Prolongation of the QT interval during methadone use: how important is dose?

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ABSTRACT

Recent studies have shown that methadone is one of many medications that prolong the QT interval, possibly in a dose-dependent fashion. This study was done to further assess this relationship, as well as to investigate practical issues with ECG monitoring in a local methadone treatment service.

Three staff members were interviewed and 12 staff questionnaires were collated. ECG analysis and data collection were performed retrospectively. Overall, 71 ECG printouts were interpreted from 60 clients. Detailed analyses of corrected QT (QTc), methadone dose, and other factors were carried out on 39 ECGs from 31 clients on prescribed methadone, with doses of 40mg - 360mg and QTc ranging from 360ms - 520ms. The study found a significant correlation ($r=0.57$, $p=0.0002$) between QTc and methadone dose.

32 ECGs done before the start of treatment were also available for analysis and comparison with the ECGs done during treatment, showing a significantly longer mean QTc for those on prescribed methadone ($p=0.0057$).

This study adds to existing evidence that methadone prolongs the QT interval in a dose-dependent fashion. It is the first New Zealand correlation study. It also highlights practical issues and uncertainties which still surround ECG monitoring for clients on methadone treatment.

INTRODUCTION

Methadone is a prominent drug in addiction medicine - being effectively used in opioid substitution therapy[1-3] and in chronic pain management. Recently, however, its use has been linked with arrhythmia and sudden cardiac deaths[1,4-6], which are thought to be mediated through prolongation of the electrocardiogram (ECG) variable, the QT interval. Studies have now shown that methadone causes lengthening of the QT interval and the associated ventricular arrhythmia, torsade de pointes (TdP)[2,7-11], as well as revealing a molecular mechanism[12]. QT interval prolongation (medication-induced in particular) and its associated risks have become a significant issue in contemporary medicine and pharmacology. Recommendations have now been published regarding risk management and monitoring in methadone treatment[4,9,13]. Of particular importance in the New Zealand setting are recommendations made from the New Zealand Government Medicines and Medical Devices Safety Authority, Medsafe, in late 2005[4]. The most significant recommendation was that all patients with a methadone dose greater than 150 milligrams (mg) should have ECG monitoring.

There are still, however, considerable uncertainties surrounding the issue of methadone and QT prolongation. The exact relationship between these two factors is yet to be defined clearly. Methadone, particularly in high doses, prolongs the QT interval[5,6,8,10], and recent evidence points to a moderate dose-dependent relationship[2,11,14]. Nevertheless, more work needs to be done in this area. There are many other factors which can contribute to QT interval lengthening[12,15,16]. It is likely that an interplay between various factors results in prolonged QT intervals, and the clinical presentations of arrhythmia and sudden death. Given this current level of understanding, there is uncertainty about the appropriateness of Medsafe's 'threshold' value of 150mg for ECG monitoring. Some practices have introduced ECG monitoring at lower doses[17].

Contributing to the uncertainty, staff are faced with situations where the clinical reality at times appears contradictory to the evidence. There are anecdotes about patients who have had their methadone doses reduced only for their QT intervals to increase, or vice versa, without any other obvious explanation[18,19]. There are also anecdotal accounts of sudden death when a previous ECG was normal, as well as patients with known prolonged QT intervals living without incident while taking methadone. Many staff have had clients on high doses for long periods without any cardiological problems. Furthermore, there is doubt about the precision of QT interval measurement. Intrinsic and extrinsic variability is well recognised[13,16], and there are cases showing significant fluctuation in the value even within minutes[18,19].

Staff face difficulties when dealing with patients with prolonged QT intervals. Some patients strongly oppose any decrease of their methadone dose, leaving clinicians with an ethical dilemma. Staff are unable to provide an accurate risk-benefit analysis, as the risks and benefits in such situations are currently unclear.

Some clients have been resistant to having an ECG recordings performed, as they have correctly perceived that it could lead to a recommendation for reduction of their methadone dose.

