Q J Med 2003; **96**:369–374
doi:10.1093/qjmed/hcg062

Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants

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Received 27 August 2002 and in revised form 5 February 2003

Summary

Background: Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine have been regarded as less toxic in overdose than tricyclic antidepressants (TCAs). Within the TCAs, dothiepin has greater toxicity. Venlafaxine may be more toxic than SSRIs.
Aim: To assess the toxicity in overdose of venlafaxine and SSRIs compared to TCAs, and of dothiepin compared to other TCAs.
Design: Cohort study of prospectively collected data from the Hunter area, NSW, Australia.
Methods: First admissions with antidepressant deliberate self-poisoning (DSP) (November 1994 to April 2000) were identified; the presence of seizures, life-threatening arrhythmias, coma, serotonin toxicity or ICU admission, and QRS duration were noted.
Results: There were 538 admissions, with no deaths. The odds ratio (OR) for seizures with dothiepin vs. other TCAs was 3.4 (95%CI 1.2–9.9). Seizures occurred in 7/51 (14%) venlafaxine overdoses; all patients with seizures consumed $\geqslant$900 mg. The OR for seizures vs. TCAs was 4.4 (95%CI 1.4–13.8). Coma was less likely with venlafaxine and SSRIs. SSRIs, but not venlafaxine, were less likely to prolong the QRS to $\geqslant$100 ms. ICU admission was less likely for SSRIs. Serotonin toxicity was much more common with venlafaxine and SSRIs.
Discussion: Venlafaxine and dothiepin are pro-convulsant in overdose. Venlafaxine is more likely to cause serotonin toxicity, but less likely to cause coma than TCAs. SSRIs are less likely to cause coma, require ICU admission, or prolong the QRS, but are more likely to cause serotonin toxicity. Antidepressants other than TCAs or venlafaxine should be considered in patients at risk of seizure or suicide.

Introduction

Venlafaxine is a hydroxycycloalkylphenylethylamine-derivative bicyclic antidepressant which is structurally and pharmacologically related to the analgesic tramadol, but not to any of the conventional antidepressant drugs, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) or reversible inhibitors of monoamine oxidase (RIMAs) such as moclobemide. Like the tricyclic antidepressants, venlafaxine inhibits monoamine uptake (serotonin > noradrenaline $\gg$ dopamine) and has been termed a serotonin noradrenaline reuptake inhibitor (SNRI). It does not inhibit monoamine oxidase, and unlike the

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tricyclic antidepressants is neither antimuscarinic nor has any appreciable affinity for alpha-adrenergic or histaminergic binding sites.[1]

The SSRIs are a structurally unrelated group with a common mode of action. In studies of relative mortality from overdose of antidepressants, the numbers of deaths per million prescriptions are lower for SSRIs than for TCAs.[2] This, and the adverse effect profile of the SSRIs, has led some authors to suggest that the potential exists for negligence claims to be brought against medical practitioners who prescribe TCAs (rather than the newer agents) for reasons other than established need.[3] Others have suggested that such a strategy is not cost-effective.[4] In these discussions, venlafaxine has usually been included with the SSRIs. More recent fatal toxicity indices suggest that venlafaxine is more toxic than the SSRIs and as toxic as at least two TCAs, clomipramine and nortriptyline.[5]

In pre-clinical trials of venlafaxine, there were 14 cases of overdose all of whom recovered without sequelae.[6] One of these patients had multiple seizures and QTc prolongation,[6] and more recent cases suggest that seizures,[7–12] life-threatening cardiac toxicity[7,13] and death[14,15] may occur after venlafaxine overdose. An abstract describing the features of venlafaxine overdose in 626 adults reported seizures in 5%.[16] These features are clinically similar to those seen after TCA overdose, particularly the more proconvulsant dothiepin.[17]

Venlafaxine was placed on the Australian Register of Therapeutic Goods on November 16, 1994. We hypothesized that the clinical toxicity in overdose of venlafaxine may be greater than that of the SSRIs and similar to that of the TCAs. We also hypothesized that the increased seizure activity previously demonstrated after dothiepin overdose[17] would be conformed in this new dataset.

