ARTICLE

Risk assessment of drug-induced QT prolongation

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SUMMARY

Drugs can cause prolongation of the QT interval, alone or in combination, potentially leading to fatal arrhythmias such as torsades de pointes.

When prescribing drugs that prolong the QT interval, the balance of benefit versus harm should always be considered.

Readouts from automated ECG machines are unreliable. The QT interval should be measured manually.

Changes in heart rate influence the absolute QT interval. Heart rate correction formulae are inaccurate, particularly for fast and slow heart rates.

The QT nomogram, a plot of QT interval versus heart rate, can be used as a risk assessment tool to detect an abnormal QT interval.

Introduction

Over the last two decades, intense research has improved our knowledge of the mechanisms and risks of drug-induced QT prolongation.[1] Most of this research has been conducted by the pharmaceutical industry and has arisen following market withdrawals of medicines that caused torsades de pointes arrhythmia, such as cisapride and some non-sedating antihistamines. Little of this information has flowed to clinicians and there remains a paucity of clinically relevant data to guide patient management.

The QT interval is the duration between the start of the Q wave and the end of the T wave on an ECG (Fig. 1). Methods of measuring the QT interval, correcting for heart rate and determining what is an abnormal interval are outdated and provide a poor risk assessment for patients.[1] Confusion also remains about the safety and level of risk with many drugs that have been associated with QT prolongation.

Drug regulatory bodies and pharmaceutical companies have placed restrictions on some drugs which appear to have a low risk of torsades de pointes (for example quetiapine). Conversely, other drugs with clear evidence of risk have the same level of restriction (for example amisulpride).

Drugs implicated in QT prolongation and torsades de pointes

Most drugs known to cause QT prolongation block the rapid component of the delayed rectifier potassium channel. This prolongs the action potential and lengthens the QT interval (Fig. 2).[2] Delayed ventricular repolarisation will lead to early after-depolarisations, which can result in re-entrant pathways or focal activity and torsades de pointes (Fig. 3).

Many drugs have been implicated in QT prolongation, but the actual risk of this occurring is unclear in most cases. Table 1 lists common drugs which cause QT prolongation and have been associated with torsades de pointes. Other sources provide longer lists of drugs, but in many cases the evidence for QT prolongation is a single case report in which only the QTc interval (QT interval corrected for heart rate) is long. In some cases, this is due to over-correction with Bazett's formula. To complicate matters there are some drugs, such as amiodarone, that cause QT prolongation, but rarely, if ever, cause torsades de pointes.

For some drugs, such as sotalol, amisulpride and citalopram or escitalopram, there is a lot of information on the risk of QT prolongation and torsades de pointes (Fig. 4). Conversely, for other drugs such as quetiapine, venlafaxine and risperidone there is a large amount of normal QT interval data to support a very low risk of torsades des pointes.[1]

Drug interactions

QT prolongation may be due to multiple factors or more than one drug. It is important to consider both pharmacodynamic and pharmacokinetic drug interactions when prescribing drugs.

Concomitant use of two drugs that prolong the QT interval, such as escitalopram and sotalol, will

increase the risk of QT prolongation and torsades de pointes due to a pharmacodynamic interaction.

Pharmacokinetic interactions can also lead to QT prolongation, such as erythromycin inhibiting the metabolism of cisapride via cytochrome P450 (CYP) 3A4.[3]

Other factors that increase the QT interval

Congenital long QT syndromes and a number of acquired conditions cause QT prolongation. Congenital cardiac channelopathies include autosomal dominant Romano-Ward syndrome and the rarer Jervell and Lange-Neilsen syndrome.[4]

Genetics account for a large amount of the variability in the QT interval in healthy individuals.[1,5] This may explain why some individuals are more predisposed to QT prolongation. Physiological factors also influence the QT interval. Female sex and older age are associated with longer QT intervals, and there is diurnal variation in the QT interval.[6]

QT prolongation is also associated with a number of pathological conditions, including electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), cardiac ischaemia, cardiomyopathies, hypothyroidism and hypoglycaemia.[1]

When is the QT interval long or abnormal?

