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Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects

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\textbf{ABSTRACT}

\textbf{Context:} Desvenlafaxine is used to treat major depression. Desvenlafaxine is also the active metabolite of venlafaxine. Venlafaxine overdose can cause serotonin toxicity, seizures and cardiovascular effects, but there is limited information on desvenlafaxine overdose.

\textbf{Objective:} We aimed at investigating the clinical effects and complications from desvenlafaxine overdose.

\textbf{Materials and methods:} This was a retrospective observational study of desvenlafaxine overdoses over a six-year period. Demographic details, dose and timing of the overdose, together with clinical effects, treatment and complications were extracted from a local hospital network database or the medical records of patients following hospital admission with a desvenlafaxine overdose.

\textbf{Results:} There were 182 cases of desvenlafaxine overdose included in the study. From the 182 cases, 75 were desvenlafaxine (± alcohol) only ingestions and 107 included one or more co-ingested drugs. In single-agent desvenlafaxine ingestions, median age was 25 years (range: 13–68 years) with a median ingested dose of 800 mg (range: 250–3500 mg). Interquartile range (IQR): 600–1400 mg, and 54/75 (72%) were female. The Glasgow Coma Score (GCS) was 15 in 68/74 (92%) patients, 13–14 in 5/74 (7%), and was seven in one patient following aspiration. Mild hypertension (systolic blood pressure [BP] >140–180 mmHg) occurred in 23/71 patients (32%), and tachycardia occurred in 29/74 (39%) patients. There were no abnormal QT intervals and no QRS >120 m s. Serotonin toxicity was diagnosed by the treating physician in 7/75 (9%) patients, but only one of these met the Hunter Serotonin Toxicity Criteria. None of the 75 patients who took desvenlafaxine only (± alcohol) had seizures, were admitted to intensive care or died. In comparison, the 107 patients taking desvenlafaxine in overdose with other medications developed more pronounced toxicity. Generalised seizures occurred in 5/107 (5%), but in three of these cases co-ingestants were possible proconvulsants. Fifteen patients had a GCS <9 and none had an abnormal QT or QRS. Severe effects appeared to be associated with coingestants.

\textbf{Conclusion:} Desvenlafaxine overdose causes minor effects with mild hypertension and tachycardia. The risk of seizures or serotonin toxicity is low.

\textbf{Introduction}

Desvenlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) which was approved in the United States (US) and Australia for the treatment of major depressive disorder in 2008.\textsuperscript{[1,2]} Desvenlafaxine (O-desmethylvenlafaxine) is available commercially as an extended release formulation of the synthetic succinate salt.\textsuperscript{[3]} It is also the major active metabolite of the parent drug, venlafaxine.

Although there have been no head-to-head trials to directly compare the effectiveness of desvenlafaxine with venlafaxine, an indirect comparison of clinical trials of desvenlafaxine with clinical trials of venlafaxine in major depressive disorder determined that the equi-effective doses were desvenlafaxine 50 mg and venlafaxine 75 mg.\textsuperscript{[4]} In short term trials, desvenlafaxine was effective in the treatment of major depressive disorder in dose range of 50–400 mg/day, but no greater effectiveness was seen with doses >50 mg/day.\textsuperscript{[5–8]} Desvenlafaxine has also been used in the treatment of anxiety associated with depression,\textsuperscript{[9]} pain associated with diabetic neuropathy,\textsuperscript{[10]} and the vasomotor symptoms of menopause.\textsuperscript{[11]}

Venlafaxine is metabolised to desvenlafaxine via the cytochrome 2D6 (CYP2D6) hepatic enzyme.\textsuperscript{[12]} Therefore, the use of desvenlafaxine eliminates the requirement to metabolise a drug to an active form and also reduces the risk of potential adverse effects due to increased venlafaxine exposure in patients with defective CYP2D6 metabolism (poor metabolisers).\textsuperscript{[13,14]} Following oral therapeutic administration of desvenlafaxine, its bioavailability is approximately 80%, time to maximum plasma concentration ($T_{\text{max}}$) approximately 7.5 h, and the elimination half-life is approximately 11 h.\textsuperscript{[3,15]} Desvenlafaxine is primarily excreted unchanged in the urine (46%), or via glucuronidation (19%), together with minor
involvement of the CYP3A4 pathway. No involvement with the CYP2D6 pathway has been demonstrated.

