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Pharmacokinetics of 38% Silver Diamine Fluoride in Children

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Pharmacokinetics of 38% Silver Diamine Fluoride in Children

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Pharmacokinetics of 38% Silver Diamine Fluoride in Children

Hellene Ellenikiotis

ABSTRACT

Objective

38% silver diamine fluoride (SDF) is a topical agent used to prevent and arrest caries lesions. Small quantities can be swallowed and absorbed. We conducted a pharmacokinetic study in children, 3-13 y, with ≥1 lesion to determine the pharmacokinetics of silver and fluoride.

Methods

SDF was applied to study participants at the UCSF Pediatric Dental Clinic and blood was obtained at 1 randomly selected timepoint (2, 4, 6, 24, 48, 96,168 h) post-application. Serum fluoride and silver were analyzed, and pharmacokinetic parameters were estimated using population pharmacokinetic modeling and used to simulate silver exposures in cohorts of children.

Results

55 children completed the study (6-10 per timepoint with 10-55 mg SDF applied). Following SDF application, serum fluoride concentrations ranged from 6-36 ng/mL with no discernable temporal pattern. Silver concentrations ranged from 1.4-46.2 ng/mL. A 1 compartment model with first-order absorption and elimination with weight as a covariate best fit the data. Based on the estimated parameters, silver PK was simulated for cohorts of children from 15 to 50 kg. Compared to previously published data in adults, the predicted time to peak concentration in children was comparable (C: 4.4-5.9

h; A: 5.3 ± 5.8 h) and predicted peak silver concentrations were within the same range (C: 12.8-22.0 ng/mL; A: 3.0-29.0 ng/mL), though observed silver concentrations were higher in some children. The predicted half-life of silver was longer in children compared to adults (C: 4.0-15.5 days; A: 1.9 ± 1.1 days).

Conclusions

Following SDF application, fluoride serum concentrations fluctuated around previously reported baseline levels, and some silver concentrations in children exceeded concentrations in adults. As expected, the predicted silver exposure was greater in children with lower weights. Regardless, low dosage and intermittent use mitigate risk and support continued development of SDF as a minimally invasive, safe, and efficacious treatment for caries in children.

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1. INTRODUCTION

38% silver diamine fluoride (SDF) is a topical agent used to prevent and arrest dental caries (Horst and Heima 2019). Its efficacy (Contreras et al. 2017; Oliveira et al. 2019) and clinical safety (Duangthip et al. 2018; Milgrom et al. 2018) in children are well-documented. Furthermore, it is a minimally-invasive, easy to use, and cost-effective treatment option that has expanded access to dental care for children (Crystal et al. 2017; Yeung and Argaez 2017; Crystal et al. 2019).

38% SDF is applied in milligram quantities to teeth, after which small amounts can be swallowed and absorbed. Vasquez and colleagues (2012) conducted a pharmacokinetic study in which 38% SDF was applied topically to intact buccal surfaces of 3 teeth without caries lesions in 6 healthy adults. Over the 4 h observation period, serum silver concentration peaked at 2.5 h. Fluoride exposure was below the United States Environmental Protection Agency (US EPA) oral reference dose (IRIS 1987), and occasional silver exposure was well below concentrations associated with toxicity (IRIS 1989). Lin and colleagues (2019) applied 38% SDF topically to 5 teeth without caries lesions, in 16 healthy adults who were observed for 24 h. Over the observation period, serum silver concentrations peaked at 3 h and the estimated elimination half-life was approximately 46 h. In both studies, dose and time to peak serum silver concentration were comparable, although peak concentrations were higher in the first study. Taken together, the results of the 2 studies suggested a 400-fold safety margin based on US EPA guidelines (IRIS 1989). Nevertheless, the adult PK studies had limitations. The Vasquez study had a small number of subjects and short follow-up, which prevented estimation of an elimination half-life and calculation of the exposure to

silver (i.e., area under the curve serum concentration vs. time curve). Although the Lin study captured a more comprehensive PK profile, the follow-up period over 24 h was too short to have a robust estimate of the elimination half-life of silver or the return of serum silver concentrations to baseline levels. Neither studied children or application of SDF to carious lesions.

