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PHARMACOGENETICS

CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine

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SUMMARY

Background: **Venlafaxine (V) is a mixed serotonin and noradrenaline reuptake inhibitor used as a first-line treatment of depressive disorders. It is metabolized primarily by the highly polymorphic cytochrome P450 (CYP) enzyme CYP2D6 to yield a pharmacologically active metabolite, *O*-desmethylvenlafaxine (ODV), and to a lesser extent by CYP3A4, to yield *N*-desmethylvenlafaxine (NDV).**

Objectives: **The aim of this study was to assess whether the O-demethylation phenotype of V has an impact on the pharmacokinetics and clinical outcome.**

Method: **In 100 patients treated with V, serum concentrations of V, ODV and NDV and the ratios of concentrations ODV/V as a measure of O-demethylation were determined. Individuals exhibiting abnormally high or low metabolic ratios of ODV/V were selected for genotyping. Clinical effects were monitored by the Clinical Global Impressions Scale and side effects by the UKU (Udvalg for Kliniske Undersogelser Side Effect Rating Scale) rating scale.**

Results: **There was wide inter-individual variability in ODV/V ratios. The median ratio ODV/V was 1·8 and the 10th and 90th percentiles 0·3 and 5·2, respectively. Individuals with ODV/V ratios below 0·3 were all identified as poor metabolizers (PM), with the genotypes *6/*4 ($n = 1$), *5/*4 ($n = 2$) or *6/*6 ($n = 1$). Individuals with ratios above 5·2 were all ultra rapid metabolizers (UM, $n = 6$) due to gene duplications. Five individuals with intermediate metabolic activity (ODV/V, 1·1 ± 0·8) were heterozygotes with the CYP2D6*4 genotype, and one patient with an intermediate metabolic ratio of 4·8 had the genotype *4/2x*1. Clinical outcome measurements revealed that patients with ODV/V ratios below 0·3 had more side effects ($P < 0·005$) and reduced serum concentrations of sodium ($P < 0·05$) in comparison with other patients. Gastrointestinal side effects, notably nausea, vomiting and diarrhoea were the most common. Differences in therapeutic efficacy were not significant between the different phenotypes.**

Conclusion: **The O-demethylation phenotype of V depends strongly on the *CYP2D6* genotype. A PM phenotype of CYP2D6 increases the risk of side effects.**

***Keywords*: clinical response, CYP2D6, depression, molecular genetics, side effects, venlafaxine**

INTRODUCTION

Venlafaxine (V) is a bicyclic antidepressant, which inhibits the reuptake of serotonin, noradrenaline and, to a lesser extent, of dopamine (1–7). It is

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biotransformed in humans by the cytochrome P450 (CYP) isozyme 2D6 to its major metabolite in serum, *O*-desmethylvenlafaxine (ODV), and in parallel to *N*-desmethylvenlafaxine (NDV) and *N*,*O*-didemethylvenlafaxine by several CYP isoenzymes including CYP3A4, CYP2C19 and CYP1A2 (7–13). The major metabolite ODV possesses the same biologic activity as the parent compound, while no pharmacological activity has been ascribed to the other metabolites (11). ODV/V ratio can thus be considered as a measure of the activity of CYP2D6 in depressed patients. More than 70 different alleles of CYP2D6 gene are currently known to occur at variable frequencies in different ethnicities (see http://www.imm.ki.se/CYPalleles/cyp2d6.htm) (14), and they have been linked to three classes of phenotypes based on the extent of drug metabolism (15–18). Extensive metabolism of a drug substrate is characteristic of the wild-type genotype, or extensive metabolizer (EM), with two functional alleles (*1 or *2). Poor metabolizers (PM) have typically an autosomal recessive trait caused by mutation and/or deletion of both alleles; and ultra rapid metabolizers (UM) have an autosomal dominant trait arising from functional gene duplications and amplification (19–21). As the concentrations of V and ODV are mostly dependent on the CYP2D6 metabolizer state, it was suggested that the clinical response and side effects of V are related to CYP2D6 genotype (7, 22). The aim of this study was to investigate possible associations of the O-demethylation phenotype of V with genotype, and pharmacokinetic and pharmacodynamic differences in patients treated with V.

