CYP2D6: Venlafaxine

AUC: area under the concentration-time curve, BID: twice a day, Css: steady state plasma concentration, DV: *O*-desmethylvenlafaxine, EM: extensive metabolizer, IM: intermediate metabolizer, MR: metabolic ratio, NS: not statistically significant, PM: poor metabolizer, S: statistically significant, UM: ultrarapid metabolizer, V: venlafaxine.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Hermann M et al. Serum concentrations of venlafaxine and its metabolites O-desmethylvenlafaxine and N-desmethylvenlafaxine in heterozygous carriers of the CYP2D6*3, *4 or *5 allele. Eur J Clin Pharmacol 2008;64:483-7 PMID: 18214456	4	IM: A PM: A	43 patients, 20x EM, 18x IM (2x *1/*3, 13x *1/*4, 3x *1/*5), 5x PM (all *4/*4). Venlafaxine XR was dosed in response to therapeutic drug monitoring. No relevant concomitant medication. Some of the patients were smokers. Compared to EM: IM: - Css[a] V+DV increased from 5.0 to 6.1 nM/mg (NS, by 22%) - DV/V ratio decreased from 3.1 to 1.5 (S, by 52%) PM: - Css[a] V+DV increased from 5.0 to 8.5 nM/mg (NS, by 70%) - DV/V ratio decreased from 3.1 to 0.2 (S, by 94%) The decrease of the DV/V ratio is mainly the result of the increase of V Css[a]. Note: *3-*8 and gene duplications were assessed.	Conclusion authors: 'The study showed a shift in the metabolic pathway resulting in substantially higher levels of N-desmethylvenlafaxine in HEMs than in EMs. The metabolic pattern of venlafaxine in HEMs was similar to previous observations in PMs and possibly represents an increased risk of venlafaxine-related side effects in HEM patients.' Css[a] V+DV compared to EM: IM: 122% PM: 170%
ref. 2 McAlpine DE et al. Cytochrome P450 2D6 genotype variation and venlafaxine dosage.	3	IM: C	39 patients who had either adverse effects or the absence of a therapeutic response to V. 5x IM (gene dose 0.5), 33x IM+EM+UM (gene dose 1). Compared to gene dose 1:	Conclusion authors: 'In an outpatient psychiatric practice, patients who did not have at least 1 fully active allele of the 2D6 gene were not successfully treated with dosages of venlafaxine

Mayo Clin Proc 2007;82:1065-8. PMID: 17803873			Gene dose 0.5: - Percentage of patients with > 75 mg/day V decreased from 79% to 0% (S, by 100%). Details of the 5 IM (gene dose 0.5) - 44-year-old woman (*3/*9) diagnosed with dysthymic disorder and was treated with 75 mg/d of V. She initially experienced dry mouth and an increase in appetite. However, she also reported a decrease in depressive symptoms. Her dosage subsequently was increased to 112.5 mg/day, at which time her depression became worse and she experienced fatigue. Her dosage was consequently decreased to 75 mg/d, and she did well for 4 months with this dosage. - 16-year-old girl (*3/*9) diagnosed with attention-deficit/hyperactivity, depression, psychotic symptoms and bipolar disorders. She had to discontinue V 75 mg/day because of excessive somnolence and a lack of improvement in her mood. - 54-year-old woman (*4/*17) diagnosed with major depressive disorder. She discontinued use of her V 37.5 mg/day after 4 days because of intolerable nausea, insomnia, and decreased appetite. - A 46-year-old man (*4/*41) diagnosed with generalized anxiety disorder became more anxious and developed heart palpitations in response of V 37.5 mg/day. When he discontinued use of venlafaxine, his anxiety symptoms improved. - 15-year-old girl diagnosed with major depressive disorder had to discontinue her treatment with V 75 mg/day because of intolerable adverse effects.	greater than 75 mg/d. Physicians should be alert to the possibility that an adverse reaction may indicate a slow metabolizer and consider genotyping such patients.'
ref. 3 Shams ME et al. CYP2D6 polymorphism and clinical effect of the antidepressant	4	PM: C IM: A UM: A	25 patients treated with V exhibiting abnormally high or low metabolic ratios of DV/V were genotyped. 10x EM (9x *1/*1, 1x *1x2/*4), 5x IM (*1/*4), 4x PM (2x *4/*5, 1x *4/*6, 1x *6/*6), 6x UM (all *1x2/*1). No concomitant CYP2D6 inhibitors.	Conclusion authors: 'A PM phenotype of CYP2D6 increases the risk of side effects.' Css V+DV compared to EM:

