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Therapeutic Drug Monitoring of Venlafaxine in an Everyday Clinical Setting: Analysis of Age, Sex and Dose Concentration Relationships

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Abstract: Venlafaxine is a commonly used antidepressant agent. We aimed to provide detailed information on the associations between venlafaxine dose and concentrations of venlafaxine, by patient age and sex. From a therapeutic drug monitoring (TDM) database located at Odense University Hospital, Denmark, we identified all adults for whom the treating physician had requested clinical advice on the TDM result for venlafaxine between 2002 and 2012. We identified 1,077 TDM samples of venlafaxine from 334 males and 743 females (median age 45 years), and the median daily dose was 225 mg. Median plasma concentration of venlafaxine and o-desmethyvenlafaxine (ODV) were 306 nmol/L and 861 nmol/L, respectively. The median dose-corrected serum level for venlafaxine was 1.49 nmol/L/mg., while the dose-corrected serum level of men and women were 1.21 nmol/L/mg and 1.60 nmol/L/mg, respectively. The dose-corrected sum of venlafaxine and ODV was 8.91 nmol/L/mg (IQR 6.56-12.26) *versus* 5.52 nmol/L/mg (IQR 4.16-7.52) for patients above 64 years and below the age of 65 years, respectively. Dose-corrected plasma concentrations of venlafaxine and ODV are increased to a clinically significant degree in patients above the age of 64, and initiation of venlafaxine therapy in the elderly should be made cautiously and supported by drug measurements.

Depression is a common mental disorder in the adult population (1). Epidemiological data have demonstrated a prevalence of all depressive syndromes deemed clinically relevant of 13.5% (2). Women tend to be at higher risk of late-life depression than men (3). A variety of pharmacological agents exist today as treatment for depression, and drug monitoring services are available for many of these drugs to support clinical observations. The clinical value thereof is subject to some controversy (4).

Venlafaxine is an antidepressant that inhibits both serotonin and norepinephrine reuptake (5). Venlafaxine is metabolized to its active metabolite O-desmethylvenlafaxine (ODV) in the liver by the cytochrome P450 enzymes, with CYP2D6 playing a dominant role, along with, although to a lesser degree, CYP2C19 and CYP3A4, the formation of another, less important, metabolite N-desmethyl venlafaxine, is primarily catalyzed by CYP2C19 (6). The concentration of the active metabolite ODV, venlafaxine and the ratio of ODV to venlafaxine depends on the level of CYP2D6 activity (7). CYP2D6 is polymorphically expressed resulting in distinct different phenotypes among individuals (8). Together with other factors, such as age and sex, physiological factors and pharmacokinetic drug-drug interactions, this may influence the plasma drug concentration achieved at a given drug dose. Hence, the dose itself is not necessarily the only predictor of plasma concentration, adverse reaction profile or clinical efficacy. Therapeutic drug monitoring (TDM) provides a reasonable indirect estimation measurement of the relevant concentration in the central nervous system, since there is generally a correlation between plasma concentrations of psychotropic drugs and the concentration in the central nervous system (9). The approved dose for venlafaxine is 75 – 375 mg per day (10). Treatment within this range of doses is usually sufficient to reach a serum level (VEN + ODV) within the recommended therapeutic range of about 400 - 1500 nmol/L. This suggested therapeutic range is largely based on observational studies and expert opinion, whereas the true association with clinical efficacy remains unclear (4). The age- and sex-related dose-concentration relationship for venlafaxine is still insufficiently elucidated (11–14) .

We present a large study on the associations between age, sex, venlafaxine dose and concentrations of venlafaxine and ODV within an everyday clinical setting of a Drug Monitoring Service.

Methods

Setting

At the Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, a TDM service providing analysis of venlafaxine and its main metabolite has been available since 2002. This service is offered to patients in the Region of Southern Denmark, comprising about 1,200,000 inhabitants. Dose and total venlafaxine concentrations have been entered in a database and annotated with clinical advice to physicians requesting such. Values of venlafaxine and ODV are automatically stored in the laboratory database and encoded with a unique personal identifier that automatically encodes age and sex. We merged these data to create a dataset containing information on the following variables: dose, total venlafaxine, venlafaxine and ODV concentrations, age and sex.

