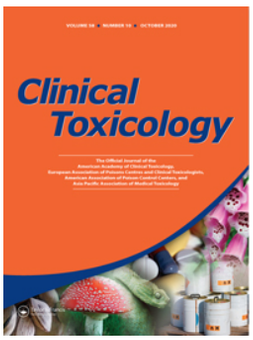

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CLINICAL RESEARCH

Seizure in venlafaxine overdose: a 10-year retrospective review of the California poison control system

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ABSTRACT

Background: The optimal observation time period with respect to seizures after venlafaxine overdose is unclear. We conducted a 10-year retrospective review of calls to the California Poison Control System to describe the time of onset of seizures in adult and pediatric overdose of venlafaxine.

Methods: Inclusion criteria included adult and pediatric patients with exposure to venlafaxine, who were admitted to a health care facility and who had at least one seizure. We did not exclude cases in which co-ingestions of other drugs were reported. Data extraction of *a priori* defined variables was recorded. Descriptive statistics were used to characterize the cohort of patients, including means, medians, and interquartile ranges.

Results: The total number of cases included in the data analysis was 123 (12.9% of all venlafaxine ingestions). The longest time to last seizure was 24 h. Twenty-five percent of participants had a seizure from hour 7 to 24 h. This did not differ significantly between IR and XR formulations.

Conclusions: Optimal observation time with respect to seizures after overdose of immediate-release formulation of venlafaxine is 18 h (24 h if ingested with other medications), and 21 h for patients who are poisoned with the sustained-release formulation.

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KEYWORDS
Poison control centers; venlafaxine; seizure

Introduction

Venlafaxine, a selective serotonin reuptake inhibitor (SSRI) at low doses and a dual action SSRI/serotonergic and norepinephrine reuptake inhibitor at high doses, was first introduced in 1993 and is licensed for the treatment of major depressive disorder, generalized anxiety disorder, panic disorder, and social phobia [1]. It is available in immediate or sustained release formulations and marketed under the brand name Effexor® and Effexor XR®. Venlafaxine is used off-label for the treatment for diabetic neuropathy, chronic pain syndromes, migraine prophylaxis, and hot flashes [2–4]. Prescriptions for venlafaxine increased nearly seven-fold in the first decade of its introduction and between 2006 and 2016, approximately 15.9 million prescriptions of venlafaxine were issued per year [5,6].

The usage of venlafaxine has been associated with a number of side effects, including seizures. The toxicity profile of venlafaxine has been described as a hybrid between standard selective serotonin reuptake inhibitors and tricyclic antidepressants with regard to effects on cardiac conduction, serotonin syndrome, and coma [7]. However, venlafaxine is associated with increased rate of seizures than either medication class. During pre-marketing testing, seizures were reported in 0.26% (8/3082) of venlafaxine-treated patients [3]. Despite the small proportion of seizures that occur after therapeutic doses of venlafaxine [8,9], there are numerous reports of seizures occurring in overdose. The authors of a 2003 retrospective review of 390 calls to the California Poison Control System (CPCS) reported that venlafaxine ingestion was associated with seizures in 23 cases (5.9%) [10]. Subsequently, case reports and abstracts reported delayed seizures, particularly from the sustained release preparation of venlafaxine. There have been various case reports of delayed seizures more than 12 h post-overdose with venlafaxine or similar [11,12]. In addition, venlafaxine-induced seizures can be mitigated by gastrointestinal decontamination procedures, such as single dose activated charcoal and whole bowel irrigation, which can increase decrease medication absorption and increase clearance, respectively [13].

Currently, the CPCS recommends clinicians to observe poisoned patients for 6 h after overdose of immediate release formulations of venlafaxine and 18–24 h for sustained-release preparations. However, a prior study shows that delayed seizures are not uncommon, with 23% of seizures occurring after 8 h or more post-ingestion of venlafaxine, 11% at 16 h or more, and 4% at 24 h or more [13]. Therefore, the optimal observation time period is unclear. Our goal is to describe the time of onset of seizures in adult and pediatric overdose of venlafaxine tablets. The findings of this study are significant as it can either substantiate current recommendations

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Supplemental data for this article can be accessed here.

or offer a more optimal guideline for observation of the venlafaxine-poisoned patient.