Many different cut-offs have been suggested to determine if the QT interval is abnormal. A QT or QTc interval greater than 500 millisecond (msec) is sometimes regarded as abnormal, but this is problematic for patients with tachycardia and it is unclear which heart rate correction formula should be used.

One study of Holter measurements in healthy volunteers showed that the 95% confidence limit of the average 24-hour QTc interval was 440 msec in men and 460 msec in women (450 msec overall).[7] Lower cut-offs, such as 440 msec, are too sensitive and a considerable number of patients would require evaluation (outpatient) or monitoring (inpatient) because they have a QT interval greater than 440 msec, when actually they have no risk of torsades de pointes (false positives). These cut-offs are difficult to apply in clinical practice, and a sensitive and specific cut-off that incorporates heart rate correction is required.

Measuring the QT interval

There continues to be debate over the best method for measuring the QT interval. Standard ECG machines

Fig. 1 **ECG showing the different intervals during a heart beat**

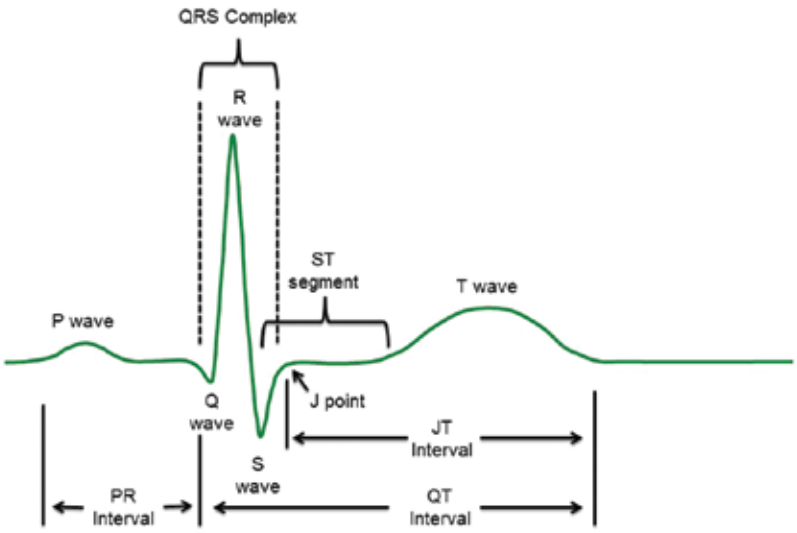

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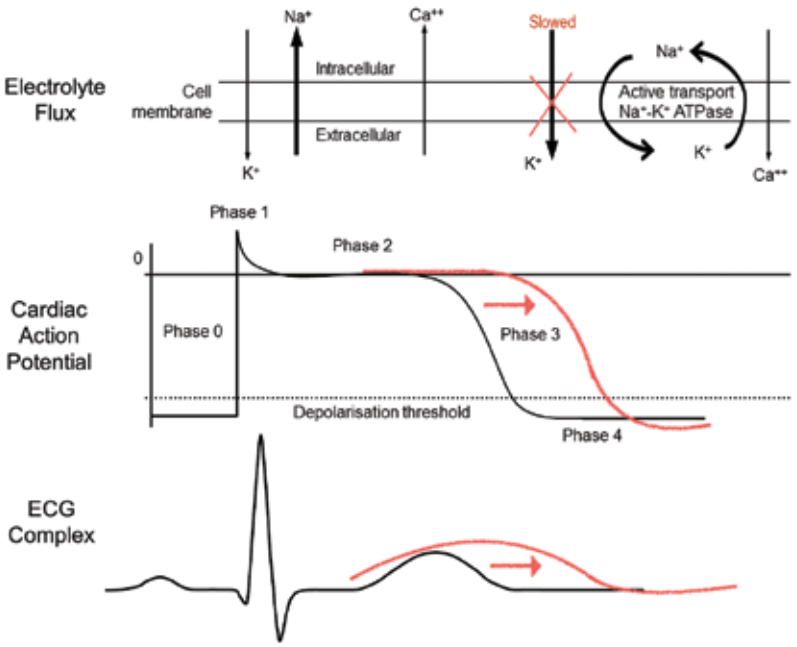
Fig. 2 **QT prolongation showing electrolyte fluxes, action potentials and ECG phases 0–4 on the electrocardiogram**



phase 0 rapid depolarisation due to rapid sodium influx
phase 1 initial repolarisation due to potassium and chloride efflux
phase 2 the plateau where there is a balance of potassium efflux and calcium influx
phase 3 rapid repolarisation due to potassium efflux
phase 4 the resting membrane potential before the next depolarisation
——— indicates QT prolongation and its associated pathophysiology

