Sertraline Pharmacokinetics in HIV-Infected On ARV and Uninfected Youth

Nathan Hanan[1], Mary Paul[2], Yanling Huo[3], Edmund Capparelli[1], Suad Kapetanovic[4], JL Ariansen[5], Elizabeth Smith[6], Pim Brouwers[7], Brookie M. Best[1], IMPAACT P1080 Protocol Team

[1]University of California, San Diego, San Diego, CA, USA, [2]Baylor College of Medicine, Houston, TX, USA, [3]Harvard School of Public Health, Boston, MA, USA, [4]University of Southern California, Los Angeles, CA, USA, [5]FHI 360, Durham, NC, USA, [6]NIH National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [7]NIH National Institute of Mental Health, Rockville, MD, USA

Nathan J. Hanan
University of California, San Diego
9500 Gilman Drive, MC 0641
La Jolla, CA 92093-0641
E-mail: nhanan@ucsd.edu

P810

Abstract

Background. Antidepressant sertraline (SRT) is an SSRI eliminated by hepatic metabolism by cytochrome P450 (CYP) enzymes: 2B6, 2D6, 2C9, 2C19 and 3A4, glucuronyl transferases, and monoamine oxidase A & B. SRT is often titrated to effectiveness. Due to comorbidities and interactions, the appropriate starting dose and titration range may require adjustment in pediatrics. This is the first report of SRT pharmacokinetics (PK) in HIV-1 infected youth.

Methods. IMPAACT P1080 is a multicenter, pilot study to describe PK of psychiatric medications prescribed in youth. Target enrollment was 45 subjects >6 to <25 years per arm: 15 uninfected (HIV-), 15 HIV-1 infected on a ritonavir-boosted protease inhibitor (PI/r), and 15 HIV-1 infected on efavirenz (EFV). Six PK samples were collected: pre-dose, 2, 4, 6, 12 and 24-hours post-dose. A validated LC-MS/MS method quantitated SRT and its metabolite N-desmethylsertraline (D-SRT) in plasma. CYP2D6 activity was assessed by urinary dextromethorphan/dextrorphan (DXMO/DXO) ratio using LC-MS/MS. Noncompartmental methods estimated PK parameters, and HIV- and PI/r cohorts were compared by the Wilcoxon rank-sum test, two-sided with significance set to $p<0.05$.

Results. Final results included 31 participants who completed PK visits (16 HIV-, 12 PI/r, and 3 EFV). The median (range) values for weight, age, and dose were 69.5 (31.5-118.2) kg, 21.8 (9.1-24.7) years, and 75 (12.5-150) mg once daily. SRT exposure was highest for HIV- and lowest for EFV cohort. $AUC_{0\text{-}24}$, C_{24}, C_0 and C_{min} were significantly higher in HIV- compared to PI/r (Table 1). Oral clearance (dose-independent) did not differ significantly between cohorts, whereas the DXMO/DXO ratio was significantly higher in HIV- compared to PI/r cohorts. Two HIV- participants were CYP2D6 poor metabolizers (log(DXMO/DXO) of > -0.5). Participants in the EFV cohort had markedly higher oral clearance and lower sertraline exposures than HIV- and PI/r. However, accrual was too low to include in statistical comparisons.

Conclusions. HIV- participants had the highest SRT exposure compared to HIV-infected cohorts, potentially from higher daily doses. Differences between SRT exposure in HIV- and PI/r participants appear modest and unlikely to have a large impact on dose titration. Although greater in magnitude, the potential impact of EFV on SRT needs further investigation due to limited numbers of EFV participants.

Introduction

- The lifetime prevalence of major depression in patients with HIV has been estimated at 22-45%, far exceeding what is seen in the general population.[1]
- Children infected with HIV are twice as likely to use psychiatric medications as uninfected children.[2]
- SRT is often titrated to effectiveness. However, the typical starting dose and titration range may need to be adjusted in HIV youth to produce exposures that are both safe and effective.
- This is the first report of SRT PK among HIV-infected children and adolescents.

Objectives

Primary. To describe the pharmacokinetics of SRT currently prescribed in HIV-infected and uninfected children and adolescents

Secondary.

•To compare SRT exposure between HIV- infected vs. uninfected children.

•To compare SRT PK in HIV-infected taking RTV vs. EFV vs. Uninfected (no ARVs).

Methods

•IMPAACT P1080 is an observational pilot study of psychiatric and antiretroviral medication concentrations in HIV-1 infected and uninfected children and adolescents

➢The sertraline arm of this study enrolled subjects taking FDA-approved doses of sertraline for clinical care from 20 national sites into three strata: (1) HIV-uninfected subjects (HIV-), (2) HIV-infected subjects taking a concomitant efavirenz (EFV)-based antiretroviral regimen, and (3) HIV-1 infected subjects taking a concomitant ritonavir-boosted protease inhibitor (PI/r) regimen.

•Pharmacokinetic samples were drawn pre-, 2, 4, 6, 12, and 24 hours post-dose.

•Sertraline was assayed by liquid chromatography-mass spectrometry, with a lower limit of quantification of 1 ng/mL.

•Raw sertraline plasma concentrations were normalized (corrected) to a dose of 100 mg once daily and a weight of 70 kg.

•Metabolic CYP2D6 phenotyping was assessed by measuring the dextromethorphan/dextrorphan (DMXO/DXO) ratio in urine following an FDA-approved dose of DMXO.

•Urine was collected and pooled from pre-dose (t=0) to 4 hours post-dose.

