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Therapeutic Drug Monitoring of Venlafaxine and Impact of Age, Gender, BMI, and Diagnosis

Original Paper

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Abstract Depression is a common mental disorder affecting more than 264 million people in the world and 5.1% of the Slovak population. Although various antidepressant approaches have been used; still, about 40% of patients do not respond to a first-choice drug administration and one third of patients do not achieve total remission. Therapeutic drug monitoring (TDM) is a method used for quantification and interpreting the drug concentrations in plasma in order to optimize the pharmacotherapy. The aim of this study was to measure the plasma concentrations of venlafaxine, the fourth most prescribed antidepressant in Slovakia, as well as its active metabolite and interpret them with the relevant patients' characteristics.

The study was of retrospective nature and 28 adult patients in total were included. The concentrations of venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) in plasma were quantified using the validated UHPLC-MS/MS method. The effects of potential influencing factors were evaluated by a multivariate linear regression model.

Only 39% of patients reached the venlafaxine active moiety concentrations within the recommended therapeutic range. Plasma concentrations were dependent on age, gender, and duration of the therapy. Venlafaxine metabolism expressed as a metabolite-to-parent concentrations ratio was influenced by a combination of age, gender, and body mass index (BMI). We did not observe any significant difference in plasma concentrations between the patients with a single and recurrent diagnosis of depression. Combining variables made an additive effect on plasma concentrations, for example, active moiety plasma concentrations were higher in older women. In contrast, drug metabolism was higher in older men and men with lower BMI. TDM of venlafaxine is recommended in clinical practice, especially in the elderly when beginning the pharmacotherapy.

Keywords *Venlafaxine – major depressive disorder – therapeutic drug monitoring*

INTRODUCTION

Depression is a relatively common mental disorder affecting nowadays more than 264 million people all around the world. The disorder is a leading cause of disability worldwide and significantly contributes to the overall global burden of disease (WHO, 2019). Prevalence in Slovakia is 5.1% in all age groups (WHO, 2017). Women have a higher prevalence rate of depression compared to men since adolescent age (Luppa et al., 2012). Although various antidepressant approaches have been used, about 40% of patients do not respond to a first-choice drug administration and one third of patients do not achieve total remission (Cai et al., 2017). Therapeutic drug monitoring (TDM) is a beneficial patient management tool for quantification and subsequent interpretation of drug concentrations in blood in order to individualize and optimize pharmacotherapy. TDM enables individual dose adjustments according to the properties of the drug, patient characteristics, and measured concentration in blood. Therefore, it is considered as an important tool mainly in patients with variabilities in pharmacokinetics such as patients suffering from comorbidities, patients with impaired function of elimination organs as liver and kidneys, older patients, children, pregnant women or when

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occurring drug-drug interactions (Hiemke et al., 2018). In neuropsychopharmacology, TDM provides a reasonable indirect estimation measurement of the relevant psychotropic drug levels in the central nervous system (CNS) as a result of the investigated correlation factors between concentrations in plasma and in CNS.

Although the plasma concentrations' quantification of a variety of neuropsychopharmacological drugs has become a clinical routine abroad, apart from the monitoring of the drugs with a narrow therapeutic range, it does not belong to standard care in Slovakia.

Venlafaxine (VEN) has been registered at the Slovak market for more than 20 years, and nowadays, it is the fourth most prescribed antidepressant in Slovakia (NHIC, 2019; SIDC, 2020). It belongs to the group of serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressants as its mechanism of action is the inhibition of serotonin and norepinephrine reuptake from the synaptic cleft (Hansen et al., 2017). Venlafaxine is predominantly metabolized by cytochrome CYP2D6 enzyme to an active metabolite *O*-desmethylvenlafaxine (ODV). Half-lives of the extended-release formulations of venlafaxine are 4–14 hours and 10–20 hours for its metabolite ODV. Thus, steady-state concentrations are reached within 4 days of drug administration (Alventa SPC, 2019; Hiemke et al., 2018). It was found that both parent drug and active metabolite ODV penetrate well into the cerebrospinal fluid and the correlation between plasma and brain concentrations of venlafaxine, ODV and active moiety (sum of venlafaxine and ODV) was established. According to the study of Paulzen et al. (2015), the calculated correlation coefficients were 0.74, 0.88 and 0.84 for venlafaxine, ODV and active moiety, respectively.

The therapeutic plasma concentrations of active moiety should be within the range 100–400 ng/mL, and the critical levels are over 800 ng/ml (Hiemke et al., 2018). The concentrations over the critical levels should lead to dose adjustment if the adverse reactions are present. Hypertension, vasodilation leading to flushes, headaches, palpitations, nausea, constipation, dry mouth, insomnia, nervousness, and tachycardias are the most common side effects (Alventa SPC, 2019).

The aim of our study was to evaluate the plasma concentrations of venlafaxine and ODV in plasma of depressive patients treated in standard clinical settings and to explore factors influencing these concentrations.