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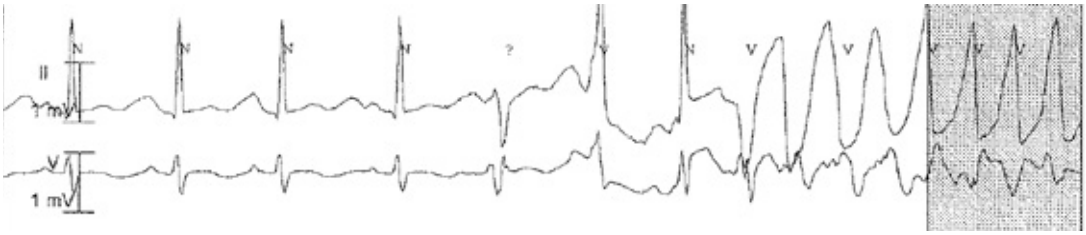
Fig. 3 **Torsades de pointes on a rhythm strip**



ECG tracing of leads II and V in a patient with a prolonged QT and then onset of torsades de pointes showing the R on T phenomena
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Table 1 **Drugs that have been associated with a high risk of QT prolongation and torsades de pointes**

Antidepressants	selective serotonin reuptake inhibitors: citalopram, escitalopram
	moclobemide
	tricyclic antidepressants†
	lithium‡
Antihistamines	loratadine
	diphenhydramine
Antimicrobials	ciprofloxacin, moxifloxacin
	erythromycin, clarithromycin
	fluconazole, voriconazole
	pentamidine
Antipsychotics	amisulpride
	chlorpromazine
	haloperidol
	ziprasidone
Cardiac drugs	amiodarone‡
	sotalol
	disopyramide
Other drugs	cisapride
	ondansetron, dolasetron
	methadone
	arsenic
	chloroquine

† Although QT prolongation is traditionally associated with tricyclic antidepressants, this is almost always due to QRS widening without lengthening of the JT interval (QT interval minus the QRS duration)

‡ Drugs where there appears to be QT prolongation, but a much lower risk of torsades de pointes

A longer list of drugs associated with QT prolongation can be found at http://crediblemeds.org, but many may only have a low risk of torsades de pointes and possibly no risk

can be unreliable and taking the automated reading from the ECG machine in clinical practice may be inaccurate, particularly in patients with a long QT. The best method is to use continuous digital 12-lead Holter recordings, extracting multiple 12-lead ECGs and using a combination of computer algorithms and onscreen manual measurement with overlapped views and calipers.[8] However, this is not possible in clinical practice and manual methods using standard ECGs have been shown to be reproducible[9] and close to digital Holter methods.[8] A simple manual method is presented in Table 2.[1] The QT interval is measured from the beginning of the Q wave to the end of the T wave (Fig. 1). Although it requires measuring the QT interval in six leads and taking the median, this can be done in a few minutes or less with practice, and its value and importance make this worthwhile.

