Published in final edited form as:

Cardiol Young. 2016 February ; 26(2): 354–362. doi:10.1017/S1047951115000359.

Pharmacokinetics of Intravenous Sildenafil in Children with Palliated Single Ventricle Heart Defects: Effect of Elevated Hepatic Pressures

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Abstract

Aims—Sildenafil is frequently prescribed to children with single ventricle heart defects. These children have unique hepatic physiology with elevated hepatic pressures which may alter drug pharmacokinetics. We sought to determine the impact of hepatic pressure on sildenafil pharmacokinetics in children with single ventricle heart defects.

Methods—A population pharmacokinetic model was developed using data from 20 single ventricle children receiving single dose intravenous sildenafil during cardiac catheterization. Nonlinear mixed effect modeling was used for model development and covariate effects were evaluated based on estimated precision and clinical significance.

Results—The analysis included a median (range) of 4 (2–5) pharmacokinetic samples per child. The final structural model was a two-compartment model for sildenafil with a one-compartment model for des-methyl-sildenafil (active metabolite), with assumed 100% sildenafil to des-methyl-sildenafil conversion. Sildenafil clearance was unaffected by hepatic pressure (clearance = 0.62 L/H/kg); however, clearance of des-methyl-sildenafil (1.94 × (hepatic pressure/9)$^{-1.33}$ L/h/kg) was predicted to decrease ~7 fold as hepatic pressure increased from 4 to 18 mm Hg. Predicted drug exposure was increased by ~1.5 fold in subjects with hepatic pressures ≥ 10 mm Hg versus < 10 mm Hg (median area under the curve = 533 μg*h/L versus 792 μg*h/L).

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CONFLICTS OF INTEREST:

None

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the United States guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional review board of Duke University Medical Center.

Clinicaltrials.gov identifier: NCT01169519

Discussion—Elevated hepatic pressure delays clearance of the sildenafil metabolite, des-methyl-sildenafil and increases drug exposure. We speculate that this results from impaired biliary clearance. Hepatic pressure should be considered when prescribing sildenafil to children. These data demonstrate the importance of pharmacokinetic assessment in patients with unique cardiovascular physiology that may affect drug metabolism.

Keywords

single ventricle; sildenafil; pharmacokinetics; hepatic dysfunction

INTRODUCTION

Population pharmacokinetics refers to the study of drug kinetics in target populations with unique pathophysiology that might affect the drug dose-concentration relationship.[1] Children with palliated single ventricle heart defects have very unique physiology including a propensity for elevated venous/hepatic pressures with associated hepatic congestion. These factors may alter drug pharmacokinetics, particularly for drugs undergoing hepatic metabolism and therefore these patients represent an ideal population for population pharmacokinetic assessment.[2–7]

Sildenafil is a phosphodiesterase type-5 inhibitor that is often used to lower pulmonary vascular resistance in children and adults with single ventricle heart defects.[8–11] Sildenafil undergoes predominantly hepatic metabolism (cytochrome P450 3A4 [major route] and cytochrome P450 2C9 [minor route]) and is converted to an active metabolite, des-methyl-sildenafil, which has approximately 50% of the *in vitro* potency for phosphodiesterase type-5 as the parent drug.[12] In adult patients with hepatic congestion secondary to pulmonary arterial hypertension or hepatic dysfunction (e.g. cirrhosis), sildenafil clearance is reduced by 50–80% with effects on clearance of both sildenafil and des-methyl-sildenafil.[13] Although single ventricle patients frequently demonstrate hepatic dysfunction and congestion, no prior studies have evaluated sildenafil pharmacokinetics in single ventricle patients. Sildenafil dosing in children has been the source of recent controversy after the “sildenafil in Treatment-Naive Children, Aged 1–17 Years, with Pulmonary Arterial Hypertension” (STARTS) trials demonstrated increased mortality in children with pulmonary hypertension randomized to medium or high dose sildenafil when compared to low dose therapy.[14,15]

In the present study we sought to determine the pharmacokinetics of intravenous sildenafil in children with surgically palliated single ventricle heart defects. We tested the hypothesis that clearance of sildenafil and des-methyl-sildenafil would be directly related to surgical stage and hepatic pressures.

MATERIALS AND METHODS

Study Population

The study design, samples analysis (limits of quantification = 0.05 μg/L) and detailed cohort demographics have been previously described.[16,17] Briefly, blood samples were collected as part of a prospective dose escalation pharmacokinetic and hemodynamic efficacy study of intravenous sildenafil. Children ages 6 months – 10 years and status post stage II or stage III single ventricle surgical palliation and undergoing electively scheduled cardiac catheterization were eligible for inclusion. Children with significant hepatic dysfunction defined as either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ two times the upper limits of normal were excluded from participation. Dosing groups included 0.125 mg/kg (n=2), 0.25 mg/kg (n=5), 0.35mg/kg (n=8) and 0.45 mg/kg (n=5). The study was approved by the Duke University Medical Center Institutional Review Board and written informed consent for trial participation was obtained from the parent or guardian of each study subject.