METHODS

Adult patients who were hospitalised with a diagnosis of depression at the Psychiatric Clinic of University Hospital Martin were included in this retrospective study. The Ethics Committee of Jessenius Faculty of Medicine, Comenius University approved the study as well as publication of the outcomes. The patients were administered venlafaxine or its combination with other psychotropic drugs. Two blood samples (at admission day and at the day of discharge) were obtained from 28 adult patients (11 men, 17 women). The blood samples were collected at the trough level, that is, just before administering the next dose after a 24-hour interval and after reaching a stable state concentration of an applied medication and dose regimen. Immediately after the blood sampling and centrifugation, the plasma samples were stored at -80°C until the analysis. Developed and validated method based on ultra-high pressure liquid chromatography coupled with tandem mass spectrometry was used for the quantification of venlafaxine and ODV in plasma (for more details, see Kertys et al., 2020). Only the one-step sample preparation procedure was used as a sample pre-treatment method. The patients' basal characteristics, diagnosis, venlafaxine dose, duration of steady-state concentration of the drug in the applied daily dose, hepatic functions, and any information about co-medication were documented. Dose-corrected concentrations (DCC) of venlafaxine, ODV and active moiety were calculated to evaluate the influence of various dose regimens. The effect of potential influencing factors was quantified by a multivariate linear regression and the model was selected by Akaike Information Criterion (AIC). All the statistical analyses were performed in R (R Core Team, Vienna, Austria) ver. 3.5.2. P-value < 0.05 was considered as statistically significant.

RESULTS

In total, 28 adult patients suffering from major depressive disorder (MDD) were included in the study (39% men, 61% women), with median age 50 years (range 18–70 years). The MDD diagnosis was confirmed by a specialist-psychiatrist according to DSM-5 (APA, 2018). Majority of patients (n = 25; 89%) were taking venlafaxine at the single daily dose of 300 mg, 2 patients at the single daily dose of 225 mg, and one patient at the single daily dose of 375 mg. Almost all patients were administered another psychomedication or combination of these; the most frequently co-administered antipsychotics were quetiapine, olanzapine, sulpiride, or a combination of two antidepressants venlafaxine and trazodone. Only 2 patients were taking venlafaxine alone. Therefore, we could not evaluate any potential effect of concomitant drugs on the levels of venlafaxine in plasma. Hepatic functions (alanine transaminase - ALT, aspartate aminotransferase - AST, gama-glutamyltransferase - GMT) in all the patients were normal or slightly increased; however, no clinically important alterations were observed. The information about smoking habits and about renal functions of the patients was not available, as these tests were not performed as a routine examination.

The dose of venlafaxine was individually titrated for each patient according to its clinical efficacy and side effects' occurrence. Patients in our study reached a stable concentration of venlafaxine and the blood sample was collected on 4^{th}–29^{th} day.

Only 39% of the measured concentrations were within the therapeutic range (100–400 ng/mL) according to the

Table 1: Medians of plasma concentrations (VEN and ODV; ODV+VEN) and metabolite to parent drug ratios (ODV/VEN) in patients treated with venlafaxine at the single daily dose of 300 mg (F32 – single episode of MDD; F33 – recurrent episode of MDD)

	Patients	VEN [ng/mL]	ODV [ng/mL]	ODV/VEN	ODV+VEN [ng/mL]
All	**25**	**182**	**345**	**1.85**	**452**
Females	15	255	370	1.85	693
Males	10	148	261	1.75	389
Age < 65	21	132	304	1.92	417
Age ≥ 65	4	345	511	1.55	859
F32	7	128	280	2.00	435
F33	18	198	356	1.74	553

Table 2: Medians of dose-corrected plasma concentrations (DCC) of venlafaxine active moiety (F32 – single episode of MDD; F33 – recurrent episode of MDD)

	Patients	DCC [ng/mL/mg]
All	**28**	**1.46**
Females	16	2.07
Males	12	1.30
Age < 65	24	1.39
Age ≥ 65	4	2.86
F32	8	1.46
F33	20	1.61

Consensus Guidelines for TDM in Neuropsychopharmacology (Hiemke et al., 2018). 17 patients (61%) had active moiety concentrations above this range. The sum of the levels of venlafaxine and ODV ranged between 188 and 1426 ng/mL with median of 426 ng/mL. Median dose-corrected plasma levels were 0.59 ng/mL/mg for venlafaxine, 1.06 ng/mL/mg for ODV, and 1.46 ng/mL/mg for the sum of both.

The results of median plasma concentrations of venlafaxine, ODV and an active moiety at 300 mg dose regimen are summarized in Table 1. Dose-corrected plasma concentrations of venlafaxine active moiety in the subgroups of patients are shown in Table 2.

A statistically significant positive correlation of plasma concentration counted as DCC of active venlafaxine moiety with age was observed (in females $p = 0.004$, in males $p = 0.04$). The increase was steeper in female patients than in male patients. We observed a negative and statistically significant correlation of DCC with the duration of the therapy (counted as days of stable concentration in the blood; $p = 0.03$). Coefficient of determination of the AIC selected model was relatively high (adj. $R^2 = 0.37$). The results are shown in Figure 1.