MATERIALS AND METHODS

The study design was approved by the local ethics committee.

Patients

All eligible patients with an episode of major depression, dysthymia, or depressive adjustment disorder, according to DSM-IV criteria, and demanding antidepressant therapy were included.

Inclusion criteria were: female and male patients, age 18–65 years, no additional severe medical condition, particularly no contraindication for V. Exclusion criteria were: acute suicidality, pregnancy, admission to the hospital by legal commitment or for crisis intervention, therapeutic drug monitoring (TDM) request forms lacking a relevant information, e.g. patient's name (or identification code), age, sex, name of the medication, dose or concomitant medication and drug–drug interference because of an analytical interference which prevented the quantification of the drug and/or main metabolite in serum or plasma.

Overall, 100 patients who were treated with V immediate release tablets once or twice daily, were recruited for TDM. From the large sample, patients were selected for genotyping when exhibiting abnormally high or low ratios of concentrations of ODV to V, [ODV/V] (Fig. 1).

The Clinical Global Impressions Scale (CGI, item 2) was used as global improvement rating. A short version of the UKU (Udvalg for Kliniske Undersogelser Side Effect Rating Scale) was used to assess the severity of side effects (23). Clinical chemistry routine, at least sodium measurement was applied.

Blood sampling

For analysis of the trough serum concentration blood was taken under steady-state conditions in the morning (9·00 hours) according to the usual clinical schedule of blood sampling before the first morning dose and after at least 7 days of a con-

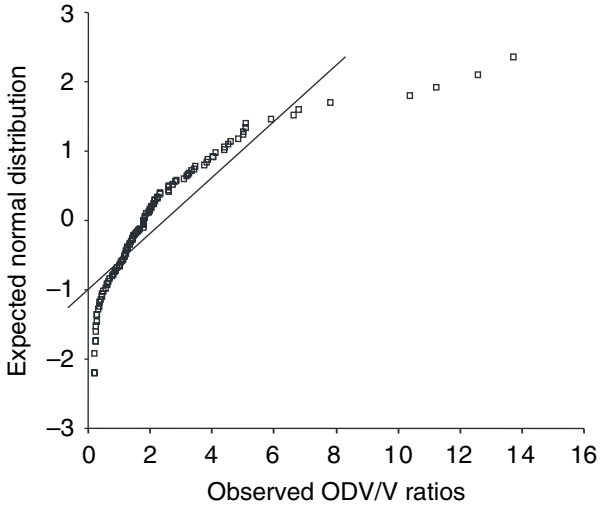

Fig. 1. Q-Q frequency of distribution of *O*-desmethylvenlafaxine (ODV)/venlafaxine (V) ratios in 100 depressed patients who were treated with venlafaxine.

tinuous drug therapy which is in accordance with the recommendations of recently reported consensus guidelines (24). The procedure for collecting and handling the serum samples was as follows: about 7 ml venous blood was collected in a container (monovette) without additives. The blood was left to clot in the test tube for 30–60 min at room temperature, followed by centrifugation at 1500 *g* for 10 min. The serum was then transferred to a polypropylene tube and if the analysis was not performed immediately, the samples were frozen and maintained at −20 °C until thawed and analysed.

