Population Pharmacokinetics of 38% Silver Diamine Fluoride in Children

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Abstract

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Purpose: The purpose of this population pharmacokinetic study was to further characterize the pharmacokinetics of silver and fluoride in healthy children 13-months to 13-years of age receiving SDF for the treatment of dental caries.

Methods: SDF was applied to lesions teeth of participants, and participants were randomized to blood draw timepoints post-SDF application (early: 2, 4, or 6 hours; intermediate: 24, 48 or 96 hours; and late: 7, 14, or 21 days). Serum fluoride and silver concentrations were determined using fluoride ion selective electrode and inductively coupled plasma-mass spectrometry, respectively. Concentration versus time data were analyzed simultaneously using population pharmacokinetic analysis with nonlinear mixed effects modeling using Phoenix NLMEsoftware. Thirty two children 2-13 years old with at least one carious lesion were recruited at the University of Washington Center for Pediatric Dentistry. The first child began the study on March 21st, 2023 and the last blood sample was taken on June 10th 2023.

Results: Twenty-three participants completed the study. Serum fluoride had no discernable temporal pattern. Silver concentrations were best described by a one-compartment model with first-order absorption and elimination following application of SDF. Simulated 12 kg children had a predicted peak concentration that was 3.3-fold higher than simulated 40 kg children (22 ng/mL vs. 6.6 ng/mL) and an exposure that was 2.5-fold higher (60 ng·day/mL vs. 24 ng·day/mL). The simulated half-life was 10.6 days in 12 kg children and was slightly longer in 40 kg children (14.3 days).

Conclusions: The observed data and subsequent population pharmacokinetic modeling suggest that the absorption and elimination of silver after SDF application may differ depending on the weight of the child. No fluoride or silver concentrations observed were of clinical or toxicological concern.

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I. Introduction

Thirty-eight percent silver diamine fluoride (SDF) is a topical agent utilized for the treatment of dental hypersensitivity and arrest of dental caries.[1,2] SDF has profound utility in pediatric dentistry for the treatment of carious lesions, by eliminating or delaying need for definitive dental treatment under general anesthesia and/or other sedation modalities in some cases.[3] The safety of SDF is well documented and described in both pediatric and adult patients.[4,5] SDF is a low cost, minimally invasive, easy-to-use, efficacious treatment for use in patients with dental caries.[6-10]

The American Academy of Pediatric Dentistry (AAPD) provides guidelines for the application and utilization of SDF.[11] SDF is applied directly to sites of dental caries in small topical doses. The AAPD recommends that the initial application be followed by a two-to-four-week examination for assessment of effectiveness and reapplication. For continued arrest, reapplication twice annually is suggested if caries activity restarts.

Small amounts of SDF can be swallowed during application, especially in young children. This may lead to systemic uptake of silver and fluoride. Pharmacokinetic studies in adults did not show an appreciable increase of fluoride serum levels from baseline values.[5,12] However, silver levels were detectable with an estimated half-life of two days.[5,12] Subsequently, a physiologically based pharmacokinetic (PBPK) model was developed for children by utilizing adult human and animal PK parameters for silver.[13] This model predicted higher plasma silver concentrations for young children than older peers, with relative values decreasing with greater age and weight. Moreover, the model predicted that application of SDF at standard doses would not result in toxic levels of silver or fluoride in young children. The validity of the predictive model was supported by a recent pharmacokinetic study of silver and fluoride following SDF application in children.[14] Each pediatric participant had a single blood draw at a single timepoint (up to 7 days) after SDF application and resulting silver concentrations were analyzed using population pharmacokinetic

modeling. However, the pediatric study had certain limitations including no data from young children (less than 3 years) and the duration of the study was insufficient to precisely estimate the half-life of silver.

Currently, SDF is classified as a Class II medical device for the treatment of dental hypersensitivity in adults.[15] It is used "off-label" for the arrest of dental caries with specific utility for pediatric patients. While the aforementioned studies provide substantial evidence to support the safety of SDF in children, there is insufficient data available to confidently predict the half-life of silver and covariates (e.g., age or weight) that might impact the disposition of silver. PK data derived from blood sampling at multiple time periods are needed to establish a pediatric safety profile of SDF and obtain U.S. Food and Drug Administration (FDA) approval for SDF treatment of dental caries in children.

The purpose of this population pharmacokinetic study was to further characterize the pharmacokinetics of silver and fluoride in healthy children 13-months to 13-years of age receiving SDF for the treatment of dental caries.

II. Methods

This study was conducted under Investigational New Drug Authorization (IND) 124808 from the FDA and was approved by the WCG IRB 1349201; trial registration NCT05670743.. Children were enrolled from March 22nd 2023 through May 26th 2023 at the University of Washington Center for Pediatric Dentistry (CPD) from the current patient pool. The daily schedule of CPD was scanned by study personnel who looked for patients that fit the criteria of English or Spanish speaking children aged 2 through 13 years old, in good health, not taking any prescription or over-the-counter medications(except "as needed" inhalers or allergy medications). Each participant had at least one carious lesion into enamel or dentin. Patients were ineligible to participate if they had SDF applied

within the last three months, were scheduled to have general anesthesia within the timeframe of their participation with the study, had oral mucositis or ulcerative lesions, or had a known sensitivity to fluoride or silver. If a patient met the study criteria, researchers informed the scheduled provider of the patient. The pediatric dental resident or faculty member then approached the patient and parent to determine interest in participation. If interested, one of two investigators enrolled participants.

Informed consent and confirmation of study eligibility were obtained in the parent or caregiver's primary language (English or Spanish). Consent was obtained in the patient's native language by study investigators. Signed assent was obtained for children seven years or older. Verbal assent was obtained from the younger children.

Randomization for blood sampling was performed by random assignment of blood draw periods within each of the three age cohorts: Cohort A, 13 to less than 36 months; Cohort B, 36 to 84 months; Cohort C, 84 to 156 months. The blood draw periods were divided into early (2, 4, and 6 hours), intermediate (24, 48, and 96 hours), and late (7, 14, and 21 days) timeframes. Cohort A and B were randomized to blood draws in the early and late periods. Cohort C utilized all three periods. All participants within each cohort were randomized to a unique sequence of blood draw timepoints via random selection from their respective sampling periods. The unique sequence was created by generating note slips with every possible sequence of blood sampling times within each cohort. When a patient was enrolled, a note slip was randomly selected from their respective cohort pool of slips. Once selected, that unique sequence could not be occupied by another participant within the respective cohort to ensure adequate distribution of timepoints across the study for children of various age groups.

The test product was aqueous SDF (Ag(NH3)2 F) (CAS Registry no. 33040-28-7), 38.3 to 43.2 percent in purified water, 5.0 to 5.9 percent (w/v) fluoride, and 24.4 to 28.8 per cent (w/v) silver (Advantage Arrest, Elevate Oral Care LLC, West Palm Beach, Fla., USA). Advantage Arrest involvement in the study was limited to donation of materials. The product was from a single lot and certified by the manufacturer. It was stored according to the manufacturer's instructions.

