Eur J Clin Pharmacol (2004) 59: 883–891
DOI 10.1007/s00228-003-0710-3

PHARMACOKINETICS AND DISPOSITION

**Marianne Gex-Fabry · Androniki E. Balant-Gorgia
Luc P. Balant · Serge Rudaz · Jean-Luc Veuthey
Gilles Bertschy**

Time course of clinical response to venlafaxine: relevance of plasma level and chirality

Received: 1 September 2003 / Accepted: 19 November 2003 / Published online: 24 December 2003

Abstract *Objective*: Early clinical response to antidepressant treatment is an important therapeutic goal, considering the psychological, social and economic consequences of depression. The aim of the present study was to investigate the relationship between the time course of response and the concentration of venlafaxine (V), its active metabolite O-desmethylvenlafaxine (ODV) and enantiomeric ratios V(+)/V(−) and ODV(+)/ODV(−).
Methods: Depressed inpatients ($n=35$) received V orally at a fixed 300 mg daily dose. Accepted comedication included clorazepate (maximum 60 mg/day), zopiclone (maximum 15 mg/day) and low-dose trazodone (maximum 200 mg/day). Severity of depression was assessed on days 0, 4, 7, 11, 14, 21 and 28 (Montgomery and Åsberg Depression Rating Scale). Blood samples were taken on day 14 and day 28 and submitted to stereoselective determination. All measurements reflected trough steady-state values. First, pattern analysis was used to provide a categorical perspective of clinical response (50% improvement from baseline depression score). Patients displaying non-response, transient response, early persistent response and delayed persistent response were compared with respect to racemic concentrations and enantiomeric ratios. Second, in a dimensional perspective, mixed-effects modelling was used to analyse severity of depression versus time curves with respect to the possible influence of concentrations and enantiomeric ratios.
Results: Comparison of patients with and without persistent response did not reveal any significant difference for V, ODV, V + ODV plasma levels or enantiomeric ratios. Persistent response was significantly associated with less frequent pre-study antidepressant medication and less frequent comedication with zopiclone (day 14) and clorazepate (day 28) during the study. Focus on patients with persistent response ($n=19$, 54.3%) indicated that early response, first observed before day 14, was associated with significantly higher V + ODV concentration than delayed response (median 725 ng/ml versus 554 ng/ml, $P=0.023$). No difference was found for pre-study medication or comedication during the study. Shorter time to onset of response was significantly associated with lower V(+)/V(−) enantiomeric ratio ($r_s=0.48$, $P<0.05$). Mixed-effects modelling of depression severity versus time curves in patients with persistent response confirmed that either higher V + ODV plasma level or lower V(+)/V(−) ratio were significantly associated with more rapid decrease of depression score (likelihood ratio tests, $P=0.012$ and $P=0.046$, respectively).
Conclusion: Considering its modest sample size, naturalistic design and limited observation period, the present study provided preliminary indication that earlier clinical response may occur with higher V + ODV plasma level, extending previous dose-response studies. The hypothesis was also raised that exposure to a more potent noradrenergic therapeutic moiety, as reflected by a lower V(+)/V(−) ratio, may be relevant to early improvement of depression.

Keywords Venlafaxine · Concentration-response relationship

M. Gex-Fabry (✉) · A. E. Balant-Gorgia · L. P. Balant
Clinical Research Unit, Department of Psychiatry,
2 chemin du Petit-Bel-Air,
1225 Chêne-Bourg, Switzerland
E-mail: Marianne.Gex-Fabry@medcli.unige.ch
Tel.: +41-22-3055793
Fax: +41-22-3055799

S. Rudaz · J.-L. Veuthey
Laboratory of Pharmaceutical Analytical Chemistry,
School of Pharmacy, Geneva University,
Geneva, Switzerland

G. Bertschy
Clinic of Adult Psychiatry, Department of Psychiatry,
Geneva University Hospitals,
Geneva, Switzerland

Introduction

The antidepressant venlafaxine (V) is characterised by a positive dose-effect relationship both for clinical

response and occurrence of adverse reactions [1, 2, 3]. In addition, emerging evidence indicates that earlier response may be achieved with a higher daily dose [4, 5]. Onset of response to antidepressant treatment has been the focus of much debate in recent years, earlier clinical response being not only beneficial to the patient and the family, but also associated with decreased societal and economic burden [6, 7, 8]. V, among other drugs, has been postulated as a fast-onset antidepressant, based on different lines of evidence. Preclinical studies have suggested rapid onset of action to be associated with rapid desensitisation of the beta-adrenergic receptor system [9]. Placebo-controlled studies have shown significantly greater clinical improvement with V than with placebo as early as week 1 [6, 10, 11]. In comparative studies, faster onset of response was documented with V than with imipramine [12] or serotonin (5-HT)-specific reuptake inhibitors [13]. Nevertheless, earlier onset of response when compared with alternative treatment options has not always been observed [14, 15], possibly because of methodological differences between studies. With speed of action becoming a central issue for pharmaceutical companies, specific methodological recommendations have been proposed for studies aimed at estimating onset of response [16, 17]. According to Leon et al. [16], key features include: (1) a prospective, operational definition of early onset of response; (2) frequent assessments of depression severity during the early phase of treatment; (3) strategies to minimise bias and heterogeneity of response, e.g. adequate dosage achieved within a short period of time and (4) statistical approaches capable of capturing the dynamic nature of symptomatic change.

The pharmacology of putative early onset antidepressants has recently been reviewed [18, 19], with accumulating data suggesting a possible association between early response and a dual mechanism of action on serotonin (5-HT) and noradrenaline (NA) reuptake inhibition. Over V clinically relevant dose range, 5-HT and NA uptake inhibition are sequentially engaged [20], leading to the hypothesis of the NA system being crucial in faster onset of response at higher dose. Pharmacological properties of V enantiomers may also be invoked, V(+) selectively inhibiting 5-HT reuptake and V(−) displaying both noradrenergic and serotonergic activity [21]. Due to stereoselective disposition in humans [22] and large inter-individual pharmacokinetic variability [23], different patients may be exposed to different pharmacological profiles at a given dose. Despite potential clinical relevance, the concentration–response relationship of V has been little investigated and has been restricted to racemic concentrations of parent compound and its active metabolite, O-desmethylvenlafaxine (ODV) [24, 25, 26].