Chromatographic determination of venlafaxine and its metabolites

Racemic V and its metabolites, ODV and NDV, in serum of depressed patients, who were treated with V, were quantified by an automated high-performance liquid chromatography with online sample preparation and fluorescence detection at an excitation wavelength of 220 nm and an emission wavelength of 305 nm. The method was adopted from a method described for the determination of dextromethorphan and metabolites (25). Pure reference material of V, ODV and NDV was used for calibration. It was kindly donated by Lederle Lab. Div., Pearl River, NY, USA. The retention times of V, ODV and NDV were 17·9, 17·0 and 14·2 min, respectively. Interferences with other drugs were not found. The limit of quantification was 10 ng/mL for all analytes, with interassay ($N = 9$) coefficients of variation being 9·3 , 14·7 and 10·8 for V, ODV and NDV, respectively. Linearity between nominal concentrations and detector signal was given between 10 and 800 ng/mL, with a correlation coefficient always >0·99.

Genotyping

For genotyping, a LightCycler® (Roche Molecular Systems, Indianapolis, IN, USA) and the Roche LightCycler®-software version 3·5, LightCycler® capillaries, EDTA vacutainer (Sarstedt, Nümbrecht, Germany), Eppendorf Centrifuge (Engelsdorf, Germany) and blood centrifuge (Rotina 48 R, Tuttlingen, Germany) were used.

Chemicals were purchased for genotyping procedure such as binding buffer, proteinase K, isopropranol, inhibitor removal buffer, washing buffer, elution buffer, magnesium chloride stock solution and AmpliTaq Gold polymerase enzyme (Roche DNA Isolation Kit, Berlin, Germany). Amplification primers and hybridization probes were purchased from TIB MOLBIOL Syntheselabor (Berlin, Germany).

EDTA blood was drawn and stored at −20 °C until isolation of genomic DNA (Roche DNA Isolation Kit). Real-time PCR reaction used the LightCycler®. Each mutation was investigated separately. Genotyping analysis was performed on patients' DNA and screened for the major alleles CYP2D6*3, *4, *6, and *9. The complete allele deletion (CYP2D6*5) and gene duplication of CYP2D6 were also detected by a quantitative PCR reaction (18).

Data management and statistical analyses

Mean values ± standard deviation (SD) and medians with 25th and 75th percentiles of V, ODV, NDV serum concentration (ng/mL), and ODV/V ratios were calculated. Serum concentrations in relation to the daily doses [concentration-over dose (C/D) (ng/mL/mg)] were calculated. To study the relationship between therapeutic outcome and incidence of side effects in relation to different genotype states and ODV/V ratios, CGI were scored (very good effect = 3, moderate effect = 2, weak effect = 1 and no effect = 0). The sum of therapeutic effects and the occurrence of side effects per number of patients were compared between these different groups.

The computer software SPSS version 10 (Chicago, IL, USA) was used for statistical computations. For group comparison, non-parametric Mann–Whitney *U*-test (between-group comparisons) was calculated. Statistical significance was predefined as $P \leq 0{\cdot}05$.

RESULTS

A group of 100 patients (54 men) with a mean age ± SD (52 ± 11 years) who were treated once to twice daily with the recommended oral doses of V immediate release tablets were recruited for TDM of V. The co-administered medications with V are demonstrated in Table 1.

Twenty-five depressed patients (14 men) with a mean ± SD age of 49·0 ± 12·7 were selected for

Table 1. List of co-administered drugs of the patients treated with venlafaxine

Co-medication	No. of patients (n = 100)
None	30
Psychotropic drugs	
Antidepressant drugs	
Doxepin	2
Mirtazapine	19
Paroxetine[a]	1
Reboxetine	2
Trimipramine	5
Antipsychotic drugs	
Amisulpride	1
Haloperidol	1
Melperone[a]	5
Olanzapine	5
Promethiazine	1
Quetiapine	2
Risperidone	8
Sulpride	1
Benzodiazepines/hypnotics	
Alprazolam	4
Lorazepam	32
Zolpidem	13
Mood stabilizers	
Lamotrigin	2
Lithium	12
Sodium valproate	7
Non-psychotropic drugs	
Acetyl salicylic acid	6
Allopurinol	2
Ascorbic acid	1
Etilefrin	1
Folic acid	2
Isorbid dinitrate	1
Levodopa + benserazide	2
L-thyroxin sodium	8
Medroxyprogestron	1
Metformin	1
Metoprolol[a]	7
Potassium chloride	1
Ramipril	2
Theophylline	1

[a]CYP2D6-inhibiting drugs.

genotyping analysis because of their abnormal metabolic ratios of concentrations between ODV and V [ODV/V]. No inhibitors of CYP2D6 such as metoprolol, moclobemide, celecoxib, propranolol, melperone, haloperidol or paroxetine were co-administered in this group of patients.

