Published in final edited form as:

J Clin Pharmacol. 2013 February ; 53(2): . doi:10.1177/0091270012445793.

Population Pharmacokinetic Modeling of Sertraline Treatment in Alzheimer's Disease Patients: The DIADS-2 Study

Claire H. Li^{1,2,*}, Bruce G. Pollock³, Constantine G. Lyketsos⁴, Vijay Vaidya⁵, Lea T. Drye⁵, Margaret Kirshner⁶, Denise Sorisio⁶, and Robert R. Bies^{1,2,3} For the DIADS-2 Research Group

¹Indiana University, Indianapolis School of Medicine, IN, USA

²Indiana Clinical and Translational Sciences Institute (CTSI), Indianapolis, IN, USA

³Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

⁴Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁵Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

⁶University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Keywords

Sertraline; Alzheimer's disease; Population pharmacokinetics

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease associated with a number of neuropsychiatric symptoms (NPS). One commonly found NPS is depression, affecting as many as 60% of AD patients [1]. The antidepressant sertraline, a selective serotonin reuptake inhibitor (SSRI), has been used for the treatment of depression in AD patients [2]. It is the second most potent inhibitor of serotonin reuptake. [3]. In a study of 117 randomized controlled trials from 1991 to 2007, sertraline was proposed as the best first line treatment for moderate to severe depression in adults based on an overall evaluation of benefits, acceptability and other factors [4]. Sertraline is orally administered with high plasma protein binding affinity [5]. The average elimination half-life of sertraline is approximately 26 hours and the peak plasma concentration (C_{max}) is reached at 6–8 hours [6]. Sertraline is mainly eliminated by hepatic metabolism to its major metabolite, N-desmethylsertraline, by multiple cytochrome p450 enzymes including CYP2B6, CYP2D6, CYP2C9, CYP2C19 and CYP3A4 [7]. This metabolite has 5–10% of sertraline's serotonin reuptake inhibitor potency; thus its clinical effect on sertraline response is negligible [8].

Address for correspondence: Claire Li, Division of Clinical Pharmacology, Wishard Memorial Hospital, 1001 West 10th Street, WD Meyers Building, W7123, Indianapolis, IN 46202, Phone: 317-630-8795, Fax: 317-630-8185, clali@iupui.edu.

Conflict of Interest

Bruce G. Pollock, receives research support from the National Institute of Health, Canadian Institutes of Health Research, American Psychiatric Association and the Foundation of the Centre for Addiction and Mental Health. Within the past two years he has been a faculty member of the Lundbeck International Neuroscience Foundation (LINF) (last meeting was April 2010).

Constantine Lyketsos was involved in another trial for which Pfizer donated a different drug; he also was involved in research sponsored by Forest to study escitalopram and citalopram and Pfizer to study sertraline and donepezil; Dr. Lyketsos served as a consultant for Organon, Eisai, GSK, Lilly, Wyeth, and Pfizer.

Robert R. Bies is funded through the Indiana Clinical Translational Sciences Institute from a gift of Eli Lilly and Company. Dr. Bies is also a scientific advisory board member for the Metrum Institute.

Claire H. Li, Vijay Vaidya, Lea T. Drye, Margaret Kirshner, and Denise Sorisio report no conflicts of interest.

The pharmacokinetic profile of sertraline has been broadly explored in previous clinical studies where patient ages spanned broad ranges [9–11]. In a pharmacokinetic study of 16 elderly (≥ 65 years of age) patients treated with 100 mg sertraline once daily for 14 days, plasma sertraline clearance was approximately 40% lower compared to similarly studied younger (25–32 years) patients [6,12]. A comparable result was found in a 21 day study (n=44), with the elimination rate constant (0.019/hr) in elderly individuals 16 to 63% lower than that observed in young adults [13].