The present investigation was part of a study on lithium augmentation of V therapy in hospitalised patients with depression [27]. Its general objective was to determine whether chiral determination of plasma concentration might contribute to a better understanding of pharmacokinetic and pharmacodynamic variability in patients. Pharmacokinetic variability has been the focus of an earlier publication in this journal [23]. In the present article, the concentration–response relationship was analysed through two different statistical approaches, taking into account enantiomers of V and ODV. First, pattern analysis [28] proceeded by classification of patients according to whether onset of clinical response was early (< 2 weeks) or delayed and whether response was persistent or transient. Group comparison with respect to plasma levels, enantiomeric ratios and comedication was then performed. Second, mixed-effects models [29], conceptually similar to models used in population pharmacokinetics, were used to describe the time course of clinical improvement and its relationship to concentration, taking into account heterogeneity of profiles among patients.

Materials and methods

Patients

The present study included 35 inpatients who participated in an open fixed-dose study of V, with low-dose trazodone augmentation for severe and persistent insomnia and lithium augmentation for non-responders at week 4 [27]. Inclusion criteria were age range 18–65 years, diagnosis of moderate or severe depressive episode without psychotic symptoms (ICD-10 criteria [30]) and a score at inclusion ≥25 on Montgomery and Åsberg Depression Rating Scale (MADRS [31]). Exclusion criteria were pregnancy, schizophrenia, schizoaffective disorder, dependence syndrome, presence of a somatic illness that was a contraindication to the prescription of venlafaxine, trazodone or lithium and previously documented hypersensitivity to these drugs. Patients were also excluded if they were receiving mood stabilising drugs at inclusion and if they were non-responders to previous V treatment at a daily dose ≥225 mg. Description of the patients is provided in Table 1. For the 14 patients with pre-study antidepressant medication, distribution of drugs was as follows: citalopram ($n = 5$), paroxetine ($n = 2$), sertraline ($n = 1$), low-dose venlafaxine ($n = 2$), trazodone ($n = 2$), nefazodone ($n = 1$), moclobemide ($n = 1$) and low-dose trimipramine ($n = 1$). No washout period was considered necessary in these patients. When present at inclusion visit ($n = 5$), antipsychotic medication at a low to moderate dose was discontinued.

Protocol and informed consent form received approval from the ethics committee of the Department of Psychiatry, Geneva University Hospitals. After receiving a complete description of the study and possible side effects, each patient provided written informed consent before being enrolled.

Treatment

After inclusion, patients were rapidly titrated to a 300-mg daily dose of V, which remained constant from day 3 onward (150 mg b.i.d.). Accepted psychotropic comedication included clorazepate (maximum 60 mg/day), zopiclone (maximum 15 mg/day) and trazodone, introduced at low-dose (maximum 200 mg/day) in case of severe and persistent sleep disorder (MADRS sleep item ≥4 for at least 1 week). The present study focused on data collected up to day 28, i.e. before lithium was introduced in non-responders. Psychotropic comedication during the study is documented in Table 1. Comedication prescribed for somatic disorders was present in 15, 18 and 20 patients on days 0, 14 and 28, respectively. Most frequent classes of drugs were hormonal preparations ($n = 6$–7 patients), analgesic and anti-inflammatory products ($n = 5$–8),

Table 1 Patient description ($n = 35$). *ICD-10* International Classification of Diseases, 10th revision [30], *MADRS* Montgomery and Åsberg Depression Rating Scale [31]

Age (median, range)		44	22–60
Gender (*n*, %)			
Males		14	40.0%
Females		21	60.0%
Psychiatric diagnosis according to ICD-10 criteria (*n*, %)			
Depressive episode (F32)		20	57.1%
Recurrent depressive disorder (F33)		13	37.1%
Bipolar affective disorder, current episode depression (F31)		2	5.7%
Specific or mixed personality disorder (F60–F61)		12	34.3%
Anxiety or obsessive–compulsive disorder (F40–F42)		7	20.0%
Baseline MADRS depression score (median, range)		38	25–52
Pre-study psychotropic medication (*n*, %)			
Antidepressants		14	40.0%
Antipsychotics		5	14.3%
Benzodiazepines		30	85.7%
Other hypnotics		11	31.4%
Psychotropic comedication during the study (*n*, %)			
Clorazepate	Day 0	32	91.4%
	Day 14	30	85.7%
	Day 28	29	82.9%
Zopiclone	Day 0	32	91.4%
	Day 14	25	71.4%
	Day 28	23	65.7%
Trazodone	Day 0	1	2.9%
	Day 14	6	17.1%
	Day 28	14	40.0%

laxatives ($n = 3$–4) and medications for the cardiovascular system ($n = 2$–5).

Blood samples were taken on day 14 and day 28 for therapeutic drug monitoring purpose. A majority of samples (80%) were obtained at 14 h post-dose (range 12–16 h) and reflected trough values, with usual intake times at 1800 hours and 0800 hours. Because half-lives are about 4 h for V and 10 h for ODV [32], and posology was kept constant from day 3 onward, patients were considered at steady-state for parent compound and metabolite. All patients had chiral determination of V and ODV.

As reported previously [23], inter-individual variability was larger for the parent compound (77%) than for the metabolite (33%) and the active moiety V + ODV (31%). Estimates for V(+)/V(−) and ODV(+)/ODV(−) enantiomeric ratios were 47% and 70%, respectively. Intra-individual variability arising from repeated measurements on day 14 and day 28 was below 20% for V, ODV, V + ODV and enantiomeric ratios. The present article focused on concentrations measured on day 14, postulated to reflect exposure to drug treatment throughout the 4-week observation period.

