Evaluation of a QT nomogram for risk assessment after antidepressant overdose

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Overdose with citalopram is associated with QT prolongation and torsades de pointes, whereas this arrhythmia has not been reported after venlafaxine or mirtazapine overdose.
- Uncertainty exists concerning the best means of identifying poisoned patients at greatest risk of arrhythmia, and a nomogram comparing QT and heart rate has recently been proposed based on published cases of torsades de pointes.
- Few data are available concerning the performance of the nomogram in patients that present to hospital after antidepressant overdose.

WHAT THIS STUDY ADDS

- After antidepressant overdose patients had a broad range of heart rate and QT values, which were below the nomogram in 98% of cases (95% confidence interval 96, 99%).
- Citalopram overdose was associated with a higher proportion of patients with QT values above the nomogram than venlafaxine and mirtazapine overdose, especially in those who had low heart rates.
- The nomogram allowed discrimination between the different antidepressant agents and may have a role in predicting arrhythmia in clinical practice.

AIMS

A QT-heart rate nomogram has recently been proposed as a means of identifying patients at risk of torsades de pointes after antidepressant overdose, based on published cases of drug-induced torsades de pointes. The present study sought to examine the performance of the nomogram in patients who ingest an antidepressant overdose but do not develop arrhythmia.

METHODS

A retrospective case control study of patients presenting to hospital after overdose of citalopram, mirtazapine and venlafaxine was carried out. The primary outcome variable was QT higher than the nomogram, and was compared with occurrence of QT_c (QT corrected by Bazett's formula) greater than ≥ 440 ms and QT_c ≥ 500 ms, with comparison between drugs. Data are expressed as proportions in each group with 95% confidence intervals.

RESULTS

There were 858 electrocardiograms from 541 patients. QT was higher than the nomogram in 2.4% (1.4, 4.1%), whereas QT_c was ≥ 440 ms in 23.1% (95% CI 19.8, 26.8%), and QT_c was ≥ 500 ms in 1.1% (0.5, 2.5%). Citalopram overdose was more likely to be associated with QT higher than the nomogram compared with the other agents (difference 7.0%, 95% CI 2.9, 11.9%, $P = 0.001$) and more likely to be associated with QT_c ≥ 440 ms (difference = 11.0%, 95% CI 2.6, 19.0%, $P = 0.013$).

CONCLUSIONS

The QT nomogram was associated with a lower false positive rate than widely accepted QT_c criteria, and allowed detection of different effects of individual drugs. The nomogram offers potential advantages over QT_c criteria and merits further investigation in a clinical setting.

Introduction

Torsades de pointes is an unusual and important adverse effect of a broad range of different drugs. It is thought to be due to blockade of the inward rectifier potassium channel current, which manifests as QT prolongation on an electrocardiogram (ECG) although the relationship between QT prolongation and risk of torsades de pointes is complex [1, 2]. In clinical practice, the QT interval is widely relied upon as a surrogate marker of drug cardiotoxicity and may indicate an increased risk of arrhythmia [3]. QT values are subject to wide inter- and intra-individual variability and are confounded by heart rate, autonomic tone and electrolyte concentrations. The relationship with heart rate is complex, and may be expressed in any individual as the slope of the R-R interval (inverse of heart rate) and QT across a range of heart rate values [4]. This allows QT values to be determined with reference to heart rate whilst taking account of inter-individual differences. This approach may be useful in the setting of a controlled clinical trial, but it is rarely applicable in the context of acute drug overdose because baseline data are lacking.

Generalized formulae attempt to limit the confounding effect of heart rate, for example that of Bazett $QT_c = QT / (R-R)^{1/2}$ and Fridericia $QT_c = QT / (R-R)^{1/3}$ [5]. However, these do not address intra-individual differences and are unreliable at extremes of heart rate. Correction by the Bazett and Fridericia formulae can introduce significant errors in the assessment of drug-induced QT effects [6]. Not surprisingly, ECG data correlate only weakly with the risk of arrhythmia after antidepressant overdose [7]. A QT-heart rate nomogram has recently been proposed [8]. It is based on work by Fossa and colleagues who proposed that a 'cloud' of paired QT and R-R intervals could be plotted, and a 95% reference range constructed to identify values outside the range that might indicate patients at greatest risk of arrhythmia [9]. The nomogram incorporates heart rate rather than R-R interval, and is capable of discriminating between historical reported cases of drug-induced arrhythmia and patients who ingested drugs with no known cardiac effects [8]. The nomogram is sensitive and specific in these groups, and offers the potential advantage of being readily applied in a clinical setting. However, its performance has not been examined in patients who ingest drugs capable of prolonging QT interval but who do not develop arrhythmia. This is a more representative control group to whom the nomogram would be applied in routine clinical practice. Therefore, the present study was designed to compare the performance of the nomogram with established methods of QT assessment in patients who present to hospital after antidepressant overdose but do not develop arrhythmia.