Results

- SRT exposure (Table 1.) and SRT concentrations (Fig. 1.) were highest for HIV- and lowest for EFV cohort.
- $AUC_{0\text{-}24}$, C_{24}, C_0 and C_{min} were significantly higher in HIV- compared to PI/r (Table 1.)
- Oral clearance did not differ significantly between HIV- and PI/r cohorts.
- CYP2D6 activity (DXMO/DXO) was significantly higher in the PI/r compared to HIV-

Table 1. Sertraline Pharmacokinetic Parameters, Median (IQR)[1]

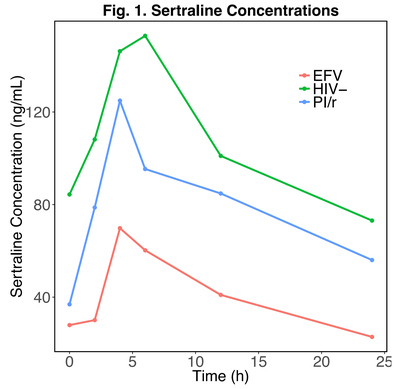
Parameter	HIV- n = 16	PI/r n = 12	p value[2]	EFV n = 3
Daily Dose (mg/kg)	1.3 (0.9, 1.5)	0.9 (0.7, 1.4)	0.24	0.7 (0.5, 1.6)
$AUC_{0\text{-}24}$ (ng*hr/mL)	865 (548, 1310)	450.6 (365, 616)	0.04	245 (196, 265)
Norm-$AUC_{0\text{-}24}$ (ng*hr/mL)[3]	1439 (738, 1814)	732 (560, 905)	0.11	553 (292, 573)
C_0 (ng/mL)	20.1 (12.6, 39.7)	10.0 (7.5, 15.9)	0.03	6.0 (3.0, 7.0)
C_{max} (ng/mL)	46.7 (36.5, 90.1)	34.3 (23.6, 41.7)	0.09	13.2 (8.8, 22.1)
T_{max} (hr)	4 (4, 6)	4 (4, 6)	1.00	6 (4, 6)
C_{24} (ng/mL)	17.5 (14.3, 40.1)	12.6 (8.6, 18.9)	0.07	4.2 (2.9, 5.9)
C_{min} (ng/mL)	14.5 (12.5, 35.6)	9.1 (6.7, 12.8)	0.02	4.0 (2.9, 5.9)
CL/F (L/hr/kg)	1.3 (0.9, 2.4)	1.8 (1.3, 2.2)	0.44	3.4 (1.7, 11.1)
$T_{1/2}$ (hr)	26.4 (14.1, 35.3)	18.1 (12.5, 23.1)	0.28	11.1 (10.2, 20.7)
D-SRT/SRT Ratio	1.5 (1.2, 1.7)	1.2 (0.7, 1.5)	0.13	2.2 (2.1, 2.6)
Log(DXMO/DXO)[4]	-2.3 (-3.0, -0.6)	-4.3 (-4.8, -3.8)	0.01	-2.35

[1]For the EFV cohort, median and range are reported
[2]p values calculated using the Wilcoxon rank-sum test for HIV- and PI/r comparisons.
[3]$AUC_{0\text{-}24}$ normalized to a 100 mg once daily dose and a weight of 70 kg.
[4]Urine DXMO/DXO ratio was measured in 12 HIV-, 6 PI/r, & 1 EFV.

Results Continued

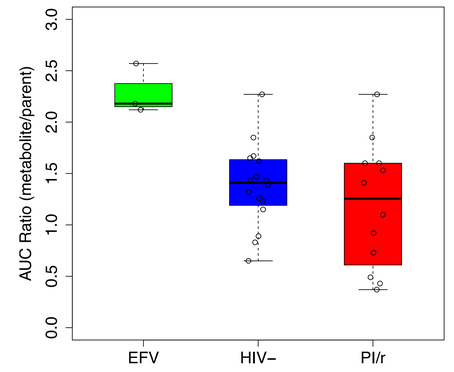
- Two HIV- participants were CYP2D6 poor metabolizers (log(DXMO/DXO) of > -0.5)
- The ratio of metabolite (D-SRT) to parent (SRT) was highest in the EFV group, while HIV- and PI/r cohorts had similar values (Table 1 & Fig. 2.).
- Participants in the EFV cohort had markedly higher oral clearance and lower sertraline exposures than HIV- and PI/r. However, accrual was too low to include in statistical comparisons.

Fig. 1. Sertraline Concentrations



Sertraline concentrations were normalized to a dose of 100 mg and weight of 70 kg

Fig. 2. AUC Ratio



Ratio of desmethylsertraline (metabolite) AUC(0-24) to sertraline (parent) AUC(0-24)

Conclusions

- HIV- patients had the highest SRT exposure compared to HIV-infected cohorts.
- Differences between SRT exposure in HIV- and PI/r participants appear modest and unlikely to have a large impact on dose titration.
- Although greater in magnitude, the potential impact of EFV on SRT needs further investigation due to limited numbers of EFV participants.

References

1. Penzak SR, Reddy YS, Grimsley SR. 2000. Depression in patients with HIV infection. Am J Health Syst Pharm 57:376 –389.
2. Chernoff M, Nachman S, Williams P, Brouwers P, Heston J, Hodge J, Di Poalo V, Deygoo NS, Gadow KD; IMPAACT P1055 Study Team. Mental health treatment patterns in perinatally HIV-infected youth and controls. Pediatrics. 2009 Aug;124(2):627-36.

Acknowledgements

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We thank the patients and their families, the study team and the site personnel for their dedication to this project.

Poster presented at the Conference on Retroviruses and Opportunistic Infections (CROI); February 13-16, 2017; Seattle, Washington, USA.