Int J Emerg Med (2008) 1:35–41
DOI 10.1007/s12245-008-0014-6

ORIGINAL ARTICLE

Assessing risk of a prolonged QT interval–a survey of emergency physicians

Amanda S. Y. Chan · Geoffrey K. Isbister · Carl M. J. Kirkpatrick · Stephen B. Duffull

Received: 23 January 2008 / Accepted: 17 February 2008 / Published online: 18 March 2008

Abstract
Background Although QT prolongation is associated with an increased risk of torsades de pointes (TdP), it is unclear how clinicians determine risk in individual patients with prolonged QT.
Aims To investigate physicians' interpretation of electrocardiogram (ECG) values in patients with a prolonged QT in reference to risk of TdP.
Methods A survey was sent to Australasian emergency physicians (EPs) to investigate interpretation of ECG data in risk assessment for TdP. The survey contained three sections: demographic information, questions on heart rate correction and six sets of ECG data which the clinician ranked from low to high risk. Risk analysis for ECG values was performed by producing histograms of the distribution of responses for each of the six sets of ECG parameters. These distributions were compared to predicted distributions based on Bazett's corrected QT>500 ms and the QT nomogram. The QT nomogram is a recently developed method for assessing whether QT-HR pairs are associated with increased risk of TdP by plotting them to determine if they are above an at risk line—the nomogram.
Results Of 720 surveys sent out, 249 were returned (35%). A heart rate correction was used by 90% of respondents and the median "at risk" QTc judged by EPs was 450 ms [interquartile range (IQR): 440–500 ms]. Respondents were divided as to whether bradycardia increased the risk of TdP, with equal numbers responding "no change" and "more caution". In four of the six sets of ECG parameters, EPs had a similar risk distribution to that predicted by Bazett. For one point predicted to be high risk by the QT nomogram, there was a uniform (undecided) risk distribution by EPs.
Conclusions EPs mainly relied on Bazett's correction as their method of TdP risk assessment, which may be problematic for bradycardic patients.

Keywords QT interval · Drug toxicity · Torsades de pointes · Nomogram · Risk assessment

Introduction

Prolongation of the QT interval and risk of torsades de pointes (TdP) are ongoing issues for both the pharmaceutical industry in drug development and for clinicians assessing patients following drug interactions or drug overdose. During drug development the potential for a drug to prolong the QT interval must be assessed on many levels, including in vitro, animal and human studies [1].

Author's contributions: GKI, CK and SBD designed the survey and study; AC undertook data collection; AC, CK and SBD undertook data analysis; GKI and AC wrote the manuscript and all authors commented on it.

A. S. Y. Chan · G. K. Isbister · C. M. J. Kirkpatrick · S. B. Duffull
School of Pharmacy, University of Queensland,
Brisbane, Australia

G. K. Isbister
Menzies School of Health Research, Charles Darwin University,
Darwin, Australia

S. B. Duffull
School of Pharmacy, University of Otago,
Dunedin, New Zealand

G. K. Isbister (✉)
Department of Clinical Toxicology, Newcastle Mater Hospital,
Edith St, Waratah, NSW 2298, Australia
e-mail: Geoffrey.isbister@menzies.edu.au

The current International Conference of Harmonisation (ICH) guidelines stipulate that cautionary labelling should be used on new drugs if QT prolongation occurs for more than 5 ms, as this denotes some risk of TdP [2]. Drugs that prolong the QT interval for more that 20 ms are considered proarrhythmic and are generally not marketed [2]. These are likely to be the upper bounds of proven safety rather than the lower bound of proven risk.

Despite this increasing focus on QT prolongation by the pharmaceutical industry and drug regulatory agencies, there remains little information available to clinicians to guide them in risk assessment of a drug-induced prolonged QT [1]. Although small changes of 5 and 20 ms may be relevant to the introduction of a new drug into the population (i.e. 20 ms in a susceptible person with mild undiagnosed congenital long QT syndrome), these criteria are less helpful for the clinician making a risk assessment for individual patients.

Unfortunately, there is no universally accepted criterion to identify the level of QT duration that is associated with a clinically significant increased TdP risk. Current methods include QT intervals corrected for heart rate (HR). These are termed QTc when corrected to a heart rate of 60 bpm. Various formulae exist for the calculation of QTc and Bazett's formula ($QTcB = QT/RR^{1/2}$) is the most commonly used in clinical practice. However, this formula is known to be less reliable for values of heart rate that differ significantly from 60 bpm and poses a problem for physicians in examining a patients' risk of developing TdP in cases of extreme bradycardia and more commonly with tachycardia [3–6]. A recent study by our group has evaluated a different approach based on pre-clinical study data by Fossa et al. using a QT nomogram [7, 8].