In the elderly, sertraline's effectiveness is comparable to the SSRI fluoxetine as well as the tricyclic antidepressants (TCAs) nortriptyline, amitriptyline and imipramine. It has lower rates of adverse side effects than the TCAs [9]. Although many studies have examined the sertraline pharmacokinetic profile in elderly subjects, non-compartmental methods were employed that have limitations in assessing sources of inter-individual variability in sertraline concentration. In fact, this is the first population pharmacokinetic (PPK) study focusing on AD patients with depression. While this analysis was based on data from a null clinical study, it provided an opportunity to capture the pharmacokinetic characteristics in elderly individuals of sertraline. In these analyses, we aim to gain insights relating to inter-individual variability in the pharmacokinetics of sertraline in AD patients. The objective is to identify covariates that contribute to variability in sertraline concentration by performing a PPK analysis of sertraline in elderly patients with AD and generating PPK parameters for this population.

MATERIALS AND METHODS

Participants and Study design

The design of the multicenter Depression in Alzheimer's Study-2 (DIADS-2) has been described in detail elsewhere [2, 14–16]. Briefly, DIADS-2 enrolled 131 AD patients with mild-to-moderate AD. Patients were randomized in a, 12-week, double-blind, placebo-controlled (n=64) antidepressant trial of sertraline (n=67; range: 25–125 mg per day). An initial treatment regimen of sertraline 50 mg QD or identical-appearing placebo was prescribed. The dosage of sertraline in the active treatment arm was increased to 100 mg QD after one week. The daily dose was adjusted depending on the response and tolerability of the treatment in the first four weeks post randomization. Single concentration samples of sertraline were collected in individual patients at weeks 4 and 12. The time of last dose and exact time of collection were available for each of these samples.

The study was approved by Institutional Review Boards at all five study sites and the coordinating center: Johns Hopkins School of Medicine, Baltimore, MD; University of Pennsylvania School of Medicine, Philadelphia, PA; Medical University of South Carolina, Charleston, NC; University of Rochester School of Medicine, Rochester, NY; University of Southern California Keck School of Medicine, Los Angeles, CA; Johns Hopkins Bloomberg School of Public Health. In addition, the PPK analysis was approved by the institutional Review Board of Indiana University School of Medicine, Indianapolis, IN.

Analytical Procedure to Measure Sertraline Concentration

Plasma sertraline concentration was determined using high-performance liquid chromatography (HPLC). The extraction of plasma was done in the mobile phase at a 3:2 ratio of 0.025 M potassium phosphate buffer, pH 2.5, and acetonitrile with a flow rate of 1 mL/min. The separation of plasma occurred in a Knauer nucleosil, C18, 100 angstrom, 150 mm × 4.6 mm column with a Supelco pelliguard LC-18, 2 cm × 4.6 mm pre-column cartridge. Ninety microliters of n-octylamine was added as a modifier to the mobile phase and degassed. The sertraline and D-sertraline assays were linearized by an internal standard,

200 ng/mL of clomipramine, in the range of 10 to 600 ng/mL. The intra-assay and inter-assay variability in the coefficient of variation (CV) ranged from 6.6% to 9.4% and ranged from 2.8% to 6.3%, respectively. With 1 mL of plasma, recovery for sertraline and metabolite ranged from 87% to 93% with a lower limit of quantification (LLOQ) of 10ng/mL. The analysis was carried out using a Turbo Chrom data system.

Population Pharmacokinetic Model Development

The population pharmacokinetics of sertraline were analyzed using nonlinear mixed effect modeling software, NONMEM, Version VII (GloboMax_LLC, Ellicott City, MD, USA) using Wings for NONMEM, Version 7 [17]. The initial model development focused on a base model structure on PK parameter assessment. One and 2 compartment models with first order absorption and elimination were evaluated using subroutine ADVAN2 TRANS2 and ADVAN4 TRANS4, respectively. A likelihood based approach (Method 3) was used to handle measurements below the quantitation limit (BQL) at 10 ng/mL [18].