All application procedures and initial blood draws were performed at CPD on selected Saturdays, based on availability of researchers. Completing study procedures on Saturdays allowed for utilization of all facilities without interrupting regular patient care. The waiting room was used for patients awaiting blood draw, the operatories were used for SDF application, and a consultation room was used for blood draws. Age, race, gender, and ethnicity information were collected at baseline along with the weight and health history. A brief visual examination was conducted to note any evidence of inflammatory or ulcerative changes to the gingiva or other oral tissues. Participants' teeth were then brushed with a soft toothbrush to remove debris. The SDF unit dose ampule and microbrush were weighed with a calibrated analytical balance prior to application. Affected areas were isolated via cotton roll and teeth dried with cotton gauze. SDF was applied to carious lesions with the manufacturer's supplied microbrush. The microbrush and remaining SDF unit dose ampule were weighed after application to determine the amount of SDF applied. A one-minute contact time was maintained with cotton roll isolation if the child was cooperative. When cooperation allowed, the participant's mouth was then rinsed with water and high vacuum suction. Three patients were not cooperative enough for water and high vacuum suction and cotton gauze was utilized to wipe the area after SDF application. Children were given a tube of non-fluoride toothpaste at the baseline appointment, with instructions that it be used through the end of the blood draw period. The patient then waited in the reception area until their first blood draw timepoint. Movies, games, toys, healthy snacks and food and water were provided

to entertain the children, and researchers were easily able to observe them. Prior to the blood draw participants were encouraged to drink a small bottle of water to increase blood volume. Additionally, participants would present to CPD on Saturdays for their respective late blood sampling assignment (7, 14, or 21 days).

Participants were brought back to the consultation room for blood draws by nurses and participant caregivers, if they wanted to be present. Toys, EMLA topical anesthetic, a vibration distraction device, and encouragement were utilized to soothe patients during the blood draw. A brief assessment for any adverse effects, including parent questioning and visual observation of the intraoral tissues, was conducted prior to dismissal. Participants were given a small bag of age-appropriate toys and provided with two $50 gift cards (one given to participant and the other to their parent). This was performed for each blood draw completed. Two $25 dollar gift cards were presented when the participant completed all assigned blood draws. For patients assigned intermediate blood draws, families were offered to return to CPD or have a nurse and researcher perform the blood draw at their home (if within 10 miles of CPD) on their respective sampling date. At 24 to 48 hours after the SDF application and initial blood draw, a follow-up parent questionnaire was administered by one of the study personnel either by phone or at the intermediate blood draw visit to capture any adverse events since SDF application.

A six mL sample of blood was drawn into fluoride-free collection tubes from each participant at CPD according to the first set of randomization times (2, 4, or 6 hours). Samples were maintained at ambient temperature and transported via car to the University of Washington School of Pharmacy for processing and storage within 4 hours. The samples were spun in a clinical centrifuge, serum withdrawn, and stored at -80°C. Actual sampling times for each participant were used in the pharmacokinetic analyses due to control for the minor variances from assigned blood draw times. Samples were analyzed for fluoride by ion chromatography and silver by ICPMS

(inductively coupled plasma mass spectrometry) by the Environmental Health Laboratory and Trace Organic Analysis Center at the University of Washington, Seattle, WA, as described in detail by Lin et. al. (2019).[12] Limits of detection for this study were 5 ng/mL (0.005 parts per million) for fluoride and 0.1 ng/mL for silver.

Data were analyzed using population PK modeling with evaluation of possible covariants (e.g., age or weight). Cmax, Tmax, half-life, and AUC were calculated.

There was no discernable temporal pattern for serum fluoride concentrations; therefore, pharmacokinetic analysis on fluoride was not performed. Serum fluoride concentrations post-SDF application were summarized in a descriptive analysis.

To select an error model, additive and multiplicative error models were tested, and the additive model was selected based on the diagnostic plots. Standard allometric scaling exponents of 0.75 and 1 were used for CL and V, respectively, to account for the relationship between bodyweight to these pharmacokinetic parameters in pediatric patients.

For clearance for a specified weight, CL,

$$CL = CL_{TV} \cdot \frac{Weight^{0.75}}{70\ kg}$$

where CL_{TV} is the typical clearance at a reference weight (70 kg), weight is total bodyweight (kg), and the allometric exponent was set to 0.75.

For volume for a specified weight, V,

$$V = V_{TV} \cdot \frac{Weight^{1.0}}{70\ kg}$$

where V_{TV} is the typical volume at a reference weight (70 kg), weight is total bodyweight (kg), and the allometric exponent was set to 1.0.

The inter-individual variability (IIV) for volume of distribution and clearance of silver was evaluated by using an additive error model as described by:

$$P_i = P_{TV} \cdot e^{n_i}$$

where Pi is the estimated parameter value (V or CL) of the ith individual, P_{TV} is the typical population value of the parameter for V and CL, and η_i is the random variable for the ith individual, which is normally distributed with mean 0 and variance ω^2. For a covariate to be retained in the model, its inclusion had to result in a decline of 3.841 for one parameter in the objective function value (ΔOFV) at $\alpha = 0.05$.

The following formulas were used to calculated individual PK parameters based on the estimated population values:

Rate constant of elimination, $ke = \frac{CL}{V}$

Time of peak concentration, $Tmax = \frac{\ln(ka/ke)}{(ka-ke)}$

Peak concentration, $Cmax = \frac{\text{Dose}}{V} e^{-ke \cdot Tmax}$

Elimination half-life, $t_{1/2} = \frac{\ln(2) \cdot V}{CL}$

Area under the curve, $AUC = \frac{Dose}{CL}$

The model was internally validated using a bootstrap analysis in Phoenix NLME, in which datasets were resampled with replacement from the original datasets and refit to the model (n=1000) and assessed using goodness-of-fit plots. To better understand the effect of weight on silver PK in theoretical cohorts of children with varying weights (12, 15, 20, 30 and 40 kg), the final population PK parameters and interindividual variability estimates were used to simulate silver

concentration versus time curves for 1000 children per cohort following application of 19 mg SDF (average amount of SDF applied).

III. Results

Thirty-two total patients were initially enrolled in the study (signed consent forms), twenty-three participants presented for the baseline appointment with application of SDF and all blood draws, and twenty-two participants completed all required blood draws. One subject (#26) was excluded from the analysis due to an invalid calculation of amount of SDF applied. Serum concentrations below the lower limit of quantification (LLOQ) were not included in the analysis. Of the 52 assigned timepoints, two samples were missing (i.e., blood samples could not be drawn from the participant) and two samples were below the LLOQ for silver.

Following SDF application, the serum fluoride concentrations ranged from <5 to 12 ng/mL (<0.005 to 0.012 ppm). (Figure 1) As baseline blood samples were not obtained, post-SDF application fluoride concentrations could not be corrected for baseline fluoride concentrations. Following SDF application, the serum silver concentrations ranged from <0.1 to 31.8 ng/mL. (Figure 2) A one compartment model with first-order absorption and elimination best described the silver concentration versus time data following application of SDF. Due to the paucity and variability in the silver concentrations at early timepoints reflecting the absorption of silver, the absorption rate constant for silver was fixed at 23.7 day-1. This value was based on published adult silver pharmacokinetic data (Lin et al., 2019). Adopting a fixed absorption rate constant resulted in estimated peak silver concentrations at ~5 hours that agreed with the observed trend in the pediatric data.