Analytical method

In a first stage, concentrations of V and ODV were determined by a gas chromatography method with nitrogen-phosphorus detection [23]. Within-day coefficients of variation for V were 3.2% at 10 ng/ml, 2.8% at 100 ng/ml and 2.0% at 200 ng/ml. They were 7.2% at 10 ng/ml, 6.7% at 100 ng/ml and 6.5% at 400 ng/ml for ODV. Between-day coefficients of variation were 2.9% at 100 ng/ml for V and 2.8% at 300 ng/ml for ODV. In a second stage, a validated stereoselective capillary electrophoresis method was used for the determination of the enantiomeric concentrations from which (+)/(−) ratios were calculated [33]. After optimisation of the method (including robustness), validation was carried out. In the tested concentration range (25–500 ng/ml), correlation coefficients were superior to 0.996. Within-day and between-day accuracy and precision were determined at three different concentrations for each enantiomer. For both analytes, within-day accuracies were superior to 95%. Day-to-day accuracy, for serum-spiked samples at a concentration of 50 ng/ml, was superior to 95.0% of the expected value with precision (relative standard deviation) inferior to 15.0%. At 250 ng/ml, day-to-day accuracies were superior to 97.0% with precision inferior to 5.0%. At 500 ng/ml, accuracy did not differ more than 1.0% of expected values, with precision inferior to 6.0%.

Clinical assessments

Severity of depression over time was assessed through MADRS total scores on days 0, 4, 7, 11, 14, 21 and 28. The MADRS depression scale has demonstrated adequate inter-rater reliability, validity and sensitivity to change in antidepressant clinical trials [31, 34]. Information about adverse events was collected at same time intervals on the basis of open questions.

Statistical analysis

Pattern analysis

Pattern analysis was introduced by Quitkin [28] with the aim of differentiating drug-specific and non-specific placebo response in individual patients. It has been used with success to assess onset of clinical response [6, 11].

In the present study, clinical response was defined as 50% improvement from baseline MADRS score. This criterion has strong precedence of use, and its clinical meaning is generally recognised [35]. Response observed before day 14 was considered as an early response, whereas response first observed on day 14 or later was considered as a delayed response. Response was further categorised as persistent if all subsequent assessments up to day 28 qualified for response and as transient if at least one of these evaluations did not meet the criterion for response. Patients were, thus, classified into one of the following four categories: non-response, transient response, early persistent response and delayed persistent response. In patients displaying persistent response, time to onset of response was defined as the time of first occurrence of response. Group comparison proceeded through Fisher exact test for categorical variables (e.g. comedication) and Mann-Whitney U-test for continuous variables (e.g. concentration). Association

between continuous variables was assessed through Spearman rank-order correlation coefficient (r_S). Statistical significance was set at 0.05.

Mixed-effects modelling

Mixed-effect modelling for the analysis of depression severity versus time curves was first introduced by Gibbons [29]. It was recently recommended to capture the dynamic process of onset of clinical improvement, while taking into account heterogeneity of individual profiles [16].

In a first stage, MADRS score y_{it} of patient i at time t was described by the following quadratic random-effects model:

$$y_{it} = \alpha_i + \beta_i t + \gamma_i t^2 + \varepsilon_{it} \quad (1)$$

where α_i, β_i and γ_i are intercept, slope and quadratic coefficients for subject i, respectively. Distributions of these individual parameters are assumed multivariate normal, with mean values α, β, γ corresponding to population values and variance terms σ_α^2, σ_β^2, σ_γ^2 reflecting inter-individual variability. The residual error term ϵ_{it} describes differences between measured and predicted MADRS scores, assumed to be normally distributed with mean 0 and variance σ_ϵ^2. Estimation of the 7-parameter model $\left(\alpha,\ \beta,\ \gamma,\ \sigma_\alpha^2,\ \sigma_\beta^2,\ \sigma_\gamma^2 \text{ and } \sigma_c^2\right)$ was performed considering all data together ($N = 133$ data, $n = 19$ patients). Bayesian post-hoc estimates of individual parameters were also provided.

In a second stage, these post-hoc estimates were plotted against potential covariables (e.g. concentration) in order to explore whether they may influence the shape of depression severity versus time curves. If a significant trend was observed, the covariable was included as a fixed-effect into the model, which was rewritten as follows.

$$y_{it} = \alpha_i + (\beta_i + bX)t + (\gamma_i + cX)t^2 + \varepsilon_{it} \quad (2)$$

where b and c are coefficients describing the influence of covariate X on slope and quadratic term, respectively. The influence of concentration was assessed in terms of variation around median value in the population. As candidate covariables generally displayed positively skewed distributions, they were log-transformed in order to ensure that outlying values may not be unduly influent. The full 9-parameter model was estimated considering all data together.

The likelihood ratio test was used for comparison of models of increasing complexity. To test whether including a covariable would significantly improve the goodness of fit, twice the difference of log-likelihoods was compared with the χ^2 distribution with two degrees of freedom. Significance level was at 0.05. Models were also assessed with respect to standard errors of parameter estimates and the following graphs: (1) observed and predicted depression scores versus time; (2) residuals (i.e. observed-predicted scores) versus time and versus prediction and (3) observed versus predicted depression scores. Graphics were considered for both population and individual post-hoc predictions. Descriptive statistics of residuals were calculated at each time and per patient. Data analysis was performed using SYSTAT 10 (Systat Software Inc., Richmond, CA, USA), which integrates the implementation of mixed models as described by Hedeker and Gibbons [36].