When desvenlafaxine was introduced it was assumed that it would cause similar effects in overdose to venlafaxine, including seizures and cardiotoxicity. Electrocardiogram (ECG) changes (minor QRS prolongation and minor abnormalities in the QT interval) and tachycardia are common in venlafaxine overdose, with ventricular arrhythmias and more serious cardiac effects associated with very large ingestions (>8 g). Recently it has been suggested that the major cardiotoxic mechanism may be arrhythmias and cardiomyopathy associated with excess adrenergic stimulation with a report of Takotsubo’s cardiomyopathy.

Currently the risk assessment for desvenlafaxine overdoses is often based on venlafaxine overdoses, so data on desvenlafaxine overdoses is required.

There is limited data on the effect of desvenlafaxine on the QT interval. In pre-marketing studies no effects on the QT or clinically relevant changes in ECG intervals were reported, although evaluation of adverse effects showed palpitations and tachycardia were common (incidence ≥1% to <10%). Orthostatic hypotension was reported following a 600 mg dose of desvenlafaxine daily for 14 days, in 6 out of 9 study participants.

Seizures are the most common serious complication of venlafaxine overdose, with the probability of seizures increasing with increased dose. Similarly, serotonin toxicity (also termed “Serotonin Syndrome”), is reported in venlafaxine overdoses. There is very limited information on desvenlafaxine overdose and the risk of seizures, serotonin toxicity and cardiac effects, with no published reports of these complications in desvenlafaxine overdoses. A comparison study of desvenlafaxine and venlafaxine ingestions reported to Poisons Centres in Texas found that the majority of desvenlafaxine ingestions resulted in no adverse effects.

In this study, we aimed at investigating the frequency of toxic effects and complications following desvenlafaxine overdose, including seizures, serotonin toxicity and cardiac toxicity.

Methods

Study design and setting

This was a retrospective observational study of desvenlafaxine overdose admissions which either presented to a toxicology unit of a tertiary referral hospital and were treated in the emergency department or admitted under the care of the toxicology treatment service, or were patient presentations from hospitals around Australia where the New South Wales Poisons Information Centre was called for advice.

Primary presentations and referrals for all adult overdose and poisoning patients from a population of over 500,000 people are managed by the toxicology unit. Clinical data and demographic information is collected for all patients treated by the toxicology service using a standard data collection form on admission. Other information relevant to treatment, monitoring and outcomes is collected during the admission, and all information are entered into a dedicated database by research assistants. Approval to use the database and patient medical records for research has been granted by the Area Health Service Human Research Ethics Committee.

Physicians from hospitals reporting desvenlafaxine overdoses to the New South Wales Poisons Information Centre were prospectively invited to participate in the study. The treating physician completed a data collection form at the time of patient admission. Approval to use the data from the Poisons Information Centre telephone calls was granted by the Health Service Human Research Ethics Committee.

Participants

All self-poisoning admissions of desvenlafaxine between April 2009 and March 2015 were identified from the toxicology database. An overdose was defined as an ingested dose of desvenlafaxine in excess of the manufacturer’s recommended maximum daily dose of 200 mg taken with the intention of self-harm or unintentionally the incorrect dose. We used the toxicology database to identify the patient admissions. For each admission the majority of the data was extracted from the database, although the medical record was reviewed to verify specific data elements (see below), such as the ECG. Information was extracted from the medical record using a clinical research form developed prior to data collection and piloted in a sample of ten records. All medical records were reviewed by two authors.

The second group of participants were recruited prospectively from telephone calls to the New South Wales Poison Information Centre between September 2009 and August 2012. The treating physician was asked to complete a data collection sheet at the time of the patient admission which included details of the patient and overdose. In addition, ECGs were provided from the patient medical record and, where available, the de-identified patient medical records were reviewed by the researchers to verify clinical details of the overdose.

Data collection

The following information was obtained for all patients where available: patient demographic details (sex, age), details of the ingestion (dose of desvenlafaxine, co-ingestants, time of ingestion and time of presentation), clinical observations (heart rate [HR], BP and Glasgow Coma Score [GCS]), complications (seizures, serotonin toxicity, arrhythmias), investigations (ECG parameters including the QT interval and QRS width), treatments provided (decontamination with charcoal, admission to the intensive care unit [ICU], intubation and ventilation), and length of hospital stay (LOS). Details of the overdose (timing, amount and co-ingestants) were cross-checked with the medical record from a number of sources where available, including patient history, ambulance or emergency services, information provided by family and/or friends, other health care providers, and empty medication packets.
In an attempt to increase reliability of the information abstracted from medical records, both authors who are familiar with medical records, independently retrieved and analysed information and confirmed findings. ECGs were reviewed in the medical record and all intervals measured manually. The diagnosis of serotonin toxicity was based on that of the attending clinical toxicologist. In addition, the medical record was reviewed and the frequency of cases of serotonin toxicity based on the Hunter Serotonin Toxicity Criteria [26] was also recorded.