Bootstrap analysis was used to verify the reproducibility and/or robustness of the final population PK model for silver. The estimated model parameters of the final population PK model were comparable to those following a bootstrap analysis (data not shown). Individual plots of the visual predictive check were created as each study participant received a different dose based on the amount of SDF applied. (Supplemental Figure 1) The diagnostic plots for the final model suggest that the model adequately described the serum silver concentration versus time data following SDF application. (Supplemental Figure 2)

The parameter estimates of the final population PK model are presented in Table 2. The relative standard error values of the parameter estimates suggest that the estimates obtained from the data were of moderate precision due to the limited number of subjects and sampling points. (Table 2) The typical value population estimates of the apparent volume (V) of silver was 10895 L and apparent oral clearance (CL) was 1205 L/day for the reference weight of 70 kg.

The summary of the individual estimated PK parameters of the children in the study is presented in Table 3. Overall, the estimated peak silver concentration was 5.3 ± 6.4 ng/mL and was estimated to occur at 5.1 ± 1.2 hr after SDF application. The estimated exposure to silver was 34 ± 44 ng·day/mL and was eliminated from the body with a half-life of 8.5 ± 13.3 days.

To explore the range in silver exposures in children, the population PK parameters and interindividual variability estimates were used to simulate serum silver concentrations at a fixed 19 mg SDF amount for 1000 children with weights of 12, 15, 20, 30 and 40 kg. Cmax, Tmax, AUC (i.e., exposure), and t1/2 were summarized by cohort (Table 4). The simulated peak concentration and AUC were highest in the smallest children and generally decreased with increasing weight (Figure 3; Table 4). Simulated 12 kg children had a predicted peak concentration that was 3.3-fold higher than simulated 40 kg children (22 ng/mL vs. 6.6 ng/mL) and an exposure that was 2.5-fold higher (60

ng·day/mL vs. 24 ng·day/mL). The simulated half-life was 10.6 days in 12 kg children and was slightly longer in 40 kg children (14.3 days).

No adverse or unanticipated effects related to SDF application were either observed at the follow-up assessment or reported by participant or parent and none were reported in response to the 24-48 hour parent questionnaire or at blood draw visits. No participant who had SDF application withdrew or was lost to follow up.

IV. Discussion

Following SDF application, the serum fluoride concentrations ranged from <5 to 12 ng/mL (<0.005 to 0.012 ppm). The serum silver concentrations ranged from <0.1 to 26.1 ng/mL. The typical value population estimate of the apparent volume (V) of silver was 10895 L and apparent oral clearance (CL) was 1205 L/day for the reference weight of 70 kg. The estimated peak silver concentration was 5.3 ± 6.4 ng/mL and was estimated to occur at 5.1 ± 1.2 hr after SDF application. The estimated exposure to silver was 34 ± 44 ng·day/mL, and silver was eliminated from the body with a half-life of 8.5 ± 13.3 days. Participant serum fluoride concentrations were similar to baseline levels in an adult PK study on SDF (10-50 ng/mL).[12] Reported fluoride varnish (approximately 3-5 mg fluoride applied or less than half of a standard 0.5 mL packet) and fluoride gel treatments (approximately 40 mg fluoride applied or 3 mL) result in higher serum fluoride concentrations compared to SDF (varnish: 60-120 ng/mL and gel: 300-1443 ng/mL).[17,18] These results suggest that a single SDF application does not appreciably increase serum fluoride levels in children.

Estimated peak serum silver concentrations based on population PK parameters were highly variable in this child population (range: 0.5-31.8 ng/mL). The peak silver concentrations were similar to adult peak concentrations in Vasquez et al. (3-29 ng/mL)[5] and higher than adult peak concentrations in Lin et al. (0.13-2.2 ng/mL).[12] The amount of SDF applied, number teeth treated,

and whether treated teeth were carious or noncarious, and post-application procedures (wait time, rinsing, etc.) differed between this pediatric study and the adult studies. However, the variability in serum silver peak concentrations and exposure may in part be due to imprecision in determining the amount of SDF applied, differences in the amount swallowed or absorbed, or differences in biliary excretion.

Ingesting excess silver results in argyria, the permanent blue or blue-gray discoloration of the skin. No other adverse health effects have been associated with silver ingestion[19] The U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) on silver sets the lowest observed adverse effect level (LOAEL) at one-gram total via intravenous (IV) dose. This is about 95-fold to 200-fold more than the average estimated total SDF that was applied in this study. The IRIS also states the oral dose conversion is 25 grams, indicating that the safety margin is about 25-fold higher when silver is provided orally. These values assume complete absorption of silver into the bloodstream or complete ingestion. This is highly unlikely, as SDF ingestion is limited by absorption into the tooth, removal by cotton roll during isolation, and removal during rinsing and suctioning. Additionally, in practice SDF is applied intermittently. This allows for clearance of silver from circulation. These factors combine to make the safety margin even higher.

A previous pediatric pharmacokinetic study that utilized a similar SDF application protocol allows for some valuable comparison with the present work.[14] The study by Ellenikiotis et al. included a larger sample size within a 7-day sampling timeframe, resulting in a RSE that was much lower for V/F and CL/F (6.8% and 16% respectively). It also had a larger average amount of SDF applied of 33 mg versus 19 mg for this study. Although a similar SDF application protocol was utilized, there is no clear explanation for the observed difference. Potential sources could be inherent provider technique differences or differences in the micro brushes used for application.

Limitations of this study include small number of participants for each time point, utilization of fixed absorption rate constant based on adult data,[12] a low number of 1 to 3 year old participants, inability to determine actual amount of SDF applied, and challenges in recruitment given the time dedication, multiple blood draws, and patients' and parents' aesthetic concerns of SDF application.[20] A clinic that sees a higher volume of new patients might provide a greater source of patients in the 12-36 months age range. Although, attempts were made to increase patient blood volume by providing water bottles after SDF application, blood samples could not be drawn at certain timepoints or from specific study participants. An additional step that could have been added to the protocol is encouragement to hydrate the morning of the SDF application appointment. The small sample size decreased the overall power of our results, increased the RSE of the total population estimate parameter model (especially for CL VII), and required a fixed absorption rate constant for silver due to paucity and variability at early time points. It is plausible that sampling points from similar studies could be added to sampling points from this study to alleviate these limitations.

Measuring the dose of SDF applied poses a unique challenge. The amount of SDF applied was estimated as the difference in the weight of the SDF unit dose ampule and application brush before and after application. The carious lesion may absorb a portion of the SDF with excess being removed via water and suction. The microbrush can pick up saliva and debris from the patient's mouth. The patient's teeth were brushed before application to minimize debris, but these factors can lead to uncertainty about the amount of SDF applied. Moreover, the actual amount of SDF swallowed vs. the amount of SDF applied is unknown. Thus, the resulting blood concentrations are a better proxy for safety than the amount of SDF applied.