Population PK model development

Sildenafil and des-methyl-sildenafil concentration-time data were analyzed using nonlinear mixed effects modeling with Phoenix NLME 1.2 software (Certara, St. Louis, MO) using the first order conditional estimation with interaction algorithm. One, two, and three-compartment structural pharmacokinetic models for sildenafil and des-methyl-sildenafil, 100% conversion of sildenafil to des-methyl-sildenafil (represented by clearance sildenafil to des-methyl-sildenafil) or <100% conversion (represented by clearance sildenafil to des-methyl-sildenafil in addition to a sildenafil elimination clearance parameter), and proportional versus proportional plus additive residual error models were explored.

Random effects on structural model parameters were considered supported by the data if shrinkage was <30% and condition number was <1000. Weight was included *a priori* as covariates for structural model parameters, using a fixed (3/4 or 1) or estimated exponent. Diagnostic plots used for model evaluation included the following: observed versus population predicted concentration and versus individual predicted concentration; conditional weighted residuals versus population predicted concentration and versus time after last dose; random effects and conditional weighted residuals histograms; and observed versus population predicted and individual predicted concentrations by patient. In addition, precision of parameter estimates and objective function values were used to assess model goodness-of-fit.

Once the base model was selected, covariates were investigated for their influence on pharmacokinetic parameters. Continuous covariates evaluated were age, weight, cardiac index (calculated from catheterization data at the time of sildenafil administration), serum creatinine, and hepatic pressure (directly measured at the time of sildenafil administration) and were centered around the median. Categorical covariates included surgical stage, race, and sex. In the final model, comparisons were made between subjects with hepatic pressures ≥ 10mm Hg versus those with hepatic pressures < 10mm Hg based on an *a-priori* estimation of the approximate cutpoint for abnormal hepatic (central venous) pressures in children of similar age. Inter-individual variability estimates in pharmacokinetic parameters were plotted against covariates, and those with a discernible physiologic and graphical relationship were evaluated for inclusion in the final model. The threshold for significance of a single covariate was reduction of the objective function by >3.84 ($p < 0.05$). A forwardaddition ($p = 0.05$), backward-elimination ($p = 0.01$) approach to covariate selection was planned for use if more than one covariate were found to be significant.

Model evaluation

Base and final model performance was evaluated based on successful minimization, goodness-of-fit plots, and precision of parameter estimates. The final model was further evaluated with bootstrap procedures and visual predictive check. The precision of the final population pharmacokinetic model parameter estimates were evaluated using nonparametric bootstrapping (1,000 replicates) to generate the 95% confidence intervals for parameter estimates. For the visual predictive check, the final model was used to generate 1,000 Monte Carlo simulation replicates of sildenafil exposure, and simulated results were compared with those observed in the study. The number of observed concentrations outside the 90% prediction interval for each time point was quantified.

Dose-exposure assessment

Individual pharmacokinetic parameters from the final model were used to simulate sildenafil and des-methyl-sildenafil concentration-time profiles after a single dose. Using Phoenix WinNonlin 6.3 software and simulated concentration-time profiles, elimination rate constants were calculated from linear regression of log concentration versus time in the elimination phase, area under the curve was calculated using the trapezoidal rule and linear up log down method, and elimination half-life ($t_{1/2}$) was calculated as ln(2)/elimination rate constant assuming linear kinetics. As des-methyl-sildenafil has 50% activity compared to sildenafil, combined area under the curve was calculated as: (sildenafil area under the curve) + ([des-methyl-sildenafil area under the curve]/2).

RESULTS

Twenty children were enrolled in the study. Indications for cardiac catheterization included: pre-Fontan evaluation (n=9), hemodynamic assessment secondary to relative cyanosis (n=3), pulmonary artery evaluation (n=4), poor function by echocardiogram (n=2), aortic arch evaluation (n=1) or suspected high pulmonary vascular resistance (n=1). Demographic features and physiologic parameters are summarized by dosing group in Table 1.

