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ORIGINAL PAPER

Pharmacokinetic correlates of venlafaxine: associated adverse reactions

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Abstract

To address the potential correlation between plasma concentrations of venlafaxine (VEN), its active metabolite *O*-desmethylvenlafaxine (ODVEN) and the active moiety, AM, (ODVEN + VEN) and adverse drug reactions (ADR) in a large naturalistic sample of in- and outpatients. We compared plasma concentrations of VEN, ODVEN and AM and dose-adjusted (C/D) levels as well the ODVEN/VEN ratios between patients complaining ADRs, following the Udvalg for Kliniske Undersogelser side effect rating scales (UKU) ($n = 114$) and patients without ADRs (control group, $n = 688$) out of a naturalistic database. We also investigated potential pharmacokinetic correlates of the four UKU categories by comparing patients complaining ADRs with those who did not. Based on previous literature we applied different ODVEN/VEN ratio values as cut-offs to split our sample into two groups at a time and compare frequencies of ADRs between the groups. No differences for demographic and pharmacokinetic variables including plasma and C/D concentrations as well as ODVEN/VEN ratios were observed between study groups. Neither the comparisons between females and males nor between elderly and non-elderly patients revealed significant differences ($p > 0.05$ in all cases). No differences were also reported exploring the patients complaining ADRs from the 4 UKU categories separately. After applying various ODVEN/VEN cut-offs, groups did not display differences in frequencies of ADRs ($p > 0.05$ in all cases). Our findings do not demonstrate a direct link between venlafaxine metabolism measures and ADRs. Therefore, additional dimensions are needed to be considered in future trials aiming to disentangle the involved aspects of ADRs in patients receiving venlafaxine.

Keywords Antidepressants · Drug metabolism · Psychopharmacology · Adverse drug reactions · Pharmacokinetics

Introduction

Venlafaxine (VEN) is a widely prescribed selective serotonin- and norepinephrine-reuptake inhibitor, SSNRI. Its complex metabolic pathway predominantly consists of a CYP2D6 and, to a lesser extent, a CYP2C19 mediated demethylation leading to *O*-desmethylvenlafaxine (ODVEN), its major active metabolite. Secondary pathways involve CYP3A4 and CYP2C19 isoenzymes leading to additional metabolites such as *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine (DDV) [1]. The apparent elimination half-life of the parent compound (VEN) is shorter than the half-life of the active metabolite (5 vs. 11 h) in the case of venlafaxine immediate release [2], and it is prolonged to 11 h for VEN and 12.5 h for ODVEN in the extended release formulation. Clinicians consider the total concentration of VEN + ODVEN (active moiety, AM) as the most relevant clinical measure due to the pharmacological activity of ODVEN [3]. The 'Consensus Guidelines for Therapeutic Drug Monitoring (TDM) in Neuropsychopharmacology' suggests a so-called therapeutic reference range for the active moiety between 100 and 400 ng/mL [3]. Tolerability issues may drastically limit the therapeutic outcome for venlafaxine-based treatment [4, 5]. Adverse drug reactions (ADR) include autonomic reactions such as nausea or dizziness [6] sometimes due to venlafaxine-related serotonin toxicity [4]. The potential to cause ADRs is at least partially related to venlafaxine's vulnerability to drug–drug interactions [7, 8], which may be a consequence of the involvement of multiple cytochrome isoenzymes in its metabolism. However, the exact mechanisms underlying venlafaxine-related ADRs remain poorly understood. There

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are several case reports of ADRs and fatal poisonings associated with venlafaxine providing data on venlafaxine blood concentrations in the literature [9–13]. However, there is a dearth of TDM studies addressing the relationship between venlafaxine and its major metabolite and reported ADRs. A study investigating samples of two previous prospective trials reported that patients with metabolite to parent ratios (MPR), ratio of ODVEN/VEN, above four, are unlikely to suffer from moderate to severe venlafaxine-associated reactions [14]. Another trial reported no significant correlations between venlafaxine AM and heart rate or QTc changes [15], contrasting the findings from an older study showing a positive correlation between venlafaxine AM and the QTc interval [16]. A study by Shams and colleagues addressed the association between venlafaxine drug concentrations and clinical outcome measures, but did not report any correlation between drug concentrations and ADRs [17]. Finally, a very recently published study assessing the impact of genetic variants on clinical outcome in venlafaxine-medicated patients displayed no link between tolerability and parent compound (VEN) serum concentrations [18].