**Clinical outcomes and measurements**

The following outcomes were defined: tachycardia (HR >100 beats per minute [bpm]), mild hypertension (systolic BP >140 mmHg), severe hypertension (systolic BP >180 mmHg), hypotension (systolic BP <90 mmHg), abnormal QT interval (defined as the QT- HR pair being above the abnormal threshold on the QT nomogram [27]) or presence of arrhythmia, seizure activity, serotonin toxicity, and altered level of consciousness defined as GCS <15. We reported the most extreme measurement from the observations recorded in the patient record during the admission for each parameter listed.

We defined the presence of serotonin toxicity in two ways: (1) from the attending clinician diagnosis during the patient admission (i.e., from the diagnosis of serotonin syndrome, toxicity or serotonergic signs written in the patient notes), and (2) according to the Hunter Serotonin Toxicity Criteria [26] using the description of the individual signs and symptoms and observations made in the patient notes during the admission; one author (GKI) made the diagnosis of serotonin toxicity according to the criteria. (See supplementary Figure 1: Hunter Serotonin Toxicity Criteria for the diagnosis of serotonin toxicity.) [26]

The QT interval was measured manually from the ECG recording by one author (JMC) using a magnifying ruler. Measurements were made visually to the closest 20 ms. The QT interval is measured from the beginning of the Q wave until the end of the T wave. The end of the T wave is the point at which the ECG trace returned to the isoelectric baseline. Six leads were used for measurement, including three chest and three limb leads (V2, V4/V5, V6, I, II and aVF/aVL), with the median of the six QT measurements taken as the QT interval.[27] The QT-HR pairs were then plotted on the QT nomogram [28] to determine if the QT was abnormal which identifies patients at risk of Torsades de Points. To ensure good agreement 25% of all QT measurements were measured by a second author (GKI) and compared to ensure consistency, with 83% of readings within 20 ms of one another, and 100% within 40 ms. The QRS interval was also taken from each ECG recording.

**Analysis**

Descriptive statistics were used to report continuous variables with medians, range and IQR using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA; www.microsoft.com). The 95% confidence intervals (CI) were calculated using the Wilson’s procedure with a continuity correction. Statistical and graphical analyses were performed using Prism version 6.05 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com). Pearson’s Correlation Coefficient was used to test for associations between dose and both BP and HR.

**Results**

There were 200 desvenlafaxine overdose admissions during the study period: 144 were from the hospital admission database and 56 from telephone calls to the Poisons Information Centre. Eighteen cases were excluded due to unknown dose (six patients), doubtful ingestion (two patients), or where a dose of 200 mg or less (nine patients) was ingested; one patient who ingested 1400 mg desvenlafaxine was excluded from the study due to death being caused by other co-ingestants in the overdose – verapamil SR (7200 mg), telmisartan (560 mg), aspirin (6000 mg) and ezetimibe (100 mg). In total, 182 admissions met the inclusion criteria (Figure 1). Eight patients were admitted on two occasions, one on three occasions, and one had four admissions. There was no difference in the demographics or outcomes in patients from the hospital admission database compared to those recruited from telephone calls to the Poisons Information Centre, except more patients took co-ingestants in the hospital database. The patients were divided into two groups depending on the ingestion of desvenlafaxine (plus or minus alcohol) alone, and desvenlafaxine with one or more additional co-ingested drugs. A summary of patient characteristics comparing the desvenlafaxine alone ingestions to those with co-ingestants is shown in Table 1.

**Desvenlafaxine alone overdoses**

There were 75/182 (41%) patients who took a desvenlafaxine only (± alcohol) overdose. The median age of patients was 25 years (Range: 13–68 years) and 54/75 (72%) were female. The median ingested dose was 800 mg (Range: 250–3500 mg; IQR: 600–1400 mg). Six patients (8%) received single dose

![Figure 1. Flow chart of the recruitment of patients from the toxicology unit and the poison centre.](Image)
activated charcoal 0.5–2 h post-ingestion. The median LOS was 14.5 h (Range: 2.7–60 h; IQR: 10–18 h; N = 71 [information unavailable for four patients]). No patient were admitted to ICU and no deaths were recorded.

