Acta Scientific Pharmacology

Volume 1 Issue 8 August 2020

Research Article

Considering Therapeutic Drug Monitoring (TDM) Data for a Good Dose Strategy in Intake of Escitalopram, Fluoxetine, and Sertraline

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Received: June 27, 2020

Published: July 30, 2020

Abstract

Objective: It is essential for the patient health that the physician reaches the data that will help with proper drug treatment in cases when Therapeutic Drug Monitoring (TDM) can not be applied. This study aims at examining the change on the plasma levels related to three antidepressants including to escitalopram (S-CT), fluoxetine (FLU), and sertraline (SRT) widely used in depression therapy and given in different daily doses, and offering prior knowledge to physicians through the obtained data in situations where TDM is not applicable.

Method: Plasma samples of the patients treated with antidepressant drugs were analyzed on TDM requests by physicians at the Clinical Pharmacogenetic Laboratory, Üsküdar University, Istanbul, Turkey. In our study, the TDM reports were obtained retrospectively from the computerized database of the laboratory for the period 2017 - 2019. The TDM reports included daily drug dose, drug plasma level, patient characteristics like gender, age.

Results: In total, 468 TDM analyses of S-CT, 803 of FLU, 730 of SRT were registered. In this study, the most commonly prescribed drug doses in the treatment were found 10 - 20 mg S-CT, 20 mg FLU and 50 mg SRT. The mean plasma levels in the samples for S-CT, FLU and SRT were about 24.03 ± 18.40 ng/mL, 110.09 ± 92.11 ng/mL, 31.49 ± 30.31 ng/mL, respectively. Also, The mean daily dose for S-CT, FLU, and SRT was about 15.31 ± 6.33 mg/d, 34.25 ± 15.78 mg/d, 86.34 ± 46.86 mg/d, respectively. For each drug on each daily dose, variability in the resulting plasma level was observed.

Conclusion: In this study, S-CT, FLU, and SRT plasma levels have been analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) for TDM analysis. Obtained data can assist in the interpretation of TDM in various daily drug doses for each patient and it can be a valuable reference. In particular, this study may also offer prior knowledge including the relationship between drug daily dose and drug plasma level to physicians through the obtained data in situations where TDM is not applicable.

Keywords: Therapeutic Drug Monitoring; Plasma level; Escitalopram; Fluoxetine; Sertraline

Introduction

Affecting physiological function in a biochemical way, drugs are chemicals commonly having bounds with specific target sites [1]. The initial step of a successful therapeutic intervention might be derived from the correct choice of drug therapy [2]. For the qualitative decision in the drug therapy, quantitative aspects are required to be taken into consideration to make sure that the drug could reach the target sites so that they could show the expected effect.

Therapeutic drug monitoring (TDM) helps know dose adjustment for the prescribed drugs by measuring drug and metabolite in plasma [3]. TDM is also used to determine whether the drug plasma level is within the accepted therapeutic drug range and this value shows the highest effectiveness and safety. Especially, for several antidepressants, TDM is used that the quantification of drug and its metabolite in plasma by a clinical routine to adjust drug dose [3,4]. Provided that the obtained value is below the therapeutic range, there might occur unresponsiveness (risk for loss of action) in drug treatment, whereas if the obtained value is over this range, the risk of toxicity might increase [3,5].

For a successful TDM, it is important that the method used in the drug analysis be selective and sensitive. For TDM, liquid chromatography-tandem mass spectrometry (LC-MS/MS) is preferred due to its high accuracy and sensitivity [6-8]. Additionally, having notably reduced runtimes and reduced sample volumes are the advantages of LC-MS/MS over other chromatographic methods [9,10]. TDM is analyzed at the point when the drug reaches the steady-state concentration and sample collection could be made at trough level which is the level where the drug is at its lowest concentration in the plasma [4,5]. Even though LC-MS/MS is commonly used the method for TDM in numerous laboratories, notable disadvantages of LC-MS/MS method are high equipment costs and the need for well-trained personnel. Therefore, it is essential for the patient health that the physicians reach the data that will help with proper drug treatment in cases when TDM can not be applied due to the disadvantages of the LC-MS/MS method.