Methods

Data collection

The study involved a retrospective analysis of ECG data collected from patients who attended the Emergency Department due to citalopram, mirtazapine and venlafaxine overdose between 2000 and 2006, as reported elsewhere [10–12]. Standard practice in the Toxicology Unit is that continuous cardiac monitoring is performed if patients have reduced conscious level, persistent tachycardia (>100 beats min^{-1}), or systolic blood pressure <90 mmHg. A 12-lead ECG is performed on admission, and repeated at >6 h after ingestion, and a further ECG if there are any electrocardiographic or haemodynamic effects or suspected cardiac symptoms. Recordings were by a Hewlett Packard device and automated determination of QT interval from the start of the QRS complex to the end of the T-wave (QT_c was derived using Bazett's formula).

Data analyses

The primary outcome variable was QT higher than the Isbister nomogram using a scatterplot of heart rate vs. QT interval [8]. Secondary variables were $QT_c \geq 440$ ms and $QT_c \geq 500$ ms to represent the upper limit of normal values and cut-off for very abnormal values, respectively. Stated quantities ingested were expressed as a multiple of the World Health Organization 'defined daily dose' for citalopram (20 mg), mirtazapine (30 mg) and venlafaxine (100 mg). Data are expressed as proportion and 95% confidence intervals determined by the Wald method, and analyses were performed using MedCalc software v.9.1.0.1 (MedCalc, Mariakerke, Belgium) [13]. Between-group comparisons were made using Mann-Whitney tests and two-tailed Yates' corrected chi-square tests, and P values <0.05 were accepted as statistically significant in all cases.

Results

Data were available for 858 ECG recordings that were taken from 541 patients with median (IQR) age 34 years (25–42 years), including 161 men (29.8%). The median stated dose ingested, as a multiple of the defined daily dose was similar between groups: citalopram 16 (10–30), mirtazapine 15 (8–27), and venlafaxine 15 (9–28). None of the patients studied developed torsade de pointes or other significant arrhythmia.

Overall, the proportion of patients with QT on or above the nomogram was 2.4% (95% CI 1.4, 4.1%), whereas that for $QT_c \geq 440$ ms was 23.1% (95% CI 19.8, 26.8%), and $QT_c \geq 500$ ms was 1.1% (0.5, 2.5%). Scatterplots of heart rate and corresponding QT interval are shown in Figure 1. Ingestion of citalopram conferred a greater likelihood of QT higher than the nomogram than ingestion of mirtazapine or venlafaxine (difference 7.0%, 95% CI 2.9, 11.9%,

Figure 1

Scatterplot of heart rate and corresponding QT interval for all ECGs taken after overdose of citalopram ($n = 424$), mirtazapine ($n = 103$) and venlafaxine ($n = 331$). The line shown is that used by Chan *et al.* [8]

$P = 0.001$). A higher proportion of patients in the citalopram group had $QT_c \geq 440$ ms (difference = 11.0%, 95% CI 2.6, 19.0%, $P = 0.013$), but not $QT_c \geq 500$ ms (difference = 2.0%, 95% CI -0.9, 5.7, $P = 0.265$). The cut-off QT values for the highest 2.5%, 5%, and 10% of each group are also shown in Table 1.

The number of ECG recordings (Figure 1) is higher than the number of patients (Table 1) due to more than one ECG being performed in 197 patients. No discernible relationship was found between interval after ingestion and QT or QT_c , either in the whole study population or the subgroup who had multiple ECG recordings.

Discussion

The nomogram recently proposed by Chan and colleagues was reported to have high sensitivity for drug-

induced torsades de pointes [8]. The present study extends these findings in an 'at risk' control group for whom the nomogram gave a low false positive rate. By contrast, conventional use of QT_c criteria in the same population was associated with a higher false positive rate, up to 23% depending on the cut-off value selected. In this setting, a high false positive rate could indicate overly conservative practice, and may result in a needlessly prolonged period of ECG monitoring in some patients. Moreover, such an approach might make it more difficult to identify patients at highest risk of significant arrhythmia. Drug-induced torsades de pointes is most likely to occur in patients with low heart rate (<90 beats min^{-1}) [8]. The present study found the greatest discrepancy between nomogram and QT_c methods was amongst patients with heart rate 30–60 beats min^{-1} , where the nomogram was more sensitive. Application of Bazett's formula in patients with low heart rate appeared to overly correct QT interval, which may limit its role in identification of patients at risk of arrhythmia.

