Netherlands
The Journal of Medicine

REVIEW

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

A.A. Kan[1]*, D.W. de Lange[1,2,3], D.W. Donker[2], J. Meulenbelt[1,2,4]

[1]National Poisons Information Centre (NVIC), University Medical Centre Utrecht, Utrecht, the Netherlands, Department of [2]Intensive Care Medicine and [3]Emergency Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands, [4]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands, *corresponding author: a.a.kan@umcutrecht.nl

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^+ (I_{Na}), K^+ (I_{Ks}, I_{Kr}) and Ca^{2+} (I_{Ca}) currents have all been implicated.[3,8-11] 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.[13,14]

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 hypokalaemia[1,2,15] hypomagnesaemia[2,16-18] and hypocalcaemia[15,19] 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.[20]

Additionally, a very important risk factor for the development of QT prolongation is the genetic background. This genetic influence can range from an increased susceptibility to develop prolonged QT in response to medication (often polygenetic and dormant),[21,22] to the relatively rare monogenetic types of congenital long-QT syndromes.[23-25]

Other contributing factors are female gender,[26,27] and increasing age.[26,28,29]

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 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.

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.[33-36] Postuma *et al.* confirmed this variability, yet showed that with clear

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

Rank	Drug (TdP risk grade)*	# Information requests in 2012
1	Quetiapine (2)	939
2	Citalopram (1)	387
3	Promethazine (2)	374
4	Venlafaxine (2)	337
5	Mirtazapine (2)	312
6	Paroxetine (3)	263
7	Olanzapine (2)	260
8	Fluoxetine (3)	229
9	Risperidone (2)	208
10	Sertraline (3)	195

***Risk grades as allocated by www.crediblemeds.org. (1) 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.).**

instructions the QT interval can be calculated manually in a very accurate way (*figure 1A, C*).[37] *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.[11]

QT interval correction for heart rate

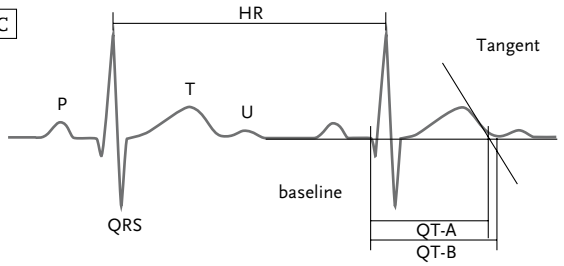
The QT interval importantly depends on heart rate. The interval is prolonged at slower heart rates and shortens as the heart rate increases. Already in the 1920s, Henry Cuthbert Bazett developed a formula to correct for this heart rate dependence and introduced what is known as the corrected QT (QTc).[38] Yet, it is well known that this formula tends to overcorrect at a faster heart rate while undercorrecting at low heart rates.[39-48] This leads to a tendency to be too conservative at high heart rates, while under-correcting at low heart rates.

Figure 1. *Two methods of manual QT interval determination*

A **Method 1**
- Measurement taken from the Q-wave to the intersection of the tangent to the steepest slope of the last limb of the T-wave and the baseline
- Read lead II or V5 if lead II is unclear
- Take the mean of three measurements

B **Method 2**
- Measurement taken from the Q-wave to the point where the T-wave returns to the baseline
- QT measured in 6 leads total: 3 limb leads and 3 chest leads
- Take the median of the six individual leads

C



Examples of the manual measurement as recommended by A) Viskin et al. 2005 (36) and Postema et al. 2008 (37) or B) by Isbister & Page 2012. (57) C) Illustration of these two methods (adapted from Postema et al. 2008 (37) with permission of Elsevier).