Overall, 140 samples (73 sildenafil and 67 des-methyl-sildenafil) were above the limits of quantification (0.05 μg/L) and 20 (7 sildenafil, 13 des-methyl-sildenafil) were below. One outlier peak sildenafil concentration and all samples below the limits of quantification were excluded. Thus, the analysis included 72 sildenafil and 67 des-methyl-sildenafil samples from 20 children. The median (range) number of sildenafil and des-methyl-sildenafil samples per child was 4 (2–5) and 3.5 (2–5). The median (IQR) sildenafil and des-methyl-sildenafil sampling times for the 1st, 2nd, 3rd, 4th and 5th samples were 20 (20, 20) min, 60 (43, 64) min; 1.9 (1.4, 3.0) hours, 4.1 (1.8, 5.1) hours and 18.8 (17.3, 20.8) hours after dose, respectively. Concentration-time profiles stratified by surgical stage are shown in Figure 1. The median (range) sildenafil and des-methyl-sildenafil concentrations were 106 (1.59–775) and 16.6 (1.08 – 96.2) μg/L, respectively.

Population pharmacokinetic model development

Figure 2 summarizes the final structural model which was a two-compartment model for sildenafil, one-compartment model for des-methyl-sildenafil, with assumed 100% sildenafil to des-methyl-sildenafil conversion, and metabolite clearance from the body represented by des-methyl-sildenafil clearance. The data only supported the addition of inter-individual variability parameters for sildenafil to des-methyl-sildenafil conversion and des-methyl-sildenafil clearance (i.e. shrinkage <30%). Body weight was included as a covariate for all base model parameters; addition of an allometric scaling (exponent = ¾) was not included as it did not improve the model fit (decrease in objective function value of −1.7).

Data describing model building steps and model evaluation are included in the on-line supplement. In the base model, surgical stage demonstrated a suggestive graphical relationship to inter-individual variability for conversion of sildenafil to des-methyl-sildenafil. Gender, surgical stage and mean hepatic pressure demonstrated a suggestive graphical relationship for inter-individual variability for des-methyl-sildenafil clearance (Supplementary Figure 1). By univariable screen, mean hepatic pressure and surgical stage were significant covariates for des-methyl-sildenafil clearance; after inclusion of hepatic pressure, no additional covariates were significant (Supplementary Figure 2 and Supplementary Table 1). Body weight was used as a covariate for all final model parameters. The final model demonstrated adequate goodness-of-fit with no significant deviation from the unity line for sildenafil model-predictions versus observed concentrations and no significant deviation from zero for residuals (Supplementary Figure 3A–D). There was under-prediction of the highest des-methyl-sildenafil concentrations found in surgical stage 3 children (Supplementary Figure 4A–B), and absence of bias in residuals (Supplementary Figure 4C–D).

Model evaluation—The number of observed concentrations outside the visual predictive check 90% prediction interval for sildenafil and des-methyl-sildenafil were 6/72 (8%) and 8/67 (12%) respectively, indicating good model predictive performance (Supplementary Figure 5). Relative standard errors of bootstrapped parameter estimates were <20%, and the percent difference between model and bootstrapped median parameter estimates was ≤5% (with the exception of the correlation coefficient), indicating precise estimation of population model parameters (Supplementary Table 2).

Dose-exposure assessment—Individual Bayesian parameter estimates are included in Table 2. As suggested by the final model, clearance of des-methyl-sildenafil was decreased and des-methyl-sildenafil half-life ($t_{1/2}$) increased in children with HP ≥10 mm Hg. Following a single dose of 0.35 mg/kg and using individual Bayesian PK parameter estimates, predicted area under the curve for sildenafil, des-methyl-sildenafil and combined for the study population increased with increasing HP (Figure 3A–C). Median (range) predicted combined area under the curve was 533 μg*h/L [284 – 1046] and 792 μg*h/L [417 – 1431] (~1.5-fold difference) for children with hepatic pressure <10 mm Hg and ≥10 mm Hg, respectively. Following the same single dose of 0.35 mg/kg in children with hepatic pressure <10 mm Hg and 0.25 mg/kg in children with HP >10 mm Hg, median (range) predicted AUC_{TOTAL} was similar between dose groups (533 μg*h/L [284 – 1046] and 565 [298 – 1022] μg*h/L, respectively [Figure 3D–F]).

DISCUSSION

This is the first population pharmacokinetic analysis of intravenous sildenafil in children and the first population pharmacokinetic analysis of any kind in children or adults with palliated single ventricle heart defects. These patients have very unique physiology often demonstrating chronically elevated central venous pressures and secondary hepatic congestion.[4–6] We demonstrate delayed clearance of the active sildenafil metabolite, des-methyl-sildenafil, with a direct relationship to increased hepatic pressures. The consequences are potentially clinically important with an estimated 1.5-fold increase in drug exposure (area under the curve) in subjects with hepatic pressures ≥ 10 mm Hg when compared to those with hepatic pressures < 10 mm Hg.