PPK analyses used the first-order conditional estimation (FOCE) LAPLACIAN method. Inter-individual variability (IIV) for PK parameters was evaluated using an exponential model $P_i = P_{TV} \times e^{\epsilon_i}$ where P_i is the parameter estimate for the i th individual, and P_{TV} is the typical value for the parameter at the population level. The variability between i th individual and population parameter values was described by ϵ_i which was assumed to be normally distributed with a mean of 0 and a variance of 1 [19]. In addition to the IIV, intraindividual variability, system noise, experimental error and/or model misspecifications was described by a residual error model. The residual error models evaluated were: additive ($y_{ij} = \hat{y}_{ij} + \epsilon_{ij}$); proportional ($y_{ij} = \hat{y}_{ij}(1 + \epsilon_{ij})$); and combined ($y_{ij} = \hat{y}_{ij}(1 + \epsilon_{ij}) + \epsilon_{ij}$); where y_{ij} and $\hat{y}_{ij}$ represents the j th observed sertraline concentration, and its corresponding model predicted concentration with the difference described by ϵ_{ij} or ϵ_{ij} . ϵ_{ij} was assumed to be normally distributed with a mean of 0 and a variance of 1. The absorption rate constant (K_a) was fixed to 0.5 based on the literature values of t_{max} and an elimination constant [13]. This was done because the estimation of K_a in this dataset resulted in unstable model runs.

To evaluate the inter-individual variability estimated by the nonlinear mixed effects modeling approach, patients' demographic characteristic (weight, height, age, sex, race and study site) were evaluated to see if these explained this variability. These factors were assessed independently in a stepwise forward addition then backward elimination approach. Covariates such as weight, height, age, sex and race were included to examine potential physiologic differences that could contribute to difference in drug elimination rate or distribution volume across this population. Given the possibility of differences in adherence to the protocol by either subjects or the study site in sample collections, etc, clinical site was also tested as a covariate.

For continuous covariates, the effects of the covariates on PK parameter estimates were tested in the following model structures:

$$\begin{aligned} P_{TV} &= \theta_1 + \theta_2 * Cov \\ P_{TV} &= \theta_1 + \theta_2 * (Cov - Med_{cov}) \\ P_{TV} &= \theta_1 * (Cov / Med_{cov})^{\theta_2} \\ P_{TV} &= \theta_1 * \exp[\theta_2 * (Cov / Med_{cov})] \end{aligned}$$

where P_{TV} is the typical population estimate of a particular PK parameter, and θ_1 and θ_2 are fixed effect estimates for a corresponding covariate, Cov normalized by the median value of the covariate, Med_{cov} . Missing data were found in both weight and height covariates. A

naïve substitution approach [20] was carried out to simply replace the missing value with the median value based on sex.

IF (WT=0 and SEX=1) THEN WT=Med_{WT,Sex=Male}
 IF (WT=0 and SEX=2) THEN WT=Med_{WT,Sex=Female}

A common allometric function of scaling the PK parameters to the 0.75 power of body weight was also tested after the missing weight values were replaced.

$$P_{TV} = \theta_1 * (WT / Med_{WT})^{0.75}$$

Categorical variables such as sex, race and site were tested in the following model structure. Each category was evaluated in a separate fashion.

IF (Cov.EQ.1) THEN $P_{TV} = \theta_1$
 Else $P_{TV} = \theta_2$

For example, each ethnic group was divided into a category, African American=1, White=4 and Hispanic/Latinos=5. In this case, θ_1 and θ_2 are the population PK parameter estimates for African Americans and other races (White and Hispanic), respectively.

Model evaluation was based on a likelihood ratio test using the objective function value (OFV) from NONMEM. The change in the OFV returned by NONMEM is approximately equal to $-2 \times \log$ likelihood. The difference in $-2 \times \log$ likelihood between two models that are nested follows a χ^2 distribution. Covariates were added to the model in a step-wise addition fashion and remained in the final model if the OFV decreased by greater than 3.84 (p-value = 0.05, df=1). The final model was further examined using goodness-of-fit plots generating using R (Version 2.13) based on the conditional weight residual distribution and fitness of predicted versus observed sertraline concentrations in both population and individual levels.

RESULTS

Patient Characteristics

A total of 131 participants entered the trial with 67 randomized to sertraline and 64 to placebo. Only the concentration measurements taken from patients in the active treatment arm (n=67) were utilized for this analysis. An average of 1.7 sertraline concentration measurements per individual was available, and 5 of the measurements were found below the LLOQ. Seventeen individuals were removed from the analysis. Specifically, 16 individuals lacked sertraline concentration information at both weeks 4 and 12, and one individual had missing dosage information for both occasions. In the remaining 50 individuals, other single observations were removed as follows: 14 individuals only had a single sertraline concentration measurement from one of the two visits (non-measured visit removed). Of these 14 observations, 11 were missing a concentration measurement, 1 was missing a dosage time associated with a concentration sample, and 2 were missing dosage amount information associated with that concentration sample. The PPK analysis was conducted using the remaining 85 PK observations from 50 individuals.

