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Electrocardiogram changes and arrhythmias in venlafaxine overdose

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The major clinical effects of venlafaxine overdose are seizures and serotonin toxicity.
- There is controversy over the risk of cardiac toxicity in venlafaxine overdose.

WHAT THIS STUDY ADDS

- Venlafaxine overdose is unlikely to cause clinically significant cardiac toxicity, including QT prolongation or malignant arrhythmias, and the commonest cardiovascular effects are tachycardia and mild hypertension.
- Massive ingestions >8 g may result in cardiac toxicity and patients should be observed carefully.

AIMS

To investigate serial electrocardiogram (ECG) parameters, haemodynamic changes and arrhythmias following venlafaxine overdose.

METHODS

The study included 369 venlafaxine overdoses in 273 patients presenting to a toxicology unit where an ECG was available. Demographic information, details of ingestion, haemodynamic effects [heart rate and blood pressure (BP)] and complications (arrhythmias and conduction defects) were obtained. ECG parameters (QT, QRS) were measured manually and analysed by visual inspection, including plotting QT–HR pairs on a QT nomogram.

RESULTS

The median ingested dose was 1500 mg [interquartile range (IQR) 600–3000 mg; range 75–13 500 mg). Tachycardia occurred in 54% and mild hypertension (systolic BP >140 mmHg) in 40%. Severe hypertension (systolic BP >180 mmHg) and hypotension (systolic BP <90 mmHg) occurred in 3% and 5%, respectively. No arrhythmias occurred based on continuous telemetry, and conduction defects were found in only seven of 369 admissions; five of these conduction defects were pre-existing abnormalities. In 22 admissions [6%, 95% confidence interval (CI) 4–10] there was an abnormal QT–HR pair, with larger doses being more likely to be associated with an abnormal QT. The median maximum QRS width was 85 ms (IQR 80–90 ms; range 70–145 ms) and the QRS was greater than 120 ms in only 24 admissions (7%, 95% CI 4–10).

CONCLUSIONS

Venlafaxine overdose causes only minor abnormalities in the QT and QRS intervals, unlikely to be associated with major arrhythmias, except possibly with large doses.

Introduction

Many of the newer antidepressants have been shown to be safer in overdose compared with the older tricyclic antidepressants. However, venlafaxine appears to be more toxic than other newer antidepressants, with a higher rate of fatalities [1], increased risk of seizures [2] and cardiac toxicity reported with massive ingestions [3]. Serotonin toxicity and seizures are the most important clinical effects commonly reported following venlafaxine overdoses and

occur across a range of doses. Cardiac effects are rare, being reported with massive ingestions, and are not well characterized [3–5].

A recent report of venlafaxine overdoses has suggested that cardiac toxicity is more common and is associated with abnormal QT prolongation. The study concluded that QT prolongation is a major problem with venlafaxine overdose and all patients require cardiac monitoring [6]. However, this study by Howell *et al*. focused on QT prolongation with single electrocardiograms (ECG) and used Bazett's correction where the majority of patients had tachycardia. They reported no serious arrhythmias and it is ultimately unclear what the potential is for clinically significant cardiac toxicity in venlafaxine overdose. The suggestion that QT prolongation is the most important parameter is also inconsistent with previous reports, where QRS widening and sodium channel blockade may be the mechanism of cardiotoxicity in massive overdoses.

The aim of this study was to assess the effect of venlafaxine overdose on ECG parameters (QT interval, QRS width), blood pressure and heart rate, and determine the frequency of arrhythmias.

Methods

This study was a review of consecutive presentations of venlafaxine overdose to a tertiary toxicology unit at the Calvary Mater Newcastle Hospital (Australia), which has a primary referral population of approximately 300 000 people. Detailed information on all admissions is recorded in a relational database. The use of this database for research purposes has previously been exempted by the Human Research Ethics Committee as an audit, and approval was obtained for prospective collection of clinical data, blood samples and ECGs from a subgroup of patients. An earlier study has reported the first 51 venlafaxine overdose admissions in a study of the relative toxicity of antidepressants [2].