V. Conclusions

After SDF treatment, participant serum fluoride concentrations (<5-36 ng/mL) were similar to previously observed fluoride concentrations in adults following SDF treatment (10-50 ng/mL) and are lower than reported after fluoride varnish or fluoride gel treatments. In children, the peak serum silver concentrations (range: 0.5-26.1 ng/mL) overlapped with the range of observed adult peak concentrations (4-hr adult PK: 3-29 ng/mL; 24-hr adult PK: 0.13-2.2 ng/mL).[5, 12] Silver was eliminated with a half-life of approximately 8.5 ± 13.3 days. The observed data and subsequent population pharmacokinetic modeling suggest that the absorption and elimination of silver after SDF application may differ depending on the weight of the child. None of the silver or fluoride concentrations observed were of clinical or toxicological concern.

VI. Figures and Tables

Figure 1. Observed serum fluoride concentrations following application of 38% SDF to children. Each dot is the measured serum fluoride concentration from a child (n=21); X represents concentrations at the limit of quantification and black dots represent serum fluoride concentrations of study participants.

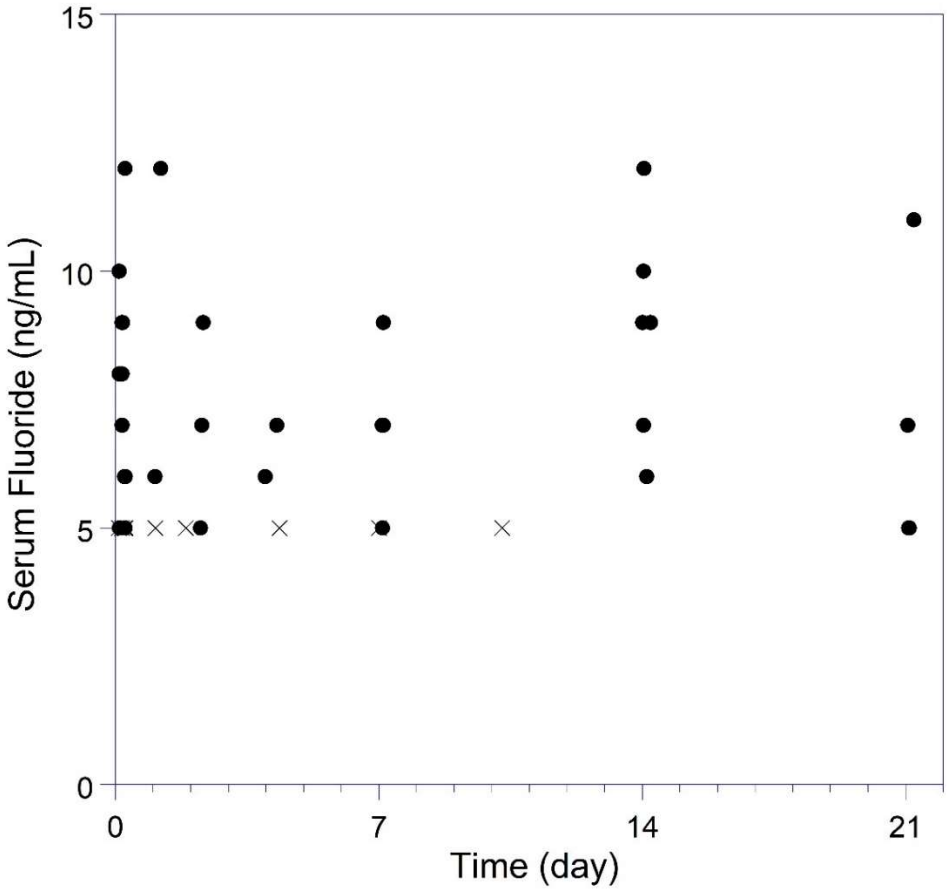


Figure 2. Simulated concentration–time curve using final parameter estimates from the population pharmacokinetic model (solid red line: average prediction; dashed red lines: 5% and 95% confidence intervals) with observed serum silver concentrations following application of 38% SDF to children. Each dot is the measured serum silver concentration from a child (n=21); X represents concentrations at the limit of quantification.

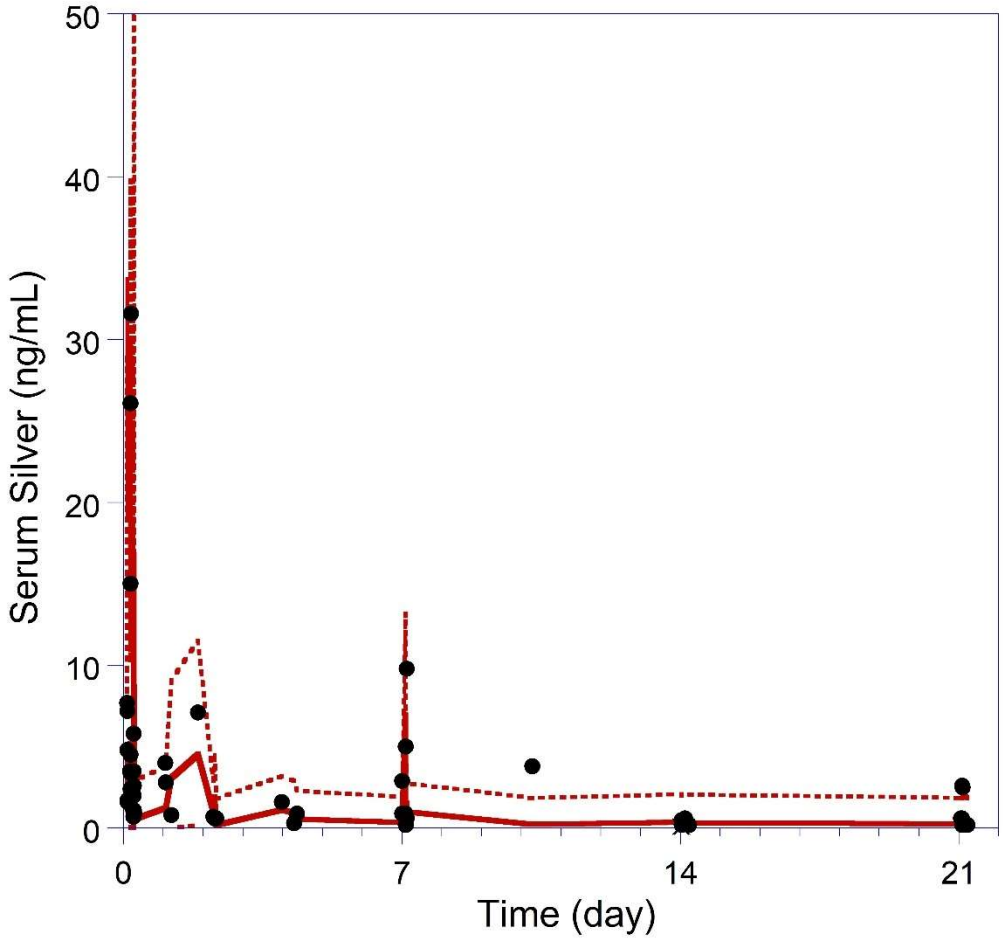


Figure 3. Average simulated serum silver concentration vs. time curves in cohorts of children following application of 34 mg of SDF (1000 simulations per cohort). Cohorts: 12 kg (gray), 15 kg (green), 20 kg (blue), and 30 kg (black), and 40 kg (pink). Inset: first 3 days after SDF application. Shaded areas are 95% confidence intervals.