Methods

The Hunter Area Toxicology Service (HATS) is a regional toxicology unit situated at the Newcastle Mater Misericordiae Hospital, which services a population of about 350 000 people and is a tertiary referral centre for a further 150 000.[18] All presentations to the service are entered prospectively into a clinical database. A preformatted admission sheet is used by medical staff to collect data on admission,[19] and these data, with additional information from the medical record, are entered into the database by two trained personnel blinded to any study hypotheses. Detailed demographic and clinical information is recorded.[20] This was a study of consecutive presentations to hospital after deliberate self-poisoning (DSP) between 16 November 1994 and 4 April 2000.

All admissions in the Hunter Area Toxicology Service database for the period of interest were assessed. From this initial dataset of 3476 deliberate self poisonings (DSPs), all admissions where an antidepressant was taken were extracted (1237 admissions). We excluded 82 admissions who took a monoamine oxidase inhibitor, including moclobemide. Thioridazine coingestion (33 admissions) was also excluded, as it has been shown to be more cardiotoxic than other antipsychotics.[21] Admissions where more than one of the drugs of interest was ingested (419 admissions) were also removed. Finally, all second and subsequent admissions (165 admissions) were excluded, to reduce any bias occasioned by individual patient factors increasing risks of study outcomes (e.g. seizure tendency). This left a dataset consisting of 538 antidepressant DSP first admissions consisting of 51 venlafaxine, 82 dothiepin, 172 other TCA (excluding dothiepin) and 233 SSRI DSP first admissions.

Descriptive variables were: age, gender (as percent female), coingested proconvulsant drugs (chloral hydrate, antihistamines, antipsychotics, beta-blockers, theophylline, and bupropion), previous anticonvulsant therapy, history of epilepsy, amount taken (as defined daily doses, DDDs) and time to presentation. The DDD is based on the assumed average daily dose of the drug when used for its main indication by adults. It is the unit approved by the World Health Organization (WHO) for drug use studies, and allows for comparisons independent of differences in price, preparation and quantity per prescription.[22]

Outcome variables were proportion of cases with one or more seizures, proportion with a life-threatening arrhythmia, mean QRS duration on admission, proportion of patients with a QRS $\geqslant$100 ms at any time,[23] mean blood pressure, mean pulse rate, mean QT interval, mean corrected QT (QTc),[24] proportion with GCS $\leqslant$10 on admission, proportion with coma level 0 or greater,[25] proportion with serotonin toxicity as defined by Sternbach,[26] hospital length of stay (LOS), proportion requiring ICU admission, and for those in ICU, LOS in ICU. Since a large number of outcome variables can increase the possibility of false-positive results arising by chance, the outcome variables of primary interest were predetermined to be seizures, life-threatening arrhythmias, Glasgow coma score $\leqslant$10, coma, QRS $\geqslant$100 ms, serotonin toxicity and ICU admission.

Dothiepin has already been shown to have a toxicological profile that differs (more proconvulsant) from other TCAs.[17] Thus, an odds ratio for seizure in dothiepin DSPs compared to other TCA DSPs was calculated to examine our previous observation, but dothiepin was excluded from comparisons with SSRIs and venlafaxine. Results are presented as median (range) or mean (SEM) and odds ratios (OR) with 95% confidence intervals (95%CI). Odds ratios were adjusted for study factors shown to be different between the groups. Dunn's multiple comparison test was used for *post-hoc* multiple comparison testing.[27] Exact tests were used where cell numbers were too small for asymptotic estimations. Statistical calculations were performed using GraphPad InStat version 3.05 for Windows 95/NT (GraphPad Software), StatXact Version 5.0.3 and LogExact Version 5.0 (Cytel Software Corporation).

Results

There were no deaths in any of the groups under study. Nine of the 82 patients who took dothiepin had a seizure (11%), while six of the 172 other TCA DSPs had a seizure (3.5%). The OR for seizures with dothiepin vs. other TCAs was 3.4 (95%CI 1.2–9.9, $p = 0.02$). None of the descriptive study variables (see Table 1) was significantly different between dothiepin and other TCAs (data not shown). However, our previous analysis[17] included adjustment for age, gender and ingested dose. When this adjustment was made, the OR for seizures with dothiepin was 8.9 (1.9–41.1, $p = 0.005$). Dothiepin was excluded from further analysis.

