Isbister, Geoffrey K.; Page, Colin B. 'Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice", Emergency Medicine Journal Vol. 29, p. 915-918 British Journal of Clinical Pharmacology Vol. 76, Issue 1, p. 48-57 (2013)

Available from: http://dx.doi.org/10.1111/bcp.12040

Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice

Geoffrey K Isbister[1,2], *BSc, FACEM, MD Colin B Page*[2,3] *MBChB FACEM M Med Sci*

[1] Discipline of Clinical Pharmacology, University of Newcastle, New South Wales, Australia;

[2] Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, New South Wales, Australia;

[3] Emergency Department, Princess Alexandra Hospital, Brisbane, Queensland, Australia.

Key words: QT prolongation, drug toxicity, Torsades de Pointes, QT interval, electrocardiogram, risk assessment, drug overdose, adverse drug effect

Funding: GKI is supported by an NHMRC Clinical Career Development Award ID 605817.

Corresponding Author: Geoffrey Isbister, Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, Edith St, Waratah NSW 2298; Tel: +612 4921 1211; Fax: +612 4921 1870; Email: geoff.isbister@gmail.com

Summary

There has been in increasing focus on drug induced QT prolongation including research on drug development and QT prolongation, following the removal of drugs due to Torsades de Pointes (TdP). Although this has improved our understanding of drug-induced QT prolongation there has been much less research aimed at helping clinicians assess risk in individual patients with drug induced QT prolongation. This review will focus on assessment of drug-induced QT prolongation in clinical practice using a simple risk assessment approach. Accurate measurement of the QT interval is best done manually, and not using the measurement of standard ECG machines. Correction for heart rate (HR) using correction formulae such as Bazett's is often inaccurate. **These formulae underestimate and overestimate the duration of cardiac repolarisation at low and high heart rates, respectively.** Numerous cut-offs have been suggested as an indicator of an abnormal QT, but are problematic in clinical practice. An alternative approach is the QT nomogram which is a plot of QT versus HR. The nomogram has an "at risk" line and QT-HR pairs above this line have been shown in a systematic study to be associated with TdP and the line is more sensitive and specific than Bazett's QTc of 440msec or 500msec. Plotting the QT-HR pair for patients on drugs suspected or known to cause QT prolongation allows assessment of the QT interval based on normal population QT variability. This risk assessment then allows the safer commencement of drugs therapeutically or management of drug induced effects in overdose.

Introduction

There has been an enormous amount of research on drug induced QT prolongation over the last few decades.[1] To date research has almost exclusively focussed on drug development and the risk of particular drugs causing QT prolongation in populations of patients taking the drug therapeutically. The removal of a number of drugs from use in the last decade due to cases of TdP,[2, 3] has intensified mainly pharmaceutical industry research and prompted the development of guidelines for the *in vitro* and *in vivo* assessment of drug effects on the QT interval.[4] This has improved our understanding of drug-interactions and balancing the risk of QT prolongation versus the benefit of the drug.[5]

Unfortunately this research and such guidelines are of limited usefulness to the clinician dealing with individual patients who have suspected or confirmed drug induced QT prolongation. A good example is a physician treating patients with methadone.[6] Methadone is known to cause QT prolongation but Torsades de Pointes (TdP) occurs only rarely and ceasing methadone is difficult because of its benefits and patient desire to continue.[7, 8] Another example is assessing patients who have taken an overdose of a drug which may or may not cause QT prolongation. There is little information on how to develop a risk assessment in these patients, including: 1) Practical measurement of the QT interval in the clinical setting, 2) Heart rate correction of the QT interval, and 3) The threshold for an abnormal QT.

An additional problem with assessment of the QT interval for an individual patient for a particular drug is that in the majority of cases QT measurements are not available for the patient prior to commencing the drug or taking a drug overdose. In many cases the risk assessment has to be made from a single electrocardiogram (ECG) at the time the patient presents for medical attention.

There are previous reviews of the topic focusing on drug development[1] and consensus criteria for assessing the QT interval for new drugs.[4] This review will focus on the assessment of drug-induced effects on the QT interval in an individual patient following either therapeutic use or an overdose of a drug. The aim is to provide a practical approach to the risk assessment of the QT interval, including the measurement, heart rate (HR) correction and determining when the QT is abnormal.