Materials and methods

This retrospective review included patients reported to the CPCS from 1 January 2006 through 31 December 2015 who had a seizure after venlafaxine exposure. This study was reviewed and approved by the University of California San Francisco Committee on Human Research.

CPCS is comprised of four poison control centers, and provides a toll-free 24-h hotline service for the public and health care professionals seeking guidance for the care of accidental and intentional poisonings, adverse drug reactions, envenomations, or environmental exposures. All calls received by CPCS are entered into an electronic database called VDL (Visual Dotlab Enterprises) and are reviewed and coded by symptom, treatment, and outcome as outlined by the American Association of Poison Control Centers (AAPCC). Patients are followed remotely by poison control staff until clinical resolution of symptoms attributed to the toxicologic emergency.

A pre-made data extraction form was developed in accordance with the study objective, which included patients' demographic and clinical characteristics. The majority of the study data were collected from VDL charts by a single abstractor (AM) after a training process, which included reviewing the first 100 charts in tandem with another investigator (KV). All data abstracted were collected securely into Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA, USA).

Study subjects

In this study, inclusion criteria included pediatric and adult patients with exposure to venlafaxine, who were admitted to a health care facility, and were described to have a seizure. We did not exclude cases in which co-ingestions of other drugs were reported.

Outcomes

The primary outcome of this study was time of seizure after venlafaxine ingestion. If the exact time of ingestion was not documented in the patient's VDL chart, we estimated the time of ingestion using the following definitions: (1) If no time is documented, it is assumed to have occurred 1 h prior to the time stamp on the record (time of the call); (2) If a time range of given, the middle of the range was used; (3) If the time of ingestion was described as "just now," the time of seizure is equal to the time of the call; (4) If the time of ingestion was described as in the "evening" without further descriptors, the time of 20:00 was used; (5) If the time of ingestion was described as "night" without further descriptors, the time of 00:00 was used; (6) If the time of ingestion was described as "yesterday" without further descriptors, the time of 13:00 was used; 7) If the time of ingestion was described as in the "afternoon" without further descriptors, the time of 16:00 was used.

Covariates

CPCS records included in the study were reviewed for demographic and clinical data utilizing *a priori* defined set of variables and definitions including: patient demographics, administration of activated charcoal as gastrointestinal decontamination, venlafaxine dose ingested, venlafaxine formulation, co-ingestions, time between ingestion and time of seizure(s), and adverse symptoms. Patient demographic data included patient age and sex. Adverse symptoms were either defined as described, or inferred by the abstractor on review of the CPCS record. Signs and symptoms included: agitation, bradycardia (heart rate $<$60 beats/min), cardiac conduction disturbances (including dysrhythmias and interval prolongation), hypertension (systolic blood pressure $>$140 mmHg), hypotension (systolic blood pressure $<$80 mmHg), lethargy, tachycardia (heart rate $>$100 beats/min), respiratory depression (respiratory rate $<$12 breaths/min), and presence of seizures.

Seizures were characterized by number of seizures and time of each seizure since emergency department presentation. Outcome measurements were time to first seizure and time of last recorded seizure. We defined the "last seizure" as the last recorded witnessed seizure. If only one seizure occurred, then this was the last recorded seizure.

Data analysis

Descriptive statistics were used to characterize the cohort of patients identified *via* the search of poison control records. Means and medians were calculated to describe the distribution of numerical variables such as age and time of last seizure. As the time of last seizure was skewed to the right, we chose to report the median and interquartile range. Categorical variables such as age, co-ingestions, and numbers of seizures were tabulated. STATA (StataCorp, 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP) was used for all calculations.