As a preliminary investigation into the kinetics of 38% SDF in children, a physiologically-based pharmacokinetic model was developed based on the adult PK parameters from the Lin study (Chen et al. 2020). The model predicted that, for a given SDF dose, the peak plasma silver concentrations were 5.2-, 4.3-, 2.7-, and 1.3-fold higher in children aged 1-2 years, 2-4 years, 5-10 years, and 12-17 years, respectively, compared to adults. The simulated half-life of silver was comparable at all ages, and plasma and tissue silver concentrations were predicted to return to baseline levels within 10 days after SDF application. Based on these predictions, younger children could have transiently higher plasma silver concentrations compared to adults.

The purpose of this study was to characterize the pharmacokinetics of silver and fluoride using population PK modeling in healthy children receiving 38% SDF treatment for dental caries lesions. This study was designed to be minimally invasive (i.e., single point blood sampling), and addresses gaps in our knowledge of the pharmacokinetics of 38% SDF in children.

2. MATERIALS AND METHODS

Participant recruitment

The study was conducted under Investigational New Drug authorization 124808 from the US Food and Drug Administration. The study was approved by the Western Institutional Review Board (20191756).

Children were enrolled from August 2019 through March 2020 from the University of California, San Francisco (UCSF) Pediatric Dental Clinic. Participants were healthy, between the ages of 3-13 years, and were not taking either prescription or over-the-counter medication, except “as needed” inhalers or allergy medication. Each child had at least 1 carious enamel or dentin lesion. Participants were excluded if they received SDF treatment within the past 3 months, had oral mucositis or ulcerative lesions, or had known sensitivity to silver or fluoride.

Procedures

Procedures were performed in the UCSF Pediatric Dentistry Clinic and the UCSF Benioff Children's Hospital Pediatric Clinical Research Center. Screening, review of medical history, and informed consent were obtained in the parent or caretaker’s primary language (English, Spanish, Cantonese) with the aid of professional medical interpreters. Assent was obtained for all participants 7 years or older. REDCap (Research Electronic Data Capture hosted at UCSF) was used to randomly assign participants to 1 of 7 timepoints for blood sampling: 2, 4, 6, 48, 72, 96, or 168 h post-SDF application. Participants were instructed to not brush their teeth on the morning of

the visit and were provided a non-fluoride toothpaste to use after treatment until their blood draw.

The test product was aqueous SDF [$Ag(NH_3)_2F$], Chemical Abstracts Service Registry No. 33040-28-7, 38.3-43.2% in purified water, 5.0-5.9% (weight by volume) fluoride and 24.4-28.8% (w/v) silver (Advantage Arrest®, Elevate Oral Care). The product was from a single lot and certified by the manufacturer. It was stored according to the manufacturer's instructions. SDF (1 to 2 drops) was dispensed from the manufacturer's multiuse bottle into a plastic dappen dish. Teeth were brushed with a soft toothbrush to remove debris. Difficult to access lesions were brushed with an orthodontic prophy angle to remove remaining debris in the cavitations. Affected areas were isolated with cotton rolls and dried with air before application of SDF. A mouth prop and saliva ejector were used to aid in maintaining isolation. SDF was applied to the carious lesion(s) with a dental applicator brush, and the teeth were isolated for about 1 minute. A water rinse, with high-volume evacuation, was performed. The amount of SDF applied was calculated as the difference in weight of the brush and dappen dish before and after SDF application. Participants were asked not to eat for 2 h after SDF application.

The blood draw was completed at UCSF Benioff Children's Hospital Pediatric Clinical Research Center at the assigned timepoint in fluoride-free collection tubes. Serum was obtained by centrifugation and stored at -80°C until analysis. Samples were analyzed by the Environmental Health Laboratory and Trace Organics Analysis Center at the University of Washington as described in detail by Lin et al. (2019). In brief, serum fluoride and silver concentrations were determined using fluoride ion selective

electrode and inductively coupled plasma-mass spectrometry, respectively. The limits of detection were 1 ng/mL (0.001 parts per million) for fluoride and 0.1 ng/mL for silver.

