Management of prolonged QT interval and torsades de pointes in the intoxicated patient

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ABSTRACT

Many drugs can significantly influence cardiac repolarisation causing an increased duration of this repolarisation phase, challenging the repolarisation reserve. This may set the stage for life-threatening ventricular arrhythmias such as torsades de pointes (TdP). TdP generally occurs in conjunction with a prolonged QT interval (QT) on the electrocardiogram. The Dutch Poisons Information Centre (NVIC) often receives information requests about drugs that can influence the QT already at therapeutic dosages. Drug-induced QT prolongation is dose dependent and hence can be particularly pronounced in overdose situations. Also, additional risk factors for the development of life-threatening arrhythmias are often present in intoxicated patients.

This review focuses on identification and management of drug-intoxicated patients who are at risk for a reduction in their repolarisation reserve, measured by their QT interval. The QT interval is strongly dependent on heart rate, which has led to the introduction of different methods to adjust the QT interval, i.e. the QTc. Bazett’s formula, which has been used for decades, lacks accuracy concerning QTc calculation at higher and lower heart rates, situations often relevant when dealing with intoxicated patients. Additionally, we highlight drugs with QT-prolonging potential that are commonly associated with an overdose setting in the Netherlands. Finally, standard treatment options specifically pointed toward the intoxicated patient at risk of QT prolongation and TdP will be discussed.

KEYWORDS

Intoxication, Torsades de Pointes, treatment, QT prolongation, QTc and Bazett’s formula

INTRODUCTION

In drug overdose, a prolonged QT interval (QT) on the electrocardiogram (ECG) is an important diagnostic tool to assess whether an individual is at risk of developing life-threatening ventricular arrhythmias.1,2 The QT can be measured on the standard ECG from the beginning of the QRS complex to the end of the T wave, thus representing the complete ventricular depolarisation and repolarisation phase.3 At the cellular level, the electrocardiographically prolonged QT interval is primarily based on a reduction of net repolarising ion channel currents resulting in a prolonged repolarisation. This, in turn, sets the stage for oscillations of the membrane potential, which can give rise to additional depolarisations during the repolarisation phase, known as early afterdepolarisations (EADs).4 If the amplitude of these EADs reaches a critical threshold, and occurs in a sufficiently large myocardial area, ectopic ventricular beats can ensue. The most common ventricular arrhythmia that can arise under these circumstances of a prolonged QT interval is torsades de pointes (TdP).5

TdP is defined as a polymorphic ventricular tachycardia exhibiting a ‘twisting of the points’ pattern around the isoelectric line of the ECG.6,7 Generally, TdP episodes are self-terminating but can also degenerate into ventricular fibrillation and thus sudden cardiac death.

The pathophysiological mechanisms underlying and favouring the development of TdP are complex and not completely unravelled. It has been shown that several disturbances in different flows of ions can be involved. Na+ (INa), K+ (IKs, IKr) and Ca2+ (ICa) currents have all been implicated.8-11 Interference of ion channels that mediate these currents, either through gain or loss of function, or regulation, has been shown to prolong the duration of the repolarisation phase.12
In the majority of cases, the mechanism by which drugs can cause a prolonged QT is due to the interaction with the human Ether-a-go-go Related Gene (hERG) subunit of the rapidly activated delayed rectifier K+ channel. This interaction blocks the inward K+ current (I_Kr), prolonging the repolarisation phase and thus increasing the likelihood of EADs.25-27

This review focuses on the identification, individual risk stratification and management of intoxicated patients (patients who have been misdosed or overdosed, intentionally or unintentionally). Depending on the situation, this subset of patients can be at particular risk for QT prolongation and subsequent malignant arrhythmias such as TdP. We review several methods recommended to determine the rate-corrected QT (QTc) for different heart rates. Additionally, we highlight which potential QT-prolonging drugs are commonly associated with an overdose setting in the Netherlands. Finally, the current advocated treatment of QT prolongation and TdP in intoxicated patients will be outlined.