Therapeutic drug monitoring

In patients who were treated with V for at least 7 days (steady-state conditions), the mean dose ± SD was 183 ± 74 mg/day. The dose-corrected serum concentrations (C/D) of V and ODV ranged between 0·05–4·3 and 0·1–4·5, respectively, as shown in Table 2. There was also a wide inter-individual variability of ODV/V ratios between 0·07 and 13·7 as shown in Table 2 and Fig. 2.

A weak relationship between V doses and serum concentrations of V or ODV in all patients (n = 100) was observed. The linear regression correlation coefficient between V doses and V serum concentrations was $r^2 = 0{\cdot}04$ ($P < 0{\cdot}05$) while $r^2 = 0{\cdot}2$ ($P < 0{\cdot}01$) was obtained between V doses and ODV serum concentrations. A marked interindividual variability of the serum concentrations of V and ODV at different doses of V were observed as shown in Fig. 2.

In 25 depressed patients who were selected for genotyping, the mean dose ±SD was 215 ± 63 mg/day and ranged between 75 and 450 mg/day. The dose-corrected serum concentrations (C/D) of V and ODV were between 0·07–1·91 and 0·07–2·61 ng/mL/mg, respectively. There was also a wide interindividual variability of ODV/V ratios in this group of patients between 0·2 and 13·7 ng/mL/mg (Table 2).

Genotype–phenotype correlation

A wide interindividual variability of ODV/V ratios was observed in all depressed patients (n = 100) and the median (10th–90th percentiles) was 1·8 (0·3–5·2). At least part of this variability could be explained by the genotype. There was a *CYP2D6* gene dose-dependent ratio of concentrations (Fig. 3). All individuals with ODV/V ratios lower than the median had at least one deficient CYP2D6 allele. Five individuals were heterozygotes with the most frequent mutant allele (CYP2D6*4), and had a mean metabolic activity (ODV/V, 1·1 ± 0·8). Three individuals were heterozygotes with two mutant alleles and revealed impaired metabolic activities [one (*6/*4) had a metabolic activity (ODV/V = 0·3) and two (*5/*4) had a mean metabolic

Table 2. Serum concentrations of venlafaxine (V) and *O*-desmethylvenlafaxine (ODV) in various patient groups

	Dose of V (mg)	V (ng/mL)	ODV (ng/mL)	V + ODV (ng/mL)	C/D V (ng/mL/mg)	C/D ODV (ng/mL/mg)	ODV/V
All patients (n = 100)							
Median	150·0	93·5	152·0	276·0	0·46	0·87	1·8
Percentiles (25th–75th)	150·0–225·0	50·2–183·0	96·5–227·7	185·0–414·2	0·32–1·1	0·55–1·3	0·87–3·6
Min.–max.	75·0–450·0	14·0–653·0	19·0–499·0	53·0–954·0	0·05–4·3	0·1–4·5	0·07–13·7
Mean (±SD)	183·0 (74·4)	143·7 (148·8)	171·3 (107·1)	315·8 (177·2)	0·86 (0·88)	1·0 (0·65)	2·8 (2·7)
Genotyped patients (n = 25)							
Median	225·0	52·0	149·0	226·0	0·23	0·66	2·5
Percentiles (25th–75th)	187·5–262·5	24·5–141·0	82·5–206·5	167·0–342·0	0·11–0·81	0·46–0·90	0·57–6·73
Min.–max.	75·0–450·0	12·0–430·0	28·0–588·0	61·0–813·0	0·07–1·91	0·07–2·61	0·2–13·7
Mean (±SD)	214·5 (62·6)	106·2 (115·1)	166·7 (112·9)	272·9 (164·4)	0·48 (0·52)	0·77 (0·52)	4·2 (4·0)

C/D, dose-corrected serum concentration.
Molecular weight of V = 277·4 and of ODV = 263·4.