These issues led to the aims of this study: an assessment of the practical issues, and staff attitudes and views on the QT interval issue and ECG monitoring (reported elsewhere); an audit of a local clinic's current practice (partially reported here); and a retrospective, descriptive investigation to further examine the relationship between methadone dose and QT interval.

METHOD

Literature Review

Factors with probable or possible effect on the QT interval were identified. These factors were used to construct a data collection template to be employed in data retrieval.

Ethical approval was granted by the Central Regional Ethics Committee.

Search of Medical Records

A manual search was performed through the paper medical records at Wellington Opioid Treatment Service, guided by a complete client list (updated 12/11/2006). This search aimed to identify ECG printouts (original or copied) or ECG referral forms in the appropriate sections of the records. An attempt was made to identify further ECGs, using the online electronic clinical record and through the medical records department of Wellington Hospital.

When an ECG printout was found, it was measured and the remainder of the client record was searched to collect appropriate additional information as outlined in the data collection template.

QTc Measurement Procedure

An average of four individual QT intervals in any one ECG recording was taken to represent the QT interval[13]. Intervals were measured preferably using the limb leads that best showed the end of the T wave - typically the standard limb leads . Two leads were usually needed to get four individual QT intervals.

Individual QT interval lengths were measured manually, from the beginning of the QRS complex to the end of the T wave to the nearest millimetre (0.04 seconds at paper speed 25mm/s), by counting millimetre marks on the printout. As the QT interval is shortened by a faster heart rate and lengthened by a slower rate[13,16], QTc (QT corrected for heart rate) was calculated using the Bazett formula - QT interval divided by the square root of the RR interval. The RR interval needed for this calculation was measured by taking the average of four non-consecutive RR intervals (measured to the nearest millimetre by counting marks) from the rhythm-strip of the ECG printout. QTc values were rounded to the nearest hundredth of a second, as this represented the degree of accuracy possible from manual measurement.

If an ECG was unable to be measured due to poor technical quality or unclear T waves, any value recorded for QTc by the reporting doctor was used. Failing this, the automated electronic calculation of QTc was used.

For this study, QTc was deemed to be prolonged if greater than 450 milliseconds (ms) in males and 470ms in females[8,16] (although other values have been used elsewhere[4,13,20]). Heart rate (beats per minute) was calculated as 60 divided by the RR interval (seconds).

Analysis of Data

The statistical programme *EpiInfo* was used for analysis. Factors included in analysis were: QTc interval, methadone dose, age, heart rate, months on methadone treatment, gender, ethnicity, QT medication score (see appendix), presence of hepatitis C infection, and use of substances - alcohol (where over ten standard drinks per week), cannabis, BDZ (prescription or illicit), other opiates. Other factors were audited: serum methadone level, presence of heart disease, other liver disease, family history of arrhythmia, HIV infection, CYP medication score (see appendix), methamphetamine use, and laboratory blood values (potassium, magnesium, calcium, creatinine). These latter data sets, however, were too incomplete to be included in analysis.

RESULTS

Audit number overview

Records were viewed for 382 of the 387 clients on the Wellington Opioid Treatment Service client list. Of the remainder, three clients were not included because they were on an alternative opioid substitution substance, not methadone. Two records were unable to be located (of which one was a deceased client).

ECGs had largely been done at cardiology outpatients at the service's request, but a few others were performed in the emergency department (ED) or during an inpatient stay.

Of the 382 clients, 71 ECG printouts were analysed. 63 individuals were identified as having had ECGs (63/382, 16.5% of client population). ECG printouts were located for 60 clients (60/382, 15.7%). Of the three clients without their ECG printouts located, one was a baseline recording and the other two were from clients each on a dose of 160mg. Multiple ECG recordings were available for four clients.

7.6% of clients (29/382) had had baseline ECGs before starting prescribed methadone (32 baseline ECGs in total - One client had four ECG recordings in ED before starting prescribed methadone), and 8.1% of all current clients (31/382) had had ECG recordings taken while already on prescribed methadone (39 ECGs taken on prescribed methadone in total). No client in this audit had both a baseline ECG and one while on prescribed methadone. 55.2% (16/29) of clients with a baseline ECG are known to have been illicit methadone opiate users before starting methadone treatment.