**Cardiovascular effects**

The median systolic BP was 138 mmHg (Range: 106–212 mmHg; IQR: 125–149 mmHg). There was an association between increasing dose and maximum systolic BP. After excluding one outlier who had underlying essential hypertension and had omitted their anti-hypertensive treatment for one week, the data was fitted using linear regression (Slope = 4.7 ± 2.5 mmHg/g, p = 0.06; Figure 2(a)). Severe hypertension was seen in two patients and mild hypertension in 23/71 (32%) patients (N = 71; information unavailable for four patients). No patient had hypotension.

The median HR was 97 bpm (Range: 51–145 bpm; IQR: 82–109 bpm) and tachycardia occurred in 29/74 (39%) patients. There was no relationship between maximum HR and dose (Figure 2(b)). ECGs were available for all but three patients. The median measured QT interval was 360 ms (Range: 280–470 ms; IQR: 340–380 ms). There were no abnormal QT-HR pairs on the QT nomogram (Figure 3). The median QRS was 92 ms (Range: 72–120 ms; IQR: 86–98 ms).

**Neurological effects**

No desvenlafaxine alone overdose patient had a seizure (0%; 95% CI: 0–6%). There were 68/74 (91%) patients with a GCS of 15. The lowest GCS recorded was seven in one patient following an ingestion of 1800 mg with alcohol and possible aspiration. Five patients who had a GCS of 13 or 14 took overdoses in the range of 500–1000 mg desvenlafaxine. One patient had no GCS documented. No patient required ICU admission or mechanical ventilation.

**Serotonin toxicity**

The diagnosis of serotonin toxicity was made in 7/75 (9%) patients by the attending physician during the admission. However, using the Hunter Serotonin Toxicity Criteria and information from the patient medical record, only one patient (1%) met the criteria for serotonin toxicity. This patient took 3500 mg of desvenlafaxine, and was
Desvenlafaxine overdoses with coingestants

A total of 107/182 (59%) admissions included coingestants with a median number of two coingestants (Range: 1–8; IQR: 2–3). The main co-ingested medications are in Supplementary Table 2.

Mild hypertension occurred in 43/99 (43%) patients, and severe hypertension in one patient. Tachycardia occurred in 59/104 patients (57%). One patient developed rate dependant bundle branch block following an ingestion of desvenlafaxine 2350 mg and temazepam 250 mg. He initially presented with sinus tachycardia (HR, 150 bpm) and 3 h post-ingestion developed a regular broad complex tachycardia with no haemodynamic compromise. This resolved without treatment 7 h post-ingestion. ECGs were available for 103 patients. The median measured QT interval was 360 ms (range: 280–440 ms; IQR: 340–380 ms). The median QRS was 94 ms (Range: 70–120 ms IQR: 88–101 ms). No patient had an abnormal QT or QRS (Figure 3).

Fifty-five patients (51%) had a GCS of 15. Fifteen patients (14%) had a GCS of ≤9, with this potentially attributed to the co-ingestant in ten patients which included benzodiazepines, opioids, quetiapine and tricyclic antidepressants either alone or in combinations. Five patients (5%; 95% CI: 1.7–11.1%) had a seizure following ingestions of 700–5600 mg (Supplementary Table 1). However, in 3/5 there were co-ingestants that can cause seizures: phenylephrine (60 mg)/pseudoephedrine (540 mg), citalopram (480 mg) and quetiapine (16,800 mg) (Supplementary Table 1). Seizures occurred between 9.75 and 14.5 h post-ingestion (time unavailable for one patient).

Seven patients (6%) had serotonin toxicity based on the Hunter Serotonin Toxicity Criteria with two of these also requiring ICU admission and ventilation for the management of coingestant toxicity (including tricyclic antidepressant with moclobemide and valproate). Five of these patients also co-ingested combinations of drugs known to cause serotonergic effects: amitriptyline, dexamfetamine, duloxetine, escitalopram, moclobemide, pseudoephedrine and venlafaxine (Supplementary Table 1).