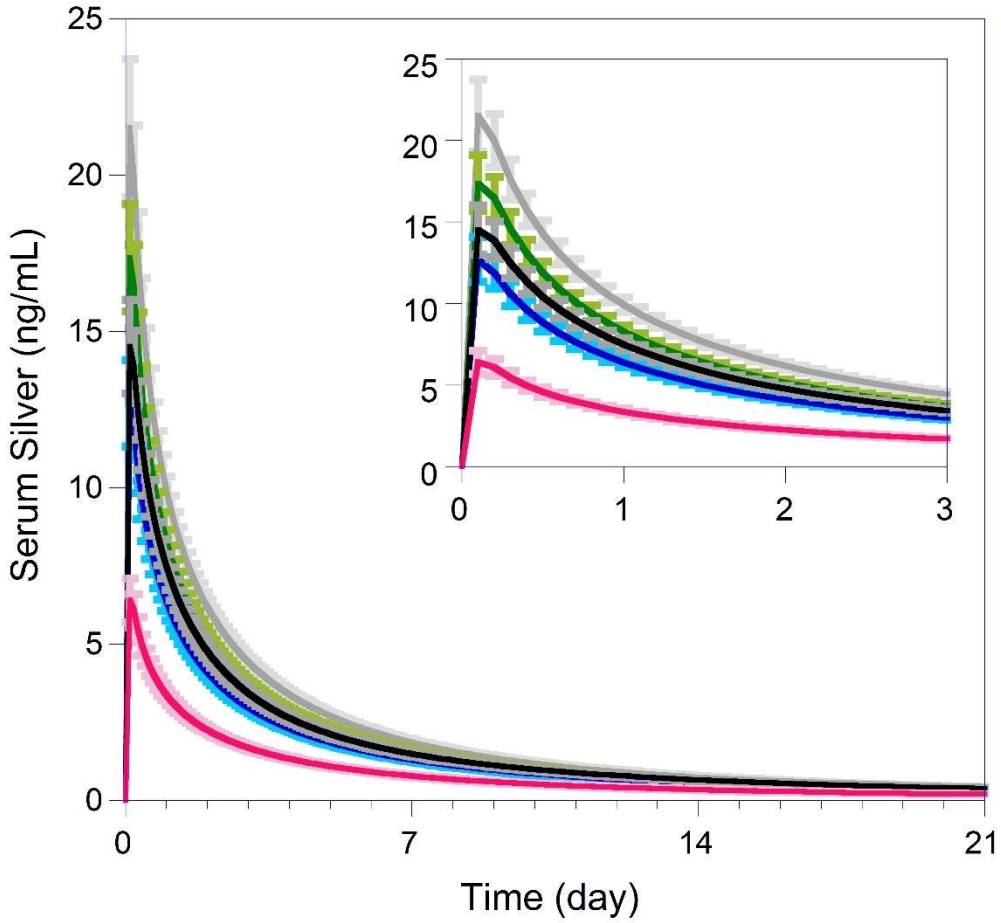


Table 1. Participant demographics and topical 38% silver diamine fluoride treatment in a PK study of healthy children treated for dental caries.

Characteristic	**Total (N = 23)**
Location	
Age	7.1 ± 3.1
Weight (kg)	33 ± 19
Gender	
Male	10 (43%)
Female	13 (57%)
Race	
American Indian/Alaska Native	1 (4%)
White	3 (13%)
Asian	0 (0%)
African American	6 (26%)
More Than One Race	8 (35%)
Unknown or not reported	5 (22%)
Ethnicity	
Hispanic or Latino	10 (43%)
Not Hispanic or Latino	13 (57%)
Amount of SDF applied (mg)*	19 ± 23
Number of teeth treated	4.2 ± 2.8

Reported as mean ± standard deviation (range) or count (%)

* SDF dosing not reportable from one participant

Table 2. Population pharmacokinetic parameter estimates of silver following SDF application to children.

ka: absorption rate constant

V: volume of distribution of silver

CL: clearance of silver

IIV: Interindividual variability of the indicated parameter

RSE: relative standard error

Parameters	**Model Parameter Estimates (RSE%)**
ka (day^{-1})	23.7 FIXED
V (L)	10895 (33%)
CL (L/day)	1205 (42%)
Interindividual variability (IIV)	
V IIV (%)	186 (33%)
CL IIV (%)	4.5 (357%)
Residual error	1.12 (23%)

Table 3. Calculated pharmacokinetic parameters of silver based on population PK parameters for each individual.

Cmax: calculated peak concentration of silver

Tmax: calculated time of peak silver concentration

V: volume of distribution of silver estimated from population PK model

CL: clearance of silver estimated from population PK model

AUC: calculated area under the curve of silver

$t_{1/2}$: calculated half-life of silver

	Parameter	
	Average ± SD	Range ± SD
Age (years)	7.1 ± 3.1	2.48 - 13.95
Weight (kg)	33 ± 19	11 - 80
Amount of SDF applied (mg)	19 ± 23	2 - 110
Number of teeth treated	4.2 ± 2.8	1 - 12
Cmax (ng/mL)	5.3 ± 6.4	0.5 - 28.6
Tmax (hr)	5.1 ± 1.2	2.5 - 7.8
V (L)	7122 ± 10020	135 - 47548
CL (L/day)	685 ± 324	251 - 1411
AUC (ng·day/mL)	34 ± 44	3 - 212
$t_{1/2}$ (day)	8.5 ± 13.3	0.3 - 63.4

Table 4. Estimated pharmacokinetic parameters of silver based on simulated silver concentration vs. time profiles for cohorts of children ranging from 12 to 40 kg (1000 simulations per cohort).
Cmax: peak concentration of silver