Non-drug risk factors and the QT interval

The classic presentation of QT prolongation and TdP is with congenital Long QT syndromes, including the more common autosomal dominant Romano-Ward syndrome and the less common Jervell and Lange-Neilsen syndrome associated with deafness.[9] Although there is now an increasing understanding of the underlying mechanisms of these congenital disorders, they are genetically and phenotypically heterogenous and associated with a variety of mutations in ion channel sub-units (potassium and sodium channels) and mutations in regulatory protein coding genes.[9, 10] Most of these **may be** associated with poor outcomes and have been reviewed in detail elsewhere.[11, 12]

In addition to congenital Long QT syndrome, there is increasing evidence that the QT interval is a heritable trait in healthy subjects,[13, 14] and genetic variants may be important for determining people who may be at higher risk from drugs that cause QT prolongation. These genetic variants in total explain more of the QT variation (except HR) than any other factor including sex. [14] However, these patients are likely to have normal ECG morphology and normal or near normal QT off the drug making identification of this group difficult without exposing them to the drug.

There are numerous other physiological and acquired pathological factors that have been associated with QT prolongation and TdP. Female sex is associated with a longer QT interval of about 20msec compared to men[15, 16]. Increasing age has been shown to be independently associated with QT prolongation.[17, 18] There is also diurnal variation in the QT interval which makes it important to consider time of day in the assessment of the QT interval.[15]

The most common pathological conditions associated with QT prolongation are electrolyte disturbance, including hypocalcaemia,[19, 20] hypokalaemia[20-23] and hypomagnesaemia.[22, 24] In a study of amisulpride overdose hypokalaemia was significantly associated with patients with QT prolongation.[25] Hypoglycaemia has also been associated with a prolonged QT.[26] Other conditions that have possible associations with QT prolongation are myocardial ischaemia, cardiomyopathies, hypothyroidism, obesity and hypertension.

So far we have considered risk factors for QT prolongation. A more difficult issue is the risk factors for TdP, independent of risk factors for QT prolongation. QT prolongation is the most important risk factor for TdP and is also the marker for TdP. However, there is little information on what independently increases the risk of TdP for patients with a prolonged QT. For example, amisulpride overdose commonly causes QT prolongation but only a small proportion of cases with QT prolongation actually develop TdP.[25]

Drugs that affect the QT interval

Numerous drugs have been associated with QT prolongation and over the last decade a number of drugs have been withdrawn from the market or restricted because of reports of QT prolongation and TdP.[2, 5, 27, 28] The list of drugs that cause QT prolongation differ between sources depending on how causality is assigned. Table 1 includes the more common drugs that have been associated with QT prolongation but is not exhaustive.

Almost all drugs that have been associated with QT prolongation block the rapid component of the delayed rectifier potassium channel (I_{KR}), which is coded by the human ether-a-go-go related gene (hERG).[29] Blocking the I_{KR} channel results in prolonging the action potential which appears as lengthening of the QT on the ECG. This delayed ventricular repolarisation leads to early after depolarisations, which can result in just focal activity or re-entrant pathways, and thence TdP.[29] However, it still remains unclear why some drugs that are potent blockers of I_{KR} and cause QT prolongation, rarely cause TdP such as amiodarone.[23, 29]

It is important to remember that QT prolongation can result from multiple factors, either multiple drugs or a combination of drugs and non-drug factors.[5] Combinations of drugs may cause QT prolongation due to pharmacokinetic interactions such as ketoconazole inhibiting the metabolism of cisapride at the cytochrome p450 enzyme 3A4, or pharmacodynamics interactions when two drugs that cause QT prolongation are combined.[5, 29] The risk assessment can be quite difficult for some drugs such as erythromycin.[30] The intravenous erythromycin formulation has been associated with QT prolongation, where is there is little evidence to support oral erythromycin by itself causing TdP.[30] However, the combination of oral erythromycin and cisapride is known to cause TdP because of erythromycin inhibiting the metabolism of cisapride, again at cytochrome p450 3A4.[5]