Results

Response patterns and relationship with concentration

Figure 1 illustrates severity of depression versus time data for individual patients and their distribution according to patterns of non-response ($n = 8$, 23%), transient response ($n = 8$, 23%), early persistent response

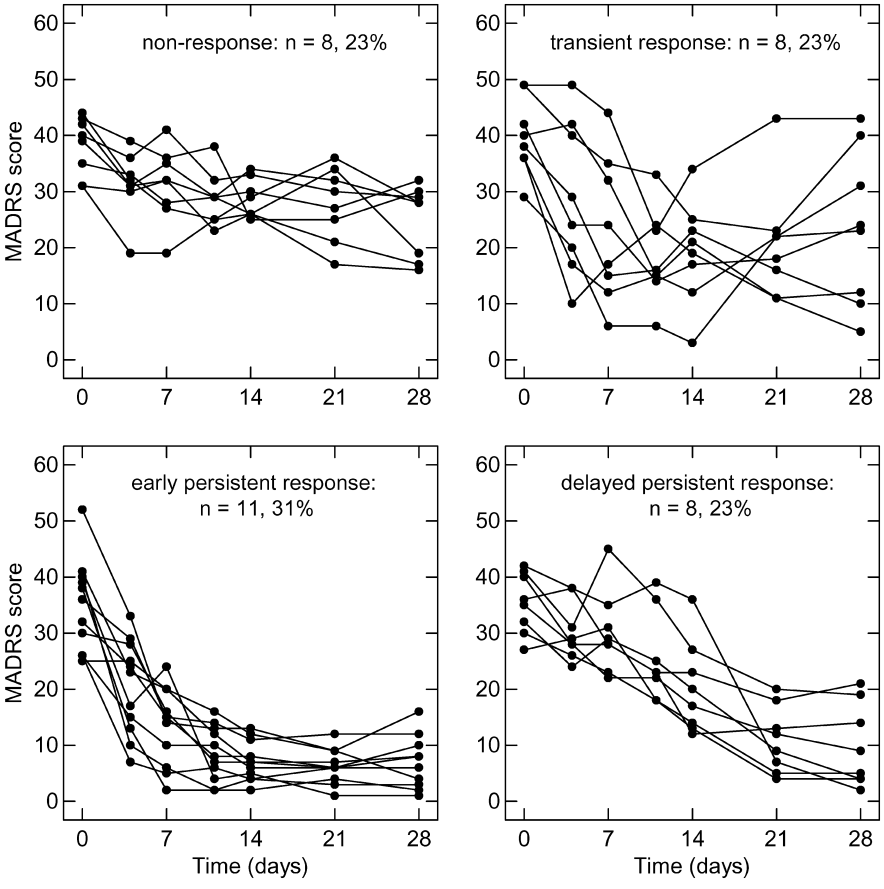

Fig. 1 Patterns of Montgomery and Åsberg Depression Rating Scale depression score versus time curves in 35 patients with venlafaxine 300 mg/day. Clinical response was defined as 50% improvement from baseline score. It was considered as persistent if all subsequent assessments met the criterion for response and as transient otherwise. Response was labelled early and delayed if first observed before day 14 or from day 14, respectively

Table 2 Response patterns and differences with respect to venlafaxine concentration on day 14. *V* venlafaxine, *ODV* O-desmethylvenlafaxine, *N.S.* not significant

		Persistent response, no		Persistent response, yes		Persistent yes versus no sign[a]	Early versus delayed sign[a]
		Non-response ($n=8$)	Transient response ($n=8$)	Early (day < 14) ($n=11$)	Delayed (day≥14) ($n=8$)		
V + ODV (ng/ml)	Median	719	576	725	554	N.S.	0.023
	Range	(466–819)	(418–803)	(458–1605)	(202–988)		
V (ng/ml)	Median	192	160	214	146	N.S.	N.S.
	Range	(37–496)	(69–393)	(74–1294)	(27–320)		
ODV (ng/ml)	Median	475	351	589	385	N.S.	N.S.
	Range	(298–569)	(285–734)	(209–772)	(175–708)		
V(+)/V(−)	Median	0.82	0.88	0.88	1.40	N.S.	0.083
	Range	(0.55–1.95)	(0.41–2.28)	(0.41–1.62)	(0.95–1.94)		
ODV(+)/ODV(−)	Median	1.12	0.98	0.93	0.96	N.S.	N.S.
	Range	(0.76–1.95)	(0.84–3.67)	(0.70–16.42)	(0.72–7.57)		

[a]Mann-Whitney U test

($n=11$, 31%) and delayed persistent response ($n=8$, 23%). In keeping with the postulate that transient response may not be clinically meaningful [35], a first series of comparisons focused on differences among patients displaying persistent response and either non-response or transient response to V therapy. Groups did not statistically differ with respect to gender, age, diagnosis of personality disorder or anxiety disorder nor MADRS depression score at inclusion. Pre-study medication did not differ, except for antidepressants, which were less frequent in persistent response (21.1% versus 62.5%, $P=0.018$). No statistical difference was seen for V, ODV or total V + ODV concentration (Table 2). Similarly, no difference was found for V(+)/V(−) and ODV(+)/ODV(−) enantiomeric ratios. However, differences appeared with respect to zopiclone and clorazepate, but not trazodone comedication during the study. Zopiclone was significantly less frequent in persistent response on day 14 (52.6% versus 93.8%, $P=0.010$), with a similar difference for clorazepate on day 28 (68.4% versus 100.0%, $P=0.022$). Since these comedications were prescribed in a large majority of patients when entering the study (Table 1), and no difference between groups was present at that time, results suggested more frequent discontinuation of zopiclone and clorazepate in patients with persistent, clinically meaningful response.

In agreement with the recommendation that analysis of onset of response should focus on treatment responders [37], a second series of comparisons concentrated on early versus delayed persistent response (Table 2). Groups did not statistically differ with respect to age, gender, diagnosis of personality or anxiety disorder, MADRS at inclusion nor pre-study medication. Whereas no difference was observed for racemic V and ODV concentrations, early response was associated with significantly higher V + ODV concentration than delayed response (median concentrations 725 ng/ml and 554 ng/ml respectively, $P=0.023$). Unlike for ODV, the enantiomeric ratio for V was lower in early persistent response, but the difference remained above statistical significance (median values 0.88 and 1.40 respectively, $P=0.083$). Interestingly, of seven patients with V(+)/V(−) ratio <1 (range 0.41–0.95), five (71.4%) simultaneously displayed total concentration >700 ng/ml. All were early responders to treatment. No difference between groups was observed for clorazepate, zopiclone or trazodone comedication on either day 0, 14 or 28.