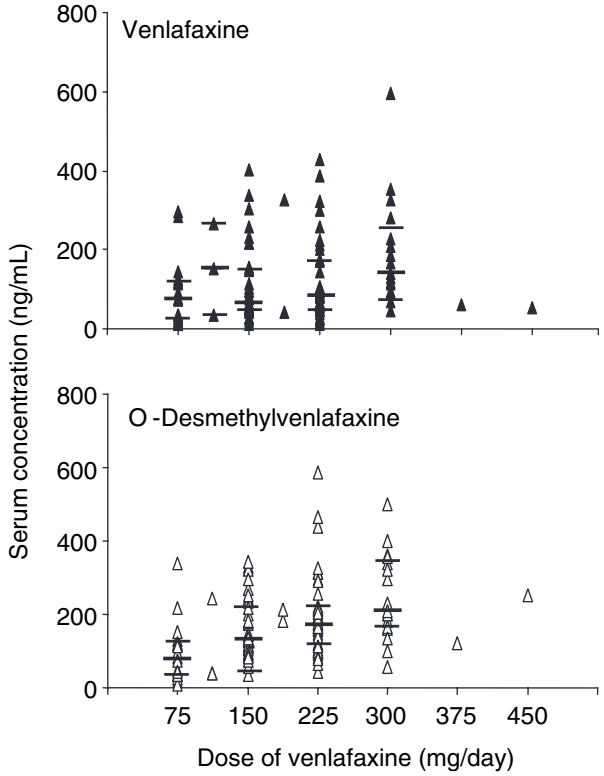

Fig. 2. Daily doses and resulting serum concentrations of venlafaxine and *O*-desmethylvenlafaxine in 100 depressed patients who were treated with venlafaxine. Horizontal bars indicate median values and 25th and 75th percentiles.

activity (ODV/V = 0·25 ± 0·01)]. Only one individual was homozygous (*6/*6) with the most impaired metabolic activity (ODV/V = 0·2). Six individuals had gene duplication and showed high metabolic ratios beyond the 90th percentile (Mean ODV/V was 10·3 ± 2·7) and can thus be regarded as UMs. Only one patient has *4/gene duplication (2 × *1) with intermediate metabolic ratio 4·8 as shown in Table 3. CYP2D6*3 and *9 alleles were not detected in these patients.

The genotyped patients received different daily dosages of V. Consequently, we used the dose-corrected serum concentration (C/D) of V, ODV and NDV to compare between them. PMs who had two mutant alleles, had significantly lower ODV/V ratios and C/D ODV serum concentrations as well as significantly higher C/D V and C/D NDV serum concentrations than *1/*1 group (EMs). In contrast, UMs who had one functional gene duplication had significantly