To further elucidate a potential association between pharmacokinetic patterns of venlafaxine, ODVEN, and AM (VEN + ODVEN) and adverse drug reactions, we analyzed a large naturalistic TDM database consisting of routinely collected plasma concentrations and information on adverse drug reactions under an ongoing antidepressant treatment with venlafaxine.

Materials and methods

Patients

Analysis of the data was conducted in cooperation between the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital, Aachen, Germany, and the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany. A large TDM database containing 1594 plasma concentrations of VEN and ODVEN from adult in- and outpatients who had been treated with venlafaxine for different indications was analyzed. Patients predominantly suffered from mood disorders. Data collection took place between 2006 and 2015 as part of the clinical routine in different institutions as part of the AGATE, 'Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen', a cooperation for drug safety in the treatment of psychiatric diseases, (for details: http://www.amuep-agate.de). AGATE is a consortium of different psychiatric hospitals predominantly in southern Germany performing therapeutic drug monitoring in terms of clinical routine and in terms of pharmacovigilance [19]. TDM was part of standard patient monitoring under long-term venlafaxine-based treatment and not part of any prospective trial. Furthermore, TDM was conducted when indicated for clinical reasons, e.g., when adverse drug reactions occurred or in situations when TDM is recommended. Data registration followed standardized protocols [20]. Retrospective analysis of clinical data was in accordance with the 1964 Declaration of Helsinki and its later amendments as well as the local regulatory authority of RWTH Aachen University hospital. For this type of study a formal patient consent is not required. Patients under concomitant medication with possible CYP2D6 inhibitory or CYP3A4, CYP2C9 or CYP2C19 inhibitory or inducing properties were excluded [21]. Samples with missing data of VEN, ODVEN and AM or clinical information were also not included in the analysis. Applying these two criteria, we excluded 689 and 103 patients, respectively, leading to a total of 802 patients included in the analysis. In a minimal number of cases, missing body mass index data were detected and were consequently substituted applying linear interpolation. Treating physicians provided detailed narrative reports of (newly occurred) ADRs shortly before blood sampling on the TDM request form. Whether or not ADRs have occurred, has to be noted on the request form and in case of ADRs, a narrative description is requested. Retrospectively, reported ADRs were classified to four major groups, psychic, neurological, autonomic and other following the categories of the Udvalg for Kliniske Undersogelser side effect rating scales (UKU). This scales specifically assesses the side effects of psychopharmacological medications [22].

Quantification of venlafaxine and *O*-desmethylvenlafaxine

Blood samples were asked to be taken just before drug administration (trough concentration) at steady state (> 5 elimination half-lives under the same drug dose). Venlafaxine and *O*-desmethylvenlafaxine concentrations were determined by HPLC with ultraviolet detection (HPLC/UV). The method was validated according to DIN 32645 (Deutsche Industrie Norm 32645), described in guidelines of GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of ISO 5725 (International Organization for Standardization) [23], FDA (US Food and Drug Administration) guidance [24] and ICH (International Conference on Harmonization) requirements. The limit of quantification was 10 ng/mL for both analytes (venlafaxine and *O*-desmethylvenlafaxine), and linearity between nominal concentrations and the detector signal was between 10 and 800 ng/mL. The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany, http://www.instandev.de).