Sample characteristics

The final dataset consists of 1,077 samples from unique individuals. A flow chart of the sample selection is presented in Fig. 1. We only used the first recorded unique patient data from the database. All included samples had to include information on daily dose of venlafaxine and a detectable VEN serum concentration. All samples were drawn as trough samples, no less than 12 hours post-dose. Phenotypically poor metabolizers, defined as having an ODV/VEN ratio below 0.3, were excluded from the analysis (15).

Analytical methods

Venlafaxine and ODV were analysed by a validated and accredited (DANAK # 221) LC/MS-MS method. Briefly, serum proteins were precipitated with acetonitrile followed by centrifugation (3000 rpm for 20 min.). The supernatant was directly injected into a Phenomenex Kinetex C18 2.6 μm 2.0x50 mm column. Mobile phases were ammonium acetate (10 mmol/L) and acetonitrile. Venlafaxine and ODV were detected by selected reaction monitoring. Levels of

detection and quantification were 10 and 30 nmol/L, respectively, for both analytes. Coefficients of variation were between 5% and 6% for venlafaxine and ODV at levels of 100 and 1300 nmol/L. Bias was between 1% and 3% for both analytes at levels of 100 and 1300 nmol/L.

Plasma concentrations given in mass units can be converted to molar units by multiplication with the conversion factor (CF) nmol/L = ng/mL x CF; such is 3.61 for VEN and 3.80 for ODV, respectively. For simplicity, we used a conversion factor of 3.70 for the sum of ODV and VEN (4).

Statistical Analysis

Data are presented as medians and interquartile range [IQR] values. Following logarithmic transformation of continuous variables (concentrations), inferential analyses were performed using ANOVA followed by Tukey's post-hoc test or unpaired t-test as appropriate; correlation coefficients were calculated using Pearson's correlation. The analysis was performed in (STATA 14, Stata Corp, Texas 14).

Results

In total 1,077 TDM samples were included in the analysis, comprising 31% (n=334) males and with a median age of 45 years (IQR 34 – 59) and 18% (n=196) being older than 64 years. The data are presented in Table 1.

Dose and serum levels

The median daily dose was 225 mg (IQR 150 – 225). Serum concentrations of VEN and ODV and the sum of both varied on different dose levels (Fig. 2a-c). The median plasma concentration of VEN and ODV was 306 nmol/L (IQR 156 –601) and 861 nmol/L (IQR 600 –1260), respectively. 60% of the analyzed serum levels were within the recommended therapeutic range;

37% were above and 3% were below. 0.1% received above and 0% below the recommended dose range in Denmark of 75-375 mg (10). The median dose-corrected serum level for VEN was 1.49 nmol/L/mg (IQR 0.77 – 2.66), 4.17 nmol/L/mg (IQR 2.99- 5.88) for ODV and for the sum of VEN and ODV it was 6.00 nmol/L/mg (IQR 4.41 – 8.28). There was a statistically positive correlation between dose and concentration for VEN, ODV and SUM with r-values of 0.35, 0.38 and 0.43, respectively ($p<0.0001$).

Sex and age

The median dose and dose-corrected serum level of (VEN + ODV) in men and women were 225 mg, 5.19 nmol/L/mg and 225mg, 6.38 nmol/L/mg, respectively. Females had a significantly higher dose-corrected serum concentration of parent compound, ODV and the sum of both compounds. The influence of sex and age on the distribution of serum concentrations in relation to the recommended therapeutic range is shown in Table 1 and Figs. 3a-b. The dose-corrected sum of the parent compound and ODV was 8.91 nmol/L/mg (IQR 6.56-12.26) *versus* 5.52 nmol/L/mg (IQR 4.16-7.52) above the age of 64 years and below the age of 65, respectively. We observed a serum concentration above the recommended therapeutic range in 42% of the females and 27% of the males. 59% of the population over 64 years of age had a serum concentration above the recommended therapeutic range.