Abnormal ECG group

Of the 60 clients for whom ECG printouts were available (71 printouts in total), 11.7% (7/60) had a prolonged QT interval on at least one ECG. 13 ECGs demonstrated prolonged QT intervals. QTc was consistently prolonged for only one of the four clients who had had multiple printouts. For one of these clients the abnormality had been noted on 2 baseline ECG recordings (performed during a quetiapine overdose), while for the remainder, prolonged QTc was present when the clients were already on prescribed methadone (6/31, 19.4%).

22 clients had a prescribed dose greater than 150mg at the time of an ECG and six of these people (6/22, 27.3%) had a prolonged QT interval. Four ECGs (from three clients) had a QTc value of 500 milliseconds (ms) or greater, the level viewed as a significant risk for TdP[9,15,16].

QTc correlation with dose

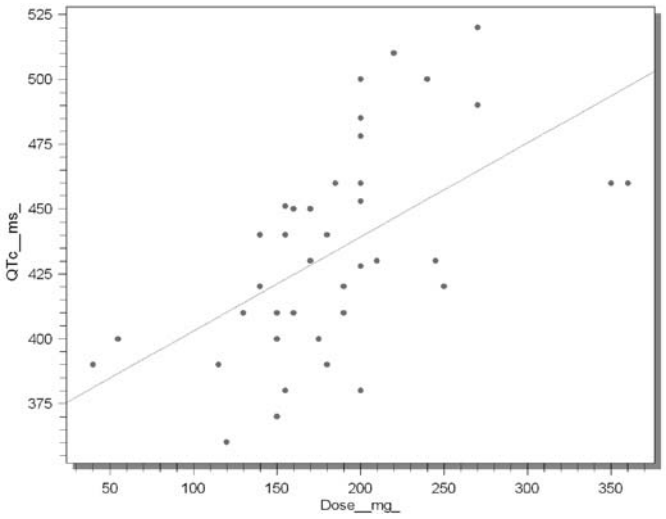
The 39 ECGs taken during prescribed methadone treatment covered a dose range of 40 - 360 milligrams (mg), median 180mg and mean 185.4mg. In this group the range of QTc was 360 - 520ms, median of 430ms and mean 434.0ms. For the 11 ECGs with prolonged QTc while on prescribed methadone, the dose range was 155 - 360mg, median 220mg and mean 242.3mg.

A moderate dose-dependent relationship between QTc and methadone dose was found on the linear regression analysis. Graph 1 shows this correlation for all available ECGs performed with clients on prescribed methadone (this included multiple ECGs for three individual patients). Methadone dose correlates significantly with QTc ($r=0.57$, $p=0.0002$); regression coefficient 0.36 (standard error = 0.087); 95% confidence interval (CI) (0.19, 0.56)Using an inverse t-test with 37 degrees of freedom. Extrapolating from this model, a 10mg methadone dose increase can be expected to increase QTc by 3.6ms (and a 100mg dose increase could increase QTc by 36ms).

This analysis was re-run using only one ECG for each client (the most recent). Eight ECGs (from the three clients with multiple ECGs) were removed in this second analysis. This still produced a significant result: $r=0.56$, $p=0.001$.

Regression analysis of the other factors showed only age to be significantly correlated to QTc ($r=0.37$, $p=0.021$). However, in a multivariate analysis including dose and age, age alone was not significant.

Graph 1. Methadone/QTc correlation for clients on prescribed methadone (39 ECGs, 31 individual clients)



High and low dose analysis

Mean QTc also proved significantly different in the methadone dose brackets used in analysis (p=0.0007) (ANOVA test for difference of means) (table 1).

