Acta Neuropsychiatrica

Acta Neuropsychiatrica 2011: 23: 156–160

DOI: 10.1111/j.1601-5215.2011.00566.x

Rapid Communications

Suicide cases and venlafaxine

Piatkov I, Jones T, Van Vuuren RJ. Suicide cases and venlafaxine.

Objective: Our aim was to establish whether the presence or absence of fully functioning cytochrome P450 2D6, 2C19 and 2C9 genetic alleles was associated with suicide in patients receiving venlafaxine treatment.
Method: Authorisation from the NSW State Coroner to perform post-mortem genetic testing was obtained for 11 samples from deceased persons who committed suicide during treatment with venlafaxine (VENADR study).
Results: All patients, but one, have at least one copy of the loss-of-function, altered or decreased cytochrome P450 enzyme activity allele. Four patients' results reveal loss-of-function genotypes, while all others were found to have diminished enzyme activity polymorphisms. Seven patients had multiple altered function polymorphisms, which included CYP2D6, CYP2C19 or CYP2C9.
Conclusion: Our preliminary limited data show that neurotoxicity development, which manifests as suicide while on venlafaxine treatment, probably correlates with a higher prevalence of gene copies of altered functioning cytochrome P450 genetic polymorphisms.

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Keywords: adverse effects; cytochrome P450; genetic polymorphisms; pharmacogenetics; suicide; venlafaxine

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Significant Outcomes

Our results showed:

- The potential role of pharmacogenomic testing in modern psychopharmacologic practice.
- A potential contribution to filling some of the scientific uncertainties in the interpretation of adverse drug reactions on venlafaxine.
- An indication for further studies to enhance recommendations for suicide prevention.

Limitations

As a result of the small sample size analysed in this preliminary study, further investigation will be required to produce significant data for clinical recommendation to suicide prevention.

Introduction

Fatal toxicity index (FTI) for drugs is calculated in terms of deaths per prescriptions. Venlafaxine is an antidepressant found to possess a higher FTI than other newer antidepressants and selective serotonin reuptake inhibitors (SSRIs). Compared with other common antidepressants, venlafaxine-positive cases showed the highest suicide frequency. In addition, the proportion of suicidal venlafaxine poisonings of all suicides was substantially higher than that of mirtazapine or SSRIs (1).

Despite a Food and Drug Administration (FDA, USA) warning for an increased risk of suicidality on venlafaxine therapy, not enough data have accumulated to confirm this association. Only several cases have been reported (2–5).

Evaluation of toxicological results includes several factors. Consideration of interactions between substances metabolised through the Phase I cytochrome P450 system and an individual's variation in enzyme activity should be used in interpreting toxicological data in relevant forensic medicine and medical practice cases.

Drug toxicology evidence is currently based on the drug to metabolite ratio in blood or urine. However, measurement of metabolites and their input into the neurotoxicity evaluation remain uncertain because of the methodology of detection and lack of scientifically based evidence. In addition, each person is unique in his or her susceptibility to toxic agents.

Recent research in the pharmacogenetics of antidepressants, venlafaxine amongst them, showed that polymorphic variations in the CYP450 genotype would necessitate modification of dosage to obtain target blood levels (6,7). Individuals who lack fully functional alleles of the relevant CYP450 gene were also shown to be less able to tolerate treatment at recommended dosages of drugs metabolised primarily by 2D6, 2C19 and 2C9 (7).

Venlafaxine is an antidepressant that is biotransformed to the active metabolite *O*-desmethylvenlafaxine, primarily by the CYP2D6 and CYP2C19 enzymes (8). According to the venlafaxine pathway (7,8), patients with loss-of-function alleles are predicted to have higher serum levels of both venlafaxine and *N*-desmethylvenlafaxine for any given dose of venlafaxine compared to patients with two functional copies of the CYP genes.

Adverse drug reactions or treatment resistance to venlafaxine are described in some publications (9–18). Serotonin syndrome induced by low-dose venlafaxine is described by Pan (15) and Bond (9).