In a *post-hoc* analysis, we verified that the observed association with age was consistent when stratifying by sex, and conversely, that the association with female sex was seen for both young and old patients (Table 1).

Discussion

This is one of the largest studies from a broad, unselected, everyday clinical setting, on the relationship between dose, age, sex and plasma concentrations of VEN and ODV. We found a clinically important impact of age on the serum concentrations of VEN and its active metabolite

ODV, with dose-adjusted serum levels increasing with age. Conversely, the higher serum levels among women compared to men is, while statistically significant, not likely to be of clinical relevance.

A major strength of this study is the large number of TDM samples (N=1,077). As the samples were from an entire region rather than a single psychiatric outpatient clinic, this adds to the generalizability of our results. It has been demonstrated that each region in Denmark is demographically representative of the entire country of Denmark (16). In Denmark, all citizens are given a unique personal identification number and this number is registered on each blood sample taken, ensuring information on both sex and age. This minimizes the need to exclude participants due to lack of basic demographic data. A main limitation pertains to selection bias as we have no way to ascertain why decisions were made to measure drug concentrations or how many per cent of actual venlafaxine-treated patients are referred for measurement of drug concentration. It is likely that the TDM database and our sampling thereof contain data from a disproportionately high fraction of patients that are clinically not responding satisfactorily. Whether these patients also display different dose-adjusted serum levels remains unknown. We did not have access to information on concomitant medications or smoking. Other studies have shown that in comparison with patients treated with venlafaxine as monotherapy, concomitant medications can significantly decrease the ratio between ODV/VEN, and smoking was shown to lead to a lower dose-corrected concentration of ODV although not statistically significant (11,14). Currently, only the extended formulation of venlafaxine is available, and we were unable to discriminate between immediate release formulations and extended release formulations of venlafaxine in the dataset.

In accordance with findings in other similar studies, we found a widespread difference in the absolute and dose-corrected interindividual serum concentrations of venlafaxine, ODV and the sum thereof (11,14). Patients above the age of 64 years had significantly higher dose-corrected

serum levels of VEN, ODV and the sum of both compounds. In this study, the difference in dose-corrected trough values of the sum amounted to 61% which is clearly of clinical relevance. In particular, it is noticeable that ODV trough concentrations rose by about 57% which, as ODV is pharmacologically active, is highly likely to be of clinical relevance. This could possibly signify that the renal elimination of ODV be compromised by the physiologically decreasing renal function in the elderly (17). Urinary recovery of ODV in its unconjugated or conjugated form accounts for about 55% of an oral dose of venlafaxine (10). In alignment with this finding, Unterecker *et al.* and Reis *et al.* reported that patients above the age of 59 and 65 years, respectively, were treated with significantly lower doses than the younger population, and had significantly higher dose-corrected serum concentrations of venlafaxine and its active metabolite ODV when compared with the younger patients (11,14). In accordance with the findings by Reis *et al.* (12), we did not observe a difference according to age in the ODV/VEN ratio.

The patients in our study were generally treated with lower doses of venlafaxine compared with similar studies (11–14). Our median dose-corrected serum level for the sum of VEN and ODV at 6.00 nmol/L/mg (see methods for conversion of units) is in accordance with the results of Sigurdsson and Unterecker, reporting 6.6 and 7.9 nmol/L/mg, respectively (13,14). Reis *et al.* reported a dose-corrected serum concentration of VEN at 1.5 nmol/L/mg and at 1.1 nmol/L/mg for ODV (11). The venlafaxine concentration is similar to our result where the median dose-corrected value for VEN was 1.49 nmol/L. However, the concentration of ODV in our study was 4.17 nmol/L/mg which is somewhat higher than the one observed by Reis *et al.* (11). Our results are, however, in accordance with Unterecker who reported a mean dose-corrected serum level of ODV of 4.9 nmol/L/mg (14).