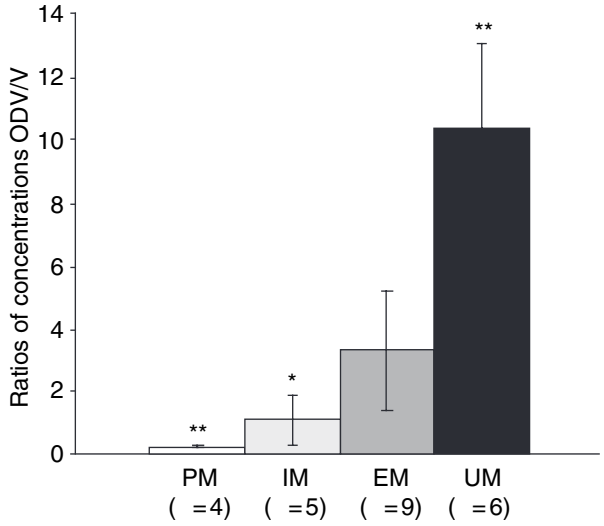

Fig. 3. Relationship between CYP2D6 genotype and ratios of concentrations *O*-desmethylvenlafaxine (ODV)/venlafaxine (V) under steady-state treatment with venlafaxine. PM, poor metabolizers who had two mutant alleles of CYP2D6; IM, intermediate metabolizers who had one active and one mutant allele (*1/*4); EMs, extensive metabolizers who had two active alleles (*1/*1); UMs, ultra rapid metabolizers who had one active and one duplicated active allele (2x*1)/*1. $^{**}P < 0{\cdot}01$, PM vs. EM and UM vs. EM, $^{*}P < 0{\cdot}05$, IM vs. EM.

higher ODV/V ratios as well as significantly lower C/D V and C/D NDV serum concentrations than *1/*1 group. Heterozygous individuals with one active allele and one deficient allele (*1/*4) had significantly lower metabolic ratios than homozygous *1/*1 allele carriers as shown in Table 3.

Clinical outcome

The sum of concentrations V plus ODV was not significantly different between the different V O-demethylation phenotypes. PMs with an ODV/V ratios below 0·3 (10th percentile), however, had significantly more side effects (Mann–Whitney *U*-test: $P < 0{\cdot}005$) and significantly lower serum concentrations of sodium (Mann–Whitney *U*-test: $P < 0{\cdot}05$) than EMs or UMs (Table 4). Gastrointestinal side effects like nausea, vomiting and diarrhoea were the most common side effects. However, no significant difference in therapeutic efficiency was observed between different genotype states as shown in Table 4.

DISCUSSION

For the new antidepressant V, concentrations of the active metabolite ODV must be considered when relating blood concentrations to clinical effects. The formation of the active metabolite is catalysed by CYP2D6. So far it is a matter of debate if CYP2D6 gene deletion or multiplication which leads to either loss or increase of enzymatic activity has clinical consequences on patients treated with this antidepressant (7, 26). The results of this study have not only shown a gene dose dependency of the formation of ODV but also given evidence that a PM status increases the risk of developing side effects.

As the CYP2D6 polymorphisms are recessive traits, the heterozygous individuals with one active allele and one mutant allele (*1/*4) had a significantly lower metabolic ratio (ODV/V, 1·1 ± 0·8, $P < 0{\cdot}05$) than other *1/*1 group and that points to a deficiency or reduction in the metabolic capacity. The individuals with these genotypes are referred to as EM and represent a great majority of the population. The individuals who had inherited two inactive alleles (*6/*6, *6/*4 or *5/*4) exhibited the poor metabolizer (PM) phenotype. They show complete absence of CYP2D6 activity and impaired ability of metabolizing V. The UM phenotype results from duplication or amplification of CYP2D6. The amplified gene product has a catalytic increased activity, which directly correlates with an excessive expression of CYP2D6 enzyme (27) and a dramatic effect on the metabolism and clearance of V. Although the individuals with UM genotype may require 'megadoses' of substrate drugs (especially those metabolized into inactive metabolites) to achieve therapeutic efficacy (28), this was not observed here for V.

The ODV/V ratio supplies useful information about the rate of V metabolism. According to our data, V metabolism can be divided into three classes by ODV/V ratios: ≤0·3, 1–5·2 and >5·2. These ratios correspond to PMs, EMs and UMs phenotypes, respectively. However, the latter phenotype was also seen for some of our EM individuals.