venlafaxine. J Clin Pharm Ther 2006;31:493-502. PMID: 16958828			Compared to EM: PM: - Identical Css V+DV of 1.29 ng/ml (NS, by 0%) - Ratio DV/V decreased from 3.45 to 0.25 (S, by 93%) - Css[a] of the inactive metabolite N-desmethylvenlafaxine increased from 0.23 to 0.75 nM/mg (S, by 232%) IM: - Css[a] V+DV increased from 1.29 to 1.30 (NS, by 1%) - Ratio DV/V decreased from 3.45 to 1.16 (S, by 66%) - Css[a] of the inactive metabolite N-desmethylvenlafaxine increased from 0.23 to 0.43 nM/mg (NS, by 90%) UM: - Css[a] V+DV decreased from 1.29 to 0.98 (NS, by 24%) - Ratio DV/V increased from 3.45 to 10.3 (S, by 199%) - Css[a] of the inactive metabolite N-desmethylvenlafaxine decreased from 0.23 to 0.09 nM/mg (NS, by 60%) Compared to EM+IM: PM: - Number of side effects increased from 0.49 to 2.3 (S, by 369%) - Sodium serum concentration decreased from 142 to 138 nmol/l (S, by 3%) - Clinical Global Impressions Scale score increased from 1.7 to 2.0 (NS, by 18%) UM: - Number of side effects decreased from 0.49 to 0.3 (NS, by 39%) - Sodium serum concentration increased from 142 to 144 nmol/l (NS, by 1%) - Clinical Global Impressions Scale score was identical with 1.7 (NS, by 0%)	PM: 100% IM: 101% UM: 76%

			The increase of the DV/V ratio with increasing gene dose is mainly the result of the decrease of V Css[a]. The increase in plasma sodium concentration was inversely related to V Css[a]. Possibly, V has a larger influence on the number of side effects than O-desmethylvenlafaxine. Note: *3-*6, *9, and gene duplications were assessed.	
ref. 4 Whyte EM et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. Int J Geriatr Psychiatry 2006;21:542-9. PMID: 16642541	3	IM+PM: A	46 elderly patients, 30x EM, 13x IM (*1/*4), 3x PM (*4/*4). V was initiated at 37.5 mg/day and titrated upward as tolerated over the next 2 weeks to reach a target dose of 150 mg/day. Concomitant medication with influence on CYP2D6 not excluded. Compared to EM: IM+PM: - Css[a] V+DV increased from 3.21 to 4.00 ng/ml per mg (NS, by 25%) - Css[a] V increased from 0.69 to 2.26 ng/ml per mg (S, by 228%) - Css[a] DV decreased from 2.52 to 1.74 ng/ml per mg (S, by 31%) - Larger decrease on the $HDRS_{17}$ scale with -7.3 vs. -7.9 (NS, by 8%). - UKU Side Effects Rating Scale score increased from 9.8 to 10.7 (NS, by 9%) - QTc interval >440 msec as measured by an ECG at week 12 increased from 6.7% to 9.1% (NS, by 36%) - Withdrawal rate was identical (NS) V Css[a] was significantly higher and DV Css[a] was significantly lower in participants who carried one or more variant alleles compared to participants who were homozygous for the WT allele. Note: *3, *4, *6-*8 were assessed.	Conclusion authors: 'Future clinical application of pharmacogenetics to examine 2D6-dependent medications may help reduce the incidence of medication adverse events particularly in those elders at higher risk for medication adverse events due to impaired renal or cardiac function.'
ref. 5	4	PM: A	12 healthy subjects. 7x EM (4x *1/*1, 3x *1/*4), 5x PM	

Eap CB et al. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 2003;13:39-47. PMID: 12544511			(1x *3/*4, 4x *4/*4). V 18.75 mg BID. Concomitant medication not reported. PM: - AUC S-V + R-V increased from 0.58 to 2.27 µmol.hour/l (S, 291%)	
ref. 6 Fukuda T et al. The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. Eur J Clin Pharmacol 2000;56:175-80. PMID: 10877013	3	IM: A	28 healthy subjects, 5x *10/*10, 11x *10 (2x *1/*10, 9x *2/*10), 11x no *10 (2x *1/*1, 4x *1/*2, 5x *2/*2), 1x other (*1/*5). V 375 – 150 mg/day, no concomitant medication. Compared to no *10: *10/*10: - AUC[a] V increased from 185.0 to 1024.5 ng.hour/ml (S, by 454%) - AUC[a] V+DV increased from 1636.9 to 1974.0 ng.hour/ml (S, by 21%) 1x *10: - AUC[a] V increased from 185.0 to 407.3 ng.hour/ml (S, by 120%) - AUC[a] V+DV increased from 1636.9 to 1742.4 ng.uhour/ml (NS, by 6%) *1/*5: - AUC[a] V increased from 185.0 to 826.4 ng.hour/ml (NS, by 347%) - AUC[a] V+DV increased from 1636.9 to 1957.0 ng×uur/ml (NS, by 20%)	AUC V+DV compared to EM: IM: 117%
ref. 7 Lessard E et al. Influence of CYP2D6 activity on the	4	PM: A	14 healthy subjects, 8x EM, 6x PM. V 18.75 mg BID. No concomitant medication. PM:	The authors report that they have seen 4 other PMs with cardiovascular side effects (syncope, palpitations, dizziness).

disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. Pharmacogenetics 1999;9:435-43. PMID: 10780263			- AUC V increased from 0.9 to 3.1 mmol.hour/l (S, bt 244%) - Clor V decreased from 100 to 23 l/hour (S, by 77%) Note: individual results of pheno- and genotyping are not reported	
ref. 8 Veefkind AH et al. Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 2000;22:202-8. PMID: 10774634	4	PM: A IM: AA UM: AA	33 patients, 3x *4/*4, 4x *1/*4, 3x *2/*4, 1x *1xn, 1x *2xn, 15x *1/*2, 6x *1/*1. V 225 mg/day, no relevant concomitant medication. Compared to no *4: *Pharmacokinetic endpoints*: *4/*4: - Css V+DV increased from 311 to 539 mg/l (NS, by 73%) - Css V increased from 64 to 476 mg/l (S, by 644%) - Css DV decreased by 74% (S) - Ratio Css DV/V decreased by 97% (S) *1/*4 + *2/*4: - Css V+DV increased from 311 to 344 mg/l (NS, by 11%) - Css V increased form 64 to 113 mg/l (NS, by 77%). - Css DV decreased by 6% (NS) -Ratio Css DV/V decreased by 56%. *1xn + *2xn: - Css V+DV decreased from 311 to 182 mg/l (NS, by 41%) - Css V decreased from 64 to 12 mg/l (NS, by 81%) - Css DV decreased by 1% - Css DV/V increased by 139% Clinical endpoint:	Css V+DV compared to EM: PM: 173% IM: 111% UM: 59%

		PM: C	*4/*4: all non-responders *1xn + *2xn: 1 responder + 1 non-responder	
ref. 9 Fukuda T et al. Effect of the CYP2D6*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. Br J Clin Pharmacol 1999;47:450-3. PMID: 10233212	3	IM: A	12 healthy subjects, 1x *5/*10, 3x *10/*10, 2x *1/*10, 2x *2/*10, 2x *1/*1, 2x *2/*2. Concomitant medication not reported. V 25-37.5 mg/day. Compared to *1/*1+*2/*2: *10/*10 + *5/*10: - AUC[b] V increased from 219.2 to1280.0 ng.hour/ml (S, by 484%) - t½ increased from 3.44 to 6.32 hour (NS, by 84%) - AUC[b] V+DV increased from 2864.7 to 3379.2 ng.hour/ml (NS, by 18%). *1/*10 + *2/*10: - AUC[b] V increased from 219.2 to 421.9 ng.hour/ml (NS, by 92%) - t½ increased from 3.44 to 4.05 hour (NS, by 18%) - AUC[b] V+DV increased from 2864.7 to 3080.1 ng.hour/ml (NS, by 8%)	Conclusion authors: 'However, concentrations of venlafaxine + O-desmethylvenlafaxine were not different between groups and since O-desmethylvenlafaxine is equally effective, the effect of genotype on pharmacokinetics is not expected to be translated into differences in response.' AUC V+DV compared to EM: IM: 114%
ref. 10 SPC Elbfaxin XR (venlafaxine) 01-11-07.	0		Dutch package insert.	

[a] adjusted for dose

[b] adjusted for dose and bodyweight

Groups at risk	IMs with concomitant use of a CYP2D6 inhibitor. IM + PM with strong CYP3A4 inhibitor

Remarks

Date literature search: 7 February 2008

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	4 C	Yes	Yes	26 March 2008
	IM	4 C	Yes	Yes	
	UM	4 A	Yes	Yes	

Action Pharmacy Technician	The metabolism of venlafaxine by CYP2D6 is decreased. Consult pharmacist
Action Pharmacist, Physician	PM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is decreased. This might result in increased venlafaxine plasma concentrations and decreased plasma concentrations of the active metabolite O-desmethylvenlafaxine. The current body of evidence does not allow the calculation of a dose adjustment. Select an alternative drug (e.g., citalopram, sertraline). If this is not possible, adjust the dose to clinical response and monitor (O-desmethyl)venlafaxine plasma concentrations. The therapeutic efficacy, but not the side effects of venlafaxine are related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations. Therefore it is not possible to calculate a dose reduction that reduces the risk for side effects for PM and IM to that of EM but remains equally effective.
	IM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is decreased. This might result in increased venlafaxine plasma concentrations and decreased plasma concentrations of the active metabolite O-desmethylvenlafaxine. The current body of evidence does not allow the calculation of a dose adjustment. Select an alternative drug (e.g., citalopram, sertraline). If this is not possible, adjust the dose to clinical response and monitor (O-desmethyl)venlafaxine plasma concentrations. The therapeutic efficacy, but not the side effects of venlafaxine are related to the sum of