All venlafaxine overdoses between January 1997 and December 2007 were reviewed and admissions where at least one ECG was available were included. The history of venlafaxine ingestion was confirmed on at least two occasions (history from ambulance officers, family, friends and empty drug containers) and blood was collected and venlafaxine quantified in a subgroup of patients. The following information was extracted from the database: patient demographic characteristics (age, sex), details of the ingestion [estimated time of ingestion and amount (mg)], co-ingested drugs, clinical effects [heart rate (HR) and blood pressure (BP)] on admission and their respective relevant maximum or minimum recordings during admission and complications (arrhythmias and conduction defects). Co-ingested drugs were classified as either having a significant potential to cause QRS widening and/or QT prolongation based on both the drug and the dose ingested.

All patients presenting with drug overdose are either managed in the Emergency Department (ED) by the toxicology unit, if their length of stay is less than about 16 h, or admitted as an inpatient under toxicology if they require intensive care admission or a longer duration of stay. All toxicology admissions have continuous telemetry while in the ED and therefore a large proportion of patients will have continuous telemetry for the duration of their hospital stay. Because of the risk of seizures, patients with venlafaxine overdose that have an inpatient admission will usually be admitted to the high dependency or intensive care unit, which also have continuous telemetry. A minority of venlafaxine overdose patients being admitted for >16 h will be transferred to the general ward without telemetry. The toxicology service has a standardized discharge policy requiring review by the medical toxicology team and the psychiatry team. Both teams are available to perform reviews on a 24/7 basis.

QT and QRS intervals were manually measured on each 12-lead ECG with a ruler. The QT interval was taken from the beginning of the Q wave up to the point where the T wave returns to baseline. QT and QRS were measured in a minimum of six leads (three chest and three limb leads) and the median interval calculated. HR was recorded from the ECG machine's automated readout and assumed to be an average measure of the RR interval for the ECG. This was confirmed in a subgroup of 57 patients where the RR interval was measured from the same point in one complex to the next complex for at least six RR intervals in the rhythm strip (lead II) and the median RR interval calculated and converted to HR.

For descriptive statistics, medians and interquartile ranges (IQR) are reported. ECG parameters were examined by visual inspection, which included plotting QT–HR pairs on a previously developed QT nomogram [7] and plots of QRS duration *vs.* time and dose.

Results

During the period of the study 317 patients presented on 436 occasions with venlafaxine overdoses. ECGs were available for 273 patients on 369 occasions where the median ingested dose was 1500 mg (IQR 600–3000 mg; range 75–13 500 mg). In a subgroup of 57 admissions where blood was collected, venlafaxine was detected in all cases. Table 1 provides the demographic details and characteristics for all 369 admissions where at least one ECG was available. Tachycardia was common, occurring in 54% of patients, as was mild hypertension (systolic BP >140 mmHg) occurring in 40%, but severe hypertension (systolic BP >180 mmHg) and hypotension (systolic BP <90 mmHg) were uncommon (Table 1).

There were 663 ECGs available for the 369 admissions. An abnormal ECG (excluding sinus tachycardia) was found in seven of the 369 admissions, which were all conduction

Table 1

Details of the 369 admissions from 273 patients reporting the median and interquartile range (IQR) or for dichotomous outcomes the number, percent proportion and 95% confidence intervals (95% CI)

	Median (IQR)	Patients *n* = 273	Admissions *n* = 369
Age	35 years (25–43)	–	–
Sex, female (%)	–	196 (72)	–
Dose ingested	1.5 mg (0.6–3 g; range 0.75–13.5 g)	–	–
Co-ingestants (%)	–	–	319 (86)
Heart rate:	103 bpm (90–117)	–	
Tachycardia (%) [HR >100 bpm]			199 (54% [49, 59])
BP (%)	138 mmHg (127–150)	–	
Systolic BP >140 mmHg			149 (40% [35, 46])
Systolic BP >180 mmHg			12 (3% [2, 6])
Diastolic BP >110 mmHg			11 (3% [2, 5])
Systolic BP <90 mmHg			19 (5% [3, 8])
QT interval	360 ms (IQR 330–390 ms)	–	22 (6% [4, 9])
Abnormal QT–HR	(Range 260–520 ms)		
QRS width	85 ms (IQR 80–90 ms)		
≥120 ms	(Range 70–145 ms)		24* (7% [4, 10])
Abnormal ECG (%)	–	–	7 (2% [1, 4])
Conduction defect			7 (2% [1, 4])
Arrhythmia			0 (0% [0, 1])

*Only two admission with QRS >120 ms (130 ms, 145 ms). IQR, interquartile range; BP, blood pressure.

defects (right bundle branch block [2], left anterior hemiblock [3], right bundle branch block and left anterior hemiblock [1], first degree heart block [1]). In five of the seven cases with a conduction defect, it was a pre-existing ECG change based on previously recorded ECGs in the medical record. No arrhythmias were reported from continuous telemetry while in the ED or intensive care unit.