Aim of the Study

This study aims at examining the change on the plasma levels related to three antidepressants including to escitalopram (S-CT), fluoxetine (FLU), and sertraline (SRT) widely used in the treatment of depression and given in different daily doses, and offering prior knowledge to physicians through the obtained data in situations where TDM is not applicable.

Materials and Methods

Plasma samples of the patients treated with antidepressant drugs are analyzed on TDM requests by physicians at the Clinical Pharmacogenetic Laboratory, Üsküdar University, İstanbul, Turkey. The TDM reports were obtained retrospectively from the computerized database of the laboratory for the period 2017-2019. The TDM reports included daily drug dose, drug plasma level, patient characteristics like gender, age. The study was approved by the Üsküdar University Ethics Committee (Approval date: 25/07/2019; approval number/ID: 61351342-/2019-352).

TDM analysis

Plasma samples were analyzed by LC-MS/MS at the laboratory. Briefly, S-CT, FLU, and SRT were extracted from plasma by protein precipitation using cold acetonitrile. Thereafter, the Agilent 6470 HP-1200 LC series (USA) liquid chromatography system was used for the analysis. ACE-3 C 8 (3 µm, 3.0 mm 150 mm) column was used for analytical separation. Quantitative analysis was carried out by multiple reaction mode with an electrospray positive ionization (ES+). Quantitation was based on monitoring precursor ion and product ion for S-CT m/z 325.1 > 109.1, for FLU m/z 310.0 > 148.0, for SRT m/z 306.1 > 275.0 and for internal standard desipramine m/z 267.0 > 72.0.

The assay data on limit of quantification (LOQ), calibration range (for eight calibration standards), accuracy (minimum- maximum, % mean) and precision (minimum- maximum, % mean CV) for five quality control samples were as follows respectively: 5.9 ng/mL, 5.9 - 441.8 ng/mL, 91.9 - 107.5%, 2.2 - 4.1% for S-CT; 14.6 ng/mL, 14.6 - 585.0 ng/mL, 95.1 - 100.0%, 5.4 - 9.9% for FLU; 5.1 ng/mL, 5.1 - 203.1 ng/mL, 94.4 - 104.0%, 4.5-10.4% for SRT. In general, the interassay coefficients of variation were less than 15%.

Statistical analysis

Data from the TDM reports containing gender, age, daily drug dose, and plasma level of drugs were performed with the software SPSS Statistics 24.0. Statistical analysis was carried out by descriptive methods. For comparisons between groups, the nonparametric statistical method (Kruskal Wallis, Mann Whitney U test) was

applied employed. Statistical significance was predefined as $p < 0.05$. Correlation coefficients (Spearman-rho) were used to calculate the relation between daily drug doses and plasma drug levels. Also, regression was applied using r^2 value.

Results

In total, 468 TDM analyses of S-CT, 803 of FLU, 730 of SRT were registered. The patients' demographic data, mean with standard deviations, median, minimum and maximum value for daily drug dose, drug plasma level (for TDM) are displayed in table 1. The percentages of females in the samples for S-CT, FLU, and SRT were about 61.5%, 45.6%, 32.0%, respectively (Table 1). The mean ages (in yrs) in the samples for S-CT, FLU, and SRT were about 40.73 ± 17.02, 31.17 ± 15.33, 35.18 ± 16.22, respectively (Table 1). The mean plasma levels in the samples for S-CT, FLU, and SRT were about 24.03 ± 18.40 ng/mL, 110.09 ± 92.11 ng/mL, 31.49 ± 30.31 ng/mL, respectively (Table 1). Also, The mean daily drug doses for S-CT, FLU and SRT were about 15.31 ± 6.33 mg/d, 34.25 ± 15.78 mg/d, 86.34 ± 46.86 mg/d, respectively (Table 1). For each drug on each daily dose, variability in the resulting plasma level was observed (Figure 1). The covariation of variables was analyzed using the r^2 of the correlation. The r^2 values between daily drug doses and plasma levels of S-CT, FLU, and SRT were 0.14, 0.35, and 0.44, respectively ($p < 0.05$) (Figure 2-4).

