Pharmacogenomics in the clinic: genetic polymorphism contributing to venlafaxine-associated heart failure

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Pharmacogenomic tests are now commercially available, but it is difficult to know which patients and drugs should trigger consideration for pharmacogenomic evaluation. Venlafaxine is a widely used serotonin–norepinephrine reuptake inhibitor indicated for the treatment of major depression disorder, anxiety and pain disorders [1]. Genetic variation is thought to play an important role in patient risk for cardiotoxicity by both acute and prolonged exposure to venlafaxine. Polymorphisms and drug–drug interactions with *CYP2D6*, and to some extent *CYP2C19*, have been shown to significantly influence the pharmacokinetics and metabolic clearance of venlafaxine and the formation of its active metabolite, O-desmethylvenlafaxine (ODV) [2–5]. Venlafaxine and ODV are both potent inhibitors of serotonin and norepinephrine reuptake. Other hepatic enzymes (*CYP3A4*, *CYP2C19* and *CYP2C9*) metabolize venlafaxine and ODV to minor, less active metabolites (Figure 1).

Several case reports have shown an association between cardiomyopathy and a poor *CYP2D6* metabolizer status in patients taking venlafaxine [6–8]. While cardiac events with venlafaxine are considered rare even at high doses, evidence suggests drug-induced cardiomyopathy and heart failure in instances of overdose and regular dosing of venlafaxine. Resolution of symptoms upon cessation of venlafaxine therapy further supports cardiovascular adverse events related to venlafaxine. The exact mechanism of cardiotoxicity remains unknown; however, some hypotheses have been made. One theory is the hypertrophic effects of dose-related sustained hypertension. Likewise, myocardial damage due to increased levels of catecholamine with inhibition of dopamine and norepinephrine reuptake is reported by the current literature [9]. The surge in catecholamine levels eventually leads to the development of cardiomyopathy resulting in left ventricular dysfunction. Patient genotyping allows for a fairly reliable estimation of *CYP2D6* and *CYP2C19* phenotypic status with respect to venlafaxine and ODV exposure, especially among ‘poor’ and ‘extensive (normal)’ metabolizers [4,5]. However, there are few case reports speculating on the clinical significance for an ‘intermediate’ *CYP2D6* metabolizer; Vinetti *et al.* report an intermediate *CYP2D6* metabolizer who presented with severe acute cardiomyopathy following a venlafaxine overdose [8]. We report a patient who developed nonischemic cardiomyopathy after 4 years of venlafaxine treatment for depression and anxiety, and who is a *CYP2D6* intermediate metabolizer and *CYP2C19* extensive metabolizer.

Case report

A 37-year-old male presented to the emergency department (ED) in 2013 with nausea, vomiting, abdominal distention, dyspnea on exertion and a 15-pound weight gain 3 weeks prior to admission despite poor oral intake. The patient was seen in the ED 6 days prior and received a 5-day course of azithromycin for suspected pneumonia. Vitals on admission were: temperature of 97°F, 98% RA, weight 290 lbs, 72 inches height, BMI 39.3 kg/m², blood pressure 174/131 mmHg and heart rate 117 beats/minute. Physical exam findings included jugular venous pressure of 18 cm above the right atrium and decreased breath sounds at half of the right thorax. Serum creatinine 1.4 mg/dl (previously recorded at 0.9 mg/dl), NT-proBNP 4921 pg/ml. The diagnosis was acute decompensated heart failure (HF).

Figure 1. Velafaxine metabolism: influence of CYP2D6 and CYP2C19 isoenzymes.

Table 1. CYP 2D6 and 2C19 allele activity status.

	Normal activity	Decreased activity	Increased activity	Null activity
CYP 2D6†	†1 †2 †2A †33 †35	†9 †10 †14 †17 †29 †41	N/A	†3-†8 †11-†13 †15 †19-†21 †38 †40 †42
CYP 2C19§	†1 †11 †13 †15 †18 †28	†9 †10 †16 †19 †25 †26	†17	†2-†8 †22 †24 †35

†Indicates allele type.
‡Pharmvar. CYP2D6. 2019 (4 September 2019).
§Pharmvar. CYP2C19. 2019 (4 September 2019).