The most abnormal QT–HR pair for each of the 369 admissions is plotted in Figure 1a on the QT nomogram, showing that in only 22 admissions (6%) was the QT–HR pair above the line and therefore abnormal. Figure 1b illustrates the QT nomogram for patients co-ingesting medications reported to cause QT prolongation. Figure 1c,d distinguishes the top and bottom 10th percentile of dose to explore the dose effect on QT. None of the patients ingesting a dose in the bottom 10% had an abnormal QT compared with four (14%) in the top 10% of doses. Figure 1e compares the QT–HR pairs in venlafaxine with a control group of overdoses of non-cardiotoxic medications [7].

The median maximum QRS width for the 369 admissions was 85 ms (IQR 80–90 ms; range 70–145 ms), and in only 24 admissions was the QRS ≥120 ms (Table 1). There was a poor and possibly no association between QRS and dose, although QRS >120 ms occurred only for doses >5 g.

Discussion

This study suggests that for the majority of cases, significant cardiotoxicity does not occur with venlafaxine overdose and the common cardiovascular effects are tachycardia and mild hypertension, consistent with it being a noradrenergic reuptake inhibitor. Malignant arrhythmias did not occur based on continuous telemetry. Abnormal QT intervals and widening of the QRS interval were uncommon, possibly associated with larger ingestions (>8 g), and were not grossly abnormal.

A previous study by Howell *et al*. on the cardiovascular toxicity of venlafaxine in overdose concluded that venlafaxine overdose is associated with a prolonged QTc and this may pose an arrhythmogenic risk, despite no cases of malignant arrhythmias occurring in their study [6]. There are also no published cases of venlafaxine overdose or ingestion being associated with torsades de pointes (TdP) [7]. It is far more likely that the dose-dependent increase in HR they report has simply translated into a dose-dependent over-correction of the QT interval using Bazett's formula [6]. Bazett's formula is known to be problematic outside of the HR range 50–70 bpm [8], and venlafaxine overdose results in a HR in the range where Bazett's formula overcorrects. This is confirmed by the fact that the reported absolute QT intervals in their study were not prolonged. This over-correction of the QT has previously been shown in other drugs that cause tachycardia in overdose such as quetiapine and bupropion [9, 10].

This study has shown that only a small proportion of venlafaxine overdoses had an abnormal QT and these cases were more likely to be larger ingestions (see Figure 1c,d) or in patients who had co-ingested other drugs known to affect the QT interval (Figure 1b). The overall pattern of the QT–HR pairs for venlafaxine over-

