The spectrum of acute heart failure after venlafaxine overdose

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Objective. Venlafaxine is a bicyclic antidepressant that may be associated with severe cardiotoxicity following large overdose. The purpose of this short case series is to present different patterns of venlafaxine-related cardiotoxicity and to discuss the potential mechanisms. Case series. Between January 2010 and July 2011, four patients were admitted to an ICU with acute left ventricular failure following large venlafaxine overdoses. The age of the four female patients ranged from 35 to 65 years. None of them had no history of cardiovascular disease. The amount of venlafaxine ingested by history ranged from 3150 to 13500 mg (extended-release preparation in two cases). The peak serum venlafaxine concentration was between 2153.3 and 9950 ng/ml. Three patients died and one recovered rapidly. The initial ECG revealed only mild abnormalities in two cases. In two patients, at least one ECG recording demonstrated a widening of QRS interval. In three patients, echocardiography disclosed a left ejection fraction of 15%–18%. Two patients presented a severe serotonin syndrome, with major rhabdomyolysis. Seizures were noted in two cases, including one patient with status epilepticus. Three patients were mechanically ventilated. The causes of death were refractory hypoxemia, malignant arrhythmias, and cardiogenic shock, respectively. Discussion. Severe and diffuse left ventricular dysfunction may be observed after large venlafaxine overdoses and this is not always associated with severe cardiac conduction function abnormalities. The mechanisms underlying venlafaxine-related cardiac failure with preserved normal cardiac conduction are discussed. A possible explanation may be a catecholamine-induced myocardial damage in relationship with the inhibition of norepinephrine (and dopamine) reuptake.

Keywords Autopsy; Cardiotoxicity; Echocardiography; Left ventricular failure; Overdose; Venlafaxine

Introduction

While there is acceptable cardiovascular safety with the use of selective serotonin reuptake inhibitors (SSRI), large overdoses of venlafaxine may lead to acute heart failure and eventually death. We report a series of four ICU cases illustrating different patterns of venlafaxine-related cardiotoxicity. During the same period (January 2010–July 2011), 76 other patients were admitted to the emergency department because of pure (17/76) or mixed (59/76) venlafaxine overdose, who did not experience serious cardiotoxicity.

Case 1

A 38-year-old depressive woman ingested 4200 mg of extended-release venlafaxine together with benzodiazepines and ethanol. Approximately 6 hours after ingestion, she was found with a Glasgow Coma Scale (GCS) score of 9/15, heart rate 106/min, and arterial blood pressure 70/40 mm Hg. Neurological examination showed ankle clonus and the admission electrocardiogram (ECG) revealed sinus rhythm, QRS duration < 100 msec and QTc interval 449 msec, with diffuse and aspecific ST changes. Hypotension persisted despite fluid replacement. After orotracheal intubation for mechanical ventilation, inotropic and vasopressive drugs were started (dobutamine, norepinephrine, and epinephrine). The patient rapidly developed acute renal failure (requiring continuous venovenous hemofiltration), rhabdomyolysis (peak CK activity 3479 IU/l, ref: 200), ischemic liver injury with cytolysis, and abnormal clotting tests. The peak value for troponin-I was 22.49 ng/ml (ref: 0.08) 40 hours post-ingestion. Venlafaxine and O-desmethylvenlafaxine (ODV) were extracted from serum samples by a liquid–liquid extraction with ethyl acetate at pH 9.2. Subsequently, concentrations have been determined by LC-MS/MS using the corresponding deutereted molecules as internal standard. Therapeutic concentrations ranged from 200 to 750 ng/ml. The peak venlafaxine serum concentration on Day 2 was 2153.3 ng/ml, with ODV of 960.1 ng/ml. Symptoms consistent with serotonin syndrome were present on Day 2. Echocardiography revealed a severe and global alteration of left ventricular (LV) contractility with a LV ejection fraction of 16%...
(Supplementary Video to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2012.763133). Cardiac arrhythmias were observed including atrial fibrillation and ventricular tachycardia. Inotropic and vasoactive drugs were progressively reduced on Day 2 but were increased again on Day 3 after evidence of Streptococcus pneumoniae septicemia and bilateral pneumonia evolving to acute respiratory distress syndrome. Echocardiography showed a significant improvement of LV function on hospital Day 10, with an ejection fraction of 59%. Unfortunately, the patient died on Day 11 from refractory hypoxemia despite ventilation with 1.0 FiO2.