Table 1. Mean QTc for methadone dose brackets

Dose bracket (mg)	Number of ECGs	Mean QTc (ms)	Std Dev
<101	2	395.0	7.1
101-150	8	400.0	26.2
151-200	20	435.8	33.8
>200	9	468.9	37.6

Baseline vs treatment ECG comparison

There was also a significant difference between mean QTc of the baseline ECGs (408.8ms) and mean QTc of all the ECGs taken on prescribed methadone (434.0ms) (p=0.0057) (ANOVA test).

Normal vs prolonged QTc comparison

Client factors from the group of ECGs with prolonged QT interval on prescribed methadone (11 ECGs in total, representing 6 clients) was compared with client factors the group of normal interval ECGs on prescribed methadone (28 ECGs), and both groups were analysed using the additional audit factors. The difference between the mean methadone dose was strongly significant between these two groups of ECGs: a mean dose of 242.3mg for prolonged QTc group, and a mean dose of 163.0mg for normal QTc group (p=0.0001) (ANOVA test) .

The only other factor showing a significant difference between these groups was alcohol use (greater than ten standard drinks) per week with RR-3.5, 95% CI (1.3, 8.9), which was still significant with one ECG per client - RR-5.1 (1.1, 24.9).

DISCUSSION

These results show a moderate dose-dependent relationship between QTc and methadone dose in this particular population (r=0.57, p=0.0002). This supports findings from several other studies. Krantz et al (2003)[11] found a significant correlation (r=0.51, p=0.03) in a series of 17 patients who developed TdP. Ehret et al (2006)[2] found a weak, but significant, dose-dependent relationship in hospitalised IV drug users receiving methadone treatment (r=0.20, p=<0.01). Cruciani et al (2005)[14] found no significant correlation overall, but a dose response for males on methadone for less than 12 months (r=0.60, p=0.02).

Two other studies [Peles et al (2006)[20] and Leavitt (2001)[21]] showed correlation (r=0.13, p=0.1 and r=0.53 respectively). These results, however, were not statistically significant. Maremmani et al (2005)[22] failed to show any correlation.

Krantz's study had patients with a mean QTc of 615ms and a mean dose of 397mg[11], both significantly higher than this study, while Leavitt had 12 patients on doses of 500mg or greater[21]. Cruciani (104 patients; 63 for opioid substitution, 41 for pain management), Ehret (167 patients) and Peles (138 patients) had study populations with reasonably similar QTc and dose values to this study[2,14,20]. The Ehret study was retrospective, while Cruciani and Peles used a cross-sectional study design. Peles also investigated serum methadone levels, but showed no correlation of blood levels with QTc[20]. Although this present study is of smaller size (39 ECGs from 31 clients), it has shown a strongly significant result. This work appears to be the first of its kind in Australasia. Possible differences with other study populations include genetic susceptibility and methadone-consumption behaviour.

This study had several limitations largely due to its retrospective design. There was no control over client information recorded by the clinic, so relevant data was not always present. Serum methadone and electrolyte levels could not be analysed as very few clients had results in close proximity to an ECG. Ehret found that several factors other than methadone dose (CYP3A4 inhibitors, low potassium levels, hepatic dysfunction) contributed to methadone-induced QTc prolongation[2]. This supports the theory that, an interplay of several variables is most important in a QT prolongation. Due to lack of data, other factors (including these three mentioned) and their influence on QTc could not be satisfactorily investigated in this study.

ECGs were taken at various times of day, in different locations, and probably, using different ECG machines - none of which are ideal. An ideal cross-sectional study would perform ECGs in one location at a similar time of day, while concurrently measuring blood electrolyte and methadone levels.

For consistent handling, manual interpretation of ECGs was used in this study,. Manual interpretation is recommended[13], but was also necessary as not all ECGs had automated or doctor-reported values. It was sometimes necessary to use the doctor-reported or automated value, as interpretation was highly technically challenging, potentially introducing small measurement bias. The interpreter in this study was a medical student (a cardiologist is recommended by some[13]). QTc measurements, although generally consistent, were found to vary by up to five percent of reported or automated values in extreme instances. No formal comparison of measurement sources was done. There has been concern raised about the appropriateness of Bazett's formula (the accepted formula in this field) for heart rate correction[13,16]. The interpreter was not blinded to client dose.