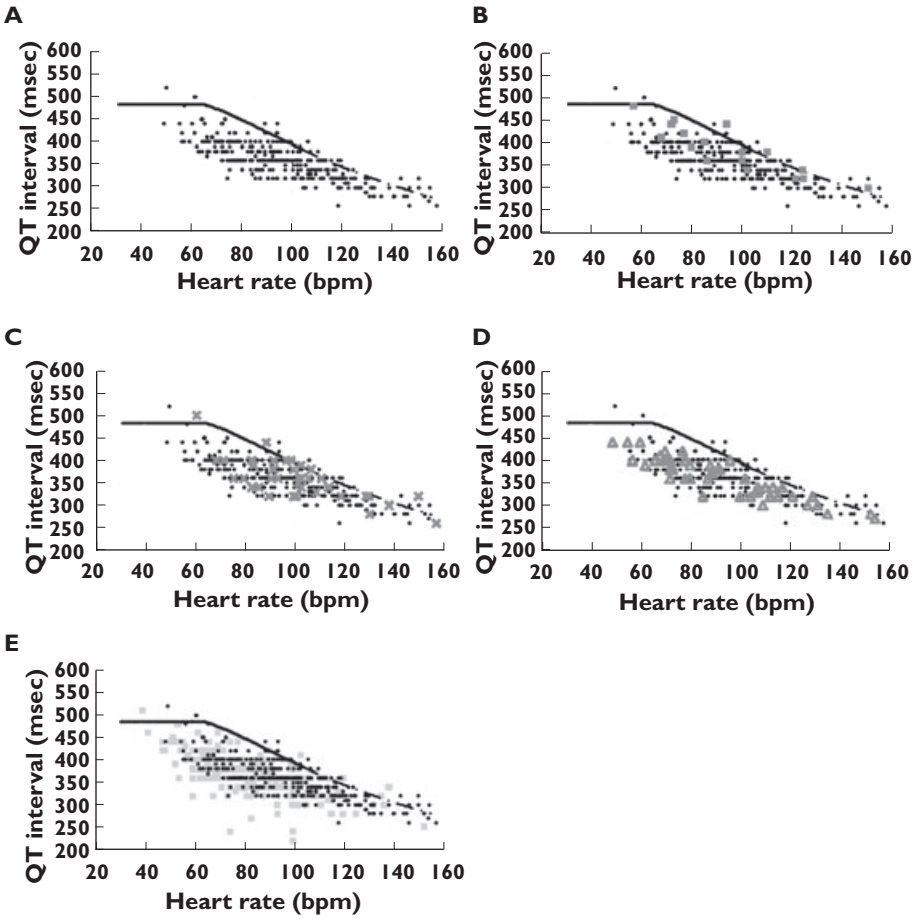

Figure 1

Plot of QT *vs.* heart rate (HR) in patients taking venlafaxine overdoses with one ECG for each patient (a). The nomogram line separates HR, QT pairs above the line associated with an increased risk of torsades de pointes compared with those below the line [7]. (b) Shows patients co-ingesting drugs known to cause QT prolongation in filled grey squares. (c) Shows patients taking the large doses (top 10%) in grey crosses and (d) has patients taking the smallest doses (bottom 10%) in grey triangles. (e) Provides a comparison with a control group of patients taking overdoses of drugs that do not affect the QT interval [7] in light grey squares

doses on the QT nomogram was only marginally different from overdoses of non-cardiotoxic medications (Figure 1e). Figure 1 therefore provides good evidence that QT prolongation is not a major feature of venlafaxine overdose, except possibly for larger overdoses, where the effect still remains moderate. This is in contrast to drugs that have been clearly associated with QT prolongation and TdP such as thioridazine [11], citalopram [12] and amisulpride [13] and sodium channel effects well known to cause severe effects in tricyclic antidepressant poisoning [14].

There have been previous reports of venlafaxine causing cardiac toxicity and death after large overdoses, consistent with our findings. There is one report of QRS widening after an overdose of 3 g; however, the patient also ingested thioridazine [15]. There is one report of a hypertensive crisis that was associated with therapeutic venlafaxine use [16]. Other reports all include doses >8 g [3–5, 17], where patients also manifest other features of venlafaxine toxicity, including seizures and serotonin toxicity [18], and there is a significant risk of death.

There were a number of limitations of the study design, including the fact that patient data were collected prospectively and the ECGs reviewed retrospectively. However, the haemodynamic parameters are objective measures that are routinely collected in all toxicology patients. ECGs were measured manually in a standardized way by the author using a previously published method [12]. Obtaining digitized ECG data using Holter monitors to record the 12-lead ECGs and on-screen measurement of the QT intervals with magnification is more accurate [19]. However, this was not possible because all the ECGs were recorded as hard copies. Automated measurement available on standard ECG machines is also inaccurate [19, 20], so was not used either.

Although all overdoses were not confirmed by measurement of venlafaxine in plasma, 100% of a subgroup

of patients where blood was available for drug assays had venlafaxine in concentrations consistent with drug ingestion. There was also the possibility of inaccuracy in the dose from patient history. However, a number of pharmacokinetic studies of drugs in overdose have demonstrated that patient estimate of dose is relatively accurate [21, 22]. Therefore, patient estimate of dose is a reasonable pharmacokinetic metric to use in studies of effects in drug overdose.

Venlafaxine remains a commonly prescribed antidepressant and will continue to be taken in overdose. Severe cardiotoxicity with arrhythmias and/or hypotension does not appear to be a major feature of venlafaxine overdose except in massive ingestions of >8 g, when other features such as neurotoxicity and serotonin toxicity are probably more important. Routine cardiac monitoring is unlikely to be necessary in the majority of cases, but all patients should have at least one ECG.

Competing interests

None to declare.

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