Data analysis

For the population pharmacokinetic analysis, silver concentration vs. time data were analyzed simultaneously using nonlinear mixed effects (NLME) modeling using Phoenix WinNonlin (version 8.3, Certara, Princeton, NJ). Model development was performed using the first order conditional estimates method with extended least squares (FOCE-ELS) estimation (with η-ε interactions). To establish the structural base model, data were fit to a 1 compartment model with first-order absorption and elimination. Due to the paucity of collected data describing the absorption of silver, the absorption rate constant for silver was fixed at 23.7 day^{-1} based on adult silver pharmacokinetic data (Lin et al. 2019), which results in peak concentrations attained at ~4 h and is in agreement with general trend in the pediatric data. The initial values for the parameters used in this process were obtained using the naïve pooled data. The estimated PK parameters were the apparent volume of distribution (V/F) and apparent oral clearance (CL/F).

To select an error model, additive and multiplicative error models were tested, and the additive model was selected based on the diagnostic plots. Given age and weight are highly correlated and weight is used by pediatric dentists for administering local anesthesia, we selected weight as a continuous covariate to evaluate for correlation with the PK parameters (V/F and CL/F). The inter-individual variability (IIV) in PK parameters of silver was evaluated by using an additive error model, as shown in

the following equation: Pi = Ptv·[weight/mean(weight)]·dPdWeight·exp(ηi), where Pi is the parameter value (either V/F or CL/F) of the ith individual, Ptv is the typical value of the population parameter, dPdWeight is the weight covariate on the parameter, and ηi is the random variable for the ith individual, which was 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 1 parameter) or 5.991 (for 2 parameters) in the objective function value (OFV) at $\alpha = 0.05$.

The model was internally validated using a bootstrap analysis in Phoenix WinNonlin, in which datasets were resampled with replacement from the original datasets and refitted to the model (n=1000). To better understand the effect of weight on silver PK in theoretical cohorts of children with varying weights (15 kg, 20 kg, 30 kg and 50 kg), the final population PK parameters and interindividual variability estimates were used to simulate silver concentration vs. time curves for 100 children per cohort following application of 33 mg SDF. The pharmacokinetic parameters (C_{max} [peak concentration], T_{max} [time to peak concentration], CL/F, V/F, $t_{1/2}$ [elimination half-life]) from these 100 simulations per cohort were estimated using non-compartmental modeling in Phoenix WinNonlin and summarized as mean values and 95% confidence intervals.

3. RESULTS

Participants

59 healthy participants were enrolled in the study and 55 children completed the study. Of those who did not complete the study, 3 children were not able to complete

the blood draw, and 1 child was lost to follow-up after SDF application. Participants were 45% female and were racially and ethnically diverse. The average age was 7.7 ± 2.9 years with 47% of participants between 3-6 years. An average of 33 ± 8 mg of SDF was applied (range: 10 to 55 mg) to an average of 7.3 ± 2.6 teeth (range: 2 to 15 teeth). The participant demographics and SDF application details are summarized in Table 1.

Fluoride and Silver Pharmacokinetics

Serum samples from 6 to 10 children were collected for each timepoint. Given some protocol deviations in the randomized blood draw times, the actual sampling times for each participant were used in the pharmacokinetic analyses.

Following SDF application, the serum fluoride concentrations ranged from 6 to 36 ng/mL (0.006 to 0.036 ppm) (Figure 1A). As baseline blood samples were not obtained, baseline serum fluoride concentrations corrections were not made to the post-SDF application fluoride concentrations. The median serum fluoride concentration was slightly higher in children during the first 6 h after SDF application (16 ng/mL) compared to subsequent sampling timepoints (i.e., 12, 11, 14, 11 ng/mL at 24, 48, 96, 148 h, respectively).

Following SDF application, the serum silver concentrations ranged from 1.4 to 46.2 ng/mL (Figure 1B). The coefficient of variation at each timepoint ranged from 46% (24 h) to 148% (48 h). A 1 compartment model with fixed absorption rate described the silver concentration vs. time data following application of SDF. Inclusion of intraindividual variability for the apparent volume of distribution (V/F) and apparent oral

clearance (CL/F) improved the model. The CV% for V/F and CL/F changed from 13% to 7% and from 39% to 16%, respectively (data not shown).