Results

During the 10-year period 2006–2015, 953 patients who ingested venlafaxine and who were admitted to an inpatient hospital facility were reported to the California Poison Control System. Of these, 128 involved only venlafaxine and 825 were multi-substance ingestions including venlafaxine. Only cases in which seizure(s) occurred were included in the primary analysis. The total number of cases included in the data analysis was 123 (12.9% of all venlafaxine ingestions).

Characteristics of study subjects

The characteristics of our study subjects are depicted in Table 1. The median age of patients was 33 years (IQR 21–44) and 40 (33%) were male. The amount of venlafaxine ingested

Table 1. Baseline characteristics of venlafaxine-overdosed patients who had at least one seizure ($N = 123$).

Age (years)	34.2 ± 14.5
Male sex	40 (33%)
Decontamination	37 (30%)
Venlafaxine formulations ingested	
Immediate release (IR)	51 (41%)
Sustained release (XR)	72 (59%)
Adverse outcomes	
Agitation	19 (15%)
Bradycardia	2 (2%)
Cardiac conduction abnormality (including dysrhythmias and interval prolongation)	18 (15%)
Death	7 (5%)
Hypertension	8 (7%)
Hypotension	23 (19%)
Lethargy	55 (45%)
Respiratory depression	12 (10%)
Tachycardia	95 (77%)
Seizures	
One	87 (71%)
Two	24 (19%)
Three or more	11 (9%)
Unknown	1 (1%)
Co-ingestants (categories)	
None	33 (27%)
Analgesic	13 (11%)
Antibiotic	3 (2%)
Antidepressant	45 (37%)
Antiepileptic	15 (12%)
Antipsychotic	29 (23%)
Benzodiazepine	8 (7%)
Caustic	1 (1%)
Co-ingestant(s) known to cause seizures	66 (54%)
Decongestant	8 (7%)
Ethanol	19 (15%)
Illicit stimulant	11 (9%)
Marijuana	6 (5%)
Stimulant	14 (11%)
Other	21 (17%)
Level of care	
Intensive care unit	107 (87%)
Medical/surgical unit	16 (13%)

Table 2. Proconvulsant coingestants in venlafaxine-overdosed patients who had at least one seizure[a].

Drug/toxin	Number of cases
Amphetamine & derivatives	12
Aspirin	1
Bupropion	28
Carbamazepine	1
Chlorpromazine	1
Citalopram	3
Clozapine	1
Diphenhydramine	4
Doxepin	1
Escitalopram	1
Fluoxetine	5
Fluvoxamine	1
Hydroxyzine	2
Lamotrigine	10
Lithium	3
Olanzapine	5
Paroxetine	3
Phencyclidine (PCP)	1
Propranolol	1
Sertraline	1
Tramadol	3
Trazodone	6

[a]Adapted from Table I-13 "Selected Drugs and Toxins Causing Seizures" in "Comprehensive Evaluation and Treatment." Poisoning and Drug Overdose, 7th edition. Kent R. Olson, et al. New York, NY: McGraw-Hill, 2018.

was recorded in only 43 (35%) of the cases, and the amount ranged from 450 milligrams to 15 grams. The median dose was 3000 milligrams (IQR 1500–6750). Decontamination, performed by administration of activated charcoal, was administered in 37 (30%) patients. A majority of patients who developed seizures ingested the sustained release formulation of venlafaxine ($N = 72$, 59%).

The most common adverse outcomes are listed in Table 1. Tachycardia was seen in 93 (77%) patients, followed by lethargy in 55 (45%) patients, hypotension ($N = 23$, 19%), agitation ($N = 19$, 15%), cardiac conduction abnormalities ($N = 18$, 15%), and respiratory depression ($N = 12$; 10%). Eight (5%) patients had hypertension and eight (5%) patients who developed seizures died.