As shown in Table 1, the median age of the patients was 75 (range: 53–89). There were 20 males and 30 females in the analysis broken down as follows: 18% African American; 72% White; and 10% Hispanic. This analysis included 4 patients with missing weight information and 9 with missing height information. The median values of weight or height without considering the missing values were 147 lb (range: 107–245) and 64 in (range: 57–72).

Population Pharmacokinetic Modeling

A 1-compartment model with first order absorption and elimination and an additive residual error model best described the sertraline data. The population parameter estimates of clearance and volume of distribution in the base model were 83.1 L/h and 6,620 L, respectively. Inter-individual variability (IIV) was estimated only for clearance because a significant correlation was found between clearance and volume of distribution. Patients at site C has plasma clearances approximately 49% lower than that seen in patients other at other clinical sites ($\chi^2 = 5.576$ df=1, $p < 0.05$). No other significant covariate relationships were found for clearance or volume of distribution. The population PK parameter estimates and goodness-of-fit plots for the final model are listed in Table 2 and supplementary Figure S1, respectively.

DISCUSSION

Nineteen percent of the variance in pharmacokinetic distribution of sertraline in these depressed AD patients was accounted for using a 1-compartment model. The population mean clearance and volume of distribution were 83.1 L/h and 6,620 L, respectively. As most patients in DIADS-2 were elderly (mean age of 75 years; range: 53–89), the mean elimination rate constant of 0.013 1/h is consistent with other literature reported values [13]. Compared to younger patients, the elderly have a longer sertraline half-life, but we found no difference between elderly healthy volunteers in the literature and these AD patients.

In our analysis, clearance estimates for the four patients with sertraline observations below the quantification limits were in the top 24% of all clearance estimates. Indeed, one patient with both observations below the quantification limit had a clearance value approximately three times higher than the typical population value. The cause of these high clearance values is not clear. Many possible factors might be considered, such as fasting, poor adherence, or genetic variance.

We also examined the effect of sex, race, age, weight, height and site on the variability of the PK parameter estimates. Previous publications have suggested that the average half-life is 1.5 times longer in women than in men [13]. We expected to detect an effect of gender on sertraline PK parameters; however, inclusion of sex as a covariate in our model yielded a statistically non-significant association. Possible differences between males and females were likely undetectable because of the small study population. In addition, a commonly reported correlation [21] between plasma clearance and body weight was not detected in this analysis.

Unexpectedly, the only covariate examined that affected PK variability was related to a single clinical site. Patients at site C had much lower clearance than other sites. This might be explained by the 3 high sertraline concentrations found in 2 patients out of a total of 9 observations from site C. Nineteen percent of the total variance in inter-individual on clearance was explained by incorporating the site as a covariate in this analysis. The model clearance estimates we present that exclude patients at the site C are likely more generalizable to the typical AD population. In conclusion, clinical site was a significant covariate contributing to the clearance change. The dosage regimen and administration

should be closely monitored in a multicenter study in order to avoid unnecessary exposures or incomplete treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support

Grant funding:

National Institute of Mental Health, 1U01MH066136, 1U01MH068014, 1U01MH066174, 1U01MH066175, 1U01MH066176, 1U01MH066177; NIMH scientific collaborators participated on the DIADS-2 Steering Committee.

Eli Lilly and Company through the Indiana Clinical and Translational Sciences Institute (CTSI)

Drug:

Sertraline and matching placebo provided by Pfizer, Inc.; Pfizer did not participate in the design or conduct of the trial; Manisha Hong, PharmD at Johns Hopkins Hospital Investigational Drug Service packaged and shipped drug

Steering Committee (responsibilities: study design and conduct)

Resource center representatives (voting):

Constantine Lyketsos, MD, MHS (study chair), Johns Hopkins School of Medicine, Baltimore

Barbara Martin, PhD (coordinating center former director), Johns Hopkins Bloomberg School of Public Health, Baltimore