Statistical analysis

The main statistical method consisted of a Mann–Whitney *U* test (M–W-*U*) with a significance level of 0.05 to compare concentrations of VEN, ODVEN and AM between the two study groups: patients reporting ADRs ($V_{ADR,}$ $n = 111$) and patients without ADRs (V_0, $n = 688$). Our primary outcome was the AM, which is considered as clinically relevant for treatment outcome [21]. The comparison also included the plasma concentration corrected by the daily dose, the so-called 'concentration-by-dose' ratio, (C/D), and the ratios of ODVEN/VEN (metabolite to parent ratio, MPR) for identification of the metabolizer status. Both were calculated in accordance with the AGNP consensus guidelines [3]. Additional analyses included comparisons between patients with and without ADRs conducted in females and males as well as elderly and non-elderly patients (age threshold 65 years) separately, to account for potential effects of sex and age on venlafaxine pharmacokinetics. We also compared the frequencies of ADRs in two different phenotype groups based on MPRs; patients with a ODVEN/VEN ratio higher or equal to one were considered average ("normal") CYP2D6 metabolizers, whereas patients with ratios lower than one were considered as poor metabolizers [25]. We repeated these comparisons using two other thresholds for the MPR (0.3 and 4), which have been previously reported as being relevant for adverse drug reactions [14, 17]. Finally, we compared frequencies of ADRs in two groups based on a cut-off level of 800 ng/mL for venlafaxine AM, which is suggested as laboratory alert level [3]. To compare expected frequencies of ADRs between the groups, we used the Pearson Chi square test (χ^2) with a significance level of 0.05. When the χ^2 test was not possible due to the small number of patients, the Fisher's exact test was conducted. Statistical analysis was carried out using IBM SPSS Statistics version 23.0 (IBM GmbH, Ehningen, Germany).

Results

Demographic and relevant pharmacokinetic data of both groups are summarized in Table 1. The daily dosage did not differ between the groups ($p > 0.05$ for M–W-*U*). Due to the skewness of the distribution, we compared groups based on the Mann–Whitney *U* test (M–W-*U*) for differences between patients with and without ADRs. The M–W-*U* test detected no differences regarding age, sex, body mass index (BMI) and daily dosage of venlafaxine between the groups ($p > 0.05$ for all comparisons). No intergroup differences were detected by comparing the distribution of the plasma concentrations of AM (VEN + ODVEN), VEN and ODVEN as well as the MPR, ODVEN/VEN ($p > 0.05$). Differences in dose-adjusted plasma concentrations (C/D) neither reached statistical significance for AM, nor for VEN or ODVEN ($p > 0.05$ for all three parameters).

Taken into account the differences in venlafaxine metabolism between males and females for venlafaxine [26], we repeated comparisons between patients with and without ADRs for each sex-subgroup separately (M–W-*U* test). In females, the two study groups did not differ in terms of demographic and clinical (for age, BMI and dosage, $p > 0.05$ for all three) or pharmacokinetic parameters (VEN, ODVEN, AM, ODVEN/VEN, C/D VEN, C/D ODVEN, C/D AM; in all cases $p > 0.05$) in 407 women without and 63 women

Table 1 Patients' demographic characteristics and pharmacokinetic parameters

	V_{ADR}	V_0
Number	114	688
Age (years)	47.0 (21–87)	48.0 (18–90)
BMI (kg/m^2)	27.0	26.0
% females	55.3	59.2
DD (mg/day)	225.0 (75.0–450.0)	225.0 (37.5–475.0)
VEN (ng/mL)	75.0 (1.3–685.0)	82.0 (1.6–3164.0)
ODVEN (ng/mL)	163.0 (13.0–635.0)	172.25 (0.6–1268.0)
VEN + ODVEN (ng/mL)[a]	265.5 (28.0–896.0)	284.5 (5.9–4432.0)
ODVEN/VEN	2.37 (0.08–40.77)	2.2 (0.002–177.5)
C/D VEN (ng/mL)/(mg/day)	0.44 (0.006–2.82)	0.41 (0.007–14.06)
C/D ODVEN (ng/mL)/(mg/day)	0.84 (0.06–4.72)	0.88 (0.002–13.95)
C/D VEN + ODVEN (ng/mL)/(mg/day)	1.42 (0.12–5.55)	1.44 (0.016–19.7)