Tmax: time of peak silver concentration

V/F: apparent volume of distribution of silver

CL/F: apparent oral clearance of silver

AUC: area under the curve of silver

$t_{1/2}$: elimination half-life of silver

	Simulated Pediatric Cohort				
Silver PK Parameters	**12 kg**	**15 kg**	**20 kg**	**30 kg**	**40 kg**
SDF Applied (mg)	19	19	19	19	19
T_{max} (hr)	5.2 (5.1 - 5.3)	5.2 (5.1 - 5.3)	5.4 (5.3 - 5.5)	5.5 (5.4 - 5.6)	5.6 (5.5 - 5.7)
C_{max} (ng/mL)	22 (20 - 24)	18 (16 - 20)	13 (12 - 14)	15 (13 - 17)	6.6 (5.9 - 7.3)
V/F (L/kg)	407 (350 - 464)	404 (344 - 464)	441 (339 - 543)	262 (221 - 303)	314 (275 - 353)
CL/F (L/day/kg)	28 (28 - 28)	26 (26 - 26)	24 (24 - 24)	13 (13 - 13)	16 (16 - 16)
AUC (ng·day/mL)	60 (59 - 61)	51 (50 - 52)	41 (40 - 42)	49 (48 - 50)	24 (24 - 24)
$t_{1/2}$ (day)	10.6 (9.1 - 12.1)	11.5 (9.5 - 13.5)	13.8 (10.3 - 17.3)	13.9 (11.8 - 16)	14.3 (12.5 - 16.1)

Reported as average and 95% confidence interval

VII. References

1. Mei ML, Lo ECM, Chu CH. Arresting Dentine Caries with Silver Diamine Fluoride: What's Behind It? Journal of Dental Research 2018;97(7):751-58.
2. Gao SS, Zhao IS, Duffin S, et al. Revitalising Silver Nitrate for Caries Management. International journal of environmental research and public health 2018;15(1):80.
3. Meyer BD, Hyer JM, Milgrom P, Downey T, Chi DL. Silver diamine fluoride-associated delays in procedural sedation in young children: A retrospective cohort study. The Journal of the American Dental Association (1939) 2023;154(4):311-20.
4. Duangthip D, Fung MHT, Wong MCM, Chu CH, Lo ECM. Adverse Effects of Silver Diamine Fluoride Treatment among Preschool Children. Journal of dental research 2018;97(4):395-401.
5. Vasquez E, Zegarra G, Chirinos E, et al. Short term serum pharmacokinetics of diammine silver fluoride after oral application. BMC oral health 2012;12(1):60-60.
6. Urquhart O, Tampi MP, Pilcher L, et al. Nonrestorative Treatments for Caries: Systematic Review and Network Meta-analysis. Journal of Dental Research 2019;98(1):14-26.
7. Zhao IS, Gao SS, Hiraishi N, et al. Mechanisms of silver diamine fluoride on arresting caries: a literature review. International dental journal 2018;68(2):67-76.
8. Craig GG, Powell KR, Price CA. Clinical evaluation of a modified silver fluoride application technique designed to facilitate lesion assessment in outreach programs. BMC oral health 2013;13(1):73-73.
9. Schwendicke F, Göstemeyer G. Cost-effectiveness of root caries preventive treatments. Journal of dentistry 2017;56:58-64.
10. Burgette JM, Weintraub JA, Birken SA, Lewis TA, White BA. Development of a Silver Diamine Fluoride Protocol in Safety Net Dental Settings. Journal of dentistry for children (Chicago, Ill.) 2019;86(1):32-39.
11. Dentistry AAoP, editor. Chairside guide: Silver diamine fluoride in the management of dental caries lesions. Chicago, Ill., USA: American Academy of Pediatric Dentistry; 2022. Dentistry AAoP, editor. The Reference Manual of Pediatric Dentistry.
12. Lin YS, Rothen ML, Milgrom P. Pharmacokinetics of 38% topical silver diamine fluoride in healthy adult volunteers. The Journal of the American Dental Association (1939) 2019;150(3):186-92.
13. Chen KF, Milgrom P, Lin YS. Silver Diamine Fluoride in Children Using Physiologically Based PK Modeling. Journal of dental research 2020;99(8):907-13.
14. Ellenikiotis H, Chen K-F, Soleimani-Meigooni DN, et al. Pharmacokinetics of 38 Percent Silver Diamine Fluoride in Children. Pediatric dentistry 2022;44(2):114.
15. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry. E11 Clinical Investigation of Medicinal Products in the Pediatric Population. International Conference on Harmonization (ICH), 2000.
16. Malin AJ, Lesseur C, Busgang SA, et al. Fluoride exposure and kidney and liver function among adolescents in the United States: NHANES, 2013–2016. Environment international 2019;132:105012-12.

17. Ekstrand J, Koch G, Petersson LG. Plasma Fluoride Concentration and Urinary Fluoride Excretion in Children following Application of the Fluoride-Containing Varnish Duraphat. Caries research 1980;14(4):185-89.
18. Ekstrand J, Koch G, Lindgren LE, Petersson LG. Pharmacokinetics of Fluoride Gels in Children and Adults. Caries research 1981;15(3):213-20.
19. The U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS): Chemical Assessment Summary. Silver; CASRN 7440-4 Available at: https://iris.epa.gov/static/pdfs/0099_summary.pdf
20. Magno MB, Silva LPd, Ferreira DM, Barja-Fidalgo F, Fonseca-Gonçalves A. Aesthetic perception, acceptability and satisfaction in the treatment of caries lesions with silver diamine fluoride: A scoping review. International journal of paediatric dentistry 2019;29(3):257-66.

Appendix

Appendix A: Demographics and Dosing. Sample ID indicates the specific patient who received the blood draw and that order in which the patient was enrolled. Notes provides reasons for serum values not being displayed.

Sample ID	Gender	Race	Ethnicity	Age (years)	Weight (kg)	Amoun appli
2	Female	Black or African American	Not Hispanic or Latino	13.95	57.8	0.0
3	Female	Black or African American	Not Hispanic or Latino	12.34	79.6	0.0
4	Female	Black or African American	Not Hispanic or Latino	10.89	78.2	0.0
5	Female	Unknown	Hispanic	6.99	22.8	0.0
6	Male	More Than One	Hispanic	2.87	13.4	0.0
7	Male	Black or African American	Not Hispanic or Latino	3.69	21	0.0
8	Male	Unknown	Hispanic	8.83	39	0.0
10	Male	American Indian/Alaska Native	Hispanic	2.48	11.1	0.0
11	Female	Black or African American	Not Hispanic or Latino	4.54	21.6	0.0
12	Female	White	Not Hispanic or Latino	9.76	39.6	0.0
13	Female	More Than One	Hispanic	7.39	21.7	0.
14	Female	More Than One	Hispanic	4.76	16.1	0.
16	Male	More Than One	Not Hispanic or Latino	6.32	22.6	0.
17	Female	More Than One	Not Hispanic or Latino	7.53	36.9	0.0
21	Female	More Than One	Hispanic	4.41	19.3	0.0
22	Male	Unknown	Hispanic	6.24	26.4	0.0
23	Male	Unknown	Hispanic	7.72	47	0.

Sample ID	Gender	Race	Ethnicity	Age (years)	Weight (kg)	Amoun appli
24	Male	Black or African American	Not Hispanic or Latino	9.52	38	0.0
25	Male	More Than One	Not Hispanic or Latino	5.47	16.7	0.0
26	Female	More Than One	Not Hispanic or Latino	4.85	20.6	-
29	Male	White	Not Hispanic or Latino	6.75	31.7	0.
30	Female	White	Not Hispanic or Latino	4.19	21.2	0.0
31	Female	Unknown	Hispanic	12.05	52.1	0.0

* Invalid dose recorded

Appendix B: Serum Concentrations of Silver and Fluoride. Sample ID indicates the specific patient who received the blood draw and that order in which the patient was enrolled. Notes provides reasons for serum values not being displayed.