The aim of this study was to assess physicians' interpretation of electrocardiogram (ECG) values in reference to risk of TdP through the use of a survey.

Methods

A survey was developed to elucidate physicians' perception of risk of QT prolongation (Appendix). Institutional ethics approval was obtained from the University of Queensland. The survey was in three parts: part one recorded the demographics, including specialty and experience (number of years after receiving specialty qualification); part two asked about use of HR correction formulae, what values of QT/QTc physicians believed confer a significant risk and whether this risk was modified by the presence of bradycardia/tachycardia (more or less cautious); part three asked the physician to rate the risk of developing TdP given various ECG values (see Appendix). Risk was given on a 5-point Likert scale where a value of 1 indicates "low risk" and 5 "high risk". Six different sets of ECG values were provided. ECG values were provided in HR, absolute QT interval and corrected QT interval according to Bazett's formula, the most commonly used in clinical practice.

Two sets of low risk and two sets of high risk values according to the QT nomogram were chosen. Another two sets of values were chosen which displayed "borderline" risk as the QT-HR pair was on the border of the QT nomogram line (see Fig. 1) [7]. When estimating the risk at the defined points using Bazett's correction factor, a different risk assessment results. The prediction was used whereby a QTc<440 ms denotes low risk and a QTc> 500 ms indicates high risk. Thus two of the survey points are considered low risk, one point medium risk and three points high risk. Differentiation between the predictive qualities of the two methods, Bazett's and the QT nomogram, were identified using three survey points. Survey points 2 and 6 are of borderline risk according to the QT nomogram, but equate to high risk according to the Bazett correction factor with QTc of 502 ms and 517 ms, respectively. Survey point 4 was high risk according to the

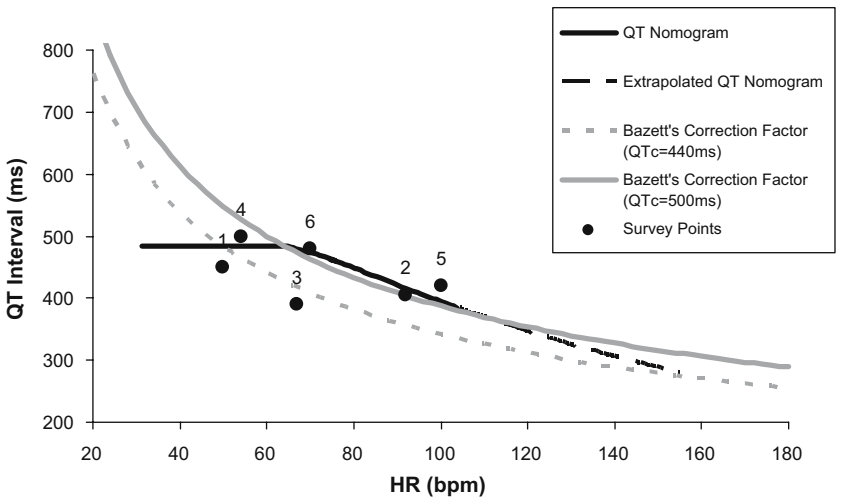

Fig. 1 Plot of survey points (QT versus HR) with Bazett's correction factor (440 ms and 500 ms) and the QT nomogram line included [7]

QT nomogram, but only considered medium risk by Bazett's (QTc=476 ms). The differences in the risk prediction by the two methods, identifiable using the survey points, will allow for discrimination of physicians' interpretation of risk.

A pilot survey was initially given to 10 clinical toxicologists and 15 emergency physicians to determine the appropriateness of the questions and survey layout. Data were collated and analysed from the pilot survey and modifications were made to improve the readability of the survey, but no major changes were made to the content. The surveys were then mailed to all emergency physicians via the Australasian College for Emergency Medicine in mid-January 2006 and included all Fellows of the Australasian College for Emergency Medicine (FACEMs). Each survey was sent with an accompanying cover letter and reply paid envelope. A repeat mailing of the survey was sent in mid-February 2006. In all cases the respondents were unidentified. Data from returned surveys were entered into a Microsoft Excel spreadsheet.