Measurement of the QT Interval

There are numerous manual and automated approaches to measuring the QT interval. Important considerations are **the method used to determine the end of the T wave,** which lead is used, whether multiple leads are used, if multiple leads are measured is the median, maximum or mean (average) QT taken **and whether a manual or automated measurement is used.**

A major problem with measurement of the QT interval is defining the end of the T wave.[1, 31, 32] Morphological abnormalities in the T wave (e.g. biphasic T waves) and distinguishing the T wave from the U wave may make determining the end of the T wave more difficult.[1] At least three methods are recognised for manual and automated measurement of the QT.[31, 33, 34] The simplest method is the visual method that identifies the point where the T wave returns to baseline (isoelectric line).[34] The differential threshold method defines the end of the T wave as the point where the differential waveform of the T wave returns to the level of the background noise and is closest to the visual method.[33] The tangent method defines the end of the T wave as the intersection of the tangent of the steepest slope of the downward part of the T wave and the baseline or isoelectric line.[31] Although the tangent method has been shown to have less inter-reader variability, it gives a shorter measurement of the QT compared to the other methods and may be more inaccurate with unusual T wave morphology.[33]

In many cases the QT is measured in only a single lead on the ECG. Lead II is most commonly used because it is more likely to have the longest QT interval. However, it only has the longest QT about 60% of the time.[1] **Other leads have been suggested because they are more likely to have measureable QT intervals. A recent study showed that lead III, V1, aVF and aVL were more likely to have non-measureable QT intervals, compared to lead I and leads V3 to V6,[33] which was consistent with the choice of six leads in a study of manual QT measurements.[34]** However, reliance on a single lead can be problematic if the tracing is unreadable in that lead.[1] A better approach is to measure more than one lead and take the median measurement.[1, 34] The median is more robust compared to the mean because an inaccurate measurement in one lead may cause a significant error in the mean. Another problem is the use of a single beat to measure the QT in each lead. More accurate approaches or algorithms will average 3 to 5 beats in each ECG lead which removes beat to beat variation and reduces artefact and noise.

Therefore to get an accurate measure of the QT interval, several beats in each lead should be averaged and then a median taken of six or more leads. This can either be done manually or automatically. A manual approach has the advantage of more accurately determining the end of the QT but is **more** time consuming because of the large number of QT intervals that need to be measured in each ECG. Automatic approaches allow the rapid measurement of large numbers of QT intervals but even the best algorithms may be inaccurate in determining the end of the QT interval.[35]

Arguably the most accurate way to measure the QT interval is to use high-resolution digital 12-lead ECGs extracted from continuous 12-lead holter recordings. A computer algorithm is then used to estimate the length of the QT from the digital 12-lead data. To increase the accuracy the digitised 12-lead ECG is displayed on-screen in a magnified view where the six limb leads and six chest leads are separately overlapped. On-screen callipers can then be adjusted by a manual operator to confirm the automatic QT measurement and correct it if required. The equipment and technology is unlikely to be available outside of pharmaceutical development, although it has been used in a limited number of clinical studies and case reports.[36-38]

Unfortunately in the clinical setting, currently the commonest way to measure the QT interval is to use the automatic measurement of the QT done by a standard 12-lead ECG machine. Although this is simple and used almost universally, it is unreliable, particularly for patients with a prolonged QT.[1, 39] This has been shown in a case of ziprasidone overdose where the automatically measured QT on the standard bedside ECG machine did not identify a prolonged QT, compared to both the automated 12-lead holter measurement and manual measurement, which found a prolonged QT interval.[36] Another example of an inaccurate measure of the QT interval in a massive valproate overdose is shown in Figure 1 where the automatic measurement has an error of about 140msec.

A better alternative in the clinical setting is using a manual measurement where more than one lead on the 12-lead ECG is measured and then the median QT interval is used. **In this approach the QT interval is measured in one complex in each of six leads. The end of the T wave is determined visually as the point where it returns to baseline – the visual method.[33] This manual approach is a compromise between the time consuming measurement of multiple complexes in all 12 leads, and taking the potentially inaccurate automatic measurement. The approach usually takes only 1 to 2 minutes with some practice. This is a small sacrifice for increasing the accuracy in the most important investigation for drug-induced QT prolongation.** Such approach has been suggested and evaluated in a recent study.[34] This method is summarised in Table 2.