The only previous study of intravenous sildenafil in the pediatric population focused on term neonates with persistent pulmonary hypertension of the newborn, demonstrating typical clearance and volume of distribution at steady state (central + peripheral) for a three day old neonate of 0.54 L/h/kg and 7.8 L/kg, respectively.[18] Studies in adults with pulmonary hypertension have reported approximate weight-normalized clearance of 0.38 – 0.59 L/h/kg with, a half-life of 2.2 – 3.9 h.[19–21] The sildenafil value of 0.62 L/h/kg reported in this study is similar to clearance values in the healthy adult (0.59 L/h/kg) and neonatal studies (0.54 L/h/kg). Based on allometric scaling, we anticipated higher weight-normalized clearance values in children relative to adults. However, the altered physiology and morbidity related to single ventricle physiology may result in the lower than expected sildenafil clearance that we observed.

Interestingly, we detected a covariate effect of increased hepatic pressure on clearance of des-methyl-sildenafil, but not for clearance of sildenafil itself. According to the model, for a child of given weight, des-methyl-sildenafil clearance is predicted to decrease ~7 fold as hepatic pressure increases from 4 to 18 mm Hg. We hypothesize that increased hepatic pressure selectively impaired des-methyl-sildenafil clearance as a result of decreased biliary clearance. In mouse, rat, and dog, des-methyl-sildenafil is excreted to bile and found in feces, while sildenafil is cleared primarily by metabolism.[12,22] Potentially selectively impaired des-methyl-sildenafil clearance due to increased hepatic pressure could be explained by unimpaired access of sildenafil to sites of metabolism in hepatocytes, but impaired des-methyl-sildenafil clearance through bile (secondary to increased hepatic pressure). This is consistent with a study in adults comparing oral sildenafil kinetics in subjects with and without liver cirrhosis. Cirrhotic subjects demonstrated reduced metabolism and clearance of both sildenafil and des-methyl-sildenafil but the effect was more substantial for des-methyl-sildenafil (48% reduction in clearance for des-methyl-sildenafil versus 24% for sildenafil).[13] Potentially sildenafil clearance was unaffected in the present study because hepatic blood flow is not sufficiently affected in the range of hepatic pressure in our study cohort. Sildenafil is an intermediate to high extraction ratio drug with clearance of 41 L/h following intravenous administration in healthy adults[19], compared to typical liver blood flow of 90 L/h. As such, we would expect sildenafil clearance to be potentially impacted only if increased hepatic pressure resulted in significantly decreased liver blood flow. However the small sample size could also play a role in our inability to detect a relationship between sildenafil clearance and elevated hepatic pressure. Also, none of our subjects demonstrated overt liver dysfunction as we excluded those with levels of either AST or ALT ≥ twice the upper limits of normal and only two study subjects demonstrated a value for either AST or ALT that was outside the normal reference range.

It is notable that inclusion of surgical stage in addition to hepatic pressures did not significantly change our overall model. Stage III surgical palliation significantly alters venous physiology, typically raising central venous and hepatic pressures.[2,8] However stage II patients can demonstrate elevated hepatic pressures as a result of impaired ventricular diastolic function and our results indicate that in these patients, sildenafil dosing should be adjusted to account for reduced clearance. These findings have broader implications for both children and adults with pulmonary hypertension where central venous and hepatic pressures may also be substantially elevated. Potentially sildenafil dosing in these patients might also require adjustment based on degree of elevation in hepatic pressures.

Beyond clearance, volume of distribution and half-life are also critical determinants of drug kinetics. Sildenafil is likely distributed to tissues and our data demonstrate a similar volume of distribution relative to adults. In previous studies in healthy adults, volume of distribution has been reported as ~105 L[21], compared to typical total body water of approximately 42 L. Weight-normalized total volume of distribution in the present study (1.81 L/kg) was within 20% of volume of distribution reported in the above adult studies (~1.5 L/kg), but was ~5-fold lower than reported in neonates.[18] This finding is consistent with elevated total body water in neonates relative to children and adults. Similarly the sildenafil half-life reported in this study (median 2.9 h) is also within the range observed in healthy adults (2.2 – 3.9 h) but is substantially below that reported for neonates (48–56 h). Consistent with the association of increased hepatic pressure and reduced des-methyl-sildenafil clearance found in this study, des-methyl-sildenafil half-life in this study (median 3.3 h) was prolonged relative to healthy adults (2.3 h).[19]