Social history included chronic alcohol use (4–6 cans of beer/night) that was stopped 3 weeks prior to admission due to nausea and vomiting. Patient had not been diagnosed with hypertension in the past but had hypertensive urgency at admission. Outpatient medications included buspirone 15 mg twice daily and venlafaxine 150 mg twice daily for 4 years. Chest computed tomography showed pleural effusion in the right lung, right lower lobe consolidation with air bronchograms and potential cardiomegaly; thoracentesis categorized the effusion as transudative. Transthoracic echocardiogram showed left ventricular ejection fraction of 25% with signs of mild/moderate mitral regurgitation and severe tricuspid regurgitation. The etiology of HF was presumed to be nonischemic dilated cardiomyopathy. The patient was started on intravenous furosemide, metoprolol tartrate, hydralazine, isosorbide dinitrate and digoxin. While hospitalized, the patient diuresed 20 pounds. Cardiac catheterization showed normal coronary arteries, severely elevated right atrial pressure (22 mmHg), elevated pulmonary capillary wedge pressure (23 mmHg), reduced cardiac index (1.5 l/min/m²), systemic vascular resistance (1337 dyn-s/cm⁵) and pulmonary vascular resistance (1.1 dyn-s/cm⁵).

The patient was discharged on day 12, with a 2-week HF clinic follow-up. During the clinic visit, consideration was given to the possibility of being a poor *CYP2D6* metabolizer resulting in high levels of venlafaxine and therefore a high catecholamine level causing HF. Genotyping showed that the patient was *CYP2D6* (*CYP2D6* *1*4) intermediate metabolizer and *CYP2C19* (*CYP2C19* *1*17) rapid metabolizer (See Table 1). Polymerase chain reaction with allele-specific primers that specifically determined *CYP2D6* *2A, 1C, *12, *15, *11, *17, *6, *8*14, *4, *3, *9, *2, *7, *41 was used. *CYP2D6* gene deletion and gene duplication were performed following polymerase chain reaction amplification. *CYP2C19* testing indicated that the patient carries one copy of the *CYP2C19**17 variant and none of the tested deficiency alleles in the *CYP2C19* gene. The testing assay can detect the wild-type allele (*CYP2C19**1) as well as ten common mutations in the *CYP2C19* gene: *CYP2C19**2, *CYP2C19**3, *CYP2C19**4,

*CYP2C19*5*, *CYP2C19*6*, *CYP2C19*7*, *CYP2C19*8*, *CYP2C19*9*, *CYP2C19*12* and *CYP2C19*17*. Patient's plasma norepinephrine (694 pg/ml), reference <420) levels were high. Venlafaxine was tapered down and discontinued over the following month. Repeat CT chest showed complete resolution of right lower lobe infiltrate and effusion at 1 month, and repeat echocardiogram at 3 months showed resolution of systolic dysfunction with left ventricular ejection fraction of 55–60% without further episodes of fluid accumulation.

Discussion

We report a case of cardiomyopathy we suspect was due to venlafaxine toxicity. Before this incident, our patient had no previous symptoms associated with heart failure. His nausea and emesis were thought to be from gut edema from fluid accumulation, as was his dyspnea on exertion and increased abdominal girth. His symptoms at presentation were potentially consistent with drug-induced pneumonitis and heart failure, which have been associated with venlafaxine toxicity. Another possible explanation for the etiology of his nonischemic heart failure is alcoholic cardiomyopathy given that his social history included chronic alcohol abuse. If alcohol were the only culprit, it seems unlikely his echocardiogram would have shown resolution of cardiac dysfunction after a 2-month follow-up. During this time, the patient was tapered off venlafaxine therapy when genotyping determined our patient to be a *CYP2D6* intermediate metabolizer (*CYP2D6*1/*4*). The cessation of venlafaxine therapy, and the combined potential for impaired metabolism – *CYP2D6* genotype is strongly suggestive of venlafaxine cardiomyopathy.