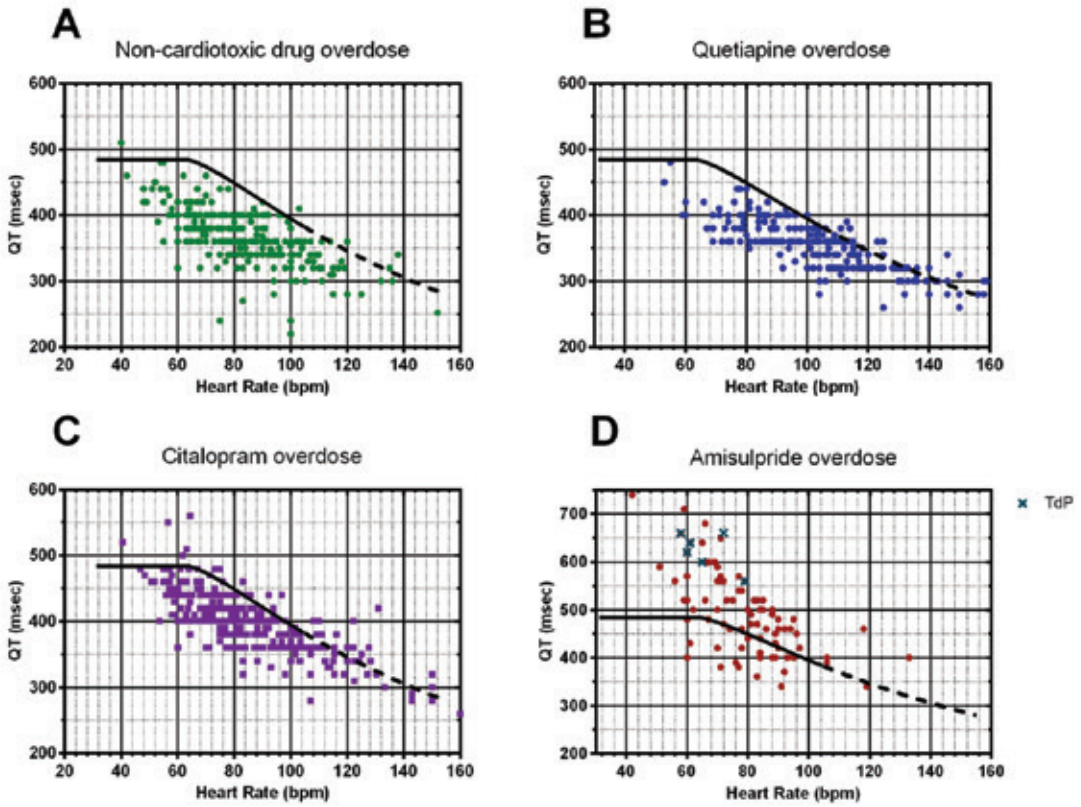
Heart rate correction

Changes in heart rate influence the absolute QT interval and therefore influence assessment of whether it is long.[6] Many heart rate formulae exist and the most commonly used is Bazett's formula. However, this is really only useful for a narrow range of heart rates and significantly over-corrects for fast heart rates and under-corrects for slow heart rates.[1,10] Fridericia's formula is better, but is still problematic for fast heart rates. Over-correction for fast heart rates is a major problem with overdoses that cause tachycardia, such as sympathomimetics (including selective noradrenergic reuptake inhibitors such as venlafaxine) and anticholinergic drugs (including drugs for which this is not their primary effect like antihistamines, antidepressants and antipsychotics such as quetiapine).[11]

QT nomogram: a risk assessment tool

An effective alternative to heart rate correction is to not correct the QT interval using a formula but

Fig. 4 **QT nomograms for various drugs in patients after overdose**



Examples of plots of QT vs heart rate for:

A non-cardiotoxic drugs (temazepam, oxazepam, diazepam, paracetamol)

B quetiapine

C citalopram

D amisulpride

• is the QT–HR pair from the ECG for an individual patient who did not develop torsades de pointes

x is the QT–HR pair from the ECG for a patient who developed torsades de pointes

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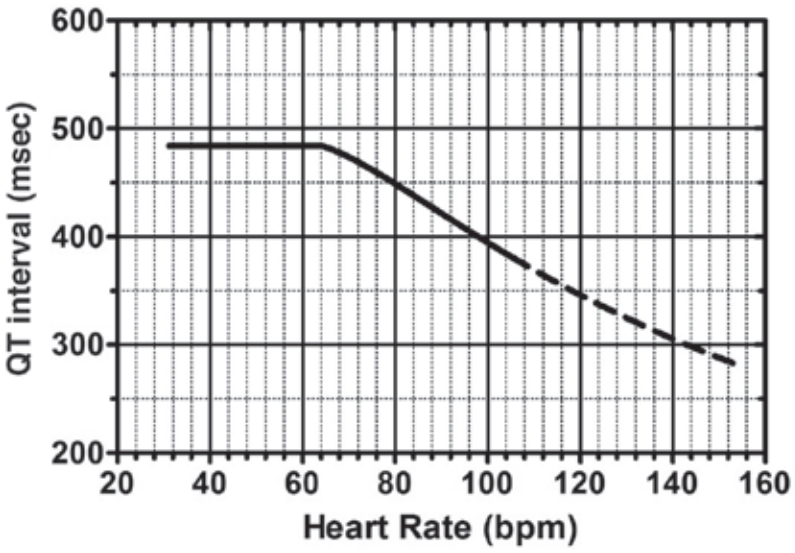
instead plot the QT interval against the heart rate on the QT nomogram (Fig. 5).[12,13] This approach incorporates heart rate correction and risk assessment in the same process. It also avoids the issue of which cut-off to use.