	venlafaxine and O-desmethylvenlafaxine plasma concentrations. Therefore it is not possible to calculate a dose reduction that reduces the risk for side effects for PM and IM to that of EM but remains equally effective.
	UM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is increased. This might result in decreased venlafaxine plasma concentrations and increased plasma concentrations of the active metabolite O-desmethylvenlafaxine. Be alert to decreased venlafaxine and increased (O-desmethyl)venlafaxine plasma concentration. Titrate the dose to a maximum of 150% of the recommended dose and monitor plasma concentrations. If this is not possible, select an alternative drug (e.g., citalopram, sertraline).

Considerations

The therapeutic efficacy, but not the side effects of venlafaxine are related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations. Since side effects and efficacy are not both related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations it is not possible to calculate a dose reduction that reduces the risk for side effects for PM and IM to the risk of EM but remains equally effective.

PM: There are case reports of cardiotoxicity (Lessard 1999) and 1 study reports all PM's to be non-responder (Veefkind, 2000). Shams et al (2006) report an increased number of side effects with identical venlafaxine + O-desmethylvenlafaxine concentrations. This indicates that the therapeutic efficacy, but not the side effects of venlafaxine are related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations. Therefore, the selection of an alternative drug that is not or less metabolized by CYP2D6 is recommended. If this is not possible, the dose should be decreased in response to clinical response and (O-desmethyl)venlafaxine plasma concentrations. Since side effects and efficacy are not both related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations it is not possible to calculate a dose reduction that reduces the risk for side effects for PM and IM to the risk of EM but remains equally effective.

The population size-weighted mean dose required to achieve a venlafaxine + O-desmethylvenlafaxine Css or AUC as EM is 72% of the recommended dose (58%-100%). A dose lower than 72% might increase the risk for therapeutic failure.

IM: Despite the fact that venlafaxine might be cardiotoxic, no cardiotoxicity has been reported for IMs. Mc Alpine (2007). reports 5 cases in which venlafaxine treatment had to be terminated due to side effects. In IM the sum of the venlafaxine en O-desmethylvenlafaxine plasma concentration shows only minor changes. In contrast to the therapeutic efficacy, venlafaxine side effects appear not be related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentration. Therefore, the selection of an alternative drug that is not or less metabolized by CYP2D6 is recommended. If this is not possible, the dose should be decreased in response to clinical response and (O-desmethyl)venlafaxine plasma concentrations. Since side effects and efficacy are not both related to the sum of venlafaxine and O-desmethylvenlafaxine plasma concentrations it is not possible to calculate a dose reduction that reduces the risk for side effects for PM and IM to the risk of EM but remains equally effective.
The population size-weighted mean dose required to achieve a venlafaxine + O-desmethylvenlafaxine Css or AUC as EM is 87% of the recommended dose (82%-99%). A dose lower than 87% might increase the risk for therapeutic failure.

UM: Only 2 studies reported results for a total of 8 patients with the UM phenotype (Veefkind, 2000; Shams 2006). None of these studies report significant effects of the UM phenotype on side effects or efficacy. As a precaution it is recommended to be alert to decreased venlafaxine and increased (O-desmethyl)venlafaxine plasma concentrations and increase the dose if required.
The population size-weighted mean of the dose adjustments calculated for the individual papers (based on the sum AUC or Css of venlafaxine + O-desmethylvenlafaxine) is 141% of the recommended dose (131% - 171%). For clinical applicability this is translated to an increase to 150% of the recommended dose. If this is not possible, select an alternative drug (e.g., citalopram, sertraline).

Mechanism

Venlafaxine is metabolized to the active metabolite O-desmethylvenlafaxine by CYP2D6. Both venlafaxine and O-desmethylvenlafaxine are metabolized by CYP3A4 to their inactive metabolites N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine, respectively. A genetic polymorphism in the gene coding for CYP2D6 may modify the plasma concentrations of venlafaxine and O-desmethylvenlafaxine (mainly E-10-hydroxy derivatives). E-10-OH-amitriptyline has approximately 30% of the potency of amitriptyline. E-10-OH-nortriptyline has approximately 50% of the potency of nortriptyline. Amitriptyline is also metabolized by N-oxidation and N-glucurunodiation. Nortiptyline is metabolized by CYP2D6 and CYP2C19 to the inactive metabolite didesmethylamitriptyline (desmethylnortriptyline).