In patients with persistent response, median time to onset of response was 11 days (range 4–21 days). Time to onset displayed significant positive correlation with V(+)/V(−) enantiomeric ratio ($r_s=0.48$, $P<0.05$), but not ODV(+)/ODV(−) nor V, ODV and V + ODV concentrations. Early relative MADRS decrease, as seen on day 7, was significantly associated with higher V + ODV concentration ($r_s=0.54$, $P<0.05$) and lower V(+)/V(−) ratio ($r_s=-0.58$, $P<0.05$), but not V, ODV or ODV(+)/ODV(−) ratio. No association remained significant when considering final MADRS decrease on day 28.

Mixed-effects modelling of depression severity versus time curves

Mixed-effects models were developed to further investigate the potential role of concentration with respect to depression severity versus time curves in patients with persistent response, taking into account heterogeneity of trends over time. Because MADRS depression score did not start decreasing before week 1 or week 2 in some patients (Fig. 1), a quadratic model was selected for the time effect. Table 3 provides a summary of the principal models tested.

The simplest random-effects model (model 1) allowed to estimate mean intercept, slope and quadratic coefficient in the population. Early decrease of depression score, estimated from average slope in the population, was −2.2 MADRS points per day. The model also

Table 3 Models for depression severity versus time curves and relationship to concentration in patients with persistent response to venlafaxine 300 mg/day ($n = 19$ patients, N = 133 data). *V* venlafaxine, *ODV* O-desmethylvenlafaxine, *SD* standard deviation, *MADRS* Montgomery and Åsberg Depression Rating Scale [31]

Parameter estimate[a]	Random effects model 1 without covariate	Mixed effects model 2 including covariate $X = \log_{10}(V + ODV/median)$	Mixed effects model 3 including covariate $X = \log_{10}(V+/V-)$
Mean (α)	34.1	34.1	34.1
Interindividual variability, SD (α)	4.9	4.9	4.9
Mean (β)	−2.22	−2.27	−2.35
Interindividual variability, SD (β)	1.00	0.68	0.81
Covariate effect b		−3.98	3.58
Mean (γ)	0.046	0.048	0.051
Interindividual variability, SD (γ)	0.039	0.028	0.032
Covariate effect c		0.154	−0.133
Residual variability, SD (ϵ)	4.6	4.6	4.6
−2 Log-Likelihood	852.8	843.9	846.6
P value[b]		0.012	0.046

[a]General model for MADRS depression score of patient i at time t was $MADRS_{it} = \alpha_i + (\beta_i + bX)t + (\gamma_i + cX)t^2 + \epsilon_{it}$
[b]Likelihood ratio test for improved goodness of fit with respect to model 1, with two degrees of freedom

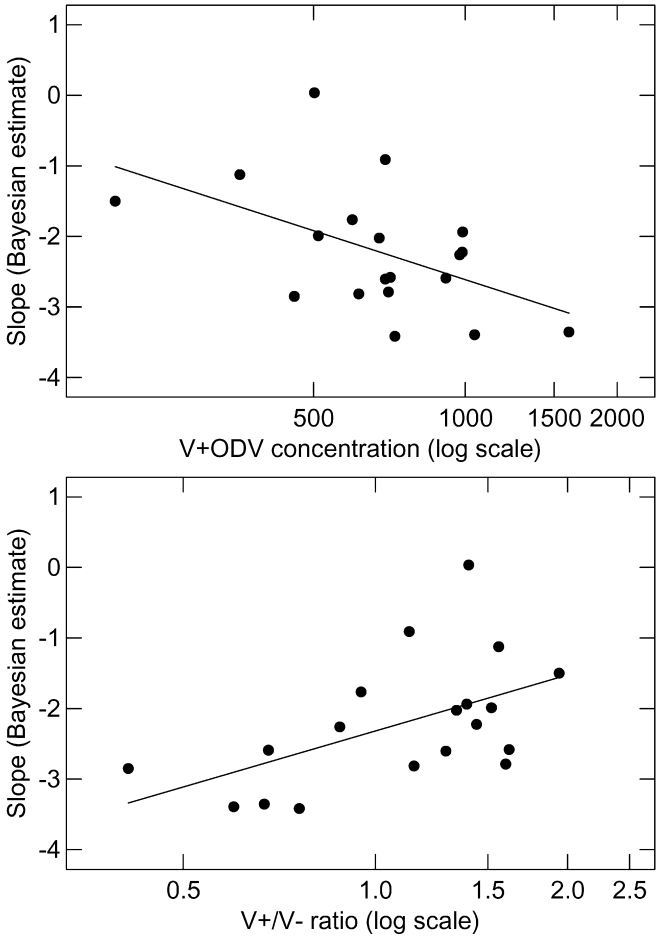

Fig. 2 Relationship between slope of Montgomery and Åsberg Depression Rating Scale versus time curve and potential covariates in 19 patients with persistent response to venlafaxine 300 mg/day. Individual Bayesian estimates of slope were obtained from a random effects model (model 1 in Table 3). Candidate covariables were total V + ODV concentration ($r_S = -0.50$, $P < 0.05$, *upper part*) and V+/V− enantiomeric ratio ($r_S = 0.55$, $P < 0.05$, *lower part*)

provided estimates of between-patient variability for intercept, slope and quadratic term. Estimated variability for slope was 45.0%, with post-hoc estimates for individual patients in a range −3.4 to 0 points per day. Search for influent covariables proceeded through plots of these individual slope estimates against V, ODV, V + ODV concentrations, as well as V and ODV enantiomeric ratios. As illustrated in Fig. 2, higher V + ODV concentration and lower V(+)/V(−) ratio were significantly associated with increasingly negative slope ($r_S = -0.50$, $P < 0.05$ and $r_S = 0.55$, $P < 0.05$, respectively). When total concentration was entered into a mixed-effects model (model 2), goodness-of-fit significantly improved (likelihood ratio test, $P = 0.012$) and inter-individual variability for slope decreased to 30.0%. Total V + ODV concentration was, thus, confirmed as a significant determinant of the slope of MADRS versus time curves. Not unexpectedly, an opposite effect was observed for the quadratic term, which correlated negatively with slope. Similarly, when V(+)/V(−) ratio was entered into the model (model 3), goodness-of-fit improved significantly when compared with a model without covariate (likelihood ratio test, $P = 0.046$). No further improvement was obtained when entering total concentration and enantiomeric ratio together in the model.