RISK FACTORS AND DRUGS THAT CAN AFFECT THE QT INTERVAL

Risk factors
A number of risk factors have been described that raise the likelihood of QT prolongation, increasing the chance to develop life-threatening ventricular arrhythmias.

The most common acquired pathological conditions that are associated with QT prolongation are electrolyte disturbances. Particularly hypokalaemia2,3,15 hypomagnesaemia2,4,16-18 and hypocalcaemia1,15 can alter cellular ionic homeostasis and thus cause electrical dysbalance and promote arrhythmias.

Moreover, a number of different pathological conditions may strongly influence cardiac repolarisation and QT prolongation, i.e., bradycardia, left ventricular hypertrophy, congestive heart failure, cardiomyopathies, myocardial ischaemia and hypertension.21

Additionally, a very important risk factor for the development of QT prolongation is the genetic background. This genetic influence can range from an increased likelihood of QT prolongation, increasing the chance to develop life-threatening ventricular arrhythmias.

This review focuses on the identification, individual risk stratification and management of intoxicated patients (patients who have been misdosed or overdosed, intentionally or unintentionally). Depending on the situation, this subset of patients can be at particular risk for QT prolongation and subsequent malignant arrhythmias such as TdP. We review several methods recommended to determine the rate-corrected QT (QTc) for different heart rates. Additionally, we highlight which potential QT-prolonging drugs are commonly associated with an overdose setting in the Netherlands. Finally, the current advocated treatment of QT prolongation and TdP in intoxicated patients will be outlined.

MEASURING THE QT INTERVAL

QT interval
A number of manual and automated approaches to measure the QT interval have been described in the literature. Nevertheless, some pitfalls in determining the ‘correct’ QT interval remain. Most experts agree that computerised measurements of QT and corrections for heart rate (QTc) are not sufficiently accurate.30-33 Manual determination of the QT also has inherent shortcomings, i.e., identifying the onset of the Q wave, and especially the end of the T wave, may be subject to considerable misinterpretation and intra- or inter-observer variability.30-35 Postuma et al. confirmed this variability, yet showed that with clear sources available that list drugs that are associated with prolonged QT. A drug list often used in literature is www.crediblemeds.org (previously www.torsades.org). This online inventory of drugs with potential QT-prolonging properties places drugs in three different risk categories for TdP. Currently 136 different drugs are listed on this website. To give insight into which drugs are commonly associated with intoxications, a ranking was made of the number of information requests concerning these types of drugs to the Dutch Poisons Information Centre in 2012 (table 1). Unfortunately, European data are not available; nevertheless, we expect that the drugs summarised in table 1 reflect the European situation.

### Table 1. Top 10 information requests at the Dutch Poisons Information Centre regarding intoxications with QT-prolonging drugs

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug (TdP risk grade)*</th>
<th># Information requests in 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quetiapine (2)</td>
<td>939</td>
</tr>
<tr>
<td>2</td>
<td>Citalopram (1)</td>
<td>387</td>
</tr>
<tr>
<td>3</td>
<td>Promethazine (2)</td>
<td>374</td>
</tr>
<tr>
<td>4</td>
<td>Venlafaxine (2)</td>
<td>317</td>
</tr>
<tr>
<td>5</td>
<td>Mirtazapine (2)</td>
<td>312</td>
</tr>
<tr>
<td>6</td>
<td>Paroxetine (1)</td>
<td>263</td>
</tr>
<tr>
<td>7</td>
<td>Olanzapine (2)</td>
<td>260</td>
</tr>
<tr>
<td>8</td>
<td>Fluoxetine (1)</td>
<td>229</td>
</tr>
<tr>
<td>9</td>
<td>Risperidone (2)</td>
<td>208</td>
</tr>
<tr>
<td>10</td>
<td>Sertraline (3)</td>
<td>195</td>
</tr>
</tbody>
</table>

*Risk grades as allocated by www.crediblemeds.org. (i) Risk for TdP: substantial evidence supports the conclusion that these drugs, at therapeutic levels, can prolong the QT interval and can have a risk of TdP in some patients. (2) Possible risk for TdP: substantial evidence supports the conclusion that these drugs, at therapeutic levels, can cause QT prolongation but there is insufficient evidence at this time that they have a risk of causing TdP. (3) Conditional risk for TdP: substantial evidence supports the conclusion that these drugs can prolong QT and therefore have a risk of TdP, but only under certain known conditions (e.g. excessive dose, drug interaction, etc.).