Heart rate correction of the QT interval

The single most important parameter that affects the QT interval is the heart rate. This has been recognised for a long time with the initial development of Bazett's formula for heart rate correction[40] and subsequent changes to improve it.[1] However, the application of such heart rate correction formulae, including Bazett's, Fridericia, Hodges and Framingham, is problematic and does not completely remove the dependence of the QT on the HR and therefore does not allow comparisons of QT for different HR.[41, 42] This is most problematic with Bazett's which will over-correct and under-correct outside a narrow physiological range of heart rates.[1, 41-44] Unfortunately Bazett's formula is the most commonly used in clinical practice, despite warnings as early as the 1960's by Simonson,[42] and numerous studies since that time.[43, 45]

Davey provides reasons for why Bazett's and other formulae fail to correct the QT interval.[41] The first reason is that the formulae do not remove the dependence of the QT on the HR, which is worst in the case of Bazett's formula which over-corrects for fast HR indicated by the positive correlation between HR and the corrected QT interval (QTc).[46] This has been confirmed for Bazett's correction in a number of studies,[47] including studies of drugs in overdose that cause tachycardia and artificially prolong the QTc.[48-50] This is a particular problem for quetiapine, a common drug taken in overdose which has been implicated as a drug causing TdP based only on cases of QTc prolongation, but no reports of TdP.[51, 52] Similarly venlafaxine overdose has been suggested to cause QT prolongation,[53] but this was not confirmed when tachycardia was considered independently.[49] Fridericia and Hodges formulae are better but will still over-correct for fast HR.

The second reason that universal heart rate correction formulae have failed is that they correct for HR at the population level.[54, 55] The formulae assume that the relationship between QT and HR is fixed for different individuals.[41] Numerous studies have demonstrated that the QT/HR relationship is stable within an individual but varies significantly between individuals.[54, 55] Therefore, accurate HR correction of the QT interval can only occur if the relationship between HR and QT is known at the individual level. Such individual HR correction is possible in clinical research studies[54] and has been done in a number of population pharmacokinetic-pharmacodynamic studies of drugs in overdose that affect the QT interval such as citalopram.[56, 57]

Individual HR correction requires good baseline ECG data off the drug for establishing the QT/HR relationship and then multiple QT measurements on the drug. This is not possible in clinical practice because the patient usually presents for medical care when they are taking the medication or have taken an overdose and baseline ECGs are not available.

A third alternative to using either population HR correction or individual HR correction is to not correct the QT interval and plot the QT interval against the HR. This is the approach taken with the QT nomogram and is discussed below.

Risk assessment: When is the QT abnormal?

Numerous cut-offs have been suggested as the definition for an abnormal QT. One study showed that a QTc>450msec in men and QTc>470msec in women was associated with an increased risk of sudden death.[58] Another study of healthy volunteers found that the 95% confidence limit of the average 24 hour QTc interval using Holter measurements was 450msec overall, but 440msec in men and 460msec in women.[15] An absolute QT or QTc greater than 500msec is often regarded as a significant risk of TdP.[5, 59, 60]

The numerous different cut-offs used for an abnormal QT interval, and whether the QTc or absolute QT should be used makes it difficult for clinicians to determine if the QT interval is abnormal in any particular individual. An approach is required that gives a relatively sensitive and specific cut-off that can be applied at a population level that takes into account individual variation between and includes HR correction.

The QT Nomogram

To attempt to circumvent the problems with HR correction and what QTc cut-off to use, the QT nomogram was developed. The QT nomogram is based on the “cloud” diagram produced by Fossa et al,[61] which is a plot of QT versus the RR interval for a population. QT-RR plots in individuals each form a unique cloud which shows the variability in the QT-HR relationship, usually over a 24 hour period. Individual clouds can be then superimposed and the inter-individual differences form a population cloud.[62] Fossa et al. suggested that any QT-RR pairs outside this population “cloud” which is the 95% “normal” range are associated with an increased risk of arrhythmia.[61] To make the QT-RR “cloud” more practical for clinical use, the QT nomogram was developed which plots QT versus HR but retains the same normal and “at risk” regions (Figure 2).[63] The advantage of this two-dimensional plot is that it does not require correction formulae and can be potentially used for single individuals.