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

Subjects studied	# Patients	Range of HR (bpm)	Formulae tested	Recommended formulae	Method of uncorrected QT measurement	Reference
Healthy subjects	10 000	40-125	- Bazett, - Fridericia - Framingham - Hodges	**M:** HR < 100: Fridericia HR > 100: Hodges **F:** HR < 100 Hodges, HR > 100 Fredericia **All:** HR < 60 Fredericia HR > 60 Hodges	Automatic (an algorithm reporting the 'true' longest interval from multiple leads excluding clear outliers)	Luo *et al.* 2004
TdP patients	129	30-160	- Bazett - Isbister nomogram	**M:** n.s. **F**: n.s. **All**: Isbister nomogram	Median of six ECG leads	Chan *et al* 2007
Pacemaker candidates without significant heart disease	41	60-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2010
Drug intoxicated patients (with & without QT- prolonging properties)	541	30-150	- Bazett – Isbister nomogram	**M**: n.s. **F**: n.s. **All**: Isbister nomogram	Median of six ECG leads	Waring *et al.* 2010
L-QT patients (TdP versus non-TdP)	29	47-79	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram – Rautaharju	**M**: Hodges **F**: Hodges **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2012
Bundle branch block patients	71	60-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram – Rautaharju	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2012
Dual-chamber device recipients with & without QT prolongation	123	52-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2010

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.[33,41,43,49,50] 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 (bmp).[11,51,52]

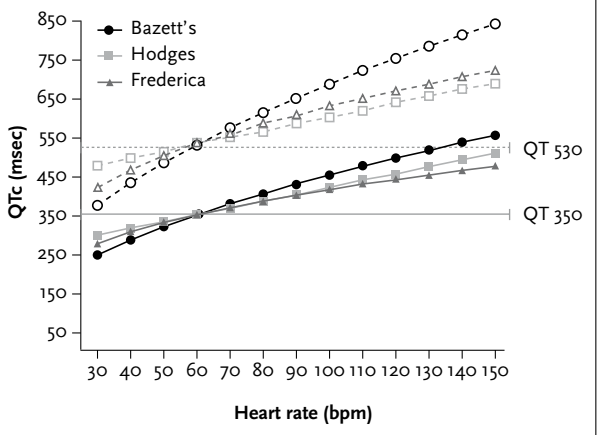
Trying to compensate for the shortcomings of Bazett's formula a number of alternative formulae have been introduced. Already in 2009 the American Heart Association, in conjunction with the Council of Clinical Cardiology and the Hearth Rhythm Society, recommended to use a different formula which is less influenced by heart rate than the Bazett's formula.[53] 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.[46] The authors compared several correction formulae by calculating the dependence of the calculated QTc by these formulae 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 Fridericia's formula are superior to Bazett's formula.[42,3,54,55]

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.[41,56,57]

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,[58,59] exhibit clear QT prolongation already at therapeutic concentrations. Drugs in a lower risk category, such as ciprofloxacin and fluconazole,[60-62] 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.[20] For citalopram, for instance, a clear relationship exists between the dose and the risk of QT prolongation and TdP.[63-65] However, for many drugs there is limited information on the risk for significant QT prolongation and TdP. Hence, cut-off values of acceptable

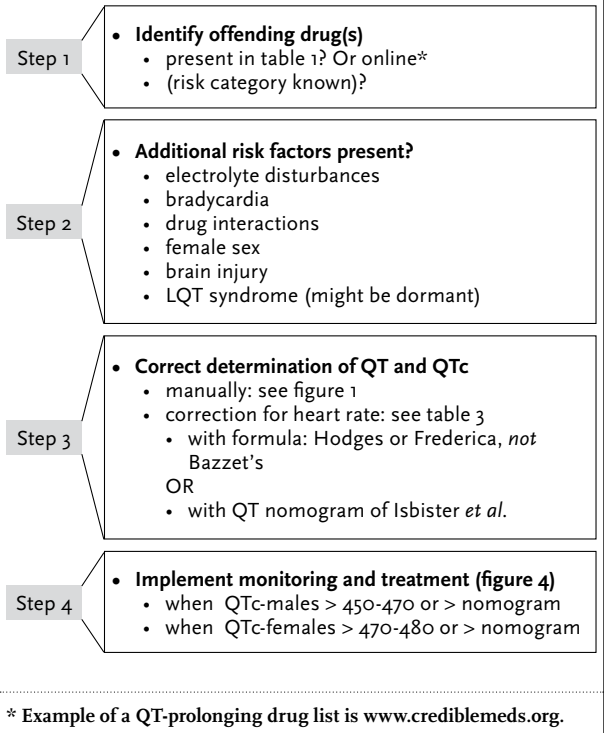
QTc times are used in the clinic, or the QT nomogram of Isbister *et al*. is used to determine the risk for TdP.
Depending on the source, a QTc >450 or 470 for males and >470 or 480 for females has been correlated to an increased risk of TdP and sudden death.[20,46,66,67] Additionally, data from congenital 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.[20,50,68-70]