Overall our pharmacokinetic data demonstrate the critical importance of population-specific pharmacokinetic assessment, particularly in patients with unique physiology that may affect drug metabolism. Population pharmacokinetic using sparse sampling methodologies have been widely applied to other patient populations but have not been commonly used in children with heart disease.[23–26] Single ventricle patients are increasingly treated with sildenafil to lower pulmonary vascular resistance.[8–11] We have previously demonstrated that intravenous sildenafil acutely improves pulmonary blood flow and cardiac output in these patients, while others have demonstrated that sildenafil improves exertional tolerance and myocardial performance.[16,17,27,28] However, there are important safety concerns associated with sildenafil drug accumulation in children. The STARTS trial demonstrated increased mortality associated with medium or high dose oral sildenafil when compared to low dose therapy.[15] These findings prompted the U.S. Food and Drug Administration to issue a safety warning recommending against use of sildenafil in children.[29] This regulatory action has been contentious and the European Medicines Agency reviewed the same data yet approved sildenafil for pediatric use at low doses (10mg three times daily for patients < 20kg and

20mg three times daily for patients > 20kg).[30] Despite difficulties in interpreting the STARTS trial results, the findings highlight the critical importance of dosing adjustments in populations with delayed sildenafil clearance.

Although our study focused on intravenous sildenafil, if our hypothesized mechanism of reduced biliary clearance of des-methyl-sildenafil is accurate, then findings may also apply to oral dosing. In healthy adults, oral sildenafil is well absorbed but undergoes significant first pass metabolism with a reported bioavailability ranging from 25%–63%.[22] Peak levels are seen 30 – 120 minutes (median 60min) after oral dosing (versus 20min after intravenous dosing in the present study) and the recommended intravenous dose is half the oral dose. Our data suggest that a child with significantly elevated Fontan pressures receiving “low dose” oral sildenafil could be exposed to drug levels (combined sildenafil + des-methyl-sildenafil) corresponding to higher doses. Reassuringly in the STARTS trial, mortality was increased only in the subset of children with idiopathic pulmonary hypertension. There are limited data for comparison of sildenafil clearance and volume between similar populations after oral and intravenous doses and PK and longer term efficacy studies are needed to evaluate both oral and intravenous sildenafil in Fontan subjects.

There are important limitations to this analysis. The sample size was relatively small and because this study was conducted in children, we employed a sparse sampling strategy with a median of 4 sildenafil samples per child. Sparse sampling is considered an appropriate approach to PK analysis in children where blood draws must be limited and we used a sampling and population PK approach that has been endorsed by both the U.S. FDA and the EMA.[23–26,31,32] Another limitation is that the study population included patients with differing surgical anatomy (approximately half were status post stage II surgery and the remainder status post stage III surgery). Surgical stage uniquely affects physiology, however we did not detect a covariate effect of surgical stage on pharmacokinetic parameters during model development, after accounting for hepatic pressures. Finally, a two compartment model for sildenafil and one compartment model for des-methyl-sildenafil described the data appropriately, with precise model parameters (model estimates nearly identical to bootstrap estimates) and good model performance (good overlap of observed and simulated data on visual predictive checks). However, there was under prediction of the highest observed des-methyl-sildenafil concentrations, occurring in stage III children. This likely resulted from the inability to incorporate inter-individual variability in volume of distribution of des-methyl-sildenafil in this model.

In conclusion, the major findings of this analysis include similar weight normalized sildenafil clearance in children with palliated single ventricle heart defects when compared to healthy adult subjects and neonates. Volume of distribution and half-life were also similar to healthy adults, but when compared to neonates, volume of distribution was almost five-fold lower resulting in a much shorter half-life of 2.9 hours (versus 48–56 hours for neonates). Notably we demonstrate an inverse relationship between hepatic pressure and clearance of des-methyl-sildenafil with estimated exposures approximately 50% greater in those with hepatic pressures ≥ 10mm Hg when compared to children with hepatic pressures < 10mm Hg. These data highlight the critical importance of pharmacokinetic analyses in patient populations with unique physiology, particularly because higher doses of sildenafil have been associated with increased mortality in previous studies in children. In our opinion there is a critical need for PK, and longer-term safety and efficacy studies in single ventricle patients for sildenafil as well as other drugs that undergo hepatic metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None

FINANCIAL SUPPORT: KDH, JSL and MCW receive support from the NIH-funded Duke Clinical and Translational Science Award (UL1TR001117). KDH and MCW receive salary support from the Department of Health and Human Services Food and Drug Administration (1UO1FD004858-01). MCW receives support from the U.S. National Institutes of Health. MRS was supported by training grant T32GM086330 from the National Institute of General Medical Sciences. This study was partially funded by an investigator-initiated research grant from Pfizer Incorporated, with additional funding provided by the Duke University Department of Pediatrics.