Based on an additive error model, weight was a significant predictor for V/F (Δobjective function value -8.99) and CL/F (Δobjective function value -11.6) and combined for V/F and CL/F (Δobjective function value -16.9). The parameter estimates of the final population PK model are presented in Table 2. The estimated model parameters of the final model were comparable to those following a bootstrap analysis (data not shown).

All relative standard error values of the parameter estimates were below 30%, indicating that the estimates obtained from the data were of relatively good precision (Table 2). 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 vs. time data following SDF application (Supplemental Figure 2).

To explore differences in silver exposures in children, the population pharmacokinetic parameters and interindividual variability estimates were used to simulate serum silver concentrations at a fixed 33 mg SDF amount for 100 children in each cohort (15 kg, 20 kg, 30 kg and 50 kg). The peak concentration (C_{max}), time to peak concentration (T_{max}), exposure (AUC; area under the curve), and elimination half-life ($t_{1/2}$) were summarized by cohort (Table 3). The simulated peak concentration and AUC were highest in the smallest children and decreased with increasing weight (Figure

2; Table 3). The simulated half-life was 15.5 d in 15 kg children and decreased to 4 d in 50 kg children.

4. DISCUSSION

The anatomical and physiological changes that occur throughout childhood affect the pharmacokinetics of compounds in the body (Chapron et al. 2021). It is, therefore, important to understand the kinetics of silver and fluoride in children after topical SDF application to assess this treatment in one of its intended use populations (U.S. Department of Health and Human Services 2000). This is the first clinical study to characterize the pharmacokinetics of silver in children following SDF treatment of dental caries lesions.

Participant serum fluoride concentrations (6-36 ng/mL) were comparable to adult concentrations (10-60 ng/mL) (Lin et al. 2019). As expected, maximum serum concentrations of fluoride with SDF were lower than those observed with fluoride varnish (60-120 ng/mL) (Ekstrand et al.1980) and fluoride gels (300-1443 ng/mL) (Ekstrand et al.1981). Our results suggest that a single SDF application does not appreciably increase serum levels of fluoride in children.

Participant serum silver concentrations ranged from 1.4-46.2 ng/mL, similar to the peak concentrations seen in adults in a study by Vasquez and colleagues (2012) (3-29 ng/mL) and higher than the study by Lin and colleagues (2019) (0.13-2.2 ng/mL). The amount of SDF applied and number carious or noncarious teeth treated differed between this pediatric study (10-55 mg SDF to 2-15 teeth) and the adult studies (3.8-11.9 mg to 3 noncarious sites (Vasquez et al. 2012); 4-11 mg SDF to 5 noncarious sites

(Lin et al. 2019)). We cannot account for the differences in serum concentrations between the adult studies, though the larger amount of SDF applied may partially explain the increased serum silver concentrations in children.

Based on the simulations, the estimated time to peak concentration was generally comparable in the simulated cohorts of children (15 to 50 kg) compared to adults (4.4-5.9 h versus 5.3 ± 5.8 h, respectively) (Lin et al. 2019). The estimated elimination half-life of silver was longer in the cohorts of children (4-15.5 d) compared to adults (1.9 ± 1.1 d) (Lin et al. 2019). Given the long half-life of silver, limited duration of the PK studies, and high degree of variability in silver concentrations in the children and adults, uncertainty remains around the true half-life of silver in children and adults. The predicted peak silver concentration for the cohorts of children (12.8-22.0 ng/mL) was within the range of peak concentrations observed in a study by Vasquez et al. (2012) (3-29 ng/mL), though observed serum silver concentrations were higher in some children. Consistent with the simulations from the physiologically based pharmacokinetic modeling of SDF in children (Chen et al. 2020), highest peak silver concentrations were observed in the smallest children (Figure 2), and the simulated silver exposure was 7.5-fold higher in 15 kg children compared to 50 kg children. This could be due to differences in body size, liver size and hepatic blood flow (Johnson et al. 2006) and may be impacted by factors such as differences in biliary excretion or the amount swallowed versus the amount absorbed in children and adults.