TREATMENT OF THE INTOXICATED PATIENT WITH PROLONGED QTC

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

Correction of electrolyte disturbances, bradycardia, acidaemia, hypotension and hypoxia is of the utmost importance (*figure 4*).[11,71,72]
Particularly hypomagnesaemia should be avoided as Mg^{2+} can suppress EADs. A Mg^{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.[73,74]

Figure 3. *Recommended approach when encountering an intoxicated patient who might be at risk for QT prolongation and TdP*



*** Example of a QT-prolonging drug list is www.crediblemeds.org.**

Raising extra-cellular Na^+ and pH through bicarbonate treatment with drugs exhibiting Na^+ channel blocking properties

If the intoxication involves a drug with Na^+ 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*).[11,75-78]

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.[11,71] Using bicarbonate treatment with other drug exposures that do not affect Na^+ channels is contraindicated, due to the inherent the risk of inducing hypokalaemia with this treatment.

Replacing slow kinetic sodium block with fast kinetic antiarrhythmic agent lidocaine treatment with drugs exhibiting Na^+ channel blocking properties

Lidocaine is an antiarrhythmic drug that also blocks cardiac Na^+ channels. It therefore seems counterproductive to treat adverse events of other Na^+ blocking drugs with this drug. Yet the pharmacological properties of lidocaine are such that it displays rapid on and off kinetics.[79] To replace Na^+ blocking drugs that have slower kinetics with lidocaine has been shown to be beneficial for antipsychotics, class 1A and 1C antiarrhythmic drugs, sotalol and cocaine.[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.[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.[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.[85-87] However, serum Mg^{2+} should be monitored as magnesium toxicity can occur when concentrations exceed 3.0. mMol/l.[88] On the other hand, whenever episodes of TdP persist, it may be necessary to repeat these magnesium infusions.[89] If potassium repletion and magnesium supplementation is not sufficient to end the TdP, then cardiac pacing can be considered to increase the heart rate.[86,87] Transvenous atrial or ventricular pacing at rates >70 bpm are recommended.[90] Additionally, treatment with isoprenaline has been suggested in drug-induced QT prolongation and TdP, provided that ischaemia or hypo-hypertension are not present.[86,87] Again, VA-ECMO should be considered as a salvage therapy.[81,82]

CONCLUSION

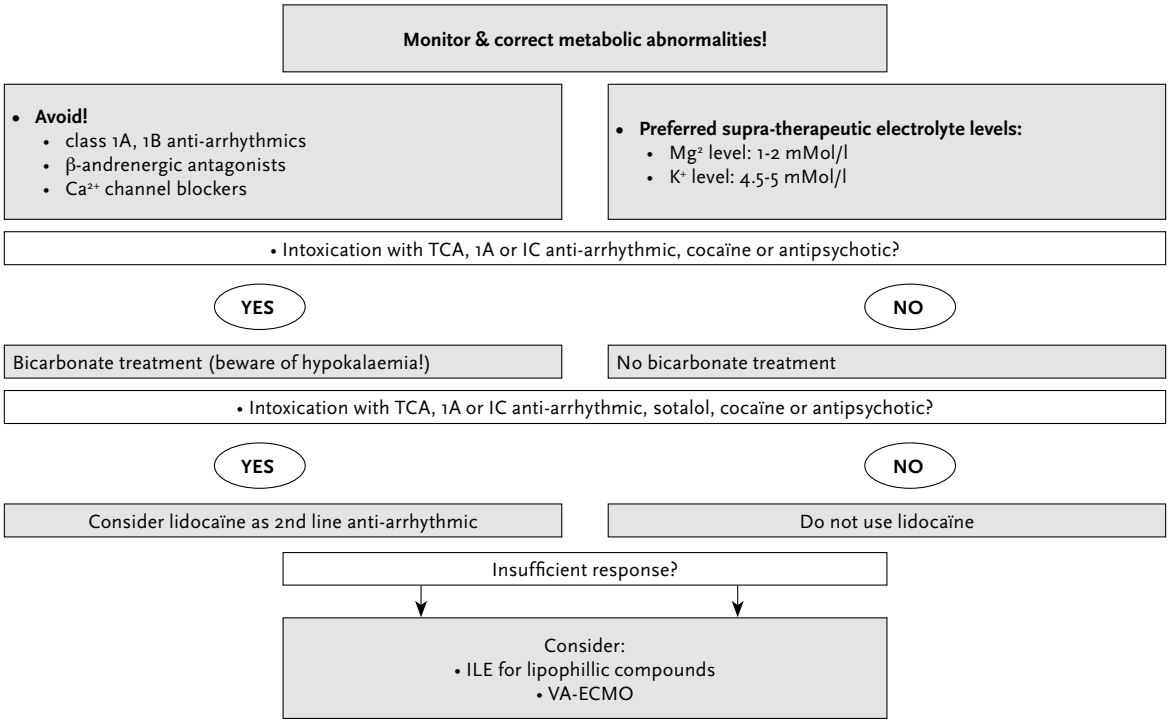
This review set out to give additional insights into the identification (*figure 3*) and management (*figure 4*) of the intoxicated patient who might be at risk for QT prolongation and possible TdP.