Substantial differences exist between the arrhythmogenic potential of various antidepressant drugs [14]. A relationship exists between citalopram dose and the risk of QT prolongation and torsades de pointes is a recognized complication of citalopram toxicity [15–17]. Administration of oral activated charcoal after overdose can prevent QT prolongation and reduce arrhythmia risk [18]. By contrast, venlafaxine causes QT prolongation and tachyarrhythmia but neither mirtazapine nor venlafaxine overdose have been reported to cause torsades des pointes [11, 19]. The scatterplots show different heart rate-QT relationships between the selected agents, and the citalopram group had a more heart rate values in the range typically associated with torsades de pointes, namely <90 beats min^{-1} . Therefore, the nomogram was sufficiently sensitive to discriminate between agents; a higher proportion of the citalopram group were identified as at increased risk, which is in keeping reported clinical outcomes. By contrast, $QT_c \geq 500$ ms did not allow discrimination between the effects of the different agents.

The nomogram could readily be incorporated in a clinical setting as a means of interpreting QT interval. The concept of a nomogram has already been shown to be acceptable to healthcare staff and can be implemented into routine treatment of poisoned patients, for example, the Prescott nomogram and its subsequent modifications that is widely used to determine risk after paracetamol overdose. A possible limitation of the nomogram approach is that it addresses only one aspect of toxicity, namely arrhythmia risk. Other aspects of toxicity require consideration such as generalized seizures, which occurred in 42 patients (7.7%) of the present study population [20]. Nonetheless, the nomogram may offer a considerable advance in our ability to predict arrhythmia, and further work is required to explore its utility across a larger patient population.

Table 1

Data concerning QT interval after antidepressant overdose shown as the proportion (95% confidence interval) of patients in each group; QT_c = QT corrected by Bazett's formula. Nomogram is that used by Chan *et al.* [8] which relates QT to heart rate (see also Figure 1). *P* values are for two-tailed Yates' corrected chi square comparison to the citalopram group

	Citalopram <i>n</i> = 215	Venlafaxine <i>n</i> = 223	Mirtazepine <i>n</i> = 103	Total <i>n</i> = 541
QT _c ≥ 440 ms	68 32% (26, 38%)	41 18% (14, 24%) <i>P</i> = 0.002	16 16% (10, 24%) <i>P</i> = 0.004	125 23% (20, 27%)
QT _c ≥ 500 ms	4 2% (1, 5%)	2 1% (0, 3%) <i>P</i> = 0.651	0 0% (0, 4%) <i>P</i> = 0.392	6 1% (1, 3%)
QT ≥ nomogram	10 5% (2, 9%)	3 1% (0, 5%) <i>P</i> = 0.075	0 0% (0, 4%) <i>P</i> = 0.060	13 2% (1, 4%)
Highest 2.5%	QT > 461	QT > 402	QT > 421	
Highest 5%	QT > 440	QT > 396	QT > 414	
Highest 10%	QT > 423	QT > 383	QT > 392	

A limitation is that the ECG data were determined from surface recordings analyzed by an automated algorithm, which may be less accurate than recordings that are subject to visual and semi-automated assessment of the QT interval. Nonetheless, this reflects a common approach to ECG interpretation that is generally relied upon for day-to-day assessment of patients who present after drug overdose and clinical decision-making. A further limitation is that none of the study population developed arrhythmia so that the positive predictive value of the nomogram and false negative rate cannot be explored. Despite this, the study extends the nomogram to a patient population considered to be at risk of arrhythmia due to antidepressant ingestion, and excludes false positives in this group. The stated antidepressant dose was based on patient self-reporting, and confirmatory laboratory measurements were not undertaken. However, this appears to be valid approach because a qualitative relationship exists between the stated drugs ingested and those detected by laboratory analyses, and a positive relationship exists between the stated quantity ingested and plasma drug concentration after self-poisoning [21–23]. We cannot exclude the possibility of confounding by co-ingested drugs; overdose in our experience involves a single agent in 45% of cases, two agents in 30%, and three or more in 25%. A limitation is that comparison cannot be made easily between groups. Nonetheless, mirtazapine does not block sodium channel conduction and so is an important negative control.

In conclusion, the risk of arrhythmia must be considered in all patients who attend the Emergency Department after antidepressant overdose. Classical approaches to QT evaluation have emerged from a regulatory perspective but these do not assist in the setting of drug overdose, and there is an urgent need to develop better risk prediction tools. Citalopram is associated with prolonged QT and

torsades, whereas this arrhythmia has not been reported after mirtazapine or venlafaxine. Consistent with this, the nomogram proposed by Chan and colleagues [8] indicated a higher proportion of cases 'at risk' after citalopram overdose than in the other groups. Future studies are needed to develop better risk assessment strategies, and the nomogram requires prospective evaluation of its utility in a clinical setting.

Competing interests

There are no competing interests to declare.

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