Drugs associated with prolonged QT
Many different drugs can cause QT prolongation, some already at regular therapeutic dosages and others particularly in an overdose setting. There are several
instructions the QT interval can be calculated manually in a very accurate way (figure 1A, C). Figure 1 provides two examples of manual approaches that have proven to give reliable and reproducible measurements of the QT interval; with some practice they take only 1-2 minutes (figures 1A and 1B). A third and quick option in cases of emergency is suggested in Goldfrank’s toxicological emergencies, where only the bipolar limb lead that best shows the end of the T wave is measured and averaged over 3 to 5 beats.

**QT interval correction for heart rate**

The QT interval importantly depends on heart rate. The interval is prolonged at slower heart rates and shortens as the heart rate increases. Already in the 1920s, Henry Cuthbert Bazett developed a formula to correct for this heart rate dependence and introduced what is known as the corrected QT (QTc). Yet, it is well known that this formula tends to overcorrect at a faster heart rate while undercorrecting at low heart rates. This leads to a tendency to be too conservative at high heart rates, while undercorrecting at low heart rates.

**Table 2. Studies comparing different heart rate correction formulae**

<table>
<thead>
<tr>
<th>Subjects studied</th>
<th># Patients</th>
<th>Range of HR (bpm)</th>
<th>Formulae tested</th>
<th>Recommended formulae</th>
<th>Method of uncorrected QT measurement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>10 000</td>
<td>40-125</td>
<td>Bazett, Fridericia, Framingham, Hodges</td>
<td>M: HR &lt; 100: Fridericia HR &gt; 100: Hodges F: HR &lt; 100 Hodges, HR &gt; 100 Fredericia ALL HR &lt; 60 Fredericia HR &gt; 60 Hodges</td>
<td>Automatic (an algorithm reporting the ‘true’ longest interval from multiple leads excluding clear outliers)</td>
<td>Luo et al. 2004</td>
</tr>
<tr>
<td>TdP patients</td>
<td>129</td>
<td>30-160</td>
<td>Bazett, Isbister nomogram</td>
<td>M: n.s. F: n.s. ALL: Isbister nomogram</td>
<td>Median of six ECG leads</td>
<td>Chan et al. 2007</td>
</tr>
<tr>
<td>Pacemaker candidates without significant heart disease</td>
<td>41</td>
<td>60-100</td>
<td>Bazett, Fridericia, Sagie-Framingham, Hodges – Karjalainen nomogram</td>
<td>M: n.s. F: n.s. ALL: Hodges</td>
<td>Max QT in any of 12 leads</td>
<td>Chilakadis et al. 2010</td>
</tr>
<tr>
<td>Drug intoxicated patients (with &amp; without QT prolonging properties)</td>
<td>541</td>
<td>30-150</td>
<td>Bazett – Isbister nomogram</td>
<td>M: n.s. F: n.s. ALL: Isbister nomogram</td>
<td>Median of six ECG leads</td>
<td>Waring et al. 2010</td>
</tr>
<tr>
<td>Dual-chamber device recipients with &amp; without QT prolongation</td>
<td>123</td>
<td>53-100</td>
<td>Bazett, Fridericia, Sagie-Framingham, Hodges – Karjalainen nomogram</td>
<td>M: n.s. F: n.s. ALL: Hodges</td>
<td>Max QT in any of 12 leads</td>
<td>Chilakadis et al. 2010</td>
</tr>
</tbody>
</table>