Two enzymes, *CYP2D6* and *CYP2C19*, contribute significantly to the metabolism of venlafaxine [3,8,10]. Genetic polymorphisms in these enzymes can result in a loss or a gain of function. There are more reports suggesting a 'poor' *CYP2D6* genotyping, meaning two null alleles, is at particular risk for venlafaxine toxicity. In this case, we describe a patient who is an intermediate *CYP2D6* metabolizer (one null copy and one normal copy), and rapid *CYP2C19* metabolizer (one normal copy and one enhanced gain of function copy). It is generally assumed such individuals may be at greater risk for drug interactions given that lower enzyme expression is more saturable. The metabolic clearance of venlafaxine should be studied within the context of both *CYP2D6* and *CYP2C19* activity as it has been shown that both are involved in venlafaxine biotransformation, and a case report of fatal venlafaxine poisoning was observed in a young man with a both 'poor' *CYP2D6* and *CYP2C19* genotypes [4,7]. We identified two reports of patients with one null *CYP2D6* allele who presented with adverse reactions with venlafaxine therapy [6,8]. The report by Chau *et al.* involved a patient with two novel variants of *CYP2D6* and *CYP2C19* (but one functional copy of each), implying an impaired metabolic phenotype [6]. Vinetti *et al.* report a patient with a *CYP2D6*1/*5*, very similar to our own and also an 'intermediate' *CYP2D6* metabolizer [8]. Most interestingly, our patient and the case in Vinetti *et al.* had a *CYP2C19*17* allele, which is associated with increased activity and a 'rapid' *CYP2C19* genotype.

These data are suggestive that *CYP2C19* may not completely compensate diminished *CYP2D6* function, or may play a role in producing a metabolite which is additively or synergistically cardiotoxic with its parent. The clinical significance of the intermediate *CYP2D6* genotype, and to what extent enhanced *CYP2C19* activity can compensate is not well understood. One reason it may have taken this patient years to develop heart failure is that the *CYP2D6* was intermediate not poor metabolizer. While these patients may tolerate venlafaxine therapy for months, even years, caution should be exercised as case reports indicate risk for heart failure and death even with normal dosages [11]. Given the strong association with venlafaxine-induced heart failure, an alternative therapy should be considered. The Dutch Pharmacogenetics Working Group recommends that for poor and intermediate venlafaxine metabolizers of *CYP2D6*, an alternative drug should be used (e.g., citalopram, sertraline), or the dose of venlafaxine should be adjusted based on clinical response, and ODV plasma levels should be monitored [12]. On the contrary, the US FDA recommends no dose adjustments for poor and extensive (normal) metabolizers because the total exposure (AUC) of venlafaxine and ODV is similar in both groups [13].

This case highlights the need for more detailed studies on the clinical significance of *CYP2C19* polymorphisms and their interaction with *CYP2D6*. Clinicians should be aware that the 'intermediate' *CYP2D6* genotype may have clinical relevancy for venlafaxine cardiomyopathy, particularly in patients on concomitant medications which are substrates for *CYP2D6*, or who abuse alcohol. Our main recommendation is that if a clinician is seeing a younger patient with a nonischemic cardiomyopathy also taking venlafaxine, then consideration for pharmacogenomic testing for *CYP2D6* and *CYP2C19* should be given. Furthermore, pharmacogenetics-based prescribing guidelines recommend to consider testing of *CYP2D6* prior to initiating venlafaxine [12].

Author contributions

All authors vouched to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. H Singh and B Dubois contributed to the acquisition, analysis or interpretation of data for the work as well as the manuscript drafting. T Barret provided substantial contributions to conception or design of the work. Z Al-Jammali, B Dubois and T Barrett contributed to the final review and approval of the manuscript version to be published.

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