Drug	Sample (N; %)	Statistics	Age (yrs)	Dose (mg/d)	TDM (ng/mL)	p value (Dose-TDM)
S-CT	468; 100 (T)	Minumun	10	5	1	< 0.05*
	288; 61.5 (F)	Maximum	90	30	98.15	
	180; 38.5 (M)	Median	39	20	19.07	
		Mean ± Std Dev.	40.73 ± 17.02	15.31 ± 6.33	24.03 ± 18.40	
FLU	803; 100 (T)	Minumun	6	10	0.31	< 0.05*
	366; 45.6 (F)	Maximum	90	80	527.22	
	437; 54.4 (M)	Median	27	40	85.85	
		Mean ± Std Dev.	31.17 ± 15.33	34.25 ± 15.78	110.09 ± 92.11	
SRT	730; 100 (T)	Minumun	6	25	1.21	< 0.05*
	234; 32.0 (F)	Maximum	90	200	231.91	
	496; 68.0 (M)	Median	34	100	22.16	
		Mean ± Std Dev.	35.18 ± 16.22	86.34 ± 46.86	31.49 ± 30.31	

Table 1: Results of descriptive statistic for age, dose, TDM.

N: Number of sample. %: Percentage of Samples, F: Female, M: Male, T: Total.

'*': Represent significant differences ($p < 0.05$) by Kruskal-Wallis test with 95% confidence interval.

Figure 1: Relationship between drug daily dose and plasma level (TDM, ng/mL) for S-CT, FLU and SRT ($p < 0.05$).

Figure 2: Relationship between S-CT daily dose and S-CT plasma level (TDM;ng/mL).Regression lines with 95% confidence interval; r^2: 0.14.

Figure 3: Relationship between FLU daily dose and FLU plasma level (TDM;ng/mL).Regression lines with 95% confidence interval; r^2: 0.35.

Figure 4: Relationship between SRT daily dose and SRT plasma level (TDM;ng/mL).Regression lines with 95% confidence interval; r^2: 0.44.

Figure 5: Mean plasma level (TDM; ng/mL) as a function of gender. '*' among groups (female and male for FLU) represent significant differences ($p < 0.05$) by Mann Whitney U test.

Influence of gender on TDM in the various daily dose

The gender distribution for each drug is presented in table 1 and 2. The percentage of females in the study was 61.5% for S-CT, 45.6% for FLU, 32.0% for SRT (Table 1). The percentage of female prescribed S-CT was higher than male in each daily drug dose while the percentage of female prescribed FLU and SRT were lower than male in each daily drug dose except in 10 mg, 40 mg FLU (Table 2). Females had a significantly higher mean plasma level of FLU in 40 mg, 60 mg doses ($p < 0.05$). There was no significant difference between males and females in the mean plasma levels of S-CT and SRT ($p > 0.05$) (Table 2). Plasma level was found within the therapeutic range in 58.3% of patients using S-CT, in 34.7% of patients using FLU and, in 79.0% of patients using SRT (Table 2).

S-CT	5 mg		10 mg		20 mg		30 mg		Total		Therapeutic range (below/within/ above (%))
	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	
Female	21; 84.0	8.80 ± 5.21	126; 60.6	16.71 ± 10.64	128; 61.2	34.55 ± 21.09	13; 50.0	32.26 ± 26.73	288; 61.5	24.90 ± 19.30	41.3; 57.3; 1.4
Male	4; 16.0	7.20 ± 2.21	82; 39.4	14.09 ± 9.01	81; 38.8	28.45 ± 15.09	13; 50.0	45.65 ± 28.03	180; 38.5	22.63 ± 16.81	38.9; 60.0; 1.1
Total	25; 100.0	8.55 ± 4.86	208; 100.0	15.68 ± 10.09	209; 100.0	32.15 ± 19.17	26; 100.0	40.45 ± 27.35	468; 100	24.03 ± 18.40	40.4; 58.3; 1.3
p		NS**		NS**		NS**		NS**		NS**	