bpm = beats per minute; F = female; HR = heart rate; M = male; n.s. = not specified; TdP = torsade de pointes.
This tendency to underestimate the QT interval at low heart rates is particularly treacherous as the risk of TdP increases when the heart rate decreases.\textsuperscript{35-45,49-50} Nevertheless, to date Bazett’s formula is routinely used in automated ECG measurement to determine the corrected QT interval (QTc) for heart rate. It should be noted that Bazett’s formula adequately corrects for heart rates varying between 50 and 90 beats per minute (bpm).\textsuperscript{31,33,34}

Trying to compensate for the shortcomings of Bazett’s formula a number of alternative formulae have been introduced. Already in 2009 the American Heart Association, in conjunction with the Council of Clinical Cardiology and the Hearth Rhythm Society, recommended to use a different formula which is less influenced by heart rate than the Bazett’s formula.\textsuperscript{33} No consensus about which formula is best has been reached, however. A literature search about this topic in the last decade shows that the formulae of Hodges and Fredericia and the QT nomogram of Isbister have been suggested as better alternatives for the Bazett’s formula (table 2). These alternatives are especially valuable for patients with bradycardia or tachycardia, as differences ranging from 30 to >100 msec can be calculated depending on the heart rate of a patient (figure 2).

The largest study concerning this topic in the last decade was performed in 2004 and involved 10,000 ECG recordings.\textsuperscript{46} The authors compared several correction formulae by calculating the dependence of the calculated recordings on heart rate. Depending on sex and heart rate, they found different formulae superior to Bazett’s formula (where the smallest correlation between heart rate and QTC was deemed best) (table 2). A potential confounding factor in this study is that the measurements were all performed automatically. Other studies in smaller patient groups and with manual ECG reading in patients, suffering from different heart conditions, confirmed that Hodges’ formula and Fredericia’s formula are superior to Bazett’s formula.\textsuperscript{43-54,55}

Isbister et al. decided not to use a direct correction for heart rate anymore, but to plot the heart rate against the uncorrected QT interval in a nomogram. The studies they performed using this approach have shown good specificity and sensitivity with regard to predicting patients at risk for developing TdP at various heart rates. The nomogram performed particularly well at low heart rates, making this method of heart rate correction particularly valuable in bradycardic situations when the risk for TdP is increased.\textsuperscript{41,55-57}

In all, several strategies have been developed to measure the QT and to determine the QTc, a true golden standard has not generally been accepted, however. It therefore seems wise to follow the FDA’s recommendation when analysing a patient who might be at risk for QT prolongation, which is to conduct a ‘thorough QT study’ in vulnerable patients (www.fda.gov). This means that an automated measurement with Bazett’s correction for heart rate is not sufficient for patients at risk. The aforementioned approaches for QT and QTc measurements are all valuable tools for this thorough QT study.

**Figure 2. Comparison of three heart rate correcting formulae based on two values of uncorrected QT (350 ms and 530 ms)**

Bazett’s correcting formula clearly gives higher values of QTc at faster heart rates and lower values with slower heart rates. These differences can lead to different risk stratifications.