The QT nomogram has been evaluated in a systematic review of cases of drug-induced TdP. This study showed that QT-HR pairs above the nomogram line were associated with TdP and that the QT nomogram was more accurate than Bazett’s QTc of 440 or 500msec.[63] **The QT nomogram had a sensitivity of 97% and specificity of 99% compared to Bazett’s formula with a sensitivity of 99% and specificity of 67% (QTc=440ms) and a sensitivity of 94% and specificity of 97% (QTc=500ms), respectively.**

A subsequent study has independently demonstrated that the QT nomogram is better than QTc criteria, with a lower false positive rate.[64] The QT nomogram has been used in numerous studies of overdose patients as a risk assessment tool for QT prolongation and TdP,[25, 49, 51, 56, 57, 65, 66] and examples of QT-HR plots are shown in Figure 3.

Like criteria based on a QTc cut-off, the QT nomogram only indicates the presence or absence of an abnormal QT-HR pair, and does not quantify the risk or probability of TdP occurring. A recent study of amisulpride overdoses showed that the magnitude of the QT interval, by any of the common measures, is associated with **an increasing** risk of TdP.[67] **Therefore, the greater the orthogonal distance above the QT nomogram line, the greater the risk of TdP for amisulpride. This suggests there is a relationship between**

the magnitude of the QT and the probability of TdP, but it is likely to differ for different drugs.

Assessing the risk of QT prolongation

Although QT prolongation can occur with the therapeutic use of drugs or drug interactions, it is more likely to occur in the setting of drug overdose. A difficult issue when assessing the risk of TdP is combining prior information on the drug that has been ingested with clinical information from the individual patient being assessed. For a limited number of drugs there is good evidence that the drug does or does not cause TdP. For example there are studies of amisulpride[25] and citalopram overdose[56] that clearly demonstrate a relationship between the drug and TdP, and in the case of citalopram a dose-effect relationship that has been used to develop clinical guidelines.[68] Conversely, a large study of quetiapine overdoses provides good evidence that quetiapine is highly unlikely to cause QT prolongation or TdP in overdose and patient do not require cardiac monitoring.[51]

For other drugs there is limited information on the risk of TdP and the main issue for the treating clinician is at what cut-off value of the QT interval should patients be monitored. Measuring the QT interval manually using the method suggested in table 2 and plotting the QT versus the HR on the QT nomogram is a simple and practical way to assess the risk of QT prolongation in individual patients. This will assist in the decision to, or continue to cardiac monitor the patient.

Prescribing drugs known to cause QT prolongation

A more difficult issue is deciding when the benefits of a drug that causes QT prolongation outweigh the risk of TdP. A good example of this is the prescription of methadone which is used widely as an opioid substitute and has significant benefits. Other examples are the use of antibiotics associated with a small risk of TdP or antidepressants and antipsychotics.

If it is decided that a drug known to cause QT prolongation and TdP is to be prescribed then it is important that there is appropriate baseline assessment and then monitoring while on the drug. A stepwise approach is recommended starting with a baseline ECG which is the minimum that should be done (Figure 4). However, a more accurate baseline assessment would be a number of ECGs at different times of the day or if available a holter assessment of the QT.[36] This initial assessment is to determine if the patient has an "off" drug abnormal QT which would preclude the use of any drug that prolongs the QT.

Once the patient is started on the medication it is important to follow up with ECGs on the drug to determine if there is evidence of QT prolongation. The approach in Table 2 can be used to determine if there is an abnormal QT. It is also essential to avoid other drugs that cause QT prolongation or other non-drug risk factors such as electrolyte abnormalities. Ultimately the use of QT prolonging drugs can be a difficult balance of benefit versus risk for the treating clinicians.