Only thirty-three (27%) patients had single substance ingestions. A majority of patients who had a seizure had multi-substance ingestions. More than half of these patients ($N = 66$; 54%) also ingested one or more medications known to cause seizures. Co-ingestants known to cause seizures and the number of cases they were involved in are depicted in Table 2, with bupropion ($N = 28$), amphetamine ($N = 12$), and lamotrigine ($N = 10$) being the most common. Other common co-ingestants included other antidepressant medications ($N = 45$; 37%), antipsychotics ($N = 29$; 23%), and ethanol ($N = 19$; 15%).

There were six deaths in our cohort of patients who had at least one seizure after venlafaxine overdose (Table 4). None of the deaths were directly related to seizure activity. Five patients died from cardiac arrest, while one patient died from sepsis and acute respiratory distress syndrome.

Seizures

Most patients ($N = 87$, 71%) had only one seizure (the time to first and last recorded seizure are the same). Twenty-four (19%) patients had two seizures, while 11 (9%) patients had 3 or more seizures. In one case, the number of seizures was not documented/unknown based on the CPCS record. The median number of seizures was 1 (IQR 1–2).

The timing of the seizures in the 123 patients who seized is depicted in Figures 1 and 2. The time of seizure is right skewed, with the majority of seizures occurring soon after ingestion. The median time to first seizure after overdose of immediate release venlafaxine was 1.5 h (IQR 1.0–6.3), while it was 3.0 h (IQR 1.0–6.5) after extended release. The median time to last seizure after ingestion of immediate-release and extended-release venlafaxine was 2 h (1.0–7.5) and 4 h (IQR 1–7), respectively, with the longest time to last seizure of 24 h. 25% of participants had a seizure from hour 7 to 24 h. This did not differ significantly between IR and XR formulations, despite a slight trend in time to seizure in the XR group. The association between dose and last seizure is shown in Figure 3, while Figure 4 (supplementary data) shows that the time of last seizure is not statistically shorter in the presence of co-ingestants known to cause seizures (Wilcoxon rank-sum (Mann–Whitney) test; p-value 0.15).

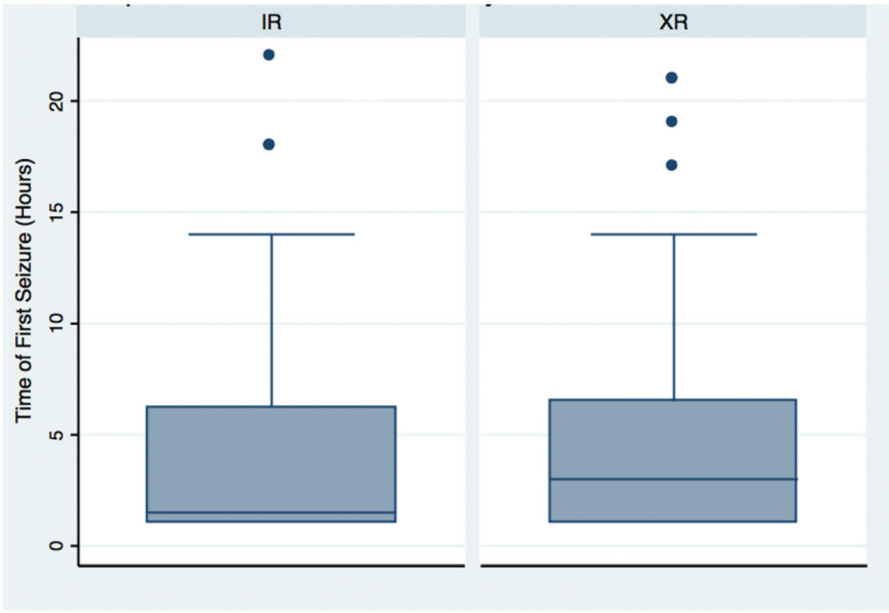

Figure 1. Time to first seizure by formulation.