**RISK ASSESSMENT OF THE INTOXICATED PATIENT FOR TDP**

The drugs listed on crediblemeds.org have all been implicated in QT prolongation to different degrees. High-risk drugs, such as erythromycin, methadone and haloperidol,\textsuperscript{58,59} exhibit clear QT prolongation already at therapeutic concentrations. Drugs in a lower risk category, such as ciprofloxacin and fluconazole,\textsuperscript{60-64} are likely to require additional risk factors, such as electrolyte disturbances, drug interactions, overdosage or bradycardia before resulting in QT prolongation and possible TdP. These risk factors are more likely to be present in the intoxicated patient (especially when a patient has been exposed to large amounts or combinations of drugs). Additionally, with virtually all QT-prolonging drugs the risk of prolonged QT times, and possible TdP, increases as a function of plasma drug concentration.\textsuperscript{65} For citalopram, for instance, a clear relationship exists between the dose and the risk of QT prolongation and TdP.\textsuperscript{55,56} However, for many drugs there is limited information on the risk for significant QT prolongation and TdP. Hence, cut-off values of acceptable...
QTc times are used in the clinic, or the QT nomogram of Isbister et al. is used to determine the risk for TdP. Depending on the source, a QTc >450 or 470 for males and >470 or 480 for females has been correlated to an increased risk of TdP and sudden death.\textsuperscript{40,46,66-67} Additionally, data from congenital LQT studies and case reports and small series of patients with drug-induced TdP show that a QTc of >500 ms is associated with a 2- to 3- fold higher risk of TdP.\textsuperscript{20,50,68-70}

**Treatment of the Intoxicated Patient with Prolonged QTc**

Correction of metabolic and electrolyte disturbances: particularly Mg\textsuperscript{2+} and K\textsuperscript{+}

Correction of electrolyte disturbances, bradycardia, acidemia, hypotension and hypoxia is of the utmost importance (figure 4).\textsuperscript{11,71,72} Particularly hypomagnesaemia should be avoided as Mg\textsuperscript{2+} can suppress EADs. A Mg\textsuperscript{2+} level of 1-2 mMol/l is recommended (physiological levels: 0.7-1 mMol/l).

With regard to potassium levels it is recommended to maintain serum potassium between 4.5 and 5 mMol/l (physiological levels: 3.8-5.5 mMol/l) as this shortens the QT interval.\textsuperscript{73,74}

Raising extra-cellular Na\textsuperscript{+} and pH through bicarbonate treatment with drugs exhibiting Na\textsuperscript{+} channel blocking properties

If the intoxication involves a drug with Na\textsuperscript{+} channel blocking properties (e.g. tricyclic antidepressants, cocaine, IA and IC antiarrhythmics, or antipsychotic drugs) bicarbonate therapy can be used to lessen the degree of sodium channel blockade through increased extra-cellular sodium (figure 4).\textsuperscript{11,77,78}

Saline appears to be less effective than sodium bicarbonate because some QRS-prolonging drugs are proposed to have a pH-dependent binding to the sodium channels, with less extensive binding at higher pH. The recommended pH level with bicarbonate treatment is between 7.50 and 7.55.\textsuperscript{11,71} Using bicarbonate treatment with other drug exposures that do not affect Na\textsuperscript{+} channels is contraindicated, due to the inherent risk of inducing hypokalaemia with this treatment.

Replacing slow kinetic sodium block with fast kinetic antiarrhythmic agent lidocaine treatment with drugs exhibiting Na\textsuperscript{+} channel blocking properties

Lidocaine is an antiarrhythmic drug that also blocks cardiac Na\textsuperscript{+} channels. It therefore seems counterproductive to treat adverse events of other Na\textsuperscript{+} blocking drugs with this drug. Yet the pharmacological properties of lidocaine are such that it displays rapid on and off kinetics.\textsuperscript{79} To replace Na\textsuperscript{+} blocking drugs that have slower kinetics with lidocaine has been shown to be beneficial for antipsychotics, class 1A and 1C antiarrhythmics, sotalol and cocaine.\textsuperscript{11,72} Additionally, in poisonings with tricyclic antidepressants (TCA) a beneficial effect of lidocaine has been reported, especially with TCAs displaying particularly slow on- and off-kinetics such as amitriptyline and nortriptyline.\textsuperscript{71,80} The use of lidocaine in TCA poisoning is only recommended, however, when the cardiotoxicity is refractory to bicarbonate treatment.