Discussion

Desvenlafaxine alone in overdose causes minor effects and is only associated with mild hypertension (32%) and tachycardia (39%). It may cause serotonin toxicity in some patients but rarely central nervous system depression. Seizures occurred in five patients in 182 overdoses (2.8%; 95% CI: 1.0–6.6%), and there were none in overdoses without coingestants. The risk appears lower than with venlafaxine; 5.6% of venlafaxine overdoses in the same hospital cohort had seizures.[24] The frequency of serotonin toxicity in desvenlafaxine-only overdoses as diagnosed by the attending physician (9%), was similar to that reported with serotonin reuptake inhibitors and venlafaxine [26,29,30] but was lower when the Hunter Serotonin Toxicity Criteria was used (1%).

Our findings are consistent with previous studies including the findings from desvenlafaxine only ingestions in 47 patients reported by Forrester et al., where the majority of ingestions resulted in no adverse effects.[25] The study by Forrester included more paediatric patients where the median ingested dose reported was much lower (median: 257 mg; range 25–1050 mg) compared to our study (median overdose: 800 mg). However, consistent with our results the most frequently reported cardiovascular effects were hypertension with an incidence of 6.4% and tachycardia with an incidence of 10.6%. We found a trend towards elevation in systolic BP with increasing dose, which has also been demonstrated in high-dose venlafaxine therapy.[31]

We found no effect of desvenlafaxine overdose on the QT or QRS intervals in patients who had taken desvenlafaxine alone or in combination with other medications. Venlafaxine has been associated with fatal arrhythmias,[32,33] although in a study of 273 patients who took venlafaxine in overdose, arrhythmias or cardiac toxicity was not a feature of the overdose except where large doses were ingested (>8 g venlafaxine).[20] To our knowledge there are no reports of arrhythmias or cardiotoxicity with desvenlafaxine. In our series one patient developed rate dependent bundle branch block that has been reported with other agents causing tachycardia.

Five patients had seizures, all of whom had taken one or more coingestants. Three patients with seizures took drugs in doses that are proconvulsant. Kumar et al., showed the frequency of seizures in venlafaxine overdose was lower with benzodiazepine co-ingestion.[24] The mechanism by which desvenlafaxine or venlafaxine causes seizures is not understood, although the incidence of seizures with desvenlafaxine appears lower than with venlafaxine. Studies in rats have shown that low doses of venlafaxine have anticonvulsant properties whereas higher doses precipitate seizure activity.[34] It is not apparent if it is venlafaxine itself or one or more of the metabolites, including desvenlafaxine, or patient factors such as metaboliser status, or biochemical causes, that are responsible for the seizure activity seen. Shams et al.
has shown that there is significant correlation between the cytochrome P450 2D6 metabolising enzyme genotype and phenotype status of patients taking venlafaxine and the incidence of adverse effects in those with poor metaboliser status.[35] This is proposed as a possible mechanism for seizures from venlafaxine overdose,[36] but this mechanism is unlikely for desvenlafaxine which is not influenced by CYP 2D6.

Interestingly the median ingested dose of 800 mg, was similar to daily doses of up to 900 mg used in pre-clinical trials of desvenlafaxine, where doses up to 750 mg/day were well tolerated, with no reported changes in ECG or routine laboratory tests.[23,37]

Serotonin toxicity diagnosed using Hunter Serotonin Toxicity Criteria was seen in only one patient following a desvenlafaxine alone overdose of 3500 mg, and in seven patients who had taken co-ingestants. In five of these patients (with or without co-ingestants) serotonin toxicity occurred following larger desvenlafaxine overdoses (2100–5600 mg). This suggests that serotonin toxicity is seen particularly after larger ingestions in susceptible individuals or in combination with drugs which have serotonergic effects.[38]

There are a number of limitations to our study. We conducted a retrospective observational study by extracting data from a prospective database and via telephone calls to the Poisons Information Centre, but still required additional data from the patient medical record. A limitation with this design is that not all the information required will be recorded, leading to bias with missing data. The dedicated toxicology database attempts to avoid this problem because most data items are collected prospectively on toxicology admission forms during the admission.

Conclusions

The main effects of desvenlafaxine overdose were mild cardiovascular effects, including mild hypertension and tachycardia, and were associated with higher ingested doses. Seizures were uncommon. The potential for arrhythmias appears low with no prolonged QRS or abnormal QT intervals. Serotonin toxicity was seen with higher dose ingestions or when taken in combination with other serotonergic antidepressants. Doses under 800 mg are highly unlikely to cause significant toxicity based on results from this study and pre-clinical studies of desvenlafaxine.

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Disclosure statement

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