In New Zealand, there is widespread illicit use of methadone by opioid dependent individuals. This could confound the results in several ways. Clients could have been taking extra methadone in addition to their prescribed dose, which could impact negatively on the QTc-dose correlation. As shown in this audit, a significant number of clients already use methadone before beginning methadone treatment (55% in this sample). This needs to be considered in interpreting the result for the difference between the mean QTc values for baseline ECGs and ECGs performed on a prescribed dose.

Non-compliance with the regular prescribed dose is a possible confounding factor of the QTc-dose correlation in this study. New Zealand clients are required to consume their methadone under supervision on at least three days per week, allowing up to four 'take-away' doses. This creates the possibility for clients to 'double-up' their dose, or to sell their methadone illegally. Prospective studies could better test urine and blood levels (showing methadone use at baseline and subsequent non-compliance), but it would be very difficult to prevent clients supplementing their prescribed dose, given its availability on the black market in NZ.

This analysis largely approached QTc and methadone dose as continuous

variables, which is appropriate. This avoided, for the most part, making judgements regarding the exact point where QTc should be deemed prolonged, or where dose is deemed too high. In comparing those with prolonged and normal QTc, cut-off points of 450ms for males and 470ms for females were used in this study. There is no clear consensus about what values constitute a prolonged QTc[20], and using different values could have altered this comparison.

There is evidence that QTc is intrinsically labile[13,16], and some cases show significant fluctuation even over short periods of time (Two local cases[18,19] showed QTc fluctuations of 364ms to 450ms, and 500ms to 444ms (automated values), with the repeat ECGs taken one minute later.); potentially, an individual could show a prolonged QTc one day and a normal one the next. Hence, placing rigid cut-off points for describing prolonged QTc could be quite inappropriate. There appears to be a tendency (quite understandably) among staff to categorise clients as having either a normal or prolonged QTc, without reference to the actual value. Management is vastly different for these two results, including a dose reduction that can be both distressing for clients and ethically challenging for clinicians, and given the uncertainty of describing defining values, any rigid cut-offs needs to be questioned.

This study provides an indication of prevalence of QT prolongation for clients on methadone treatment in NZ. Again, this prevalence and any comparisons are influenced by the cut-off values used, which vary between studies. Six of 31 clients on prescribed methadone showed a prolonged QTc in this study (19.4%). Ehret reported 50/ 167 as prolonged (29.9%)[2], Peles 22/ 138 (15.9%)[20], and Cruciani 33/ 104 (31.7%)[14].

This study has also shown a significant difference in proportions of alcohol use (>10 standard drinks per week) between the prolonged and normal QTc groups. Alcohol use is not currently reported as a risk factor for QTc prolongation. It is possible that this result is confounded, perhaps by effects on liver metabolism or other organs. More work needs to be done before any conclusions can be made.

The audit of this service has demonstrated difficulty in following ECG monitoring policy. Qualitative data reveals this is mainly due to clients' reluctance to attend cardiology appointments, but that there is also staff uncertainty around QT interval issues. These results further indicate that the practical implications of the QT interval issue, as well as the scientific understanding (especially concerning medications), are still developing. ECG monitoring policy for patients on methadone treatment will inevitably become more refined as further evidence becomes available.

CONCLUSION

A dose-dependent relationship is present between QTc and methadone in this NZ population of opioid dependent people on MMT. While giving further evidence about the role of methadone, much is still unknown about QT prolongation in this context. Other factors, as well as methadone, are clearly involved, but the contribution of each to QT prolongation, arrhythmia, and sudden cardiac death is uncertain. Further well-designed studies are needed to bring more clarity to this important issue.

APPENDIX

QT prolongation risk score: from a well-recognised database[23], medications with a known risk of QT prolongation were assigned 3 points, those with some association 2 points, and those with weak association 1 point. Points were added for each client's score.

CYP score: for medications affecting CYP3A4[24], an inhibitor was assigned +1, and inducer -1, and a total calculated.

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