George Niederehe, PhD (scientific collaborator), National Institute of Mental Health, Bethesda

Clinic directors (voting):

Paul Rosenberg, MD, Johns Hopkins School of Medicine, Baltimore

Jacobo Mintzer, MD, PhD, Medical University of South Carolina, Charleston

Daniel Weintraub, MD, University of Pennsylvania School of Medicine, Philadelphia

Anton Porsteinsson, MD, University of Rochester School of Medicine, Rochester

Lon Schneider, MD, University of Southern California Keck School of Medicine, Los Angeles

Other non-voting members:

Anne Shanklin Casper, MA, CCRP, Johns Hopkins Bloomberg School of Public Health, Baltimore

Lea Drye, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore

Crystal Evans, MS, Johns Hopkins School of Medicine, Baltimore

Curtis Meinert, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore

Cynthia Munro, PhD, Johns Hopkins School of Medicine, Baltimore

Peter Rabins, MD, MPH, Johns Hopkins School of Medicine, Baltimore

References

1. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2008; 23(2):170–177. [PubMed: 17607801]
2. Martin BK, Frangakis CE, Rosenberg PB, et al. Design of Depression in Alzheimer's Disease Study-2. *Am J Geriatr Psychiatry*. 2006; 14(11):920–930. [PubMed: 17068314]
3. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacology & Therapeutics*. 2000; 85:11–28. [PubMed: 10674711]
4. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009; 373(9665):746–58. [PubMed: 19185342]
5. Owen MJ, Morgan WN, Plott SJ, et al. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *JPET*. 1997; 283:1305–1322.
6. Warrington SJ. Clinical Implication of the pharmacology of sertraline. *Int Clin Psychopharmacol*. 1991; (Suppl 2):11–21. [PubMed: 1806626]
7. Kobayashi K, Ishizuka T, Shimada N, et al. Sertraline N-Demethylation is catalyzed by multiple isoforms of human cytochrome P-450 in vitro Drug metabolism and disposition. *DMD*. 1999; 27(7):763–766.
8. Sprouse J, Clarke T, Reynolds L, et al. Comparison of the effects of sertraline and its metabolite demethylsertraline on blockade of central 5-HT reuptake in vivo. *Neuropsychopharmacology*. 1996; 14:225–231. [PubMed: 8924190]
9. Muijsers RB, Plosker GL, Noble S. Sertraline: a review of its use in the management of major depressive disorder in elderly patients. *Drugs & Aging*. 2002; 19(5):377–92. [PubMed: 12093324]
10. Schneider LS, Nelson JC, Clary CM, et al. An 8-Week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. *Am J Psychiatry*. 2003; 160(7):1277–85. [PubMed: 12832242]
11. Axelson DA, Perel JM, Birmaher B, et al. sertraline pharmacokinetics and dynamics in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2002; 41:9.
12. Zoloft® product information. New York: Roeg. Division of Pfizer Inc; 2001. [http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/019839s053S054lbl.pdf]
13. Ronfeld RA, Tremaine LM, Wilner KD. Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. *Clin Pharmacokinet*. 1997; 32 (Suppl 1):22–30. [PubMed: 9068932]
14. Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer's disease. *Am J Geriatr Psychiatry*. 2010; 18(2):136–145.
15. Weintraub D, Rosenberg PB, Drye LT, et al. Sertraline for the treatment of depression in Alzheimer's disease: Week-24 outcomes. *Am J Geriatr Psychiatry*. 2010; 18(4):332–340.
16. Drye LT, Martin BK, Frangakis CE, et al. Do treatment effects vary among differing baseline depression criteria in depression in Alzheimer's disease study ± 2 (DIADS-2)? *Geriatric Psychiatry*. 2011; 26:573–583. [PubMed: 20672243]
17. Holford NHG: Wings for NONMEM. [<http://wfn.sourceforge.net/>]
18. Ahn JE, Karlsson MO, Dunne A, et al. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. 2008; 35:401–421.
19. Feng Y, Pollock BG, Ferrell RE, et al. Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. *Br J Clin Pharmacol*. 2006; 61:558–569. [PubMed: 16669849]
20. Yang, Y. Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0). [<http://support.sas.com/rnd/app/papers/multipleimputation.pdf>]
21. Mahmood I. Prediction of drug clearance in children: impact of allometric exponents, body weight, and age. *Ther Drug Monit*. 2007; 29(3):271–278. [PubMed: 17529882]