FLU	10 mg		20 mg		30 mg		40 mg		60 mg		80 mg		Total		Therapeutic range (below/within/ above (%))
	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	
Female	5; 55.6	28.52 ± 28.83	166; 46.1	70.07 ± 47.77	3; 42.9	52.90 ± 36.46	152; 50.7	157.00 ± 84.35	36; 33.3	275.53 ± 119.44	20; 29.4	241.04 ± 158.77	366; 45.6	127.54 ± 99.56	57.4; 42.3; 0.3
Male	4; 44.4	32.51 ± 19.70	194; 53.9	45.82 ± 43.02	4; 57.1	97.08 ± 47.98	148; 49.3	115.84 ± 76.79	72; 66.7	162.45 ± 87.77	48; 70.6	231.49 ± 108.40	437; 54.4	95.47 ± 84.32	71.4; 28.4; 0.2
Total	9; 100.0	30.30 ± 23.78	360; 100.0	57.00 ± 46.80	7; 100.0	78.15 ± 46.39	300; 100.0	136.69 ± 83.17	108; 100.0	200.14 ± 112.46	68; 100.0	233.50 ± 115.57	803; 100	110.09 ± 92.11	65.0; 34.7; 0.2
p		NS**		< 0.05*		NS**		< 0.05*		< 0.05*		NS**		< 0.05*	

SRT	25 mg		50 mg		75 mg		100 mg		150 mg		200 mg		Total		Therapeutic range (below/within/ above (%))
	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	N;%	TDM (mean ± std dev)	
Female	14; 34.1	8.56 ± 7.78	91; 31.3	16.75 ± 12.09	8; 26.7	32.44 ± 18.25	89; 49.7	37.59 ± 18.44	12; 37.5	65.16 ± 27.47	20; 29.4	75.63 ± 42.65	234; 32.0	32.24 ± 27.17	17.5; 82.1; 1.4
Male	27; 65.9	7.37 ± 9.51	200; 68.7	14.98 ± 12.28	22; 73.3	21.08 ± 14.27	179; 50.3	38.09 ± 19.79	20; 62.5	45.34 ± 24.17	48; 70.6	84.64 ± 58.46	496; 68.0	31.14 ± 31.71	20.8; 77.6; 1.6
Total	41; 100.0	7.78 ± 8.87	291; 100.0	15.54 ± 12.22	30; 100.0	24.11 ± 15.93	268; 100.0	37.92 ± 19.32	32; 100.0	52.77 ± 26.85	68; 100.0	81.99 ± 54.13	730; 100	31.49 ± 30.31	19.7; 79.0; 1.2
p		NS**		NS**		NS**		NS**		NS**		NS**		NS**	

Table 2: Distribution: Mean values and standard deviation of drug plasma level (TDM) as a function of gender and each drug daily dose.

N: Number of Sample; %; Percentage of Samples. '*' represent significant differences ($p < 0.05$) between TDM and gender by Mann Whitney U test with 95% confidence interval.. NS** represent no significant diffirences ($p > 0.05$).

Influence of age on TDM in the various daily dose

When the relationship between drug plasma level and age groups was examined using the Kruskal Wallis test, statistically significant differences were found between patients up to 45 years and older than 45 years in patients using 20 mg S-CT ($p < 0.05$) in table 3. Also, the statistically significant difference was found between older than 65 years and up to 45 years in patients using 10 mg S-CT ($p < 0.05$) in table 3. For FLU, statistically significant differences were found between older than 65 years and the other age groups in patients using 40 mg ($p < 0.05$) in table 3. In patients using 50 mg SRT, statistically significant differences were found between older than 65 years and up to 45 years ($p < 0.05$) in table 3. The daily drug dose range of S-CT and SRT was found 5 - 30 mg and 25-200 mg in age groups. While the daily FLU drug dose range was found 10 - 80 mg in patients up 45 years, it was found 20 - 80 mg in patients 46 - 65 years and 10 - 40 mg in patients > 65 years.