A clinical outcome in humans who ingest too much silver is argyria, a permanent bluish-gray discoloration of the skin with no associated adverse health effects (IRIS 1989). To avoid this cosmetic effect, the US EPA set the lowest observed adverse effect

level to 1 g total intravenous dose, which is approximately 90- to 500-fold above the amount of silver applied in this study and assumes a worst-case scenario in which the entire amount of SDF applied was ingested and absorbed. We know, however, that the amount applied is not the amount absorbed. SDF can stay within the tooth, be suctioned during isolation, soaked into a cotton roll, rinsed, and a small fraction can be swallowed and absorbed. Given these factors, the safety margin is likely larger. The EPA estimates that a 25 g oral dose is roughly equivalent to the 1 g intravenous dose (IRIS 1989), so the safety margin could be even larger, 2,000- to 10,000-fold. Additionally, low SDF dosage and intermittent use decrease risk. SDF treatment was well tolerated by participants and no adverse effects were observed or reported. This is consistent with other studies that have demonstrated the safety of this treatment (Duangthip et al. 2018; Milgrom et al. 2018).

The recruitment of a large population of ethnically diverse children across a broad age spectrum increases the generalizability of these results. The use of standard in-office methods of SDF application to carious lesions in therapeutic doses strengthens the clinical applicability of these results. Additionally, because participants had a high burden of dental caries necessitating treatment of multiple teeth, our data support the safe use of SDF for treating multiple caries lesions in children.

To minimize the invasiveness of this study, we drew a single blood sample per child at a specified timepoint and generated population pharmacokinetic parameter estimates. Additionally, we fixed the absorption rate constant based on the adult data (Lin et al. 2019) due to insufficient early timepoints. To fully capture the pharmacokinetics of silver and the return of serum silver concentrations to baseline

levels, a 2-month study in children with multiple early blood draws and weekly blood sampling may be necessary. Additional participants would permit more robust estimates of the pharmacokinetic parameters. However, a pediatric study of this design would involve more blood sampling and pose ethical and logistical challenges. As with the adult PK studies, we were unable to confirm the amount of silver absorbed by measuring the amount of silver excreted. It would be impractical to collect fecal samples for 2 months or longer given that silver has a long half-life and undergoes biliary excretion as its primary route of elimination (Klaassen 1979). Despite these limitations, these data are useful in evaluating the safety of SDF treatment and can serve as a foundation for future studies of SDF in children.

5. CONCLUSION

In conclusion, after SDF application in healthy children, serum fluoride concentrations fluctuated around previously reported baseline levels. Some serum silver concentrations in children exceeded concentrations observed in adults, and as expected, predicted silver exposures increased with decreasing weight. The low dosage and intermittent use of SDF mitigate risk. Our results support the continued development of SDF as a minimally invasive, safe, efficacious treatment for caries in children.