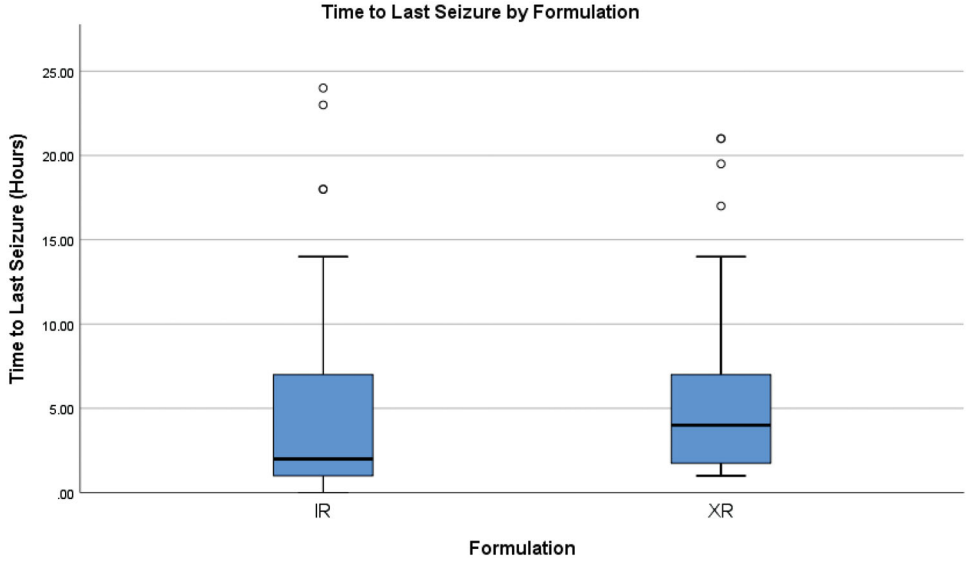

Figure 2. Time to last seizure by formulation.

Characteristics of patients who had delayed seizures after 7 h are shown in Table 3. No patient (0/123; 95% CI = 0–3%) in our cohort had a delayed seizure that occurred after 24 h since time of ingestion. Thirteen of 51 patients (25%) who had an overdose of an immediate-release formulation of venlafaxine developed their last seizure after 7 h time. Of these, seven cases were confounded by the co-ingestion of another medication well known to cause seizures. None of these patients received gastric decontamination with activated charcoal and the dose ingested was unknown. In one case, a 53-year-old woman ingested venlafaxine, diphenhydramine, and a decongestant and developed two seizures at 22 and 23 h, respectively. The last seizure in a case of immediate-release venlafaxine ingestion occurring at 24 h in one case in which a 33 year old man ingested venlafaxine, in addition to bupropion, diphenhydramine, methamphetamine, and quetiapine. The last seizure occurred at 21 h in two cases of ingestions of the extended-release formulation of venlafaxine. In one case, a 50-year-old woman ingested venlafaxine, in addition to lamotrigine and ethanol and presented to the hospital with confusion, agitation, hypertension, and tachycardia. She was treated with activated charcoal and a sedative medication, and had a good recovery. While she did co-ingest a medication well known to cause seizures (lamotrigine), our second case of seizure at 21 h involved a 38-year-old man who ingested 4500 mg of sustained-release venlafaxine. He presented to the hospital with vomiting and tachycardia, was not given activated charcoal, and had a single seizure.

Limitations

Limitations of this study include those inherent to retrospective studies of this type, such as inability to establish