Research group

Resource centers (responsibilities: study administration)

Chairman's Office, Johns Hopkins School of Medicine, Baltimore:

Constantine Lyketsos, MD, MHS, chairman

Crystal Evans, MS, coordinator

Cynthia Munro, PhD, study neuropsychologist

Peter Rabins, MD, MPH

Krissi Boehmer, BA

Adrian Mosely, MSW

Dimitrios Avramopoulos, MD, PhD

Coordinating Center, Johns Hopkins Bloomberg School of Public Health, Baltimore

Curtis Meinert, PhD, director

Barbara Martin, PhD, former director

Lea Drye, PhD, epidemiologist

Constantine Frangakis, PhD, biostatistician

Anne Shanklin Casper, MA, CCRP, coordinator

Vijay Vaidya, MPH

Jill Meinert

Project Office, National Institute of Mental Health, Bethesda

George Niederehe, PhD, scientific collaborator

Jovier Evans, PhD, project officer

Joanna Chisar, RN

Louise Ritz, MBA

Elizabeth Zachariah, MS

Clinics (responsibilities: data collection)

Johns Hopkins School of Medicine, Baltimore:

Paul Rosenberg, MD, director

Ann Morrison, RN, PhD, coordinator

Crystal Evans, MS
Pramit Rastogi, MD, MPH
Krissi Boehner, BS
Chiadi Onyike, MD
Medical University of South Carolina, Charleston
Jacobco Mintzer, MD, PhD, director
Crystal Longmire, PhD, coordinator
Warachal E. Faison, MD
Martie Hatchell, RN
Marilyn Stuckey, RN
University of Pennsylvania School of Medicine, Philadelphia
Daniel Weintraub, MD, director
Ira Katz, MD, PhD, former director
Trisha Stump, RN, coordinator
Joel Streim, MD
Suzanne DiFilippo, RN
Kate O'Neill
University of Rochester School of Medicine, Rochester
Anton Porsteinsson, MD, director
Bonnie Goldstein, RN, coordinator
Jeanne LaFountain, RN
Colleen McCallum, MSW
Laura Jakimovich, MNS
Kim Martin
Margaret McGrath, RN
University of Southern California Keck School of Medicine, Los Angeles:
Lon Schneider, MD, director
Sonia Pawluczyk, MD
Karen Dagerman, MS

Randall Sanabria

Liberty Teodoro, RN

Yanli Wang, MS

Ju Zhang

Liberty Teodoro

Table 1

Patient demographics

	N (%)	Mean (SD)	Median(range)
Sample size	50		
Number of observations	85		
Gender			
Male	20 (40)		
Female	30(60)		
Race			
Black/African American	9 (18)		
White	36 (72)		
Hispanic/Latino	5 (10)		
Clinical sites			
JHU	15 (30)		
MUSC	11 (22)		
PENN	6 (12)		
ROCH	8(16)		
USC	10(20)		
Baseline Age (years)		75 (7.76)	76 (53–89)
Baseline Weight (lb) Without 4 missing values		159 (37.08)	147 (107–245)
Baseline Height (In) Without 9 missing values		64 (4.45)	64 (57–72)
Sertraline dose administered (mg)		92.47 (18.62)	100 (25–100)
Sertraline concentrations (ng mL ⁻¹) Without 5 BQL values		62.94 (47.62)	49 (9–229)

Table 2

Population pharmacokinetic parameter estimates of sertraline in the final model

Parameters	Population estimate (% SE)	Inter-individual variability (% SE)
CL _{site=C} , L/h	43.8(34)	59.33% (31.3)
CL _{site=others} , L/h	89.1(12.2)	59.33% (31.3)
V, L	6470(70.5)	
Ka, 1/h (fixed)	0.5	
Residual variability	19.6 ng/mL (11.6)	

CL_{site=C}; clearance from site C; CL_{site=others}; clearance from other clinical sites V, Volume of distribution; Ka, rate of absorption; SE, standard error