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 acidaemia, 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*



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.

REFERENCES

1. Chvilicek JP, Hurlbert BJ, Hill GE. Diuretic-induced hypokalaemia inducing torsades de pointes. Can J Anaesth. 1995;42:1137-9.
2. Foglia PE, Bettinelli A, Tosetto C, et al. Cardiac work up in primary renal hypokalaemia-hypomagnesaemia (Gitelman syndrome). Nephrol Dial Transplant. 2004;19:1398-402.
3. Bayes de Luna A. The Electrophysiological Basis of the ECG: From Cell Electrophysiology to the human ECG. Clinical Electrocardiography: A textbook. Fourth Edition ed. John Wiley & Sons, Ltd.; 2012. p. 34-53.
4. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. Trends Pharmacol Sci. 2003;24:619-25.
5. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. Curr Opin Cardiol. 2007;22:39-43.
6. Dessertenne F. [Ventricular tachycardia with 2 variable opposing foci]. Arch Mal Coeur Vaiss. 1966;59:263-72.
7. Smith WM, Gallagher JJ. "Les torsades de pointes": an unusual ventricular arrhythmia. Ann Intern Med. 1980;93:578-84.
8. Bailie DS, Inoue H, Kaseda S, Ben-David J, Zipes DP. Magnesium suppression of early afterdepolarizations and ventricular tachyarrhythmias induced by cesium in dogs. Circulation. 1988;77:1395-402.
9. Holstege CP, Eldridge DL, Rowden AK. ECG manifestations: the poisoned patient. Emerg Med Clin North Am. 2006;24:159-77, vii.
10. Lionte C, Bologa C, Sorodoc L. Toxic and Drug-Induced Changes of the Electrocardiogram. In: Millis RM, editor. Advances in Electrocardiograms-Clinical Applications. InTech; 2012. p. 271-96.
11. Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE. Goldfrank's Toxicologic Emergencies. 9 ed. New York, NY, USA: McGraw-Hill; 2011.
12. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. Pharmacol Rev. 2010;62:760-81
13. Redfern WS, Carlsson L, Davis AS, et al. 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 1;58:32-45.
14. Zareba W. Drug induced QT prolongation. Cardiol J. 2007;14:523-33.
15. 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;23:1378-86.
16. Keren A, Tzivoni D. Torsades de pointes: prevention and therapy. Cardiovasc Drugs Ther. 1991;5:509-13.
17. Roden DM, Iansmith DH. Effects of low potassium or magnesium concentrations on isolated cardiac tissue. Am J Med. 1987;82:18-23.
18. White CM, Xie J, Chow MS, Kluger J. Prophylactic magnesium to decrease the arrhythmogenic potential of class III antiarrhythmic agents in a rabbit model. Pharmacotherapy. 1999;19:635-40.
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;73:523-6.
20. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2010;55:934-47.
21. Newton-Cheh C, Larson MG, Corey DC, et al. 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;2:277-84.
22. Newton-Cheh C, Eijgelsheim M, Rice KM, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. Nat Genet. 2009;41:399-406.
23. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104:569-80.
24. Roberts JD, Gollob MH. The genetic and clinical features of cardiac channelopathies. Future Cardiol. 2010;6:491-506.
25. van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. Br J Clin Pharmacol. 2010;70:16-23.
26. 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;27:76-83.
27. 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;18:1000-6.
28. 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;32:326-31.
29. Mayuga KA, Thattassery E, Taneja T, et al. Circadian and gender effects on repolarization in healthy adults: a study using harmonic regression analysis. Ann Noninvasive Electrocardiol. 2010;15:3-10.
30. Berling I, Isbister GK, Calver L, Clunas S. Digital Holter measurement of QT prolongation in ziprasidone overdose. Clin Toxicol (Phila). 2011;49:694-6.
31. 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.
32. Kautzner J. QT interval measurements. Card Electrophysiol Rev. 2002;6:273-7.
33. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. Drug Saf. 2001;24:323-51.
34. LaPointe NM, Al-Khatib SM, Kramer JM, Califf RM. Knowledge deficits related to the QT interval could affect patient safety. Ann Noninvasive Electrocardiol. 2003;8:157-60.
35. Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. Circulation. 2007;115:2613-20.
36. Viskin S, Rosovski U, Sands AJ, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm. 2005;2:569-74.
37. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. Heart Rhythm. 2008;5:1015-8.
38. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353-70.
39. Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JE, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. Pacing Clin Electrophysiol. 1999;22:1397-401.
40. Bai R, Yan GX. Accurate interpretation of the QT interval: a vital task that remains unaccomplished. Heart Rhythm. 2005;2:575-7.
41. Chan A, Isbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM. 2007;100:609-15.
42. Chiladakis J, Kalogeropoulos A, Arvanitis P, Koutsogiannis N, Zagli F, Alexopoulos D. Heart rate-dependence of QTc intervals assessed by different correction methods in patients with normal or prolonged repolarization. Pacing Clin Electrophysiol. 2010;33:553-60.
43. Chiladakis J, Kalogeropoulos A, Zagkli F, Koutsogiannis N, Chouchoulis K, Alexopoulos D. Predicting torsade de pointes in acquired long QT syndrome: optimal identification of critical QT interval prolongation. Cardiology. 2012;122:3-11.
44. Desai M, Li L, Desta Z, Malik M, Flockhart D. Variability of heart rate correction methods for the QT interval. Br J Clin Pharmacol. 2003;55:511-7.
45. Karjalainen J, Viitasalo M, Manttari M, Manninen V. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. J Am Coll Cardiol. 1994;23:1547-53.