The descriptive study variables are shown in Table 1. SSRI DSPs were significantly younger, took more drug and had more proconvulsant drugs than TCA DSPs. Venlafaxine DSPs also took more drug than TCA DSPs. Venlafaxine DSPs presented significantly longer after their overdose than SSRI DSPs but not longer than TCA DSPs. Other variables were not significantly different between the groups.

Significant venlafaxine DSPs had a unique toxicological profile that was a hybrid of TCA and SSRI toxidromes. Serotonergic toxicity, minor QRS changes and seizures were common but there was little or no sedation or anticholinergic effect in most overdoses (Table 2). Seizures were more common in venlafaxine DSP than either TCA or SSRI DSP. ICU admission was more common in venlafaxine DSP than SSRI DSP but TCA DSP resulted in more ICU admissions than either. SSRIs were less likely to cause tachycardia, hypotension, and prolongation of the QRS and QTc than TCAs, while venlafaxine was not significantly different from TCAs in these parameters. SSRI DSPs spent significantly less time in hospital than TCA DSPs while venlafaxine DSPs were not different from TCA DSPs. TCAs were much more likely to produce coma, and much less likely to produce serotonin toxicity than either venlafaxine or SSRIs.

Odds ratios (unadjusted and adjusted for age, coingested proconvulsant drugs, amount taken and time to presentation) for the major outcomes for venlafaxine and SSRIs versus TCAs are shown in Table 3. They confirm the differences shown in Table 2, and give an indication of the strength of those differences. Seizures were very much more evident in the venlafaxine group than the TCAs (OR 4.4, 95%CI 1.4–13.8). Both venlafaxine (OR 35.4, 95%CI 7.8–161.7) and the SSRIs (OR 20.4, 95% CI 4.9–85.1) were very much more likely to produce serotonin toxicity than were the TCAs. Adjusting for possible confounders did not materially change the results.

Table 1 Study factors in patients who had ingested venlafaxine, a TCA (not dothiepin) or an SSRI

	Venlafaxine ($n = 51$)	TCAs ($n = 172$)	SSRIs ($n = 233$)	$p^{\ddagger}$
Age (years)	36 (15–66)	38 (14–83)	29 (13–77)***	<0.0001
Female	35 (68.6)	108 (62.8)	156 (67.0)	0.61
Coingested proconvulsant drugs (see text)	9 (17.6)	13 (7.6)	37 (15.9)*	0.03
Previous anticonvulsant therapy	4 (7.8)	13 (7.6)	17 (7.3)	0.99
History of epilepsy	2 (3.9)	5 (2.9)	11 (4.7)	0.65
Amount taken (DDDs)	10.9 (0.8–82.5)* [$n = 48$]	6.7 (0.3–66.7) [$n = 155$]	16 (0.5–150.0)*** [$n = 222$]	<0.0001
Time to presentation (h)	3.7 (0.6–21.0)† [$n = 48$]	2.8 (0.3–40.8) [$n = 161$]	2.5 (0.3–68.5) [$n = 229$]	0.02

Data are medians (range) or numbers (%) of patients For cells with missing values, the actual n is indicated. ‡Kruskal-Wallis test. *$p < 0.05$ vs. TCAs, **$p < 0.01$ vs. TCAs, ***$p < 0.001$ vs. TCAs; $^{\dagger}p < 0.05$ vs SSRIs by Dunn's Multiple Comparisons test.

Table 2 Outcome measures in patients who had ingested venlafaxine, a TCA (not dothiepin) or an SSRI