Metabolite to parent drug ratio (MPR, ODV/VEN), that is, a parameter reflecting the drug biotransformation, was significantly higher in older men ($p = 0.0004$) and men with lower BMI ($p = 0.002$). For female patients, age did not seem to play a statistically significant role in the MPR parameter in our study ($p = 0.06$). The adjusted R^2 for this model was 0.36 and results are presented in Figure 2. According to these results, the combination of age, gender, and BMI exert some impact on the rate of venlafaxine metabolism. The difference in plasma concentrations between patients with a single depressive episode and recurrent episodes failed to reach statistical significance, although subjects diagnosed for the first time tend to have lower concentrations.

DISCUSSION

In the present study, the measurements of venlafaxine plasma concentrations were performed in hospitalized depressive patients. A total of 28 patients were included in this retrospective study. Only 39% patients had venlafaxine active moiety plasma concentration within the recommended therapeutic range, the rest of the patients reached levels above the range, out of which 3 patients (11%) had the levels above laboratory alert level (800 ng/mL). However, no dramatic adverse effects were noticed, only abdominal pain and gastrointestinal discomfort with a short duration were reported. This means that even higher plasma concentrations of venlafaxine were well tolerated. The same conclusion reached Unterecker et al. (2012) in his study with 478 patients taking venlafaxine. Hiemke (2008) observed that interindividual variations in patients' pharmacokinetics led to 30–50% of sub- or supraoptimal concentrations in the blood even if the recommended dosage regimen was maintained. Because of the fact that only hospitalized patients were included in the study, patients' compliance was cautiously controlled by the health care providers (oral cavity check after the drug administration, observation of the patients' behaviour). The drugs were taken strictly at the scheduled dose and time.

According to our results, the venlafaxine plasma concentration is influenced by the combination of age, gender and duration of venlafaxine steady-state concentration. The last can be just an effect of the therapy adjustment in the beginning. Other

studies also confirmed the effects of gender and age, but they also included other factors, for example, smoking habits (Hiemke et al., 2008). Co-medication with other psychotropic drugs was associated with decreased MPR (Unterecker et al., 2012), suggesting inhibition of metabolism. As most of our patients also took other psychotropic drugs, we could not evaluate this as a potential influencing factor. The plasma concentration of ODV, as well as the value of MPR, depend on CYP2D6 metabolic activity (Otton et al., 1996).

Based on our results, the patients over 65 years, especially female patients, had higher concentrations of venlafaxine active moiety even if the same dose was administered as to the younger patients. This finding is in accordance with the results of other authors (Hansen et al., 2017; Reis et al., 2009; Sigurdsson et al., 2015; Unterecker et al., 2012). Additionally, weight-corrected doses with active moiety plasma concentrations were correlated and we found that they are non-significant predictors when controlling also for age and gender. MPR parameter was found significantly higher in men with lower BMI and in older men. The latter was likewise found in the study of Reis et al. (2009). In the same study, the negative correlation between the dose and MPR was observed, however, we could not confirm this as the majority of our subjects took the same dose of venlafaxine – 300 mg once daily.

Sex-related peculiarities influence different pharmacokinetic parameters such as gastric acidity, intestinal motility, body weight and composition, blood volume, liver enzymes, renal excretion and can also account for a different sensitivity to the positive but also unwanted effects and toxicity of psychotropic drugs (Marazziti et al., 2013). Women tend to have higher plasma concentrations of psychotropic drugs and one of the reasons might be a different expression of CYP enzymes and thus variable hepatic clearance of drugs (Reis et al., 2009).

Kloiber et al. (2007) demonstrated that depressive patients have on average higher BMI and the effect of antidepressants is decreased compared to the patients with lower BMI. Venlafaxine is a lipophilic drug and when body fat decreases, the volume of distribution of these drugs is reduced (Turnheim, 2003). A negative correlation between BMI and MPR parameter was found in men, however, no correlation between plasma concentrations and BMI was observed.

According to the study of Reyes-Barron et al. (2016), response to antidepressants can be genetically determined from 42 to 50%. This might be also the case of our 3 patients with supratherapeutic or even toxic concentrations of the drug active moiety. CYP2D6, the major enzyme involved in venlafaxine metabolism as well as in other almost 20% most frequently prescribed medications, has a highly polymorphic gene. More than 100 variant alleles cause up to 200-fold variability in drug metabolism (Tirona & Kim, 2017).

In this study, the influence of the final diagnosis was assessed on the venlafaxine active moiety concentrations in plasma. Based on our results, a non-significant increase was observed in patients with recurrent episodes. However, the number of patients in this study could be considered as a limitation of our observation, and thus, this parameter should be revised in larger studies.

To summarize our findings, we confirmed that women and older patients reached higher plasma concentrations of venlafaxine active moiety, although none dose adjustments are mentioned in the summary of product characteristics of the relevant medicinal products. Dose adjustment seems to be advisable due to an additive effect of the variables, especially when administering the very first doses of venlafaxine to the elderly patients. The retrospective nature of this study provides only explorative data, but they confirm that TDM of venlafaxine therapy, controlling influences of the drug pharmacokinetics, should be recommended in clinical practice.

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