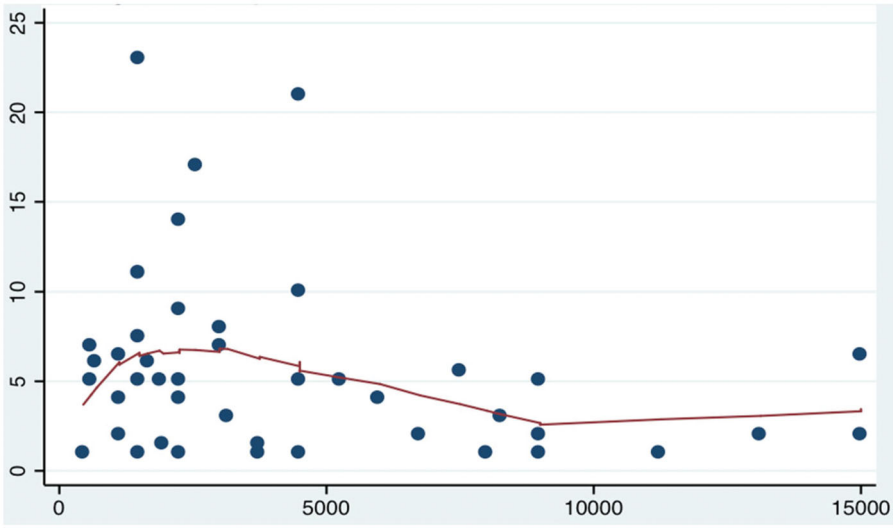

Figure 3. Last seizure versus estimated dose ingested.

Table 3. Characteristics of patient presentations with seizures occurring > 7 h.

Age/sex	Formulation	Decontamination	Time of last seizure (h)	Number of Seizures	Coingestants
1/M	IR	No	10	1	None
15/F	IR	No	17	1	None
16/F	XR	No	14	1	Aripiprazole
18/F	IR	Yes	7.5	1	Diphenhydramine, ibuprofen
20/F	IR	No	18	1	None
20/M	IR	No	14	1	Aripiprazole
20/F	XR	Yes	8	1	Aripiprazole, fluvoxamine
21/F	IR	Yes	12	1	Flurazepam
21/M	XR	No	12	1	Ethanol
22/F	XR	Yes	10	1	Bupropion
25/F	IR	Yes	8	4	Acyclovir, amphetamine
26/F	IR	Yes	10	3	Acetaminophen, citalopram, codeine, promethazine
26/F	XR	Yes	19.5	3	Ethanol, fluoxetine
31/F	XR	Yes	8	1	Bupropion
32/F	XR	No	14	1	Non
33/M	IR	Yes	24	2	Bupropion, methamphetamine, quetiapine
35/F	XR	No	11	1	None
36/F	XR	No	10	1	None
37/F	XR	No	10	1	Paliperidone
38/M	XR	No	21	1	None
40/F	IR	No	18	1	Alprazolam, diazepam, zolpidem
40/M	XR	No	10	1	None
44/F	XR	No	9	2	None
44/F	XR	No	10	1	Ethanol, Ditropan
50/F	IR	Yes	14	2	Bupropion, zolpidem
50/F	XR	Yes	21	1	Ethanol, lamotrigine
52/F	XR	No	9.5	1	None
53/F	IR	Yes	23	–	Diphenhydramine
63M	IR	Yes	13	1	Chlordiazepoxide, ethanol, prazosin, trazodone

Table 4. Characteristics of patients who died after experiencing seizure(s) after venlafaxine overdose.

Age/Sex	Formulation	Dose (mg)	Number of seizures	Co-ingestant(s)	Cause of death
29/F	IR	13125	1	Ethanol	Cardiac arrest
32/M	IR	6000	1	Methamphetamine	Sepsis, refractory acute respiratory distress syndrome
42/F	XR	Unknown	3	Aripiprazole, bupropion, lamotrigine	Multi-organ system dysfunction, cardiac arrest
49/M	XR	15000	1	None	Ventricular arrhythmia, cardiac arrest
52/M	IR	Unknown	1	Paroxetine, THC	Ventricular arrhythmia, cardiac arrest
63/F	XR	Unknown	2	Acetaminophen, bupropion, clonazepam, ethanol, eszopiclone, hydrocodone, topiramate	Ventricular arrhythmia, cardiac arrest

causation or determine the directionality of relationships. Additionally, as our methodology involved a single abstractor, we did not assess for agreement or interrater reliability of our data.