Provided values are medians (ranges)

BMI body mass index, *C/D* dose-adjusted plasma concentration, *DD* daily venlafaxine dosage, *ODVEN* *O*-desmethylvenlafaxine plasma concentration, V_0 patients without adverse venlafaxine-related reactions V_{ADR} patients with adverse venlafaxine-related reactions, *VEN* venlafaxine plasma concentration

[a]Based on the provided values, the addition of VEN and ODVEN levels does not provide the active moiety, which is due to the fact that these values are medians and not means

with reported ADRs. In males, no differences were found between patients with and without ADRs ($p > 0.05$ for M–W-*U* in all comparisons with 281 men without and 51 men with reported ADRs). We then analyzed pharmacokinetic patterns in elderly vs. non-elderly patients (< 65 years old) separately (122 elderly vs. 688 non-elderly patients). Comparisons did not yield significant differences in any case of patients with and without reported ADRs ($p < 0.05$ for M–W-*U* in all cases).

Mostly reported UKU types were autonomic ADRs in 44 patients (38.6%), followed by psychic ADRs in 27 patients (23.7%), other ADRs in 25 patients (21.9%) and neurologic ADRs in 18 patients (15.8%). In three cases, information about the type of ADRs was not acquired and was, therefore, not included in the analysis. Comparing the UKU subgroups of ADRs pair-wisely with the control group found no differences in demographic characteristics (age, sex and BMI; $p > 0.05$ in all cases), daily venlafaxine dosage ($p > 0.05$ for all comparisons) and pharmacokinetic parameters (VEN, ODVEN, AM, ODVEN/VEN, C/D VEN, C/D ODVEN, CD AM; $p > 0.05$ overall). Finally, we compared the frequency of ADRs in two phenotype groups; poor and non-poor CYP2D6 metabolizers according to the metabolite to parent ratios ($n = 215$ and $n = 587$, respectively). No significant differences were detected between the two groups (14.42% in poor vs. in 14.13% non-poor metabolizers, $p > 0.05$ for χ^2). Furthermore, when using a cut-off of 0.3 for the MPR with 54 patients below and 748 above this cut-off and when using a cut-off of 4 ($n = 595$ below and $n = 207$ patients with a MPR above), frequencies of ADRs did not differ between groups as well ($p > 0.05$ for χ^2 in both cases).

When dichotomizing patients into those with AM concentrations > 800 ng/mL ($n = 21$) and patients with AM concentrations ≤ 800 ng/mL ($n = 781$), no difference was reported between groups for the frequency of reported ADRs (Fisher's exact test, two-tailed, $p = 0.593$).

Discussion

In our naturalistic sample we sought for possible relationships between the distribution of concentrations of VEN, ODVEN and AM with reported adverse drug reactions under an ongoing pharmacotherapy with venlafaxine. Our study addresses the issue of pharmacokinetic correlates of various ADRs in a large sample receiving various daily doses under real-life clinical conditions. Previous investigations used small groups or focused on a particular ADR [14–16, 18]. We did not find particular patterns for our primary outcome, the AM, or any other of the different compounds of venlafaxine between patients with and without ADRs.

We then repeated comparisons for males and females separately, given the differences of venlafaxine pharmacokinetics between sexes as well as the higher susceptibility of females to ADRs [4, 27]. However, results did not highlight the role of the plasma concentrations of VEN, ODVEN and active moiety or dose adjusted drug concentrations. This was also the case when performing comparisons in two different groups based on an age threshold of 65 years; neither in elderly nor in non-elderly patients, pharmacokinetic parameters differed between the group of patients with vs. the group of patients without ADRs. As differences in ODVEN/VEN ratios were also not associated with ADR patterns, we decided to conduct additional analyses based on three different cut-offs for ODVEN/VEN ratios (0.3, 1 and 4). Patients with ODVEN/VEN ratios below 1 have previously been classified as poor CYP2D6 metabolizers [25]; intuitively, we expected this subgroup of patients to be more vulnerable to ADRs. However, the frequency of ADRs did not deviate significantly from the expected frequency. Therefore, we may hypothesize that poor CYP2D6 metabolizer status is not necessarily related to venlafaxine-associated ADRs contrasting evidence from two case reports describing toxic venlafaxine levels in a patient with poor CYP2D6 activity [28, 29]. Moreover, Shams et al. reported an increase in prevalence rates of ADRs such as gastrointestinal side effects for four patients with ODVEN/VEN below 0.3 (poor CYP2D6 metabolizers) with the small number of patients classified as poor metabolizers ($n = 4$) as a major limitation of this study [17]. In our larger sample we found 54 patients with a ratio below 0.3. Another trial from a small Chinese sample ($n = 29$) reported that patients with ODVEN/VEN above 4 were unlikely to display adverse events [14]. This threshold did not have any predictive value in our sample.