Co-medication is more common among the elderly due to multiple comorbid conditions that increase the risk of drug-drug interactions. A study in 877 older patients in nursing homes showed that drug-drug interactions were a potential issue among 26% (18). It is possible that

part of the high serum concentration among the elderly in our study is due to, in our dataset, unverifiable drug-drug interactions.

We found a statistically significant difference between men and women as women had a 23% increased trough value of the sum of venlafaxine and ODV. A part of the explanation might be due to the female physiology, as women tend to have lower bodyweight and a smaller blood volume. The volume of distribution for venlafaxine and ODV is about 6-7 L/kg (10). At such distribution characteristic, reduced volume of distribution in females may result in a slightly increased plasma concentration of drug and metabolite. Hydroxylation and glucuronidation occur at a slower rate and the renal clearance is lower in women than in men, which may also contribute to the observed findings (19). These results are comparable to results from other studies (12–14).

Some differences in trough concentration levels of the sum of VEN and ODV with respect to different strata of doses were found. Generally, ODV concentrations and ODV/VEN ratio decreased with increasing doses. This may signify partial saturation of the metabolic capacity of CYP2D6. Theoretically, this observation could also be due to the presence of poor metabolizers in the older age groups. We believe this to be unlikely as all individuals classifiable as phenotypically poor metabolizers were excluded.

In conclusion, we found that age has a clinically important impact on the serum concentrations of venlafaxine and its active metabolite. We suggest that venlafaxine in the elderly be initiated carefully at a low dose and slowly titrated to the lowest effective dose supported by measurements of venlafaxine and its active metabolite.

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Figure 1: Flowchart of excluded patients and samples