Competing Interests

Both authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Figure Legends

Figure 1: Standard 12-lead ECG of a valproate overdose showing QT prolongation of 560msec by manual measurement but the automatic measurement is 422msec.

Figure 2: The QT nomogram developed by Chan et al.[63] The nomogram line separates HR,QT pairs above the line associated with an increased risk of Torsades de Pointes compared to those below the line.

Figure 3: Plots of QT versus heart rate (HR) on the QT nomogram for a control group of patients taking overdoses of drugs that do not affect the QT interval (paracetamol, diazepam, oxazepam and temazepam) [A]; ten patients given intramuscular droperidol for sedation where multiple ECGs were recorded over a period of 6 to 24 hours using a 12-lead holter recorder [B]; 83 patients taking an amisulpride overdose **including six who developed TdP (crosses)** [C]; and 260 patients taking a quetiapine overdose [D].

Figure 4: Recommended approach when commencing drugs that are known to prolong the QT interval.

References

1. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug Safety.* 2001; **24**(5): 323-51.

2. Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. *Am J Gastroenterol.* 2001; **96**(6): 1698-703.

3. Yap YG, Camm J. Risk of torsades de pointes with non-cardiac drugs - doctors need to be aware that many drugs can cause QT prolongation. *British Medical Journal.* 2000; **320**: 1158-9.

4. Shah RR. Drugs, QTc interval prolongation and final ICH E14 guideline : an important milestone with challenges ahead. *Drug Safety.* 2005; **28**(11): 1009-28.

5. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; **350**(10): 1013-22.

6. Fanoe S, Hvidt C, Ege P, Jensen GB. Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. *Heart.* 2007; **93**(9): 1051-5.

7. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf.* 2005; **14**(11): 747-53.

8. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009; **150**(6): 387-95.

9. van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol.* 2010; **70**(1): 16-23.

10. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. *Cell.* 2001; **104**(4): 569-80.

11. Roberts JD, Gollob MH. The genetic and clinical features of cardiac channelopathies. *Future Cardiol.* 2010; **6**(4): 491-506.

12. Johnson JN, Ackerman MJ. QTc: how long is too long? *Br J Sports Med.* 2009; **43**(9): 657-62.

13. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, D'Agostino RB, O'Donnell CJ. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: The Framingham Heart Study. *Heart Rhythm.* 2005; **2**(3): 277-84.

14. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet.* 2009; **41**(4): 399-406.

15. Molnar J, Zhang F, Weiss J, Ehlert FA, Rosenthal JE. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol.* 1996; **27**(1): 76-83.

16. Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. *Eur Heart J.* 1997; **18**(6): 1000-6.

17. Mangoni AA, Kinirons MT, Swift CG, Jackson SH. Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis. *Age Ageing.* 2003; **32**(3): 326-31.

18. Taneja T, Mahnert BW, Passman R, Goldberger J, Kadish A. Effects of sex and age on electrocardiographic and cardiac electrophysiological properties in adults. *Pacing Clin Electrophysiol.* 2001; **24**(1): 16-21.

19. Davis TM, Singh B, Choo KE, Ibrahim J, Spencer JL, St John A. Dynamic assessment of the electrocardiographic QT interval during citrate infusion in healthy volunteers. *Br Heart J.* 1995; **73**(6): 523-6.

20. Severi S, Grandi E, Pes C, Badiali F, Grandi F, Santoro A. Calcium and potassium changes during haemodialysis alter ventricular repolarization duration: in vivo and in silico analysis. *Nephrol Dial Transplant.* 2008; **23**(4): 1378-86.

21. Chvilicek JP, Hurlbert BJ, Hill GE. Diuretic-induced hypokalaemia inducing torsades de pointes. *Can J Anaesth.* 1995; **42**(12): 1137-9.

22. Foglia PE, Bettinelli A, Tosetto C, Cortesi C, Crosazzo L, Edefonti A, Bianchetti MG. Cardiac work up in primary renal hypokalaemia-hypomagnesaemia (Gitelman syndrome). *Nephrol Dial Transplant.* 2004; **19**(6): 1398-402.