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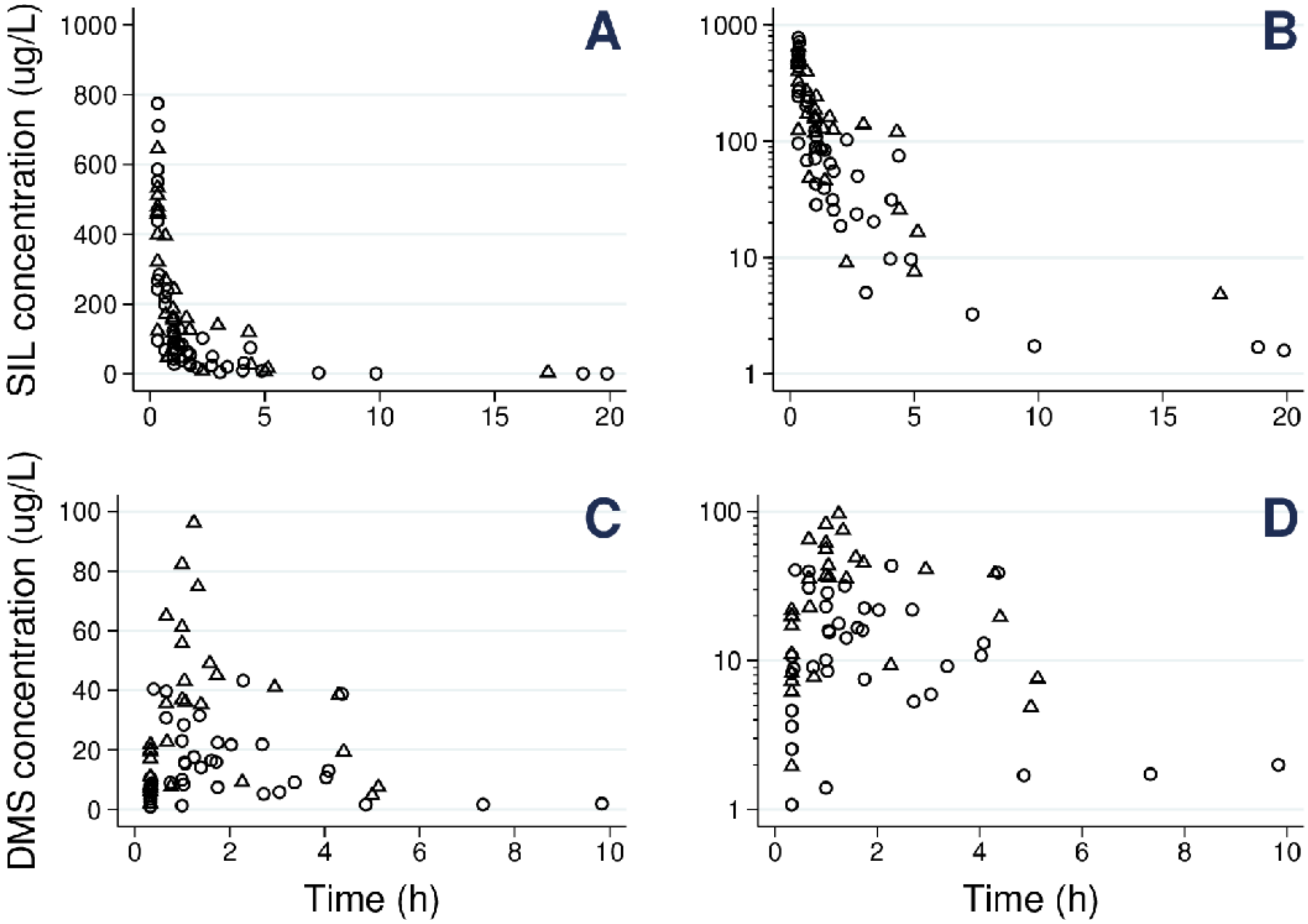

Figure 1. Concentration-time profiles

SIL = sildenafil; DMS = desmethylsildenafil; A, C = linear y-axis scale; B, D = log y-scale; circles = surgical stage 2; triangles = surgical stage 3.