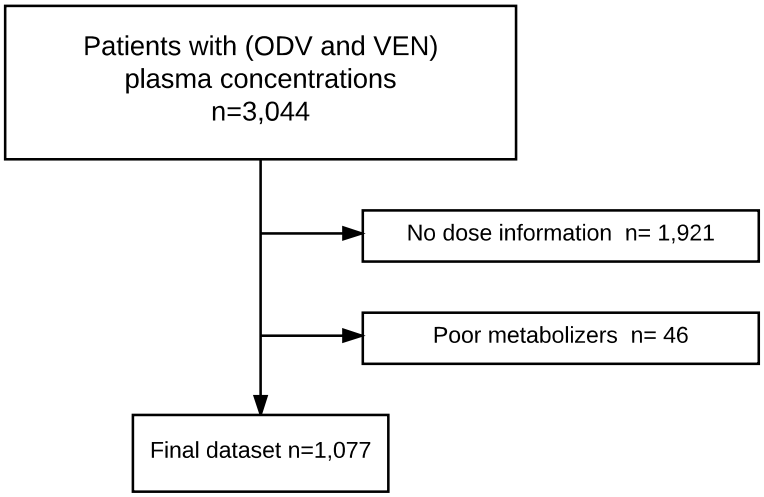


Figure 2a: Dose-concentration plots for sum of V+ODV

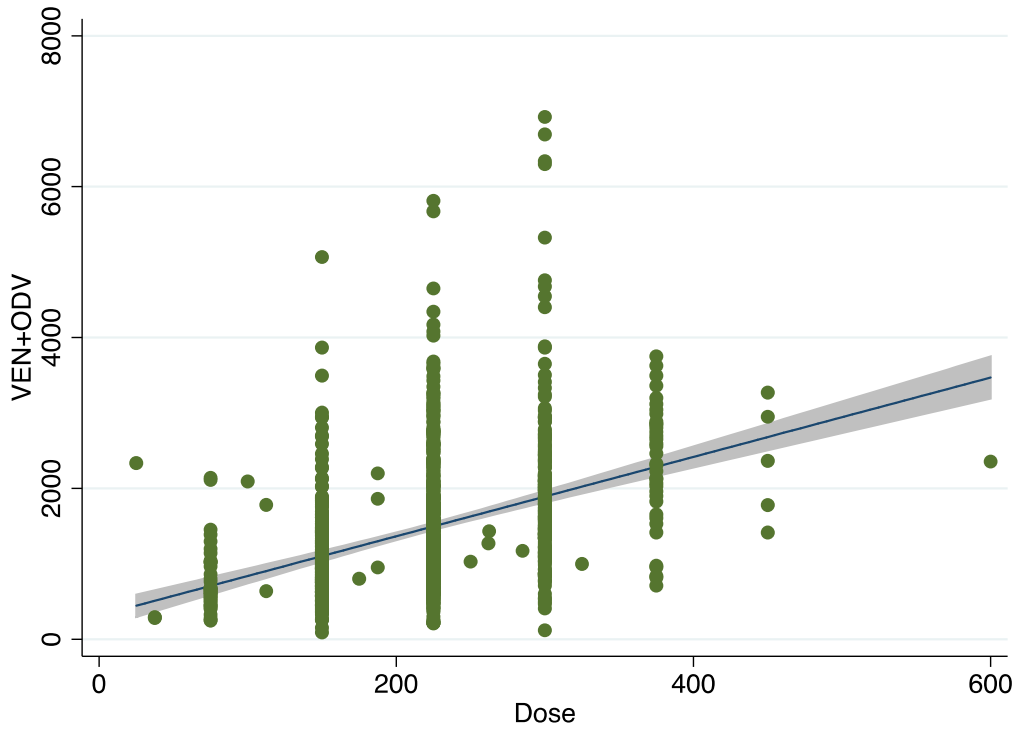