To use the nomogram the QT interval is measured manually (as described in Table 2) and then plotted against the heart rate. If the QT–heart rate pair is above the cut-off line then the QT is prolonged.

For patients with drug-induced torsades de pointes, a retrospective evaluation of the QT nomogram found it had a sensitivity of 97% and a specificity of 99%. This was compared to using Bazett's formula and cut-offs of QTc=440 msec (sensitivity 99%, specificity 67%) and QTc=500 msec (sensitivity 94%, specificity 97%).[12] There is some evidence that the further above the line the QT–heart rate pair is, the greater the risk of torsades de pointes. However, other factors such as hypokalaemia or individual (genetic) susceptibility may also play a role.

In addition to its role of providing a risk assessment tool for individuals, the QT nomogram has been used in a number of toxicology studies to provide a risk assessment for particular drugs in overdose (see Fig. 4).

Fig. 5 **QT nomogram**



——— solid line indicates heart rates that are not tachycardic[12]

– – – – dashed line is extrapolated to allow assessment of faster heart rates

The QT nomogram is a plot of the QT interval versus the heart rate. A QT–heart rate pair above the line is associated with an increased risk of torsades de pointes.[13]

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Table 2 **Step by step approach for using the QT nomogram to determine if a QT interval is abnormal** [1]

Steps	Approach
Obtain ECG	The QT interval length is manually measured in 6 leads on the ECG, usually: • 3 limb leads: I, II and aVF • 3 chest leads: V2, V4 and V6
Measure the absolute QT interval	The QT interval is manually measured from the start of the Q wave until the T wave returns to baseline On a standard ECG at 25 mm per second this is best done by counting the number of small squares • 5 small squares = 200 milliseconds • 8 small squares = 320 milliseconds Do not use the ECG automated readout or QTc
Calculate the median QT	The median is the middle number of all 6 measured QT intervals when arranged in numerical order If there are 2 middle numbers, e.g. position 3 and 4, then the average of these 2 measurements is the median
Determine heart rate	The heart rate is the average measurement derived from the RR interval on the 12 lead ECG and is most accurate when read from an automated ECG
Plot on QT nomogram	The median QT length is then plotted against the heart rate on the QT nomogram (Fig. 4). If the QT–heart rate pair is above the line on the nomogram it is a prolonged QT and there is an increased risk of torsades de pointes.

RR the distance from one R wave to the next R wave Modified from reference 1

Recommendation

Clinicians from a variety of specialities are faced with assessing whether a QT interval is abnormal. A recommended approach to the measurement of the QT interval, heart rate correction and determining if the QT is abnormal is shown in Table 2.

In addition to assessing a single QT–heart rate pair on a nomogram, it is important to consider the known risk of the drug involved and whether the patient has an underlying abnormal QT interval. This may be difficult to determine, but if old ECGs can be obtained this will provide a useful comparison.

Before prescribing a drug that causes QT prolongation and torsades de pointes, it is essential to undertake a baseline assessment. A reasonable minimum would be a single baseline ECG, but in situations where the risk is high or there are other risk factors, taking several measurements at different times of the day or a Holter recording will provide a more accurate assessment. This initial assessment establishes if the patient has an abnormal QT interval 'off' the drug which would contraindicate the use of a QT-prolonging drug. If the patient is commenced on the drug, they require serial ECGs during treatment to check for QT prolongation. It is important to avoid other drugs known to cause QT prolongation as well as preventing other causes of QT prolongation such as electrolyte abnormalities. ◀

Conflict of interest: none declared

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