in patients on methadone.(Krantz *et al.*, 2009) There remains debate on the importance of such a rare event because the risks of stopping therapy may exceed the risks of continuing with it. The identification of patients at greatest risk is essential to clinicians prescribing methadone. Although a single electrocardiogram (ECG) may be a reasonable initial screening test, an abnormal QT interval on a single ECG is insufficient to take a patient off methadone.

A 27 year male on methadone treatment for six months was referred because of concerns about a prolonged QT interval on a standard 12-lead electrocardiogram (ECG). The QT was 480msec with a heart rate of 40bpm. He had a history of polysubstance abuse, including opioid and tetrahydrocannabinoid dependence. He smoked 20 cigarettes daily, 10 to 15 cones of marijuana and occasional alcohol. He had a sciatic nerve injury and a persistent left foot drop. He had no history of cardiac disease or abnormal finding on examination and no other risk factors for a prolonged QT. His medications were 120mg methadone daily, 60mg duloxetine daily and gabapentin 300mg three times daily. He was on the methadone for chronic pain from previous injuries and had not been on it before.

The patient had two 24 hour digital holter recordings while on methadone and one four months after methadone was ceased. For the first recording he took 60mg and then a week later for the second recording he took 120mg. His methadone was weaned and stopped because of the prolonged QT and he was commenced on hydromorphone 64mg daily and had a third holter recording four month later after 64mg hydromorphone.

For each 24 hour period a 12-lead digital holter recorder (Mortara Instruments Australia P/L) was attached and digital information was recorded on a memory card and downloaded to a

computer with the proprietary software (H-Scribe) to extract high resolution digital continuous 12-lead holter recordings. From the holter recordings, high resolution 12-lead ECG recordings were extracted every hour. A second software package (E-Scribe) was used to measure the QT interval. The 12-leads are overlapped as 6 limb leads and 6 chest leads and the QT is determined by the computer. The measurement is then checked and corrected manually using magnification and on-screen callipers. The heart rate (HR) is recorded for each 12-lead ECG recording. Hourly QT-HR pairs were then plotted on the QT nomogram for the first two recordings on methadone (Figure 1A) and the third recording on hydromorphone (Figure 1B).(Chan *et al.*, 2007) The QT nomogram provides a cut-off line for an abnormal QT which has been previously evaluated for drug-induced QT prolongation.(Chan *et al.*, 2007)

We present a patient with an abnormal QT while on methadone therapy which resolved when methadone was ceased. Figure 1 illustrates the changes in the QT-HR pairs over a 24 hour period after two different doses of methadone compared to no methadone. There is considerable diurnal variability in the QT and the QT was not abnormal for the full 24 hours. Most abnormal QT-HR pairs occurred soon after each methadone dose. The use of a 12-lead ECG at a single time point may miss these abnormal QT results.

High-resolution digital holter recorders are the most accurate way to measure the QT with modern algorithms. However this still requires manual review of the QT using on-screen magnification and callipers.(Hnatkova *et al.*, 2006) The use of automated measurement of the QT interval using standard ECGs is not accurate or reliable enough to be used.(Isbister *et al.*, 2009; Malik *et al.*, 2001) Full investigation of patients taking drugs that potentially prolong the QT interval should include a 24 hour period of assessment.

It is difficult to determine the exact risk of TdP occurring in patients such as this with an abnormal QT. Although an abnormal QT based on the QT nomogram is associated with an increased risk of TdP,(Chan *et al.*, 2007) the probability of TdP occurring in a particular individual is poorly defined, including what other factors increase the risk. Further studies are required in patients on methadone to help better define the risk of TdP.

We have shown that a 12-lead holter recording provides a much better indication of the effect of methadone on the QT interval over a 24 hour period and therefore increased information to make a risk assessment for an individual patient.

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Figure 1: QT nomogram of automated measurements of the QT interval versus heart rate (HR) from two digital holter recordings in the patient while on methadone: day 1 (60mg/d; □) and day 2 (120mg/d; ▪) [A] and when the patient was taking hydromorphone [B].

A

B