Sample ID	Age (yr)	Weight (kg)	Nominal Time (days)	Actual Time (day)	Serum Ag (ng/mL)	Serum F (ng/mL)	
2	13.95	57.8	0.167	0.174	15	9	
2	13.95	57.8	2	1.878	7.1	<5	
2	13.95	57.8	21	21.097	2.5	5	
3	12.34	79.6	0.167	0.173	2.4	<5	
3	12.34	79.6	4	4.361	0.9	<5	
3	12.34	79.6	7	7.003	0.9	<5	
4	10.89	78.2	0.083	0.092	7.7	<5	
4	10.89	78.2	1	1.059	2.8	<5	
4	10.89	78.2	7	7.001	2.9	<5	
5	6.99	22.8	0.167	0.177	3.4	7	
5	6.99	22.8	14	14.045	< 0.1	12	
6	2.87	13.4	0.167	0.177	26.1	7	
6	2.87	13.4	7	7.017	nd	nd	Insuf
7	3.69	21	0.083	0.097	4.8	8	
7	3.69	21	21	21.087	2.6	5	
8	8.83	39	0.25	0.26	1.1	6	
8	8.83	39	4	4.291	0.3	7	
8	8.83	39	14	14.215	0.2	9	
10	2.48	11.1	0.25	nd	nd	nd	N
10	2.48	11.1	7	7.097	5	5	
11	4.54	21.6	0.167	0.174	4.5	8	
11	4.54	21.6	21	21.052	0.6	7	
12	9.76	39.6	0.167	0.167	3.5	8	

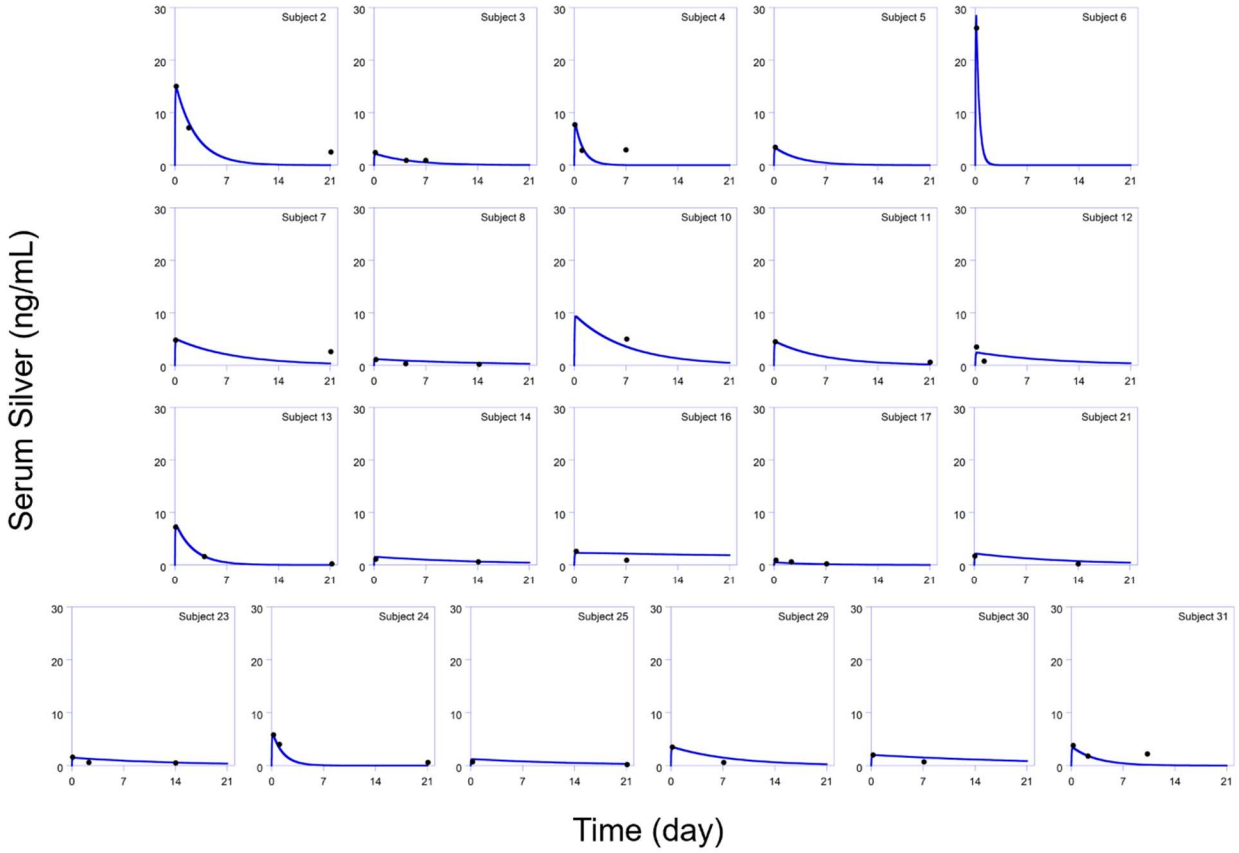
Sample ID	Age (yr)	Weight (kg)	Nominal Time (days)	Actual Time (day)	Serum Ag (ng/mL)	Serum F (ng/mL)	
12	9.76	39.6	1	1.201	0.8	12	
12	9.76	39.6	14	14.007	< 0.1	9	
13	7.39	21.7	0.083	0.097	7.2	8	
13	7.39	21.7	4	3.979	1.6	6	
13	7.39	21.7	21	21.219	0.2	11	
14	4.76	16.1	0.25	0.243	1.1	6	
14	4.76	16.1	14	14.115	0.6	6	
16	6.32	22.6	0.25	0.26	2.6	6	
16	6.32	22.6	7	7.087	0.9	7	
17	7.53	36.9	0.25	0.271	0.9	<5	
17	7.53	36.9	2	2.333	0.6	9	
17	7.53	36.9	7	7.097	0.2	5	
21	4.41	19.3	0.083	0.097	1.7	10	
21	4.41	19.3	14	14.028	0.2	10	
22	6.24	26.4	0.083	nd	nd	nd	N
22	6.24	26.4	7	nd	nd	nd	N
23	7.72	47	0.083	0.101	1.6	5	
23	7.72	47	2	2.292	0.6	7	
23	7.72	47	14	14.031	0.5	7	
24	9.52	38	0.25	0.257	5.8	5	
24	9.52	38	1	1.052	4	6	
24	9.52	38	21	21.08	0.6	5	
25	5.47	16.7	0.25	0.247	0.7	<5	
25	5.47	16.7	21	21.087	0.2	5	
26	4.85	20.6	0.083	0.104	31.6	11	Invalid
26	4.85	20.6	7	7.024	9.8	6	Invalid