Figure 3 illustrates the performance of the model including total concentration as a covariable. Figure 3 (upper part) shows individual model-predicted MADRS versus time curves in patients with persistent response, together with mean population prediction. Upward curvature of predicted curves between day 21 and day 28 was present in 11 of 19 patients, suggesting limitations of the quadratic model in some situations. Plots of predicted and observed depression scores versus time for each individual patient indicated that the model adequately described time dependence in a majority of cases ($n = 14$, 73.7%), whereas goodness-of-fit was of a lesser quality in patients with early, abrupt decrease,

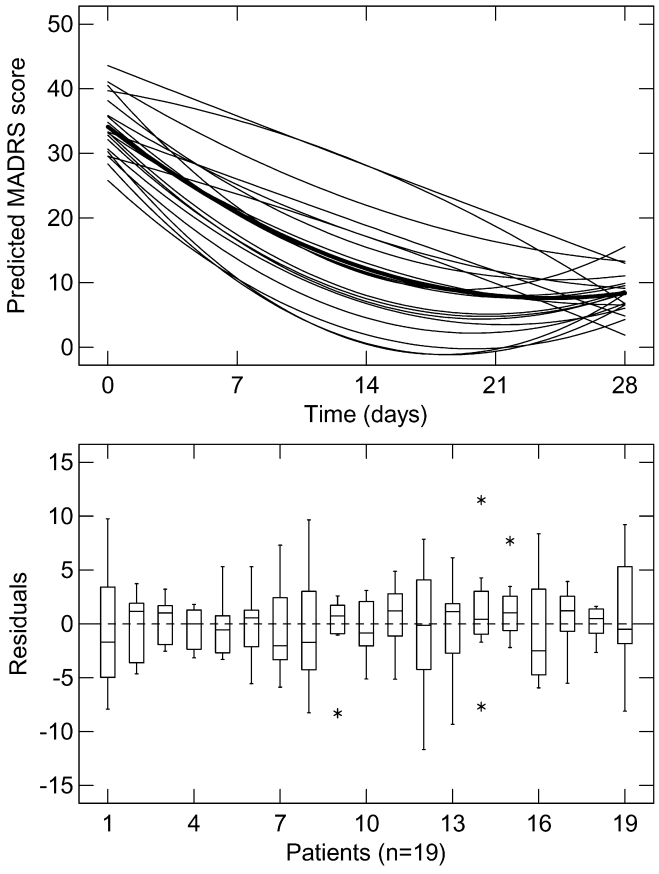

Fig. 3 Mixed-effects modelling of Montgomery and Åsberg Depression Rating Scale versus time curves, integrating V + ODV concentration as a covariate, in 19 patients with persistent response to venlafaxine 300 mg/day (model 2 in Table 3). Population prediction (*thick line*) and post-hoc individual predictions (*thin lines*) are illustrated in the *upper part*. Distribution of residuals (i.e. observed score-predicted score) is illustrated in the *lower part* as a series of box plots for each individual patient

followed by close to constant MADRS score ($n = 5$). The distribution of residual errors for each patient is depicted in Fig. 3 (lower part). Median deviation between observation and prediction was below 2.5 MADRS points in all subjects. Additional residual plots and statistics did not reveal any major departure from the hypotheses underlying linear models. Interestingly, residuals did not display any significant serial correlation across time, suggesting that an autocorrelated error structure was not needed in the model.

Discussion

In view of accumulating evidence of V early onset of action [11, 12, 13] and renewed interest in its dual mechanism on 5-HT and NA neurotransmission [9, 18], the present study offered a double perspective. First, pattern analysis provided a categorical picture of treatment response and its potential pharmacokinetic determinants. Second, mixed-effects modelling provided a dimensional perspective to depression severity versus time curves and their relationship to concentration. To our knowledge, the relationship between onset of clinical response and exposure to V and ODV enantiomers had not been investigated thus far.

Over a 4-week observation period, pattern analysis indicated absence of a clinically meaningful response in 45.7% and persistent response in 54.3% of patients prescribed a fixed 300 mg daily dose of V. Onset of persistent response occurred early, i.e. within the first 2 weeks, for 31.4% of patients. With response defined according to the Clinical Global Impressions scale (global improvement ≤ 2), early persistent response was similarly observed in 20% and 27% of patients at daily doses of 200 mg and 375 mg, respectively [11]. When comparing patients with persistent response to those with transient or no response, the absence of any significant difference with respect to V, ODV, V + ODV and enantiomeric ratios suggested that lack of response over the first 4 weeks of treatment may not depend on pharmacokinetic factors. Among possible predictors of inadequate response—misdiagnosis, psychiatric and medical comorbidity, family history of affective disorders, number of previous episodes, duration of depression prior to treatment, negative life events and poor social support—have been invoked [38]. The observation that 62.5% of patients with non-response or transient response had received prior antidepressant treatment suggested that some of them might have been treatment resistant. The limited duration of the present study, nevertheless, prevented any conclusion with respect to further clinical improvement from continuation treatment. In drug-resistant major depression, a slight but significant benefit was obtained from continuing treatment after an initial 8-week period [39].

As pointed out by Laska [40], time to response only carries relevance for those patients who respond. It was, thus, recommended that studies on onset of response should focus on treatment responders [37]. In the present study, comparison of patients showing early and delayed persistent response revealed differences with respect to exposure to total V + ODV concentration, with higher concentration significantly associated with early response. Analysis of depression severity versus time curves through mixed-effects modelling confirmed that V + ODV concentration was a significant determinant of the slope describing early improvement. These results complemented dose-ranging studies suggesting earlier onset of response at higher doses [4, 5]. Whereas significant positive associations between higher plasma levels and larger decrease of depression score have been reported [24, 26], studies have focused on endpoint analysis without considering the time factor to onset of response. The observed relationship between concentration and time course of clinical improvement in patients with persistent response also corroborated earlier studies, showing that a persistent course more likely resulted from true drug effect. Alternatively, non-persistent response reflected non-specific placebo effect,

associated with increased relapse rate on continuation treatment [41].