The high C/D NDV levels in PMs have shown that the alternative elimination route of V N-demethylation via CYP3A4 was increased as a result of reduced activity of O-demethylation by CYP2D6. In contrast, the increased activity of CYP2D6 in UMs led to a significant decrease in

Table 3. Relationship between the assayed CYP2D6 genotype states of 25 depressed patients and plasma concentrations of venlafaxine (V), *O*-desmethylvenlafaxine (ODV) and *N*-desmethylvenlafaxine (NDV)

Genotype	*6/*6	*6/*4	*5/*4	All PM	*1/*4	*1/*1	(2x*1)/*4	(2x*1)/*1
Number	1	1	2	4	5	9	1	6
Gender	Male	Male	1 male	3 males	2 males	5 males	Female	4 males
Age (years) Mean (±SD)	56	47	45·5 (4·9)	48·0 (5·8)	51·2 (11·8)	52·6 (16·2)	51	45·3 (13·5)
Dose (mg/day) Mean (±SD)	375	75	300 (106)	262 (143·6)	255 (85·5)	200·0 (64·9)	450·0	212·0 (30·6)
V (ng/mL) Mean (±SD)	106	117	310·5 (16·2)	211 (115·4)	188·8 (161·7)	77·8 (70·5)	52·0	19·0 (5·2)
ODV (ng/mL) Mean (±SD)	28	36	78 (8·4)	55 (27·2)	134·2 (41·0)	206·6 (156·5)	252·0	194·1 (63·3)
NDV (ng/mL) Mean (±SD)	287	91	183 (40·3)	172 (86·6)	110·4 (42·5)	50·8 (25·5)	44·0	24·0 (6·2)
ODV/V	0·20	0·30	0·25 (0·01)	0·25 (0·04)[a]	1·16 (0·8)[b]	3·30 (1·90)[a,b]	4·8	10·3 (2·7)[a]
C/D V (ng/mL/mg/day)	0·30	1·50	1·1 (0·4)	1·02 (0·58)[c]	0·8 (0·7)	0·35 (0·26)[c,d]	0·1	0·08 (0·01)[d]
C/D ODV (ng/mL/mg/day)	0·07	0·48	0·28 (0·1)	0·27 (0·18)[e]	0·5 (0·2)	1·00 (0·71)[e]	0·6	0·9 (0·20)
C/D NDV (ng/mL/mg/day)	0·76	1·20	0·62 (0·08)	0·75 (0·32)[f]	0·43 (0·18)	0·24 (0·09)[f]	0·1	0·09 (0·005)[f]

C/D, dose-corrected serum concentration; *1, no investigated mutant allele was detected; CYP2D6*4, G1934A, splice side defect, no activity; CYP2D6*6, T1795, deletion, premature stop codon; CYP2D6*5, CYP2D6 gene deletion; PMs, all poor metabolizers who had two mutant alleles; (2x*1), duplicated active CYP2D6 allele.

[a] $P < 0{\cdot}05$, significant difference in ODV/V ratios between *1/*4 and *1/*1.

[b] $P < 0{\cdot}01$, significant difference in ODV/V between (2x*1)/*1 and *1/*1.

[c] $P < 0{\cdot}01$, significant difference in C/D V between (2x*1)/*1 and *1/*1.

[d] $P < 0{\cdot}05$, significant difference in ODV/V between *1/*4 and *1/*1.

[e] $P < 0{\cdot}01$, significant difference in C/D NDV between (2x*1)/*1 and *1/*1.

[f] $P < 0{\cdot}01$, significant difference in C/D NDV between all PM and *1/*1 & between (2x*1)/*1 and *1/*1.

Molecular weight of V = 277·4 and of ODF = 263·4.

C/D NDV levels and a significant decrease in C/D V levels. These results are in line with data of the study of Veefkind *et al*. (7).