Chan et al. (19) reported that those who ingested venlafaxine were more likely to become confused (25% vs. 0%; $p = 0$) and have mydriasis (19.4% vs. 2%; $p \leq 0.02$) than those who took SSRIs. Compared with SSRI self-poisoners, patients who deliberately ingested venlafaxine were more likely to exhibit serious suicide intent.

Aims of this study

The variation in individual responses to psychotropic drug treatment remains a critical problem in the management of psychotic disorders. Although most patients will experience remission, some develop drug-induced adverse effects that can range from troublesome to life threatening. We aim to determine whether the presence or absence of fully functioning cytochrome P450 2D6, 2C19 and 2C9 genetic alleles is associated with suicide in patients receiving venlafaxine treatment.

Material and methods

Subjects

Authorisation from the NSW State Coroner to perform post-mortem genetic testing was obtained for 10 samples from deceased persons who committed suicide during treatment on venlafaxine (VENADR study). Ethics approval was obtained from Sydney South West Area Health Service Ethics Committee. In addition, one sample that had been previously received at the request of the Coroner was included.

Eleven (including one referred previously from the Department of Forensics) post-mortem blood samples from patients on venlafaxine therapy, who committed suicide, were analysed.

Method

DNA was extracted from the post-mortem whole blood samples stored in the NSW Forensic Department. The variant alleles of CYP2D6*2 (2850C>T), *3 (2549delA), *4 (1846G>A), *5 deletion, *10 (100C>T), *17 (1023C>T, 2850C>T), *41(2988 G>A); CYP2C9*2 (430C>T), *3 (1075A>C) and CYP2C19*2 (681G>A), *3 (636G>A), *17 (-806C →T) that affect the function of cytochrome enzymes were genotyped at the Diversity Health Institute Research Laboratory (DHIRL). DNA was extracted from blood or tissue samples using the manufacturer's protocol for the QIAGEN EZ1 Robot system. The genotyping method involves specific restriction enzyme digestion of amplified PCR products or tetra-primer allele-specific amplification PCR. The fragment analysis is based on capillary electrophoresis, the methodology of which is described in detail in our previous publication (20).

Results

The post-mortem samples from persons who had committed suicide were analysed and prevalence of loss-of-function polymorphisms was identified. They were then compared with DHIRL data for the Western Sydney Local Health Network (WSLHN), formally Sydney West Area Health Service, population which was published previously in 'Pharmacogenetics' (20). Control DHIRL laboratory population data reflect prevalence of polymorphisms in the Sydney population (Fig. 1).

All patients, but one, have at least one copy of the loss-of-function, altered or decreased cytochrome P450 enzyme activity allele (Table 1). Seven patients are heterozygous for CYP2C19*17, which linked with increased metabolism.

Four patients' results reveal loss-of-function genotypes, while all others were found to have diminished enzyme activity polymorphisms (Table 1).

As we described previously (20), the coincidence of multiple polymorphisms producing diminished enzyme activity is rare in any population, but their significance is important as it dramatically

https://doi.org/10.1111/j.1601-5215.2011.00566.x Published online by Cambridge University Press

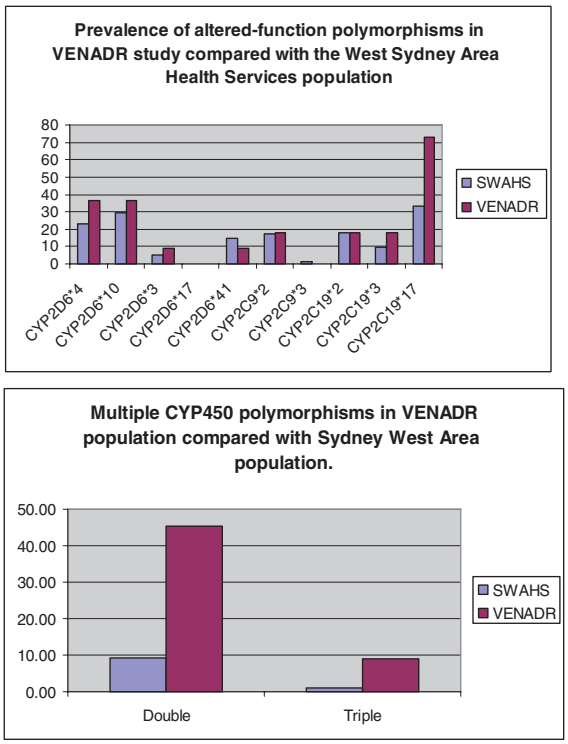

Fig. 1. Prevalence of cytochrome P450 polymorphisms.