In the present study, a lower V(+)/V(−) ratio was also significantly associated with a shorter time to onset of persistent response. Again, dimensional analysis of depression severity versus time curves confirmed that lower enantiomeric ratio was significantly associated with larger decrease of MADRS score over the initial period of treatment. Due to the different pharmacological properties of V enantiomers, patients with decreased V(+)/V(−) ratio may be exposed to a therapeutic moiety with increased noradrenergic activity [21]. Results, thus, tend to support the hypothesis that dual 5-HT and NA reuptake inhibition may be a key factor for early onset of clinical response [18]. Earlier investigation of pharmacokinetic variability in the same patients had shown that reduced V(+)/V(−) ratio was associated with reduced metabolism of the V(−) but not V(+) enantiomer [23]. It was recently confirmed that CYP2D6 isoenzyme displays marked stereoselectivity towards the (−) enantiomer, with poor metabolism and administration of CYP2D6 inhibitors associated with decreased V(+)/V(−) ratio [22]. Whereas decreased CYP2D6 activity may be associated with cardiovascular toxicity [42], its potential role with respect to onset of response to V remains to be investigated.

As methodological issues have been at the centre of the debate on onset of action, qualities and limitations of the present study require careful consideration. Several criteria generally required for investigating the time factor in response to antidepressant drugs were met in the present study. Persistent response, defined as a 50% decrease from baseline depression score, sustained over time, fulfilled the need for a widely accepted, clinically meaningful definition [35]. The fixed 300-mg daily dose achieved early and the bi-weekly clinical assessments over the initial phase of treatment were in keeping with recommendations [17]. The use of two statistical approaches provided complementary categorical and dimensional perspectives, which both proved their value in documenting onset of response to antidepressant treatment. In particular, mixed-effects models have been recently advocated [16]. With the focus being placed on the individual patient, they allow for the presence of missing data, constant or time-varying covariates and autocorrelated error structure [36]. Finally, plasma levels rather than daily doses served as indicators of actual exposure to drug and repeated measurements on day 14 and day 28 limited the possible influence of uncontrolled intra-individual variability factors, such as erratic compliance [23].

Among the weaknesses of the study, small sample size obviously limited its power to study the interplay of potentially influent factors and its external validity, prompting for replication. In particular, the respective roles of total concentration and/or enantiomeric ratio remain to be investigated in a larger population. Other difficulties arose from the naturalistic design of the study, which did not include a washout period and allowed for comedication with hypnotics, tranquillisers and low-dose trazodone during the study. V exerts a marked effect on sleep architecture, so that hypnotics or low-dose trazodone are commonly coprescribed at initiation of therapy [43]. However, it cannot be excluded that part of the observed effect might be attributed to pre-study medication or to comedication on specific components of depression, such as sleep or anxiety. Additionally, a possible role of comedication prescribed for somatic disorders cannot be excluded. Another issue is the 4-week duration of the present study, dictated by its primary focus on a lithium augmentation strategy from day 28. In clinical trials of antidepressants [44], 4 weeks is generally considered too short, but believed to provide an adequate time frame to dictate changes in therapeutic strategies in the absence of minimal improvement over that period [38]. In the present study, a majority of patients with persistent response ($n = 12$, 63.2%) displayed minimal change of depression score between day 21 and day 28 (MADRS difference ≤ 2). The predictive value of sustained response over the first 4 weeks of treatment remains to be assessed with respect to response on continuation treatment.

Keeping in mind its preliminary nature, the present study extended previous dose–response studies by documenting earlier response to venlafaxine associated with higher V + ODV concentration in patients at a fixed 300-mg daily dose. It raised the hypothesis that increased exposure to the more noradrenergic V(−) enantiomer may be relevant to early improvement of depression. The need for replication studies is further prompted by renewed interest for the role of noradrenaline in depression and onset of response in particular. Noradrenaline appears to have a significant role in social functioning by improving energy and motivation [45], leading to postulate different time courses for the different components of depression [17].

Acknowledgement This work was partially supported by a grant from Wyeth-Ayerst, Switzerland. The study complies with current laws in Switzerland.

References

1. Mendels J, Johnston R, Mattes J, Riesenberg R (1993) Efficacy and safety of b.i.d. doses of venlafaxine in a dose-response study. Psychopharmacol Bull 29:169–174
2. Kelsey JE (1996) Dose-response relationship with venlafaxine. J Clin Psychopharmacol 16:21S–26S
3. Rudolph RL, Fabre LF, Feighner JP, Rickels K, Entsuah R, Derivan AT (1998) A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry 59:116–122
4. Preskorn SH (1994) Antidepressant drug selection: criteria and options. J Clin Psychiatry 55[Suppl A]:6–22
5. Khan A, Upton GV, Rudolph RL, Entsuah R, Leventer SM (1998) The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. J Clin Psychopharmacol 18:19–25
6. Derivan A, Entsuah AR, Kikta D (1995) Venlafaxine: measuring the onset of antidepressant action. Psychopharmacol Bull 31:439–447