Drug	Age (yrs)	Sample (N; %)	Therapeutic range (below/within/above (%))	TDM (ng/mL) and drug daily dose (mg/d)	Min - Max	Median	Mean ± std dev.	p value (TDM as a function of age
S - CT	≤ 25	94; 20.1	50;50; -	TDM	1.81 - 62.51	15.14	19.13 ± 12.48	p < 0.05*
				Dose (5,10,20,30)	5 - 30	10	12.29 ± 6.34	(46 - 65, >65 yrs,20 mg)
	26 - 45	203; 43.4	47.03; 50.7; 2.0	TDM	1.14 - 98.15	16.26	21.15 ± 17.86	p < 0.05*
				Dose (5,10,20,30)	5 - 30	10	15.00 ± 6.33	(46 - 65, >65 yrs, 20mg)
	46 - 65	127; 27.1	29.1; 70.9; -	TDM	1.00 - 78.46	24.45	28.75 ± 19.18	NS**
				Dose (5,10,20,30)	5 - 30	20	17.09 ± 5.99	
	>65	44; 9.4	20.5; 75.0; 4.5	TDM	1.35 - 95.30	36.33	34.13 ± 22.37	p < 0.05*
				Dose (5,10,20,30)	5 - 30	15	16.14 ± 7.46	(≤ 25, 26 - 45 yrs; 10,20 mg)
FLU	≤ 25	353; 44.0	66.0; 33.7; 0.3	TDM	1.53 - 527.22	85.08	110.91 ± 94.77	NS**
				Dose (10,20,30,40,60,80)	10 - 80	40	33.99 ± 15.53	
	26 - 45	326; 40.6	68.7; 31.0; 0.3	TDM	0.31 - 503.71	75.35	100.42 ± 87.59	NS**
				Dose (10,20,30,40,60,80)	10 - 80	40	34.57 ± 16.33	
	46 - 65	91; 11.3	59.3; 40.7; -	TDM	0.76 - 478.41	92.95	118.40 ± 96.79	NS**
				Dose (20,40,60,80)	20 - 80	40	34.50 ± 16.62	
	>65	33; 4.1	33.7; 66.7; -	TDM	1.79 - 327.03	190.90	173.86 ± 89.02	p < 0.05* (≤ 25, 26 - 45, 46 - 65 yrs, 40 mg)
				Dose (10,20,40)	10 - 40	40	33.03 ± 10.15	
SRT	≤ 25	249; 34.1	24.5; 75.5; -	TDM	1.31 - 138.13	17.60	25.30 ± 22.72	p < 0.05*
				Dose (25,50,75,100,150,200)	25 - 200	50	77.11 ± 43.97	(>65 yrs, 75mg)
	26 - 45	312; 42.7	19.2; 78.2; 2.6	TDM	1.21 - 231.91	22.89	34.17 ± 35.52	NS**
				Dose (25,50,75,100,150,200)	25 - 200	100	93.27 ± 50.35	
	46 - 65	122; 16.7	16.4; 82.8; 0.8	TDM	2.70 - 154.16	28.05	34.44 ± 29.00	NS**
				Dose (25,50,75,100,150,200)	25 - 200	100	90.37 ± 44.12	
	>65	47; 6.4	6.4; 93.6; -	TDM	4.64 - 113.31	29.88	38.89 ± 26.50	p < 0.05*
				Dose (25,50,75,100,150,200)	25 - 200	75	78.72 ± 24.96	(≤ 25, 26 - 45 yrs, 50 mg)

Table 3: Distribution: Descriptive statistic results of drug daily dose and drug plasma level (TDM) as a function of age.

N: Number of Sample. %; Percentage of Samples. '*': Represent significant differences ($p < 0.05$) between TDM and age by Kruskal - Wallis test with 95% confidence interval. NS** represent no significant diffirences ($p > 0.05$).