alters a patient's metabolising capacity. The higher prevalence of multiple polymorphisms in the illicit drug users and akathisia patients was obvious: 21.0 and 18.0% for double alleles, compared with 13.0% in the general WSLHN population and 7.0 and 6.0% for triple alleles, compared with 0.3% in the general population (20).

Seven patients had multiple loss-of-function polymorphisms, which include CYP2D6, CYP2C19 and CYP2C9. Multiple effects of diminished enzyme activities on the venlafaxine metabolic pathway could contribute to the impairment of venlafaxine metabolism (Fig. 1).

Discussion

Some patients prescribed a psychotropic drug either do not respond to treatment or experience adverse drug reactions. If this occurs, the treatment can be modified by adjusting the dose or use of an alternative drug.

While adverse effects of a psychoactive drug can result from its physiological action, they are mainly caused by factors that affect drug pharmacodynamics or pharmacokinetics. Drug tissue distribution depends on the rate of metabolic reactions involving absorption and elimination. Individual variations in the activity of metabolic enzymes can affect drug tissue distribution and therapeutic/toxic concentration, which in turn can influence a patient's response to treatment or toxicity development.

Psychotropic drug prescribers must consider treatment-resistant patients as potential abnormal metabolisers. Nearly 80% of all drugs in use today, along with most psychotropics, are metabolised through testable metabolic pathways where the genetic code for the key enzymes can be tested.

In addition, patients with psychiatric disease are at an increased risk for being on multiple medications and complex regimes, which makes them particularly

Table 1. Drugs and cytochrome P450 polymorphisms detected in post-mortem blood samples

Patient	Sex	Age	Venlafaxine concentration (mg/l)	Traces of other drugs detected in post-mortem blood	Alcohol	CYP polymorphisms
1	Female	48	0.4	Benzodiazepam	Negative	CYP2C9 *1/*3; CYP2C19*1*17
2	Female	57	5.0	Hydrochlorthiazide, dothiepin, mitrazapine, olanzapine and amitriptyline	Traces	CYP2C9 *1/*3; CYP2C19*1*17; CYP2D6*4/*10/*41
3	Female	17	<0.1	Cannabies and benzodiazepine	Negative	Not detected
4	Male	64	1.0	Negative	Negative	CYP2C19*1*17; CYP2D6*4/*10
5	Male	52	0.2	Diazapine and olanzapine	Positive	CYP2C19*1*17
6	Male	50	0.1	Benzoylecgonine, cocaine, lamotrigine and methylamphetamine	Positive	CYP2D6*3
7	Female	40	36.0	Lamotrigine and olanzapine	Negative	CYP2C9 *1/*2; CYP2C19*1*17
8	Male	41	24.0	Diazapine, olanzapine, nordeazepine and zolpidem	Positive	CYP2C9 *1/*2; CYP2C19*1/*17
9	Male	41	0.3	Paracetamol	Positive	CYP2C19*1/*17
10	Male	59	<0.1	Negative	Negative	CYP2C19*1*2; CYP2D6*4/*10
11	Male	27	4.5	Negative	Negative	CYP2C19*1*2

https://doi.org/10.1111/j.1601-5215.2011.00566.x Published online by Cambridge University Press

vulnerable to drug interactions, with the consequence of developing toxicity. Even minor decreases in enzyme activity combined with multiple drug co-administration can change the patient's metabolising status to poor metaboliser.

In the abnormal metaboliser population, somatic symptoms associated with psychiatric diagnoses may in fact be caused by medication intolerance exacerbated by the dose adjustment. Psychotropic medications have been associated with a variety of adverse drug reactions, including neurotoxicity development. Wall et al. (21) created a list of adverse drug reactions that have been linked to abnormal metabolism of psychotropics based on the current published evidences. This list includes: extrapyramidal symptoms, tardive dyskinesia, oversedation, cardiovascular complications (i.e. tachycardia, hypertension and hypotension), weight gain, neuroleptic malignant syndrome, serotonin syndrome and suicidality.