From a methodological point of view, it was important to exclude patients with co-medication of inhibitory or inducing effects on venlafaxine metabolism. By neglecting this important issue, the significance of the MPR (ODVEN/VEN) could not have been further analyzed. Other than that (and the case of missing data) we did not apply any other exclusion criteria. As venlafaxine quantification was performed regardless of reported ADRs it is unlikely that we ended up comparing two different groups with different treatment complications.

Regarding the clinical utility of a laboratory alert level of 800 ng/ml for venlafaxine AM, our evidence is less supportive. The frequency of reported ADRs did not differ between patients with AM concentrations higher vs. lower than 800 ng/ml. Nevertheless, the small number of patients with AM concentrations above 800 ng/ml may limit the interpretation of these results.

The more specific investigation using the four UKU ADR categories did not essentially contribute to the understanding of involved pharmacokinetic mechanisms. Groups of patients suffering from ADRs classified in each of the four

categories did not differ to each other in terms of venlafaxine metabolism measures or even demographic characteristics. Therefore, the major riddle of the pathways leading to ADRs for venlafaxine remains unravelled.

Limitations

The main shortcomings of our study may derive from its retrospective, naturalistic design; e.g., patient information could be considered not as reliable as in case of a prospective study. The lack of a significant amount of clinical measures such as onset and duration of illness, response scales, comorbidities, duration of prior venlafaxine-based treatment did not enable further analyses. In particular, the duration of prior venlafaxine treatment could have crucially affected pharmacokinetic patterns related to ADRs, as these may differ between patients under long-term treatment and patients during titration. Regarding assessments of ADRs, the severity of the events was not quantified in a standardized fashion and, therefore, could not be included in the current analysis. With reference to the blood sampling, there is a large individual variation in sampling time as a result of the clinical setting, which might have, at least partially, accounted for the pronounced inter-individual variation in plasma concentrations and metabolic ratios. Further, the selectivity of the applied analytical method may be limited. Nevertheless, there are previous reports of the large inter-individual variability in VEN and ODVEN in the literature [27, 30]. Moreover, venlafaxine is a chiral drug; its enantiomers as well as those of its active metabolite differ in their pharmacodynamics and pharmacokinetics [31]. The lack of data about enantiomers did not allow further analyses. When multiple plasma concentration measurements were available, we included only the most recent analysis. Our study focused on the active metabolite of venlafaxine, ODVEN. The lack of *N,O*-didesmethylvenlafaxine concentrations (DDVEN) in our pharmacokinetic database did not allow for analyses that would have revealed the role of CYP2C19 in ADRs, as the DDVEN/ODVEN ratio is influenced by the CYP2C19 genotype [32]. Previous case reports have implied a relation between several CYP2C19 variants and ADRs [10–12, 33]. Lastly, information of genetic variations for CYP450 as well as P-gp, i.e., ABCB1 would have captured additional aspects of the related pathways.

Conclusions

Our data does not report a clear pharmacokinetic variable or combination of variables directly implicated in reported ADRs in patients receiving venlafaxine. More complex models with additional parameters such as pharmacogenetics may offer more comprehensive overviews on the mechanisms related to susceptibility to ADRs associated with venlafaxine treatment.

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