7. Blier P, Bergeron R (1997) Early onset of therapeutic action in depression and greater efficacy of antidepressant treatments: are they related? Int Clin Psychopharmacol 12[Suppl3]:S21–S28
8. Nierenberg AA (2001) Do some antidepressants work faster than others? J Clin Psychiatry 62[Suppl15]:22–25
9. Roseboom PH, Kalin NH (2000) Neuropharmacology of venlafaxine. Depress Anxiety 12[Suppl1]:20–29
10. Guelfi JD, White C, Hackett D, Guichoux JY, Magni G (1995) Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. J Clin Psychiatry 56:450–457
11. Entsuah R, Derivan A, Kikta D (1998) Early onset of antidepressant action of venlafaxine: pattern analysis in intent-to-treat patients. Clin Ther 20:517–526
12. Benkert O, Grunder G, Wetzel H, Hackett D (1996) A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res 30:441–451
13. Entsuah AR, Huang H, Thase ME (2001) Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 62:869–877
14. Clerc GE, Ruimy P, Verdeau-Palles J (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 9:139–143
15. Mehtonen OP, Sogaard J, Roponen P, Behnke K (2000) Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. J Clin Psychiatry 61:95–100
16. Leon AC, Blier P, Culpepper L, Gorman JM, Hirschfeld RM, Nierenberg AA, Roose SP, Rosenbaum JF, Stahl SM, Trivedi MH (2001) An ideal trial to test differential onset of antidepressant effect. J Clin Psychiatry 62[Suppl4]:34–36
17. Katz MM, Halbreich UM, Bowden CL, Frazer A, Pinder RM, Rush AJ, Wheatley DP, Lebowitz BD (2002) Enhancing the technology of clinical trials and the trials model to evaluate newly developed, targeted antidepressants. Neuropsychopharmacology 27:319–328
18. Blier P (2003) The pharmacology of putative early-onset antidepressant strategies. Eur Neuropsychopharmacol 13:57–66
19. Tran PV, Bymaster FP, McNamara RK, Potter WZ (2003) Dual monoamine modulation for improved treatment of major depressive disorder. J Clin Psychopharmacol 23:78–86
20. Harvey AT, Rudolph RL, Preskorn SH (2000) Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 57:503–509
21. Muth EA, Haskins JT, Moyer JA, Husbands GE, Nielsen ST, Sigg EB (1986) Antidepressant biochemical profile of the novel bicyclic compound Wy- 45,030, an ethyl cyclohexanol derivative. Biochem Pharmacol 35:4493–4497
22. Eap CB, Lessard E, Baumann P, Brawand-Amey M, Yessine MA, O'Hara G, Turgeon J (2003) Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 13:39–47
23. Gex-Fabry M, Rudaz S, Balant-Gorgia AE, Brachet A, Veuthey JL, Balant LP, Bertschy G (2002) Steady-state concentration of venlafaxine enantiomers: model-based analysis of between-patient variability. Eur J Clin Pharmacol 58:323–331
24. Charlier C, Pinto E, Ansseau M, Plomteux G (2002) Venlafaxine: the relationship between dose, plasma concentration and clinical response in depressive patients. J Psychopharmacol 16:369–372
25. Veefkind AH, Haffmans PMJ, Hoencamp E (2000) Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 22:202–208
26. Hoencamp E, Haffmans J, Dijken WA, Huijbrechts IP (2000) Lithium augmentation of venlafaxine: an open-label trial. J Clin Psychopharmacol 20:538–543
27. Bertschy G, Ragama-Pardos E, Aït-Ameur A, Muscionico M, Favre S, Roth L (2003) Lithium augmentation in venlafaxine non-responders: an open study. Eur Psychiatry 18:314–317
28. Quitkin FM, Rabkin JG, Ross D, Stewart JW (1984) Identification of true drug response to antidepressants. Use of pattern analysis. Arch Gen Psychiatry 41:782–786
29. Gibbons RD, Hedeker D, Waternaux C, Davis JM (1988) Random regression models: a comprehensive approach to the analysis of longitudinal psychiatric data. Psychopharmacol Bull 24:438–443
30. World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. World Health Organization, Geneva
31. Montgomery SA, Åsberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389
32. Klamerus KJ, Parker VD, Rudolph RL, Derivan AT, Chiang ST (1996) Effects of age and gender on venlafaxine and O-desmethylvenlafaxine pharmacokinetics. Pharmacotherapy 16:915–923
33. Rudaz S, Stella C, Balant-Gorgia AE, Fanali S, Veuthey JL (2000) Simultaneous stereoselective analysis of venlafaxine and O-desmethylvenlafaxine enantiomers in clinical samples by capillary electrophoresis using charged cyclodextrins. J Pharm Biomed Anal 23:107–115
34. Khan A, Khan SR, Shankles EB, Polissar NL (2002) Relative sensitivity of the Montgomery-Åsberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. Int Clin Psychopharmacol 17:281–285
35. Hackett D (1998) Comparing onset of effect of antidepressants: pragmatic considerations on methods and end-points. Eur Psychiatry 13:117–123
36. Hedeker D, Gibbons RD (1996) MIXREG: a computer program for mixed-effects regression analysis with autocorrelated errors. Comput Methods Programs Biomed 49:229–252
37. Katz MM, Koslow SH, Frazer A (1996) Onset of antidepressant activity: reexamining the structure of depression and multiple actions of drugs. Depress Anxiety 4:257–267
38. Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, Hawley C, Kasper S, Linden M, Massana J, Mendlewicz J, Moller HJ, Nemeroff CB, Saiz J, Such P, Torta R, Versiani M (2002) Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. J Clin Psychiatry 63:826–837
39. Schweitzer I, Burrows G, Tuckwell V, Polonowita A, Flynn P, George T, Theodoros M, Mitchell P (2001) Sustained response to open-label venlafaxine in drug-resistant major depression. J Clin Psychopharmacol 21:185–189
40. Laska EM, Siegel C (1995) Characterizing onset in psychopharmacological clinical trials. Psychopharmacol Bull 31:29–35
41. Quitkin FM, Stewart JW, McGrath PJ, Nunes E, Ocepek-Welikson K, Tricamo E, Rabkin JG, Klein DF (1993) Further evidence that a placebo response to antidepressants can be identified. Am J Psychiatry 150:566–570
42. Lessard E, Yessine MA, Hamelin BA, O'Hara G, LeBlanc J, Turgeon J (1999) Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. Pharmacogenetics 9:435–443
43. Thase ME (1999) Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 60[Suppl17]:28–31
44. Donovan SJ, Quitkin FM, Stewart JW, Ocepek-Welikson K, Harrison W, McGrath PJ, Nunes EV, Wager S, Tricamo E (1994) Duration of antidepressant trials: clinical and research implications. J Clin Psychopharmacol 14:64–66
45. Brunello N, Mendlewicz J, Kasper S, Leonard B, Montgomery S, Nelson J, Paykel E, Versiani M, Racagni G (2002) The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. Eur Neuropsychopharmacol 12:461–475