The genes that code for the enzymes involved in the metabolism of drugs are highly polymorphic and appear to be highly variable between individuals. The most commonly studied cytochrome P450 (CYP) enzymes include 2D6, 2C19 and 2C9. Polymorphisms and gene duplications in these enzymes account for the most frequent variations in Phase I metabolism of drugs, because nearly 80% of all drugs in use today, along with most psychotropics, are metabolised through these pathways (21). According to our data published in 'Pharmacogenetics' (20), patients with drug-induced akathisia have a higher prevalence of abnormal metaboliser genotypes. In addition, five patients' cases of adverse drug reactions on venlafaxine treatment referred by psychiatrists to our laboratory revealed poor or diminished cytochrome P450 metabolism.

We believe that pharmacogenomic testing has a significant role in modern psychopharmacologic practice and that these results will have an input in knowledge to fill some of the scientific uncertainties in the interpretation of adverse drug reactions on venlafaxine and recommendation for suicide prevention.

The use of pharmacogenetics in venlafaxine toxicity interpretation and prescription procedures is a subject of debate in the medical and scientific community. However, more data are needed to support FDA warnings for an increased risk of suicidality on venlafaxine therapy.

Interpretation of toxicological data in relevant forensic medicine and medical practice cases should consider the interactions between substances metabolised through the Phase I cytochrome P450 system and an individual's variation in enzyme activity.

A 10-fold higher frequency of individuals carrying more than two active *CYP2D6* alleles compared with the natural death cases ($p = 0.007$) was found among violent suicide cases (22). LLerena and colleagues described a high risk of suicide attempts among CYP2D6 ultrarapid metabolisers (23).

The high prevalence of suicides could be explained by insufficient drug treatment with anti-depressants due to an ultrarapid metabolism. Kawanishi et al. (24) have previously showed that, among depressed patients who failed to respond to antidepressants, the frequency of the *CYP2D6* gene duplication is 10-fold higher than in healthy volunteers.

Besides its expression in the liver, CYP2D6 is highly expressed in several regions of the brain, such as the hippocampus, thalamus, hypothalamus and the cortex. It was shown that CYP2D6 is present in the human brain and plays a role in the dopamine pathway. 5-Methoxytryptamine, 5-methoxy-*N*,*N*-dimethyltryptamine and pindoline have been identified as high-affinity substrates for CYP2D6 and 5-methoxytryptamine is *O*-demethylated by CYP2D6 to form serotonin (25–27). There were several publications in the past, which attempted to associate personality traits and a drug-metabolising enzyme, specifically CYP2D6. However, the cross-studies reproducibility is difficult because of the complicity of psychopathology and neurotoxicity manifestation.

Venlafaxine is metabolised to its active metabolites by cytochrome P450 2D6 (CYP2D6), 2C9 (CYP2C9) and 2C19 (CYP2C19), which are highly genetically polymorphic. Allelic variants can cause reduced activity, loss of cytochrome enzyme function or ultrarapid enzyme activity in comparison with a wild-type gene. Certain polymorphisms are associated with reduced or absent cytochrome P450 enzyme activity and low metabolite levels in venlafaxine-treated patients.

The detoxification Phase I system functions as a complex biochemical mechanism. All parts of this system play some role or another in the drug metabolic pathway. Hence, its capacity should be analysed for each individual case. Even slightly altered mechanism in combination with multiple drug treatment could influence drug toxicity or treatment resistance. Personalised medicine is developing rapidly and it engages an individualised approach to treatment and toxicity interpretation where all factors should be taken into consideration.

Acknowledgement

We would like to thank Professors Abd Malak and Steven Boyages for their support.

https://doi.org/10.1111/j.1601-5215.2011.00566.x Published online by Cambridge University Press

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https://doi.org/10.1111/j.1601-5215.2011.00566.x Published online by Cambridge University Press