	Venlafaxine ($n = 51$)	TCAs ($n = 172$)	SSRIs ($n = 233$)	$p^{\ddagger}$
Seizures	7 (13.7)**†††	6 (3.5)	3 (1.3)	< 0.0001
Life-threatening arrhythmias	0 (0.0)	4 (2.3)	1 (0.4)	0.14
Heart rate (bpm)	100 (56–138)	95.5 (60–180)	87 (54–171)***	< 0.0001
Mean blood pressure (mmHg)	103 (56–138)***	93 (49–132) [$n = 171$]	97 (53–133)**	< 0.0001
Glasgow coma score $\leqslant 10$	3 (7.0)*** [$n = 43$]	48 (30.4) [$n = 158$]	6 (2.6)*** [$n = 232$]	< 0.0001
Comatose	1 (2.1)*** [$n = 48$]	29 (17.7) [$n = 164$]	3 (1.3)*** [$n = 228$]	< 0.0001
QRS duration (ms)	90 (80–120) [$n = 38$]	90 (50–320) [$n = 153$]	82 (60–130)*** [$n = 178$]	0.0004
QRS $\geqslant 100$ ms	14 (36.8) [$n = 38$]	73 (47.7) [$n = 153$]	43 (24.2)*** [$n = 178$]	< 0.0001
QT duration (ms)	355 (260–420) [$n = 38$]	360 (200–480) [$n = 149$]	360 (200–480) [$n = 173$]	0.026
QTc ($s^{1/2}$)	436 (355–531) [$n = 37$]	439 (223–632) [$n = 149$]	428 (248–563)** [$n = 172$]	0.01
Serotonin toxicity	15 (29.4)***	2 (1.2)	45 (19.3)***	< 0.0001
ICU admission	15 (29.4)*††	79 (45.9)	17 (7.3)***	< 0.0001
Time in ICU (h)	39.5 (11.83–286) [$n = 15$]	40.62 (7.2–224.5) [$n = 79$]	32.3 (9–124.5) [$n = 17$]	0.37
Time in hospital (h)	18.5 (0.8–330.2)	23.2 (2.8–282)	15.3 (2–185.5)***	< 0.0001

Data are medians (range) or numbers (%) of patients For cells with missing values, the actual n is indicated. ‡Kruskal-Wallis test. $^{*}p < 0.05$ vs. TCAs, $^{**}p < 0.01$ vs. TCAs, $^{***}p < 0.001$ vs. TCAs; $^{\dagger\dagger}p < 0.01$ vs. SSRIs; $^{\dagger\dagger\dagger}p < 0.001$ vs. SSRIs by Dunn's Multiple Comparisons test.

Table 3 Unadjusted and adjusted odds ratios (ORs) for major complications of venlafaxine and SSRI overdose vs. TCA (not dothiepin) overdose

	Unadjusted OR (95%CI)	p	*A*djusted* OR (95%CI)	p
Venlafaxine				
Seizures	4.4 (1.4–13.8)	0.01	7.5 (1.7–34.3)	0.009
Life-threatening arrhythmias	0.6 (0.0–5.1)	0.70	NA	NA
Glasgow coma score $\leqslant 10$	0.2 (0.05–0.6)	0.005	0.1 (0.02–0.5)	0.004
Comatose	0.1 (0.01–0.7)	0.02	0.1 (0.02–0.99)	0.049
QRS $\geqslant 100$	0.6 (0.3–1.3)	0.23	0.6 (0.2–1.2)	0.14
Serotonin toxicity	35.4 (7.8–161.7)**	< 0.0001	23.9 (5.1–113.0)**	0.0001
ICU admission	0.5 (0.3–0.96)	0.04	0.3 (0.1–0.8)	0.009
SSRI				
Seizures	0.4 (0.1–1.5)	0.15	0.1 (0.02–1.4)	0.09
Life-threatening arrhythmias	0.2 (0.004–1.9)	0.21	NA	NA
Glasgow coma score $\leqslant 10$	0.1 (0.03–0.2)	< 0.0001	0.03 (0.01–0.1)	< 0.0001
Comatose	0.1 (0.02–0.2)	< 0.0001	0.04 (0.01–0.2)	< 0.0001
QRS $\geqslant 100$	0.3 (0.2–0.6)	< 0.0001	0.2 (0.1–0.4)	< 0.0001
Serotonin toxicity	20.3 (4.9–85.1)	< 0.0001	12.3 (2.9–52.8)	0.0008
ICU admission	0.1 (0.05–0.2)	< 0.0001	0.04 (0.02–0.1)	< 0.0001

*Odds ratio adjusted for age, co-ingested convulsant drugs, amount of drug taken, time to presentation. **Confidence intervals very wide due to the very small numbers of cases in the TCA group. NA, not applicable due to very small or zero numbers of events.