Data analysis

Parts one and two were summarized using descriptive statistics. For part three, histograms of the distribution of responses (low to high risk) were produced for each set of ECG values. These plots of response distributions were compared to predicted distributions (see Fig. 2): the null distribution (where every point was given uniform risk weighting), a risk weighting according to Bazett's formula and a risk weighting according to the QT nomogram line [7]. The null distribution assumed that the physician response to the risk for each QT-HR combination was uniform from low risk (1) to high risk (5). The distribution according to Bazett's correction formula was created by using QTc=440 ms and QTc=500 ms as cut-off values. QTc values of more than 500 ms were given a high risk rating, those falling between 440 and 500 were medium risk and those values less than 440 were considered low risk. The QT nomogram line was used to predict the last set of responses. Values of QT-HR falling above the line were considered high risk, those on the line were given medium risk and the values which fell below the line were considered low risk. A visual analysis between the distribution of the survey results and the predicted distributions was then performed.

Results

Seven hundred and twenty surveys were sent in each mailing and a total of 249 surveys were returned (34.6%).

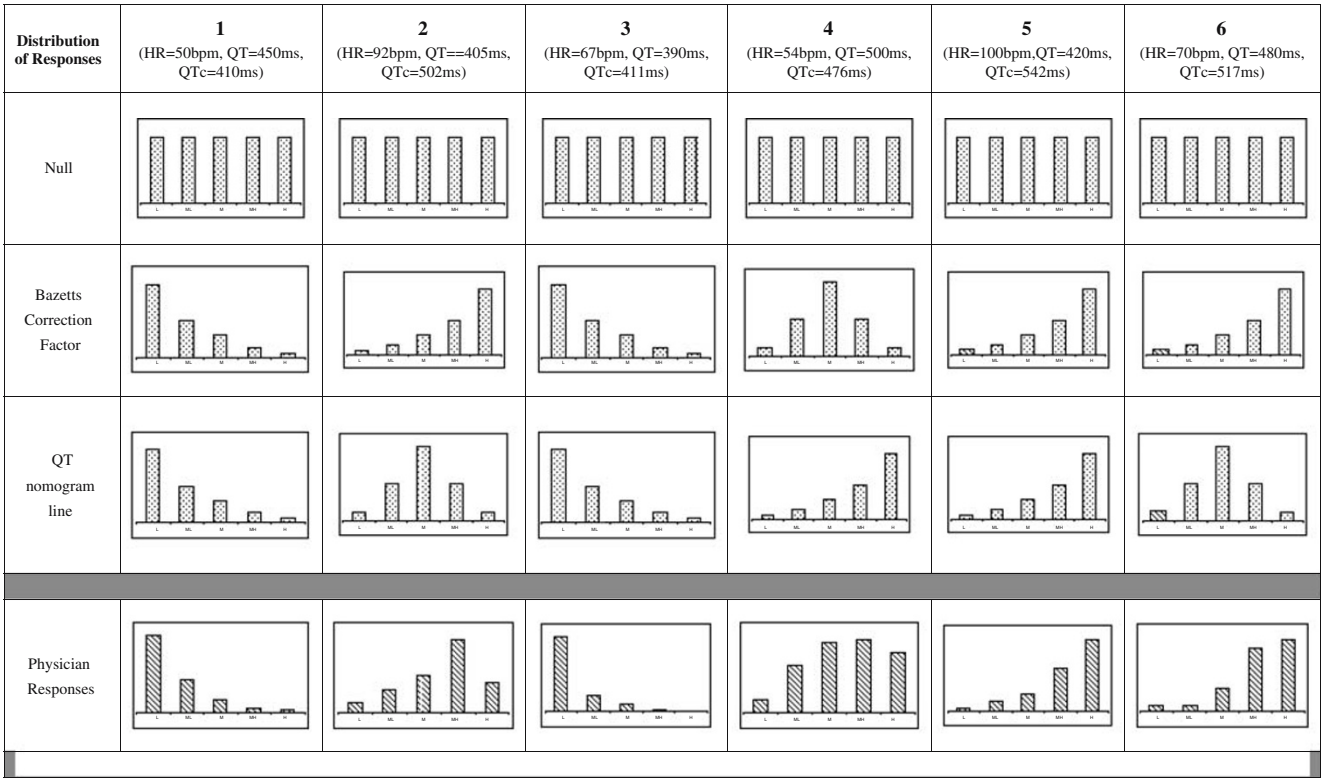

Fig. 2 Predicted responses for the null distribution, Bazett's correction factor and the QT nomogram compared to the observed distribution of responses

In addition to emergency physicians, a few responses were received from FACEM clinical toxicologists (2.8%) and FACEM intensive care specialists (1.6%) (Table 1). The majority of respondents had more than 5 years of experience (75.5%) in their specialty.