Figure 2b: Dose-concentration plots for VEN

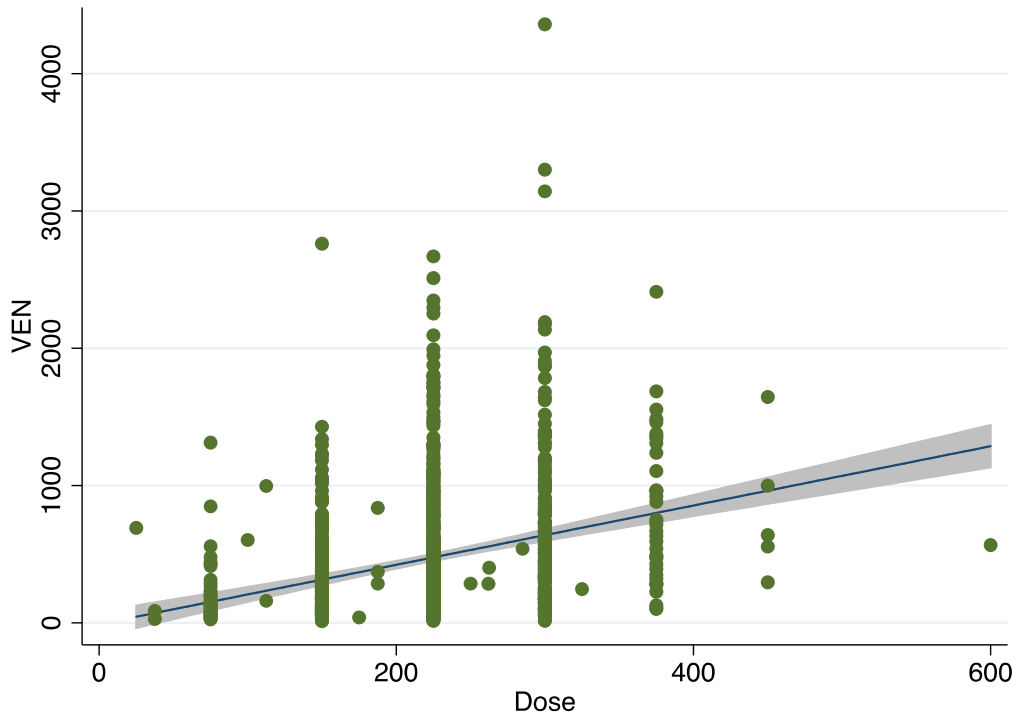
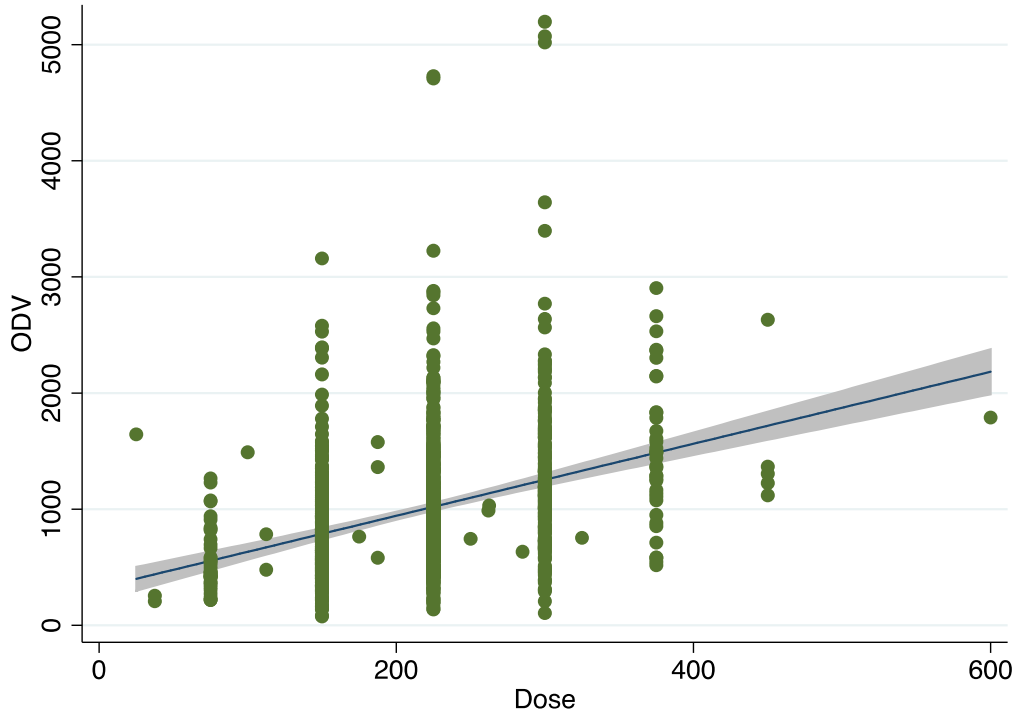