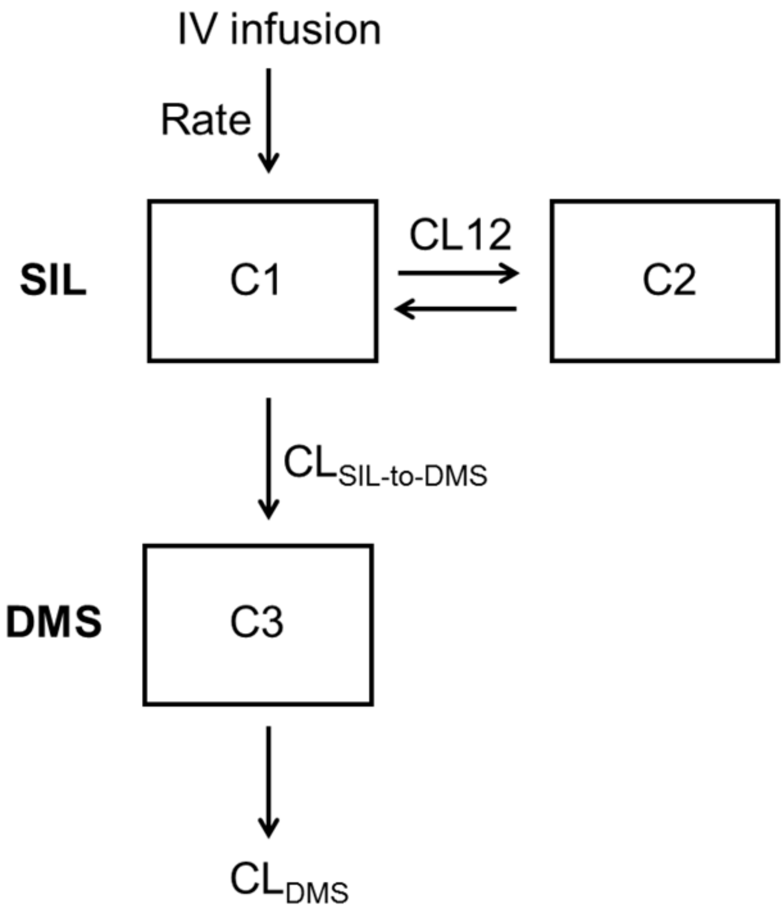

Figure 2. Final structural PK model

SIL = sildenafil; DMS = desmethylsildenafil; C1 = sildenafil central compartment; C2 = sildenafil peripheral compartment; CL12 = sildenafil intercompartmental clearance; C3 = DMS central compartment; CL$_{SIL\text{-}to\text{-}DMS}$ = sildenafil clearance (conversion to DMS); CL$_{DMS}$ = metabolite (DMS) clearance.