S-CT plasma level was found within the therapeutic range in 50.0% of ≤ 25 years, 50.7% of 26 - 45 years, 70.9% of 46 - 65 years, 75% of > 65 years. FLU plasma level was found within the therapeutic range in 33.7% of ≤ 25 years, 31.0% of 26 - 45 years, 40.7% of 46 - 65 years, 66.7% of > 65 years. SRT plasma level was found within the therapeutic range in 75.5% of ≤ 25 years, 78.2% of 26 - 45 years, 82.8% of 46 - 65 year, 93.6% of > 65 years.

Discussion

S-CT, FLU, and SRT are the most commonly utilized serotonin reuptake inhibitors (SSRIs) in depression treatment [11-13]. They show antidepressant effect because they increase serotonin levels in the brain which are caused by the inhibition of the serotonin transporter [14,15]. The pharmacokinetics of S-CT and SRT show a linear relationship between a change in dose and a change in plasma drug level while FLU shows nonlinear [16,17]. They are easily absorbed upon oral intake. While plasma protein binding of S-CT is low, the protein binding of FLU and SRT is about 95% [18]. Hepatic metabolism is the most important elimination pathway for these drugs. The elimination half time of FLU is longer than the others [17]. In contrast to S-CT and SRT, fluoxetine inhibits its metabolism and thus extends its elimination half time. S-CT, FLU, and SRT have generally used to treat depression disorder after administered with the oral dose of 10-20 mg, 20 mg, and 50 mg daily, respectively [11,19,20].

In a study by Canbolat., *et al*. (2019), it was reported that when the individual factors such as age, gender, drug interactions affect the plasma drug levels differently (above or below expected), the physician can more easily adjust the amount of daily oral dosing, by following the drug plasma levels of patients with TDM, to provide the plasma therapeutic drug range for drug effect [21]. Therefore, to examining the change in the plasma levels related to three antidepressants given in different daily doses, patients treated with antidepressant drugs in NPİstanbul Brain Hospital were selected from different age groups and both genders in this study. However, it should be recognized that this study has some weaknesses. The lack of information on concomitant medication, body weight, and smoking habits of the patients may limit an effective assessment of pharmacokinetic properties.

In this study, the most commonly prescribed drug doses in the treatment were 10 - 20 mg S-CT, 20 mg FLU, and 50 mg SRT (Table 2). In a study by Gregor., *et al*. (1994), SSRI dose titration in the naturalistic setting was examined [22]. 3350 patients treated FLU and SRT included in this study. The mean daily dose for patients receiving FLU was 21 ± 6 mg/d and for patients receiving SRT was 59 ± 28 mg/d [22]. In a study published in 2007 by Rao, the clinical pharmacokinetics of S-CT was assessed. It was found that 10-20 mg S-CT dose proved to be effective to treat depression [11]. The data obtained from our study is similar to the Gregor., *et al*. and Rao publications.

Also, it was found that the plasma level increased drug daily dose for S-CT, FLU, SRT in our study (Figure 1). All drugs gave a significantly positive correlation between plasma level and daily drug dose (Table 2 and figure 2-4). In a study published in 2009 by Reis., *et al*. serum concentration results at daily doses of 15 antidepressant drugs by the means of TDM in a naturalistic setting were assessed [23]. The r^2 values between daily drug doses and serum concentrations of S-CT and FLU were found 0.10 and 0.37 ($p < 0.05$), respectively by Reis., *et al*. [23]. Also, in the study of Lundmark., *et al*. (2000), it was stated that a closer relationship between doses and SRT plasma level (r^2: 0.79, $p < 0.001$) [24]. The r^2 values obtained from our study were similar to those of these studies (Figure 2-4). Our findings supported the findings by Reis., *et al*. in 2009 and Lundmark., *et al*. in 2000 [23,24]. Mauri., *et al*. presented clinical outcome and tolerability of sertraline in twenty-one major depression patients recently [25]. It is reported that no significant correlation between SRT dose and plasma level was found. The results of the comparison between SRT plasma level and dose in our study are different from those of Mauri., *et al*. The reason could be due to studying the small number of patients in Mauri., *et al*. study.