Figure 2c: Dose-concentration plots for sum ODV



Tabel 1

	N	Daily Dose (mg) [Median, 75% IQR]	Dose-corrected serum level (nmol/L/mg): [Median, 75% IQR]			
			VEN	ODV	VEN + ODV	Ratio ODV/VEN
males	334	225 (150 - 225)	1.21 (0.65 - 2.31)	3.70 (2.68 - 5.41)	5.19 (3.79 - 7.40)	3.33
females	743	225 (150 - 225)	1.60 (0.88 - 2.80)	4.39 (3.21 - 6.10)	6.38 (4.71 - 8.75)	3.06
t-test		0.64	<0.001	<0.001	<0.001	0.03
< 65 years	881	225 (150 - 225)	1.31 (0.72 - 2.43)	3.84 (2.86 - 5.33)	5.52 (4.16 - 7.52)	3.12
>=65 years	196	225 (150 - 225)	2.32 (1.38 - 4.22)	6.04 (4.49 - 8.63)	8.91 (6.56 - 12.26)	2.88
t-test		<0.001	<0.001	<0.001	<0.001	0.02
Male < 65 years	285	225 (150 - 225)	1.13 (0.59 - 1.98)	3.55 (2.51 - 4.77)	4.88 (3.60 - 6.76)	3.29
Women <65 years	596	225 (150 - 225)	1.43 (0.78 - 2.64)	4.04 (3.05 - 5.50)	5.91 (4.48 - 7.79)	3.10
t-test		0.99	<0.001	<0.001	<0.001	<0.05
Males >= 65 years	49	150 (150 - 225)	2.18 (1.15 - 4.17)	5.83 (3.78 - 7.31)	8.31 (5.73 - 11.42)	3.48
Women >= 65 years	147	225 (150 - 225)	2.40 (1.47 - 4.25)	6.08 (4.76 - 8.79)	9.23 (6.73 - 12.29)	2.79
t-test		0.06	0.68	0.91	0.85	0.64
<150 mg	46	75 (75 - 75)	1.83 (1.00 - 3.83)	6.27 (5.44 - 9.87)	8.74 (6.71 - 13.69)	3.54
150-225 mg	807	225 (150 - 225)	1.40 (0.74 - 2.52)	4.20 (3.03 - 5.90)	5.86 (4.38 - 8.28)	3.28
>225 mg	224	300 (300 - 300)	1.79 (0.96 - 2.98)	3.81 (2.72 - 5.31)	6.00 (4.42 - 7.72)	2.35
150-225 mg *versus* <150 mg*			0.012	<0.001	<0.001	<0.001
>225 mg *versus* <150 mg*			0.187	<0.001	<0.001	0.075
150-225 mg *versus* >225 mg*			0.118	0.015	0.580	<0.001

*ANOVA

Figure 3a. Relationship between sex and the distribution of serum levels with respect to the recommended therapeutic range.

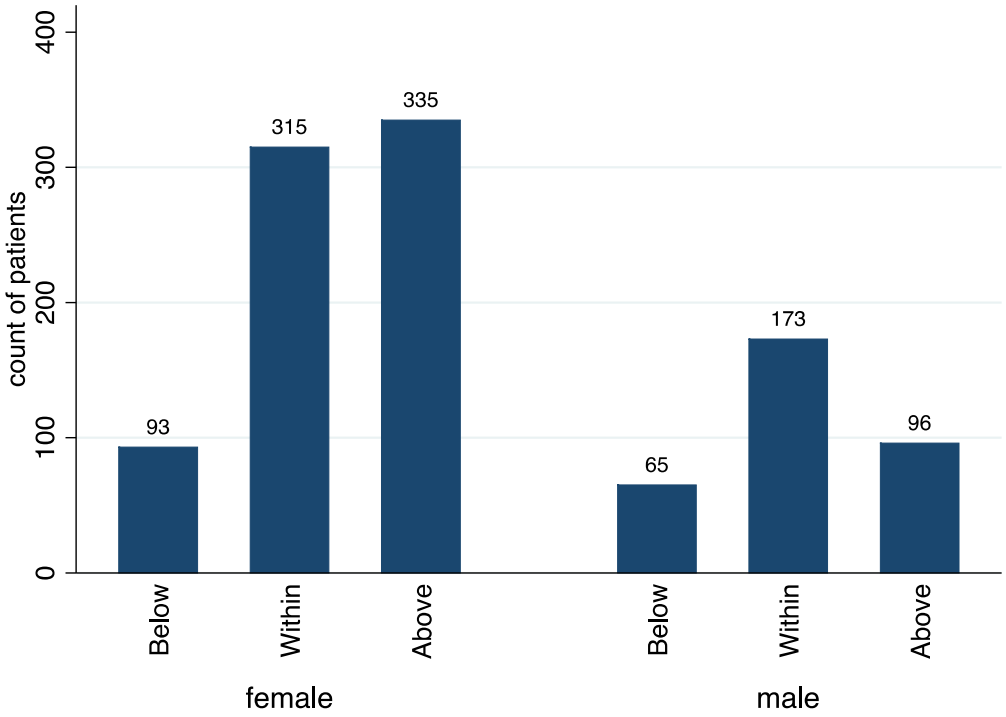


Figure 3b. Relationship between age and the distribution of serum levels with respect to the recommended therapeutic range.