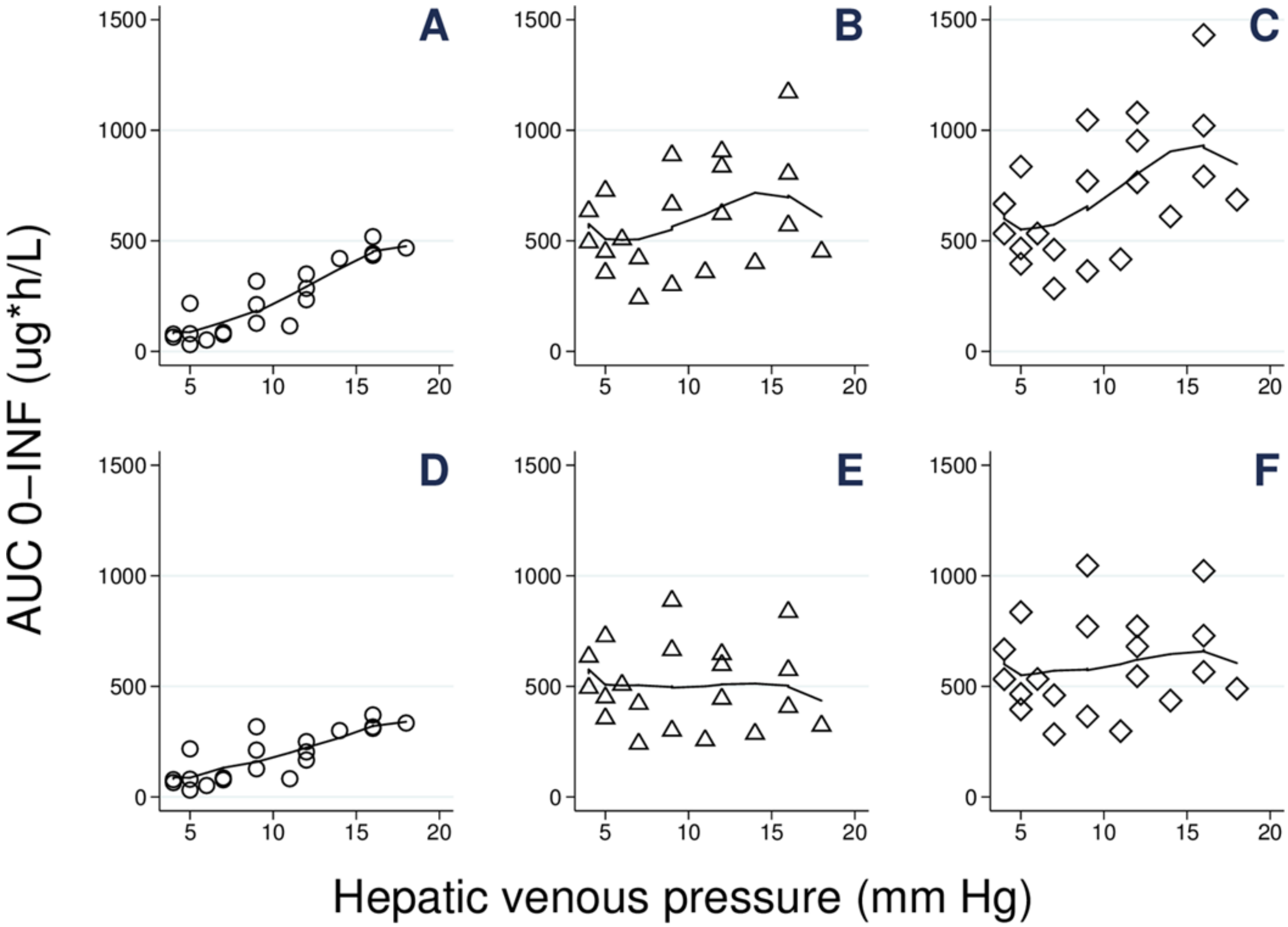

Figure 3. Predicted total exposures in the study population with and without dose reduction for hepatic pressures >10 mm Hg

HP = hepatic pressure; A–C = single dose of 0.35 mg/kg; D–F = single dose of 0.35 mg/kg for HP <10 mm Hg and 0.25 mg/kg for HP ≥10 mm Hg; Circles = DMS; Triangles = SIL; Diamonds = $AUC_{TOTAL} = AUC_{SIL} + AUC_{DMS}/2$.

Table 1

Study population

	Dosing group				
	0.125 mg/kg	0.25 mg/kg	0.35 mg/kg	0.45 mg/kg	Overall
N	2	5	8	5	20
Age (y)	1.7; 2.3	3.3 (0.8 – 5.3)	3.5 (1.1 – 5.3)	2.1 (0.9 – 5.2)	3.23 (0.8 – 5.3)
Weight (kg)	10.8; 11.7	10.8 (8.0 – 28.1)	14.5 (9.5 – 23.4)	11.5 (9.8 – 18.1)	11.9 (8.0 – 28.1)
Female	2 (10)	4 (20)	4 (20)	2 (10)	12 (60)
Caucasian	1 (5)	3 (15)	5 (25)	1 (5)	10 (50)
Serum creatinine (mg/dL)	0.3 (0.3 – 0.3)	0.3 (0.3 – 1.0)	0.3 (0.2 – 0.6)	0.3 (0.2 – 0.5)	0.3 (0.2 – 1.0)
Surgical Stage					
II	2 (10)	3 (15)	3 (15)	3 (15)	11 (55)
III	0 (0)	2 (10)	5 (25)	2 (10)	9 (45)
Hepatic Venous Pressure (mm Hg)	9, 16	9 (5 – 12)	12 (4 – 16)	7 (5 – 18)	9 (4 – 18)
Mean PA Pressure (mm Hg)	11, 16	12 (11–20)	12 (10–16)	11 (9–18)	12 (9–18)
Cardiac Index (L/min/m^2)	3.6; 7.4	2.2 (2.0 – 6.5)	3.4 (2.4 – 6.4)	4.2 (2.5 – 5.3)	3.7 (2.0 – 7.4)

Median (range) for continuous variables or N (%) for categorical variables

Table 2

Individual PK parameters

	n	Weight (kg)	HP (mm Hg)	$CL_{SIL\text{-}to\text{-}DMS}$ (L/h/kg)	CL_{DMS} (L/h/kg)	$t_{1/2,\ SIL}$ (h)	$t_{1/2,\ DMS}$ (h)
HP <10 mm Hg	11	10.8 (8.0 – 18.1)	6 (4 – 9)	0.70 (0.39 – 1.40)	4.36 (1.10 – 11.2)	2.7 (1.9 – 4.1)	2.7 (1.9 – 4.3)
HP ≥10 mm Hg	9	16.2 (9.5 – 28.1)	14 (11 – 18)	0.56 (0.30 – 0.95)	0.83 (0.68 – 3.03)	3.1 (2.3 – 5.1)	3.9 (2.2 – 6.1)
Total	20	11.9 (8.0 – 28.1)	9 (4 – 18)	0.64 (0.30 – 1.40)	1.63 (0.68 0 11.2)	2.9 (1.9 – 5.1)	3.3 (1.9 – 6.1)

HP = Hepatic Pressure; SIL = sildenafil; DMS = desmethylsildenafil; CL = clearance; $t_{1/2}$ = elimination half-life.