In the present study, the percentage of male prescribed FLU and SRT was higher than females except for S-CT (Table 1) while it was reported that the percentage of female prescribed S-CT, FLU, and SRT was higher than male in the study of Unterecker., *et al*. (2013) [26]. Also in a study published in 2009 by Reis., *et al*. the percentage of females in the various populations was found about 60% [23]. The reasons for the differences in present results between the other studies could be due to the differences in physician's approach, sampling from different races, locations, and time interval of the study.

Except for FLU in 20 mg/d, 40 mg/d, and 60 mg/d, no differences in the plasma level of antidepressants between females and males were found for all drugs (Table 2 and figure 6). Rao's (2007)

study of S-CT pharmacokinetics showed that there was no significant difference in the S-CT plasma level between females and male [11]. The recent relevant study is that Unterecter., *et al*. (2013) assessed the effects of gender and age on serum concentrations of antidepressants under naturalistic conditions [26]. When they compared serum concentrations for the male < 60 years and female 60 years, no significant differences in SRT plasma levels between females and males were found. The results of the comparison between drug plasma levels and gender in our study are similar to the results of Unterecter., *et al*. (2013) and Rao., *et al*. (2007) [11,26]. As for the influence of the age on the plasma level in literature, significant differences between age groups have been reported. Reis., *et al*. (2009) found a higher plasma level of S-CT, FLU, and SRT in elderly (>60 years) [23]. Also, in another study, Unterecter., *et al*. have reported that higher plasma levels of S-CT (47 ± 45 ng/mL), FLU (261 ± 133 ng/mL), and SRT (44 ± 21 ng/mL) have been found in elderly patients [26]. Mauri., *et al*. (2002) have reported that there was a positive correlation between age and SRT plasma levels in female patients [25].

Figure 6: Mean plasma level (TDM; ng/mL) as a function of age. '*' among groups (patients≤ 45 years (≤ 25 years and 26-45 years) and patients > 45 years (46-65 years and > 65 years) in 20 mg/d S-CT); '**' among groups (patients≤ 45 years (≤ 25 years and 26-45 years) and patients > 65 years in 10 mg/d S-CT);'***' among groups (patients> 65 yearsand the other age groups in 40 mg/d FLU);'****' among groups (patients≤ 45 years (≤ 25 years and 26-45 years) and patients > 65 yearsin 50 mg/d SRT)represent significant differences ($p < 0.05$) by Kruskal-Wallis test and One Way Anova-Post Hoc tests.

In the present study, considerable differences in the plasma level between age groups were found in 10 mg/d and 20 mg/d S-CT, 40 mg/d FLU, 50 mg/d SRT. Patients ≤ 45 years (≤ 25 years and 26 - 45 years) showed considerably lower plasma levels of S-CT in 20 mg/d than patients > 45 years (46 - 65 years and > 65 years). Also, patients ≤ 45 years (≤ 25 years and 26 - 45 years) showed considerably lower plasma levels of S-CT in 10 mg/d than patients > 65 years. Besides, while patients > 65 years prescribed 40 mg/d FLU showed significantly higher plasma levels of FLU than other age groups, plasma SRT level of patients > 65 years prescribed 50 mg SRT was found higher than patients ≤ 45 years (≤ 25 years and 26 - 45 years) (Table 3 and figure 6). The findings of the present study are in agreement with the positive correlation between age and plasma level by literature. In our results, a higher percentage of those within the therapeutic range was observed with age.

Conclusion

In this study, information was given about drug plasma levels at different daily drug doses by considering gender and age groups. This study, S-CT, FLU and SRT plasma level analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) for TDM, can give a valuable reference, and it can assist in the interpretation of TDM in various daily drug dose for each patient. In particular, this study may also offer prior knowledge including to the relationship between drug daily dose and drug plasma level to physicians through the obtained data in situations where TDM is not applicable.

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