Sample ID	Age (yr)	Weight (kg)	Nominal Time (days)	Actual Time (day)	Serum Ag (ng/mL)	Serum F (ng/mL)	
29	6.75	31.7	0.167	0.188	3.5	9	
29	6.75	31.7	7	7.122	0.6	7	
30	4.19	21.2	0.25	0.257	2	12	
30	4.19	21.2	7	7.118	0.7	9	
31	12.05	52.1	0.25	0.257	3.8	6	
31	12.05	52.1	2	2.257	1.8	5	
31	12.05	52.1	7	10.278	2.2	<5	

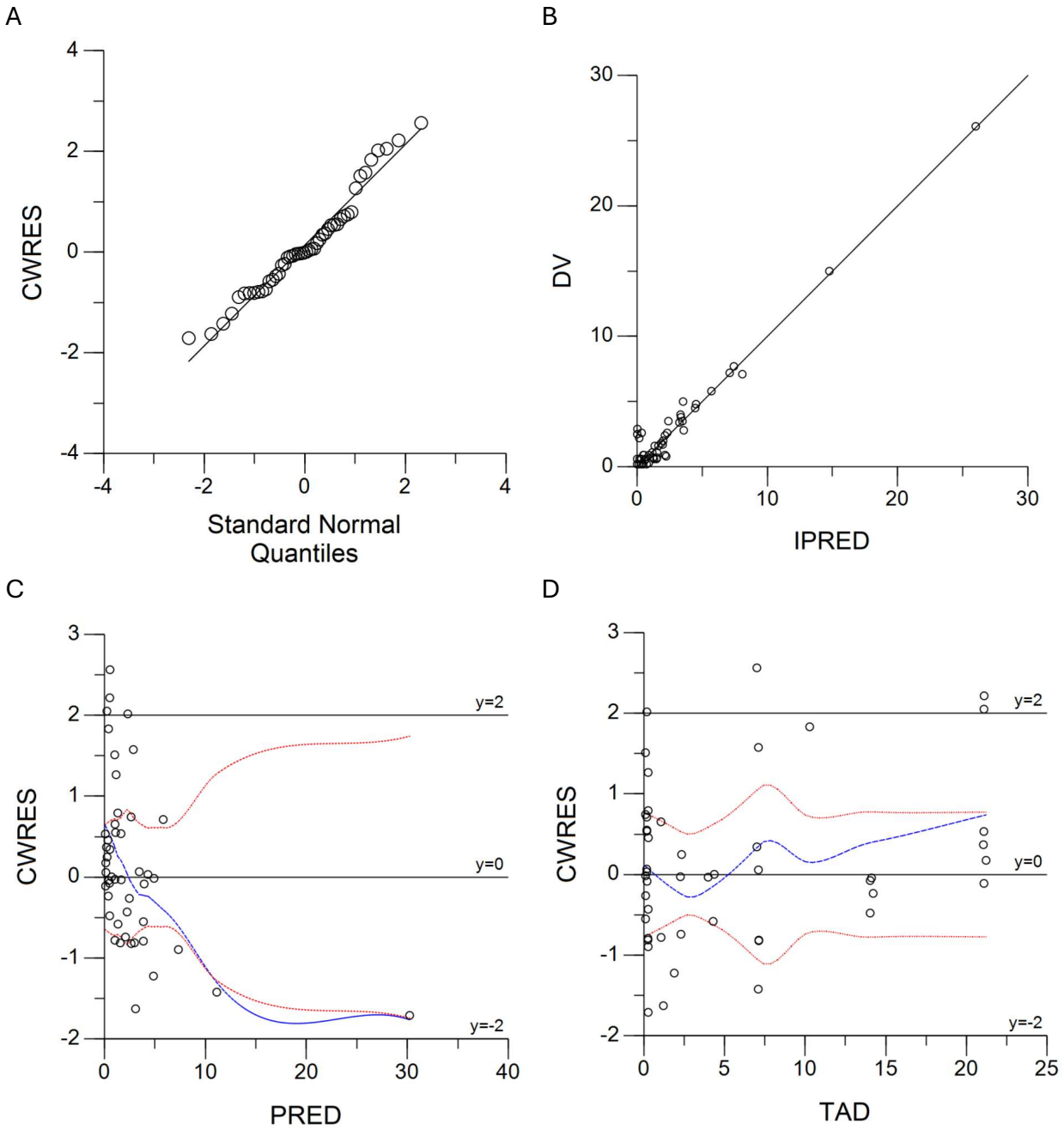
Appendix C: Clinical Supplies for SDF Application.

CLINICAL SUPPLIES			QUANTITY
GLOVES		SMALL	2 BOX
		MEDIUM	2 BOXES
		LARGE	2 BOX
DISPOSABLE GOWNS		MEDIUM	3 BOXES (50/BOX)
		LARGE	1 BOX (50/BOX)
DISPOSABLE TOOTH BRUSHES		AGE 2-7	19 INDIVIDUAL
		AGE 8-13	11 INDIVIDUAL
MASKS	**LEVEL 3**		1 BOX
	KN95 O N95		2 BOX (20/BOX)
GAUZE 2X2			2 PACKAGES
AIR W SYR TIPS			1 BAG
COTTON ROLLS			1 BOX
BIBS			1 BOX
MEDI CUP			30
WEIGHTBOATS			30
SAFETY GLASSES			3
SAFETY GLASSES-KIDS			3
HIGH VAC SUCTION			50 PER BAG
PLASTICS			30
WIPES		CAVIWIPES	2 CANISTER
MOUTH MIRROS		DISPOSABLE	30

Supplemental Figure 1. Visual predictive check (VPC) of the final model for silver pharmacokinetics for individual study participants (n=21). Observed concentrations are depicted by the dots. The predicted concentrations are represented by the lines.



Supplemental Figure 2: Goodness-of-fit plots of silver data for the final model. A) Log-value of observed serum concentrations (CWRES) vs. log-value of population predicted concentrations (Standard Normal Quantiles). B) Observed serum concentrations (DV) vs. individual predicted concentrations (IPRED). C) Conditional weighted residuals (CWRES) versus log population predictions (PRED). D) Conditional weighted residuals CWRES versus time after dosing (TAD).



VIII. Abbreviations

Full Title	Abbreviation
Silver Diamine Fluoride	SDF
American Academy of Pediatric Dentistry	AAPD
Physiologically based pharmacokinetic	PBPK
Food and Drug Administration	FDA
Investigational New Drug Authorization	IND
University of Washington Center for Pediatric Dentistry	CPD
Lower Limit of Quantification	LLOQ
Inductively coupled plasma mass spectroscopy	ICPMS
Volume of distribution	V
Clearance	CL
Inter-individual variability	IIV
Reference weight	TV
Parameter value	P
Absorption rate constant	ka
Relative standard error	RSE
Calculated area under the curve of silver	AUC
Calculated half-live of silver	$t_{1/2}$
Peak concentration of silver	Cmax
Time of peak silver concentration	Tmax
U.S. Environmental Protection Agency	EPA
Integrated Risk Information System	IRIS
Lowest observed adverse effect level	LOAEL
Intravenous	IV