46. 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.

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

48. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol. 1992;70:797-801.

49. Roden DM. Early after-depolarizations and torsade de pointes: implications for the control of cardiac arrhythmias by prolonging repolarization. Eur Heart J 1993;14(Suppl H):56-61.

50. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350:1013-22.

51. Hnatkova K, Malik M. "Optimum" formulae for heart rate correction of the QT interval. Pacing Clin Electrophysiol. 1999;22:1683-7.

52. Moss AJ. Long QT Syndrome. JAMA. 2003;289:2041-4.

53. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:982-91.

54. Chiladakis J, Kalogeropoulos A, Arvanitis P, Koutsogiannis N, Zagli F, Alexopoulos D. Preferred QT correction formula for the assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol. 2010;21:905-13.

55. Chiladakis J, Kalogeropoulos A, Koutsogiannis N, et al. Optimal QT/JT interval assessment in patients with complete bundle branch block. Ann Noninvasive Electrocardiol. 2012;17:268-76.

56. 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;70:881-5.

57. Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2012 Nov;%20. doi: 10.1111/bcp.12040.:10.

58. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. 2002;137:501-4.

59. Wilt JL, Minnema AM, Johnson RF, Rosenblum AM. Torsade de pointes associated with the use of intravenous haloperidol. Ann Intern Med. 1993;119:391-4.

60. Haring B, Bauer W. Ciprofloxacin and the risk for cardiac arrhythmias: culprit delicti or watching bystander? Acta Cardiol. 2012;67:351-4.