A comparison of study factors in those patients experiencing a seizure is shown in Table 4. Although numbers are small, seizures associated with venlafaxine and SSRIs occurred later than those associated with TCAs. Serotonin toxicity was more common with the venlafaxine-associated seizures than the TCA seizures. The median dose in those who had a venlafaxine-associated seizure was 3150 mg, and the minimum dose was 900 mg.

Discussion

In a completely new dataset, this study confirms our earlier finding that dothiepin is more proconvulsant in overdose than other tricyclic antidepressants.[17] The study also gives a biologically plausible reason why venlafaxine has a fatal toxicity index closer to that of the tricyclic antidepressants than the serotonin reuptake inhibitors.[5]

Table 4 Study factors in patients who had seizures after ingesting venlafaxine, a TCA (not dothiepin) or an SSRI

	Venlafaxine ($n = 7$)	TCAs ($n = 6$)	SSRIs ($n = 3$)	$p^{\ddagger}$
Age (years)	42 (18–66)	26 (16–32)	26 (21–29)	0.23
Female	5 (71.4)	2 (33.3)	2 (66.7)	0.38
Amount taken (DDDs)	31.5 (9–82.5)	17.5 (6.7–62.5) [$n = 4$]	30 (10.0–150)	0.77
Life-threatening arrhythmias	0 (0.0)	2 (33.3)	0 (0.0)	0.17
Comatose	0 (0.0) [$n = 5$]	3 (50.0)	0 (0.0)	0.09
QRS $\geqslant$100 ms	4 (66.7) [$n = 6$]	5 (83.3)	0 (0.0) [$n = 2$]	0.12
Time to seizure (h)	3.9 (1.5–15.1)* [$n = 6^{\dagger}$]	1.0 (0.7–2.5) [$n = 5$]	27.5 (2.0–68.5)*	0.029
Serotonin toxicity	6 (85.7)*	1 (16.7)	2 (66.7)	0.049

For cells with missing values the actual n is indicated. [†]One patient excluded who seized after venlafaxine extended release preparation. [‡]Kruskal-Wallis test. *$p < 0.05$ vs. TCAs by Dunn's Multiple Comparisons test.

When presented as DDDs rather than numbers of tablets taken, the doses of SSRI and venlafaxine were significantly larger than the doses of TCAs taken. This is most likely due to the packaging of these drugs. The DDD for most SSRIs is the equivalent of one tablet. The DDD for TCAs (usually 100 mg) is from four tablets (for the 25 mg dose) up to 10 tablets (for the 10 mg dose). The DDD for venlafaxine (100 mg) is between two and three tablets (for the 37.5 mg dose) or one and a third tablets (for the 75 mg dose). Adjusting for dose did not change the results of this study.

Venlafaxine does not have the same toxicity profile in overdose (toxidrome) as the TCAs, even though the ECG changes are similar and the propensity for seizures is greater. TCA overdoses are much more likely to be unconscious and consequently require ICU admission, and much less likely to have serotonin toxicity. A rate-dependent effect on sodium channels at micromolar concentrations may provide an explanation for both the pro-convulsant and QRS-prolonging effects of venlafaxine.[28]

This study provides further evidence for variation in toxicity between antidepressants. This occurs within a drug class (i.e. dothiepin vs. other TCAs) and between classes (i.e. venlafaxine vs. TCAs vs. SSRIs). Identifying drugs with a higher relative toxicity in overdose is important for toxicological monitoring (toxicovigilance). These data may identify drugs that may be relatively contraindicated in patients with pre-existing seizures or cardiac disease. For venlafaxine, subjects who are CYP2D6 poor metabolizers or who are taking interacting drugs may achieve concentrations similar to those found in overdose with therapeutic doses.[29,30] Data on relative toxicity in overdose should thus be considered when making prescribing and regulatory decisions for all patients. However, the main conclusion is that venlafaxine joins the TCAs as a drug that should not be prescribed to those at high, immediate risk of deliberate self-poisoning.

Acknowledgements

The authors wish to thank Dr Di O'Connell for statistical advice and Professor David Henry for his comments on the study.

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