Case 2

A 46-year-old woman ingested 3150 mg of immediate-release venlafaxine and 2100 mg of extended-release venlafaxine and was admitted 7 hours later with a normal neurological examination. The admission ECG revealed sinus tachycardia (153/min), with normal QRS duration and a QTc interval of 447 msec. Arterial blood pressure was 136/98 mm Hg. At 7 hours after hospital admission, the patient presented an episode of self-limited tonic-clonic seizure, with a mild hypotension that was responsive to fluid therapy. She regained consciousness rapidly and the ECG was not modified. Hypotension reappeared with oliguria and an increase of arterial lactate up to 2.4 mmol/l. Echocardiography was performed. The LV was severely and diffusely depressed with an ejection fraction of 18%. The troponin-I concentration remained below reference values. As tachycardia persisted, it was decided to give high doses of insulin instead of catecholamines as first-line inotropic agent. A bolus of 1 IU/kg was given, followed by a continuous infusion of 1 IU/kg/h for 18 hours. This intervention was followed by an increase of the urine output and a decrease of arterial lactate. On Day 2, the peak CK activity was 1173 IU/l. Echocardiography was repeated on Day 3 and confirmed the recovery of the LV function (ejection fraction 65%). The peak venlafaxine serum concentration was 3221 ng/ml 24 hours post-ingestion, with ODV of 2783.4 ng/ml. The patient recovered completely.

Case 3

A 35-year-old woman was admitted to the hospital 7 hours after having ingested 90 tablets of extended-release venlafaxine of 150 mg. She had a medical history of cocaine addiction. On admission to the emergency department, she presented two episodes of generalized tonic-clonic seizures that were treated by intravenous diazepam, followed by a continuous infusion of midazolam. Her vital signs were: heart rate of 134/min, blood pressure of 80/60 mmHg, and arterial oxygen saturation of 98% while breathing on ambient air. The patient was extremely agitated and confused with visual hallucinations and tremor of the extremities. Pupils were dilated but were reactive to light stimulation. A horizontal nystagmus was present bilaterally. The body temperature increased up to 39.3°C at 23 h post-ingestion. The admission ECG showed sinus tachycardia of 131/min, QRS duration of 90 msec, and QTc of 425 msec. The arterial lactate concentration was 5.9 mmol/l. No other toxin was detected at toxicological screening, but the quantitative determination of serum venlafaxine was not performed. The patient received 2 liters of crystalloids before transfer to the ICU. At 10 hours after venlafaxine overdose, a generalized tonic-clonic status epilepticus was refractory to benzodiazepine and phenytoin. A thiopentone continuous infusion was started after endotracheal intubation for mechanical ventilation. Norepinephrine (up to 1.6 mcg/kg/min) was added due to persisting arterial hypotension despite fluid loading. The echocardiography demonstrated a diffuse alteration of the LV function (ejection fraction 15%). The second ECG (13 h post-ingestion) showed sinus rhythm of 153/min, QRS duration of 133 msec, and QTc of 529 msec. Episodes of atrial fibrillation were recorded. Despite inotropic support with dobutamine (up to 8 μg/kg/min) and milrinone (up to 0.5 μg/kg/min), the patient remained hypotensive and anuric. Oxygen venous saturation in the superior vena cava was 46% and the PaO2/FiO2 ratio was less than 100 mmHg (FiO2 1.0), without lung infiltrates on the chest X-ray. Recurrent hypoglycemia was treated with hypertonic glucose infusion. At 17 hours after overdose, laboratory data showed: lactate of 9.4 mmol/l, troponine-I of 4.1 ng/ml (<0.3 ng/ml), INR of 3.2, and CK of 2968 IU/l. At 24 hours after overdose, the patient had a sudden cardiac arrest that was refractory to cardiopulmonary resuscitation.