Gastrointestinal side effects like nausea, vomiting and diarrhoea were the most common observed side effects. Adverse dysrhythmia which has been reported by other investigators (26) in patients who were PMs of CYP2D6 with high plasma levels of V was not observed. The increased number of side effects in PMs was consistent with reports of other investigators (29) who found that reduced CYP2D6 activity is associated with a higher incidence of the occurrence of side effects under treatment with antidepressants. To explain this association for V, however, it must be considered that V and ODV have comparable pharmacological properties (30) and that the sum of serum concentrations V plus ODV was similar in EM and UM. Slight differences in reuptake inhibition of noradrenaline and dopamine which are more pronounced for the mother compound than for the metabolite might explain the higher frequency of side effects which were obviously more closely related to the parent drug than to the metabolite. Moreover, it must be considered that V is a chiral drug. CYP2D6 displays marked stereoselectivity towards the (*R*)-enantiomer (31). This could have clinical consequences and thus underlie the observed differences in the occurrence of side effects in PMs and EMs. Data on differential clinical properties of (*R*)- and (*S*)-venlafaxine, however, are lacking.

A significant decrease in serum concentrations of sodium was inversely related with serum concentration of V. V, selective serotonin reup-

Table 4. Relationship between therapeutic effects quantified by the clinical global impressions (CGI) score and side effects with different venlafaxine O-demethylation phenotypes

Mean (±SD)	PMs (ODV/V ≤ 0·3)	UMs (ODV/V ≥ 5·2)	EMs [ODV/V (1–5·2)]
Total no. of patients	4	6	64
Daily dose of venlafaxine (mg)	259 ± 143	200 ± 39	190 ± 69
V serum concentration	211 ± 115	21 ± 6	97 ± 64
ODV serum concentration	55 ± 27	206 ± 50	195 ± 104
V + ODV serum concentration	266 ± 142·2	227 ± 53	292 ± 157
ODV/V	0·25 ± 0·04	10·3 ± 2·7	2·3 ± 1·1
No. of patients analysed by the CGI scale	4	6	51
No. of patients analysed for side effects	4	6	63
Mean CGI points per patient	2·0 ± 0·8	1·7 ± 0·8	1·7 ± 0·9
Mean number of side effects per patients	2·3 ± 1·0**	0·3 ± 0·5	0·49 ± 0·7
Mean sodium serum concentration (mmol/L)	138·0 ± 2·1*	144 ± 3·8	142 ± 5·4

V, venlafaxine; ODV, *O*-desmethylvenlafaxine; PMs, all poor metabolizers who had two mutant alleles; UMs, ultra rapid metabolizers who had one duplicated active CYP2D6 allele and one active CYP2D6 allele; EMs, extensive metabolizers who had a metabolic ratio ODV/V between 1 and 5·2 (This group includes nine genotyped patients who had two active CYP2D6 alleles and 42 non-genotyped patients who had the same metabolic ratios).

*Significant difference in serum level of sodium (at $P < 0·05$) between PMs and EMs.

**Significant difference in side effects (at $P < 0·005$) between PMs and EMs.

take inhibitors and angiotensin converting enzyme inhibitors are reported to be responsible for a syndrome of inappropriate secretion of antidiuretic hormone, vasopressin in normovolaemic patients which consequently results in hyponatraemia (32–34). Significant differences in therapeutic efficiency were not observed in patients with different phenotype states. This result may be due to the unaltered sum of concentrations of V and ODV. As ODV is therapeutically as active as the parent drug V (30), the obtained therapeutic effect was due to the net summation of both V and ODV.

From the results in this article we can conclude that this study revealed a significant correlation between the *CYP2D6* genotype and phenotype states of patients who were under treatment with V. Dosage adjustment of V or a selection of an alternative antidepressant drug, which is not a substrate of CYP2D6, should be advised especially for PMs with V-induced side effects including the risk of hyponatraemia. Genotyping may thus help to individualize drug treatment with V. This approach will not substitute careful clinical monitoring of the patients and TDM, as the crucial CYP2D6 phenotype might also be caused by comedication of a CYP2D6 inhibitor.

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