23. Cubeddu LX. Iatrogenic QT Abnormalities and Fatal Arrhythmias: Mechanisms and Clinical Significance. *Curr Cardiol Rev.* 2009; **5**(3): 166-76.

24. Cupisti A, Galetta F, Caprioli R, Morelli E, Tintori GC, Franzoni F, Lippi A, Meola M, Rindi P, Barsotti G. Potassium removal increases the QTc interval dispersion during hemodialysis. *Nephron.* 1999; **82**(2): 122-6.

25. Isbister GK, Balit CR, MacLeod D, Duffull SB. Amisulpride overdose is frequently associated with QT prolongation and torsades de pointes. *Journal of Clinical Psychopharmacology.* 2010; **30**(4): 391-5.

26. Eckert B, Agardh CD. Hypoglycaemia leads to an increased QT interval in normal men. *Clin Physiol.* 1998; **18**(6): 570-5.

27. Hondeghem LM, Dujardin K, Hoffmann P, Dumotier B, De Clerck F. Drug-induced QTC prolongation dangerously underestimates proarrhythmic potential: lessons from terfenadine. *J Cardiovasc Pharmacol.* 2011; **57**(5): 589-97.

28. Simons FE, Kesselman MS, Giddins NG, Pelech AN, Simons KJ. Astemizole-induced torsade de pointes [letter]. *Lancet.* 1988; **2**(8611): 624-.

29. Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res.* 2003; **58**(1): 32-45.

30. Guo D, Cai Y, Chai D, Liang B, Bai N, Wang R. The cardiotoxicity of macrolides: a systematic review. *Pharmazie.* 2010; **65**(9): 631-40.

31. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm.* 2008; **5**(7): 1015-8.

32. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. *Circulation.* 1952; **6**(3): 378-88.

33. Kasamaki Y, Ozawa Y, Ohta M, Sezai A, Yamaki T, Kaneko M, Watanabe I, Hirayama A, Nakayama T. Automated versus manual measurement of the QT interval and corrected QT interval. *Ann Noninvasive Electrocardiol.* 2011; **16**(2): 156-64.

34. Isbister GK, Calver L, van Gorp F, Stokes B, Page CB. Inter-rater reliability of manual QT measurement and prediction of abnormal QT,HR pairs. *ClinToxicol(Phila).* 2009; **47**(9): 884-8.

35. Hnatkova K, Gang Y, Batchvarov VN, Malik M. Precision of QT interval measurement by advanced electrocardiographic equipment. *Pacing and Clinical Electrophysiology.* 2006; **29**(11): 1277-84.

36. Berling I, Isbister GK, Calver L, Clunas S. Digital Holter measurement of QT prolongation in ziprasidone overdose. *Clin Toxicol (Phila).* 2011; **49**(7): 694-6.

37. Calver LA, Downes MA, Isbister GK. Assessment of QT Prolongation in High-Dose Droperidol Administration Using Continuous 12-Lead Holter Recording [abstract]. *Clinical Toxicology.* 2011; **49**(3): 2.

38. Calver L, Dunlop AJ, Isbister GK. Individual Patient Assessment of Methadone-induced QT Prolongation With Digital Holter Recording. *J Addict Med.* 2012; **6**(1): 92-3.

39. Hunt AC. Accuracy of popular automatic QT interval algorithms assessed by a 'gold standard' and comparison with a Novel method: computer simulation study. *BMC Cardiovasc Disord.* 2005; **5**: 29.

40. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart.* 1920; **7**: 353-70.

41. Davey P. How to correct the QT interval for the effects of heart rate in clinical studies. *J Pharmacol Toxicol Methods.* 2002; **48**(1): 3-9.

42. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol.* 2004; **37 Suppl**: 81-90.

43. Hodges M. Rate Correction of the QT Interval. *Cardiac Electrophysiology Review.* 1997; **3**: 360-3.

44. Rowlands DJ. Graphical representation of QT rate correction formulae: an aid facilitating the use of a given formula and providing a visual comparison of the impact of different formulae. *J Electrocardiol.* 2012; **45**(3): 288-93.

45. Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. *Am J Cardiol.* 1993; **72**(6): 17B-22B.

46. Davey PP. QT interval measurement: Q to T Apex or Q to T End? *J Intern Med.* 1999; **246**(2): 145-9.

47. Malik M. The imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes. *Pacing Clin Electrophysiol.* 2002; **25**(2): 209-16.

48. Isbister GK, Balit CR. Bupropion overdose: QTc prolongation and its clinical significance. *Annals of Pharmacotherapy.* 2003; **37**(7-8): 999-1002.

49. Isbister GK. Electrocardiogram changes and arrhythmias in venlafaxine overdose. *British Journal of Clinical Pharmacology.* 2009; **67**(5): 572-6.

50. Balit CR, Isbister GK, Hackett LP, Whyte IM. Quetiapine poisoning: A case series. *Annals of Emergency Medicine.* 2003; **42**(6): 751-8.

51. Isbister GK, Duffull SB. Quetiapine overdose: predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal. *International Clinical Psychopharmacology.* 2009; **24**(4): 174-80.
52. Gajwani P, Pozuelo L, Tesar GE. QT interval prolongation associated with quetiapine (Seroquel) overdose. *Psychosomatics.* 2000; **41**(1): 63-5.
53. Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. *Br J Clin Pharmacol.* 2007; **64**(2): 192-7.
54. Piotrovsky V. Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. *AAPSJ.* 2005; **7**(3): E609-E24.
55. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. *Heart.* 2002; **87**(3): 220-8.
56. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. *British Journal of Clinical Pharmacology.* 2006; **61**(2): 177-90.
57. van Gorp F, Duffull S, Hackett LP, Isbister GK. Population pharmacokinetics and pharmacodynamics of escitalopram in overdose and the effect of activated charcoal. *Br J Clin Pharmacol.* 2012; **73**(3): 402-10.
58. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol.* 2006; **47**(2): 362-7.
59. Fermini B, Fossa AA. The impact of drug-induced QT interval prolongation on drug discovery and development. *NatRevDrug Discov.* 2003; **2**(6): 439-47.
60. Shah RR. Drug-induced prolongation of the QT interval: regulatory dilemmas and implications for approval and labelling of a new chemical entity. *Fundam Clin Pharmacol.* 2002; **16**(2): 147-56.
61. Fossa AA, Wisialowski T, Magnano A, Wolfgang E, Winslow R, Gorczyca W, Crimin K, Raunig DL. Dynamic beat-to-beat modeling of the QT-RR interval relationship: analysis of QT prolongation during alterations of autonomic state versus human ether a-go-go-related gene inhibition. *Journal of Pharmacology and Experimental Therapeutics.* 2005; **312**(1): 1-11.

62. Batchvarov V, Malik M. Individual patterns of QT/RR relationship. *Card Electrophysiol Rev.* 2002; **6**(3): 282-8.

63. Chan A, Isbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. *QJM.* 2007; **100**(10): 609-15.

64. Waring WS, Graham A, Gray J, Wilson AD, Howell C, Bateman DN. Evaluation of a QT nomogram for risk assessment after antidepressant overdose. *Br J Clin Pharmacol.* 2010; **70**(6): 881-5.

65. Anand S, Singh S, Nahar Saikia U, Bhalla A, Paul Sharma Y, Singh D. Cardiac abnormalities in acute organophosphate poisoning. *Clin Toxicol (Phila).* 2009; **47**(3): 230-5.

66. Page CB, Calver LA, Isbister GK. Risperidone overdose causes extrapyramidal effects but not cardiac toxicity. *J Clin Psychopharmacol.* 2010; **30**(4): 387-90.

67. Joy JP, Coulter CV, Duffull SB, Isbister GK. Prediction of torsade de pointes from the QT interval: analysis of a case series of amisulpride overdoses. *Clin Pharmacol Ther.* 2011; **90**(2): 243-5.

68. Isbister GK, Friberg LE, Duffull SB. Application of pharmacokinetic-pharmacodynamic modelling in management of QT abnormalities after citalopram overdose. *Intensive Care Medicine.* 2006; **32**(7): 1060-5.