Case 4

A 65-year-old woman was admitted more than twelve hours after ingestion of 7000 mg of immediate-release venlafaxine and 40 mg lorazepam. The patient was drowsy, but arousable (GCS 14/15). Vital signs were: temperature of 36.2°C, respiratory rate of 14/min, heart rate of 105/min, arterial blood pressure of 50/40 mm Hg, and pulse oxygen saturation of 92%. The admission ECG showed sinus rhythm 102/min, QRS duration 116 msec, and QTc 310 msec. The initial hemodynamic management included colloid infusion (1000 ml) and norepinephrine infusion (1.25 μg/kg/min). The laboratory investigations revealed: arterial lactate of 3.71 mmol/l (<2.2), creatinine of 2.14 mg/dl (<1.1), and CK of 90 IU/l. The admission serum venlafaxine concentration was 9950 ng/ml. At 7 hours after hospital admission, the ECG was modified with an idioventricular rhythm (67/min) and an enlarged QRS duration (129 msec). The patient became comatose and orotracheal intubation was performed. Hemodynamic condition worsened despite fluid therapy and administration of increasing doses of epinephrine (from 0.28 μg/kg/min to 3.61 μg/kg/min) and norepinephrine (1.15 μg/kg/min). Extremely low cardiac (1 L/min) output was assessed by transcardiopulmonary thermodilution measurement. The patient died 14 hours after admission from refractory cardiogenic shock.
Discussion

Venlafaxine is a bicyclic antidepressant that inhibits neuronal uptake of norepinephrine, serotonin, and, to a lesser extent, dopamine. Due to its action of serotonin reuptake inhibition, toxic effects after overdose are likely to be similar to those observed with SSRI agents. Hypertension and tachycardia are observed after moderate venlafaxine exposures. However, some concerns appeared regarding a possible higher incidence of cardiotoxic effects with venlafaxine in comparison with SSRIs.1 With therapeutic use, a recent population-based observational study failed to demonstrate that venlafaxine was associated with a higher risk of cardiotoxicity in comparison with other commonly used antidepressants.2 Fatalities were observed after massive ingestion, and the cause of death was mainly malignant arrhythmias.3,4

The effects of venlafaxine on cardiac conduction appear to be limited, even after an overdose. In a prospective review of 273 consecutive patients presenting with a venlafaxine-alone overdose (dose ranging from 75 to 13500 mg), only minor ECG changes were noted [3]. Alteration in QRS duration was considered mild (median maximum QRS width 85 msec) and only 24 patients (7%) had a QRS of greater than or equal to 120 msec. However, doses greater than 8 g may produce significant cardiotoxicity, including a prolongation of QRS complex and QTc interval followed by ventricular arrhythmias.3

Experimental data obtained from guinea pig ventricular myocytes demonstrate that venlafaxine possesses direct cardiac electrophysiological effects by inhibiting the inward sodium current (INa).5 Block of sodium current by venlafaxine appears to be different from that described with tricyclic antidepressants and type I antiarrhythmic agents. Indeed, venlafaxine seems to block INa in its resting state. This effect has been observed for venlafaxine concentrations that could be reached in the plasma after venlafaxine poisoning in humans, even if an extrapolation of the animal experimental data must be taken with caution.

As illustrated by the present case series, the initial ECG may show only minor QRS changes even in the presence of a significant hypotension (Case 1 & 3). However, cardiotoxic manifestations may be delayed with venlafaxine extended-release preparations and the repeat ECG may then reveal an increase of QRS duration.6 Malignant arrhythmias including ventricular tachycardia have been observed in the absence of significant changes in QRS morphology or duration on the admission ECG. In a 38-year-old man who was observed one hour after having ingested 9.5 g of venlafaxine (but also lamotrigine), the QRS duration was 92 msec.7 Shortly after gastric lavage, the patient presented wide complex tachycardia (QRS duration 140 msec) and generalized seizure. After lidocaine administration, the rhythm reverted to sinus rhythm with narrow QRS.