In assessing risk of TdP, 89.9% of emergency physicians answered that they use a correction factor and 87.5% answered that they believed that a HR correction was a better predictor than absolute QT. The median QTc at which emergency physicians expressed concern about the development of TdP was 450 ms [interquartile range (IQR): 440–500; range: 400–1,000 ms]. For those who chose to use absolute QT interval, the median was 500 ms (IQR: 475–520; range: 440–1,000 ms). When asked whether bradycardia (<50 bpm) would change their risk assessment the respondents were divided with equal numbers of responses for "no change" and "more caution". With tachycardia the majority responded "no change".

In part three respondents were asked to rate the risk of developing TdP given certain ECG values. The distribution of responses where the emergency physicians' responses differed from the predicted response or when the QT nomogram predicted response differed from the Bazett prediction can be seen in Fig. 2 (columns 2, 4 and 6). For survey points 1, 3 and 5, the distribution of responses were found to be as per the predictions from the Bazett's correction factor and also the QT nomogram.

At survey point 2 (HR=92, QT=405, Fig. 2, column 2), the physicians assessed a generally medium to high risk, halfway between the medium risk predicted by the QT nomogram and high risk predicted by Bazett's HR correction formula. At survey point 4 (HR=54 bpm, QT=500 ms, Fig. 2, column 4), the responses form a relatively uniform distribution with a risk assessment of between medium-low to high, where the QT nomogram predicts a high risk of developing TdP as opposed to Bazett's formula which predicts a medium risk. Only including respondents who do not use HR correction formulae did not change this (data not shown). At survey point 6 (HR=70, QT=480, Fig. 2, column 6), the distribution of responses represented high risk which was similar to that of Bazett's correction factor, but not the QT nomogram which predicted a medium risk.

Discussion

Emergency physicians were found to mainly rely on Bazett's correction formula for their method of TdP risk assessment with responses similar to those predicted for Bazett's for four of the six points. Of the other two points one had tachycardia and the observed responses were less cautious than Bazett's. The other (point 4) was more concerning because this point is in a region of QT-HR associated with TdP (Fig. 1) and the observed responses were "undecided" with no trend in the distribution of responses.

Survey point 4 gives the most insight into current approaches to risk assessment in practicing clinicians. This point is in a region where a number of cases of TdP have been published and is above the QT nomogram line [7]. However, Bazett's formula only predicts medium risk, which has been shown to be the major problem with Bazett's formula [7]. Emergency physicians were generally undecided for this point with the number of responses at medium-low, medium, medium-high and high risk being almost identical. Although physicians appear to follow Bazett's formula there is a mixed response for this point with bradycardia, probably with some staying with Bazett's formula while others factor in the additional component of bradycardia. This is supported by the divided response on the influence of bradycardia and whether assessment should be more cautious or not.

It is concerning that no previous studies have investigated physician risk assessment of QT prolongation for TdP. Possibly this is because there are no clearly defined guidelines or methods for determining whether patients are at risk. The commonest approaches use the QTc values, but numerous cut-offs for "at risk" are defined in the literature [1, 4, 9]. There appears to be a huge gap between research being undertaken on the QT by drug regulatory agencies and the pharmaceutical industry and clinicians who are being increasingly faced with drug-induced prolonged QT in individual patients. There also appears to be little translation of the last few decades of research done on the QT interval into clinical practice. For example, despite Bazett's formula being recognized as problematic outside the HR range of 60–100 bpm [10], it is the most common

Table 1 Demographics of survey respondents

	Emergency	Intensive care	Toxicology	Other	Totals
Registrar	1	–	2	1	4
<5 years	54	2	1	-	57
5–10 years	87	2	1	–	90
>10 years	93	1	3	1	98
Totals	235	5	7	2	249

formula used in clinical practice and is calculated routinely by commercial electrocardiograph machines [3, 4]. This is supported by our survey, which demonstrates that 90% of emergency physicians use a HR correction formula, and the risk assessment is similar to Bazett's for most points and there is confusion for a point clearly associated with TdP.