Intravenous lipid emulsion (ILE) therapy or veno-arterial corporal membrane oxygenation (VA-ECMO) in non-responsive patients

If an intoxicated patient does not respond to the above-mentioned therapeutic measures, alternatives should be considered. Intravenous lipid emulsion (ILE) therapy can be considered, if the drug has lipophillic properties. If all fails veno-arterial corporal membrane oxygenation (VA-ECMO) should be considered. These treatments have been shown to be effective in several case series with severely intoxicated patients.\textsuperscript{81-84} It is important to realise that in most intoxicated patients the support of VA-ECMO is usually needed for a short time only.
Treatment of torsades de pointes
A patient who progresses into TdP should be treated with 1-2 g (4-8 mmol) IV magnesium. Intravenous magnesium can suppress episodes of TdP without necessarily shortening QT. This effect can take place even if the levels of magnesium are normal. However, serum Mg²⁺ should be monitored as magnesium toxicity can occur when concentrations exceed 3.0 mMol/l. On the other hand, whenever episodes of TdP persist, it may be necessary to repeat these magnesium infusions. If potassium repletion and magnesium supplementation is not sufficient to end the TdP, then cardiac pacing can be considered to increase the heart rate. Transvenous atrial or ventricular pacing at rates >70 bpm are recommended. Additionally, treatment with isoprenaline has been suggested in drug-induced QT prolongation and TdP, provided that ischaemia or hypo-hypertension are not present. Again, VA-ECMO should be considered as a salvage therapy.

CONCLUSION
This review set out to give additional insights into the identification (figure 3) and management (figure 4) of the intoxicated patient who might be at risk for QT prolongation and possible TdP. It has become clear that several factors need to be taken into account when doing this (figure 3). The imperative steps are firstly determining which QTc-prolonging drugs (or combinations) are involved, and secondly whether additional risk factors are present. Thirdly, the correct measurement of QT (figure 1) and QTc interval is imperative, especially for patients with bradycardia and tachycardia. For example; a bradycardic patient with a heart rate of 40 bpm and QT of 530 msec will have a QTc with Bazett’s correction of 433 ms, Hodges correction 495 ms and Fredericia 464 ms (figure 2). Both Hodges and Fredericia, and also the nomogram of Isbister, will mark this patient as increased risk, while Bazett’s correction would not.
The fourth step is to implement monitoring and treatment if necessary, focussing mostly on correcting acidemia, hypotension, hypoxia, bradycardia and electrolyte disturbances.
In all, TdP is a life-threatening rhythm disturbance that can lead to sudden death. Identifying and managing intoxicated patients who are at risk for developing TdP is vital. Such patients need close monitoring in an intensive care facility until the intoxicating drug has been eliminated from the body and further risks eliminated. Using the correct method to determine the QTc and correction of electrolyte and metabolic disturbances are critical parts of this process.

**Figure 4. Recommended treatment approach for intoxicated patients with a prolonged QT**

Monitor & correct metabolic abnormalities!

- **Avoid!**
  - class 1A, 1B anti-arrhythmics
  - β-andrenergic antagonists
  - Ca²⁺ channel blockers

- **Preferred supra-therapeutic electrolyte levels:**
  - Mg²⁺ level: 1-2 mMol/l
  - K⁺ level: 4.5-5 mMol/l

- **Intoxication with TCA, 1A or IC anti-arrhythmic, cocaine or antipsychotic?**

  YES
  - Bicarbonate treatment (beware of hypokalaemia)
  - Intoxication with TCA, 1A or IC anti-arrhythmic, sotalol, cocaine or antipsychotic?

  NO
  - No bicarbonate treatment

- **Insufficient response?**

  Consider lidocaïne as 2nd line anti-arrhythmic
  - Consider:
    - ILE for lipophillic compounds
    - VA-ECMO

ECMO = extra corporal membrane oxygenation; ILE = intravenous lipid emulsion; TCA = tricyclic antidepressants.
ACKNOWLEDGEMENTS

Dr. A. van Velzen for NVIC database information, information specialists at NVIC for information and data gathering, Dr. K. Sjauw Department of Cardiology, AMC for helpful discussions.

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APRIL 2014, VOL. 72, NO 3