61. Ibrahim M, Omar B. Ciprofloxacin-induced torsade de pointes. Am J Emerg Med. 2012;30:252-9.

62. Pham CP, de Feiter PW, van der Kuy PH, van Mook WN. Long QTc interval and torsade de pointes caused by fluconazole. Ann Pharmacother. 2006;40:1456-61.

63. Astrom-Lilja C, Odeberg JM, Ekman E, Hagg S. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. Pharmacoepidemiol Drug Saf. 2008;17:587-92.

64. de Gregorio C, Morabito G, Cerrito M, Dattilo G, Oreto G. Citalopram-induced long QT syndrome and torsade de pointes: role for concomitant therapy and disease. Int J Cardiol. 2011;148:226-8.

65. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. Br J Clin Pharmacol. 2006;61:177-90.

66. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013;346: doi: 10.1136/bmj.f288. PMCID: PMC3558546.

67. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006;47:362-7.

68. De Bruin ML, Langendijk PN, Koopmans RP, Wilde AA, Leufkens HG, Hoes AW. In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs. Br J Clin Pharmacol. 2007;63:216-23.

69. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348:1866-74.

70. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. J Am Coll Cardiol. 2007;49:329-37.

71. Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW. Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient. Philadelphia, Pennsylvania, USA: Elsevier Mosby; 2005.

72. Shannon MW, Borron SW, Burns MJ. Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose. 4th ed. Philadelphia, PA, USA: Saunders Elsevier; 2007.

73. Choy AM, Lang CC, Chomsky DM, Rayos GH, Wilson JR, Roden DM. Normalization of acquired QT prolongation in humans by intravenous potassium. Circulation. 1997;96:2149-54.

74. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. Circulation. 1996;93:407-11.

75. Bradberry SM, Thanacoody HK, Watt BE, Thomas SH, Vale JA. Management of the cardiovascular complications of tricyclic antidepressant poisoning: role of sodium bicarbonate. Toxicol Rev. 2005;24:195-204.

76. Hoffman JR, Votey SR, Bayer M, Silver L. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe cyclic antidepressant overdose. Am J Emerg Med. 1993;11:336-41.

77. Hoffman RS. Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside. BJCP. 2010;69:448-57.

78. Newton EH, Shih RD, Hoffman RS. Cyclic antidepressant overdose: a review of current management strategies. Am J Emerg Med. 1994;12:376-9.

79. Clarkson CW, Hondeghem LM. Evidence for a specific receptor site for lidocaine, quinidine, and bupivacaine associated with cardiac sodium channels in guinea pig ventricular myocardium. Circ Res. 1985;56:496-506.

80. Foianini A, Joseph WT, Benowitz N. What is the role of lidocaine or phenytoin in tricyclic antidepressant-induced cardiotoxicity? Clin Toxicol (Phila). 2010;48:325-30.

81. de Lange DW, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. Clin Toxicol (Phila). 2013;51:385-93.

82. Masson R, Colas V, Parienti JJ, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83:1413-7.

83. Presley JD, Chyka PA. Intravenous lipid emulsion to reverse acute drug toxicity in pediatric patients. Ann Pharmacother. 2013;47:735-43.

84. Waring WS. Intravenous lipid administration for drug-induced toxicity: a critical review of the existing data. Expert Rev Clin Pharmacol. 2012;5:437-44.

85. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. Circulation. 1988;77:392-7.

86. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48:e247-e346.

87. Nolan JP, Hazinski MF, Billi JE, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation. 2010t;81 Suppl 1:e1-25. doi: 10.1016/j.resuscitation.2010.08.002.:e1-25.

88. van Dijk I, Meulenbelt J. [Intoxication with magnesium, a 'forgotten' electrolyte]. Ned Tijdschr Geneeskd. 2008;152:1401-5.

89. Banai S, Tzivoni D. Drug therapy for torsade de pointes. J Cardiovasc Electrophysiol. 1993;4:206-10.

90. Pinski SL, Eguia LE, Trohman RG. What is the minimal pacing rate that prevents torsades de pointes? Insights from patients with permanent pacemakers. Pacing Clin Electrophysiol. 2002;25:1612-5.