As illustrated by Cases 1 and 2, a marked alteration of left ventricular function may also be noted despite minimal ECG changes. Recent publications have also outlined the possibility of venlafaxine-related acute heart failure, without changes in cardiac conduction. This experience

### Table 1. Literature data regarding acute left ventricular dysfunction in the absence of frank cardiac conduction disorders.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Dose VEN (mg)</th>
<th>Serum VEN (ng/ml)</th>
<th>ECG</th>
<th>Co-ingestion</th>
<th>ECG</th>
<th>Echo LVEF (%)</th>
<th>Arhythmias</th>
<th>Seizures</th>
<th>SS</th>
<th>Rhabdomyolysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malfroy F, 27</td>
<td>4500</td>
<td>Ethanol, fluoxetine</td>
<td>N/A</td>
<td>500</td>
<td>Narrow QRS</td>
<td>20</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Survival, LVEF 75% on day 10</td>
</tr>
<tr>
<td>Vinetti F, 34</td>
<td>11250</td>
<td>No</td>
<td>18015/3846</td>
<td>ST-segment depression, narrow QRS</td>
<td>No</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Survival, LVEF recovery on day 12</td>
</tr>
<tr>
<td>Caroli F., 40</td>
<td>12000</td>
<td>No</td>
<td>3678.5</td>
<td>Narrow QRS</td>
<td>No</td>
<td>35</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Survival, fractional shortening 20% at 2 months</td>
</tr>
<tr>
<td>Partridge M. 27</td>
<td>1987.5</td>
<td>Paroxetine</td>
<td>N/A</td>
<td>Left ventricular hypertrophy with strain</td>
<td>N/A</td>
<td>Fractional shortening 20% (&gt;2), hypokinesia anterior septum</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Mild</td>
</tr>
</tbody>
</table>

VEN, venlafaxine; ODV, O-desmethylvenlafaxine; N/A, not available; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; SS, serotonin syndrome.
is summarized in Table 1.\textsuperscript{8–12} The amount of venlafaxine ingested by history among these five cases ranged from 2,000 to 12,000 mg. The alteration of LV function was usually severe and diffuse. No patient experienced serious cardiac arrhythmias. In the observation published by Caroselli et al., both electrocardiographic and echocardiographic findings were suggestive for focal myocardial ischemia in the anterolateral territory with a normal coronary angiogram. After one month, the patient died and the autopsy was consistent with a focal myocardial wall rupture. Myocardial infarction with normal coronary arteries has been reported in at least two recent publications.\textsuperscript{10,13}

The mechanisms underlying venlafaxine-related cardiac failure with preserved cardiac conduction function have been discussed, but not fully elucidated. One of the most likely explanation may be a catecholamine-induced myocardial damage in conjunction with the inhibition of norepinephrine (and dopamine) reuptake. This mechanism has been suggested in the pathophysiology of “tako-tsubo” cardiomyopathy that has been occasionally observed with venlafaxine or other antidepressants.\textsuperscript{14,15} Recently, tako-tsubo cardiomyopathy has also been observed after therapeutic use of venlafaxine.\textsuperscript{16} The treatment of venlafaxine-related cardiac failure relies mainly on the administration of inotropic drugs. High-dose insulin therapy may be possibly effective, but this intervention has not been properly validated in this setting. If used, the risk of inducing hypoglycaemia is very high, as venlafaxine overdose per se may give rise to low blood glucose levels.\textsuperscript{17}

**Conclusion**

Acute heart failure following venlafaxine overdose may be due to several pathophysiological mechanisms. Interestingly, acute heart failure, with diffuse impairment of the LV function at echocardiography, may be observed in the absence of any severe intraventricular conduction abnormality. A large overdose of venlafaxine seems necessary to induce acute LV failure and there are probably also great variations in interindividual susceptibility.\textsuperscript{9,18}

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**Supplementary material available online**

Supplemental material. Echocardiography in Case 1 on Day 2, showing a severe and diffuse left ventricular dysfunction.

**References**