In summary, physicians in an emergency care setting appeared to rely on corrected QT interval, typically using Bazett's formula, for TdP risk assessment. Interpretation of risk was more varied in the presence of concurrent bradycardia, but not tachycardia. There is a need for easily accessible methods for determining risk assessment in patients with a prolonged QT and guidelines to assist in the implementation of such methods.

Limitations

A limitation of the study was that only emergency physicians were surveyed. We did not include cardiologists, intensive care physicians or general practitioners because of difficulties with obtaining mailing lists. However, emergency physicians are the group most likely and most commonly to be making risk assessments about drug-induced prolonged QT, because most patients with drug overdoses or acute drug reactions present to an emergency department and many with other causes of drug-induced QT prolongation will get referred.

Responses were generally from physicians with more than 5 years experience in the field, which may have also affected the results because they may represent a more traditional approach to the assessment of the QT interval. However, there did not appear to be a difference between respondents with less than and more than 5 years experience.

The response rate to the survey was only 35% despite it being sent out on two occasions. This may introduce some biases into the results if only emergency physicians who felt comfortable with risk assessment of QT prolongation responded.

Conflict of interest statement Nil

Funding Geoff Isbister is funded by an NHMRC Clinical Career Development Award ID300785.

Appendix: Survey

Survey – Risk Evaluation of QT Prolongation and Torsade de Pointes

Please indicate your specialty.

☐ Cardiology ☐ Emergency ☐ Intensive Care

Please indicate your experience in this specialty.

☐ Registrar ☐ < 5 years ☐ 5-10 years ☐ >10 years

(1) When assessing QT length (QT prolongation) would you use a correction factor?

☐ Yes ☐ No

(2) Is QT_C or absolute QT a better predictor of torsade de pointes?

☐ QT_C ☐ Absolute QT

(3a) At what value of QT_C/absolute QT would you be concerned about the possibility of TdP?

☐ QT_C Value:_____
☐ Absolute QT

(3b) On a scale of 1 to 5, how would you change your assessment of risk for your answer for question 3(a) if:

LC= Less Cautious SLC=Slightly Less Cautious NC=No Change SMC=Slightly More Cautious MC=More Cautious

	LC	*SLC*	*NC*	*SMC*	*MC*
	1	2	3	4	5
the patient had bradycardia. (HR<50)	☐	☐	☐	☐	☐
the patient had tachycardia. (HR>100)	☐	☐	☐	☐	☐

(4) Given the following ECG values, how would you rate the risk for development of torsade de pointes. *QTc is calculated using Bazett s formula.*

L= Low ML=Medium to Low M=Medium MH=Medium to High H=High

	L	*ML*	*M*	*MH*	*H*
	1	2	3	4	5
HR= 50, QT=450, QT_C=410	☐	☐	☐	☐	☐
HR= 92, QT=405, QT_C=502	☐	☐	☐	☐	☐
HR= 67, QT=390 , QT_C=411	☐	☐	☐	☐	☐
HR= 54, QT=500, QT_C=476	☐	☐	☐	☐	☐
HR=100, QT=420, QT_C=542	☐	☐	☐	☐	☐
HR= 70, QT=480, QT_C=517	☐	☐	☐	☐	☐

Thank you for completing the questionnaire.

References

1. Shah RR (2005) Drugs, QTc interval prolongation and final ICH E14 guideline: an important milestone with challenges ahead. Drug Saf 28:1009–1028
2. ICH Harmonised Tripartite Guideline (2005) The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. Cited 22 Aug 2006
3. Batchvarov VN, Ghuran A, Smetana P et al (2002) QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol 282:H2356-H2363
4. Malik M, Camm AJ (2001) Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. Drug Saf 24:323–351
5. Luo S, Michler K, Johnston P, Macfarlane PW (2004) A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol 37 (Suppl):81–90
6. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ (2002) Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 87:220–228
7. Chan A, Isbister GK, Kirkpatrick CM, Dufful SB (2007) Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM 100:609–615
8. Fossa AA, Wisialowski T, Magnano A et al (2005) 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. J Pharmacol Exp Ther 312:1–11
9. Moss AJ (1999) The QT interval and torsade de pointes. Drug Saf 21(Suppl)1:5–10
10. Hodges M (1997) Rate correction of the QT interval. Card Electrophysiol Rev 3:360–363