The data source used (VDL) is limited to the completeness of data recorded. For example, exact information about the ingested dose was documented in only 43 of the 123 charts. In addition, because there is no standardized procedure at the poison control center regarding timing of callbacks to hospital facilities, we do not know if all seizures were captured for all patients. Even when documented, the information was obtained over the telephone, with the risk of misinterpretation or miscommunication. Furthermore, patients may be lost to follow-up by CPCS staff for various reasons (e.g., patients may have been discharged prior to completion of follow-up or treatment teams could not be reached). In addition, patients may have been discharged at 6 h per current guidelines and may have had subsequent unwitnessed seizures.

We included cases in which other drugs, in addition to venlafaxine, were ingested. While this can cause confounding effects, particularly in cases where the co-ingestant(s) included medications known to cause seizures, we wanted to be as thorough as possible in our analysis of seizure occurrence. This meant including all cases in which seizure occurred regardless of co-ingestants. In addition, we cannot prove that other drugs, in addition to the ones tallied, were not taken, because we do not have comprehensive toxicology screening data for all of the cases.

Finally, poison control center data are not necessarily generalizable [14]. Not all cases of poisoning treated in emergency departments are reported to poison control centers, which are passive recipients of requests for consultation from clinicians.

Discussion

Venlafaxine is an antidepressant medication that blocks the reuptake of serotonin, norepinephrine and, to a lesser extent, dopamine. At low doses (e.g., 75–150 mg/day) it acts on serotonergic transmission; at moderate doses (>150 mg/day), it acts on serotonergic and noradrenergic systems; and at high doses (>225 mg/day), it affects serotonergic, noradrenergic, and dopaminergic neurotransmission [15]. These neurotransmitters play an important role in seizure genesis. An animal study investigated proconvulsant effects of high doses of venlafaxine and speculated that the blockage of reuptake of dopamine by venlafaxine can exacerbate D1 postsynaptic dopaminergic receptor effects, thereby promoting a proconvulsant effect [16]. Despite this, a majority of our overdosed patients had a single seizure and the two patients who had the greatest number of seizures (five) ingested 1500 mg and 2250 mg, respectively. One patient who ingested the largest amount, 15 grams, only had two documented seizures.

Currently, CPCS recommends poisoned patients be observed for 6 h after overdose of immediate release formulations of venlafaxine. In our cohort, only 25% of patients who had an overdose of an immediate-release formulation of venlafaxine developed their last seizure after 7 h. However, though incidence of delayed seizures is relatively low for ingestions of immediate-release venlafaxine, because seizures are associated with high morbidity and mortality, we recommend that patients with single-substance immediate-release ingestions be observed for at least 18 h and patients with co-ingestions be observed for at least 21 h. Patients who received gastric decontamination may be able to be discharged sooner, but the timing of this is unknown.

After overdose of sustained-release preparations of venlafaxine, patients referred to CPCS are observed for 18–24 h. As previously described, no patient in our cohort had a delayed seizure that occurred after 24 h since time of venlafaxine ingestion, with the last seizure occurring at 21 h in two cases. Our recommendations are in line with prior studies, one which showed a small percentage of patients develop seizures after overdose of sustained-release preparations, and another that showed time of onset of seizure after venlafaxine overdose as 3.7 h, with a range of 0.6–21 h [7,13]. Therefore, we support the current CPCS recommendation of observing patients for at least 21 h after overdose of a sustained-release venlafaxine product.

Conclusion

Venlafaxine is one of the most commonly prescribed antidepressants in the United States and seizure is, arguably, the most concerning adverse effect after ingestion. Our results are consistent with prior studies based on expected timing of seizures based on venlafaxine's pharmacokinetic profile. Optimal observation time with respect to seizures after overdose of immediate-release formulation of venlafaxine is 18 h (24 h if ingested with other medications), and 21 h for patients who are poisoned with the sustained-release formulation. Our findings regarding the optimal time of observation of the venlafaxine-poisoned patient are useful poison control staff and treating clinicians who play a vital role in the monitoring and treatment of drug-related complications.

Disclosure statement

No potential conflict of interest was reported by the authors.

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