FIGURES

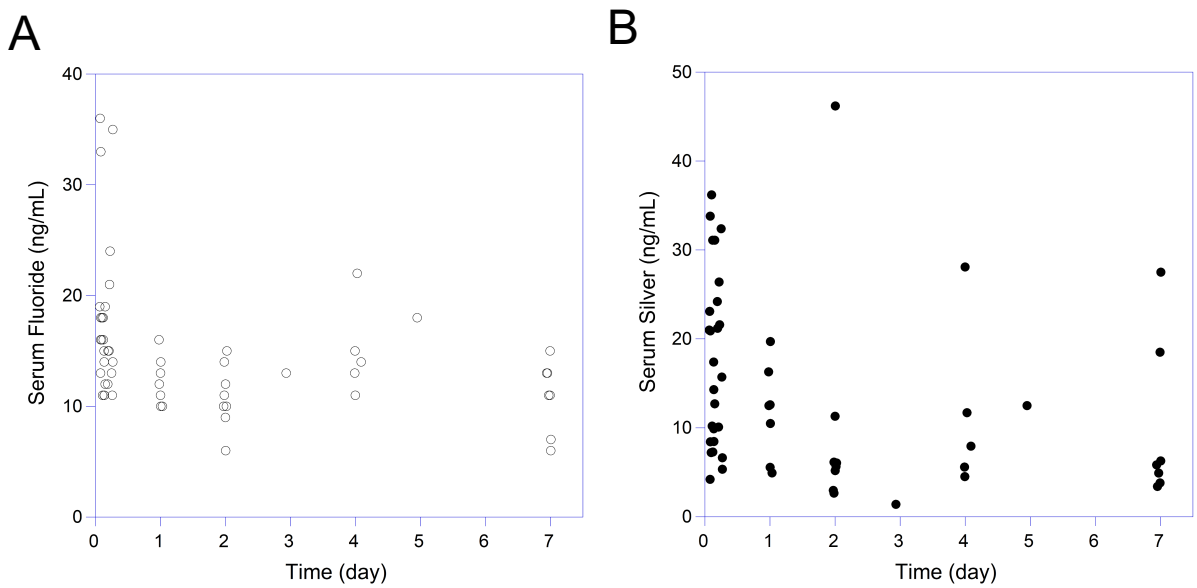


Figure 1. Observed serum fluoride and silver concentrations following application of 38% SDF to children. A) Serum fluoride concentrations. B) Serum silver concentrations. Each dot represents the measured serum concentration at the actual sampling time from a single child.

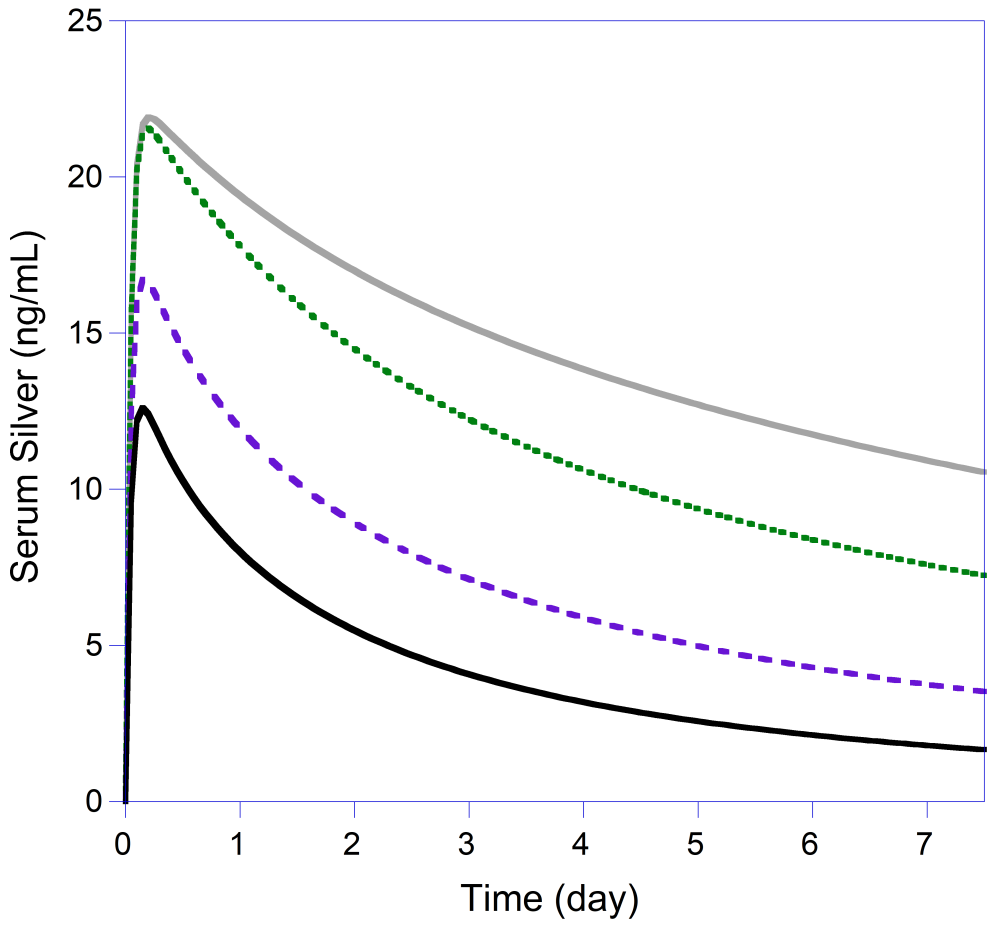
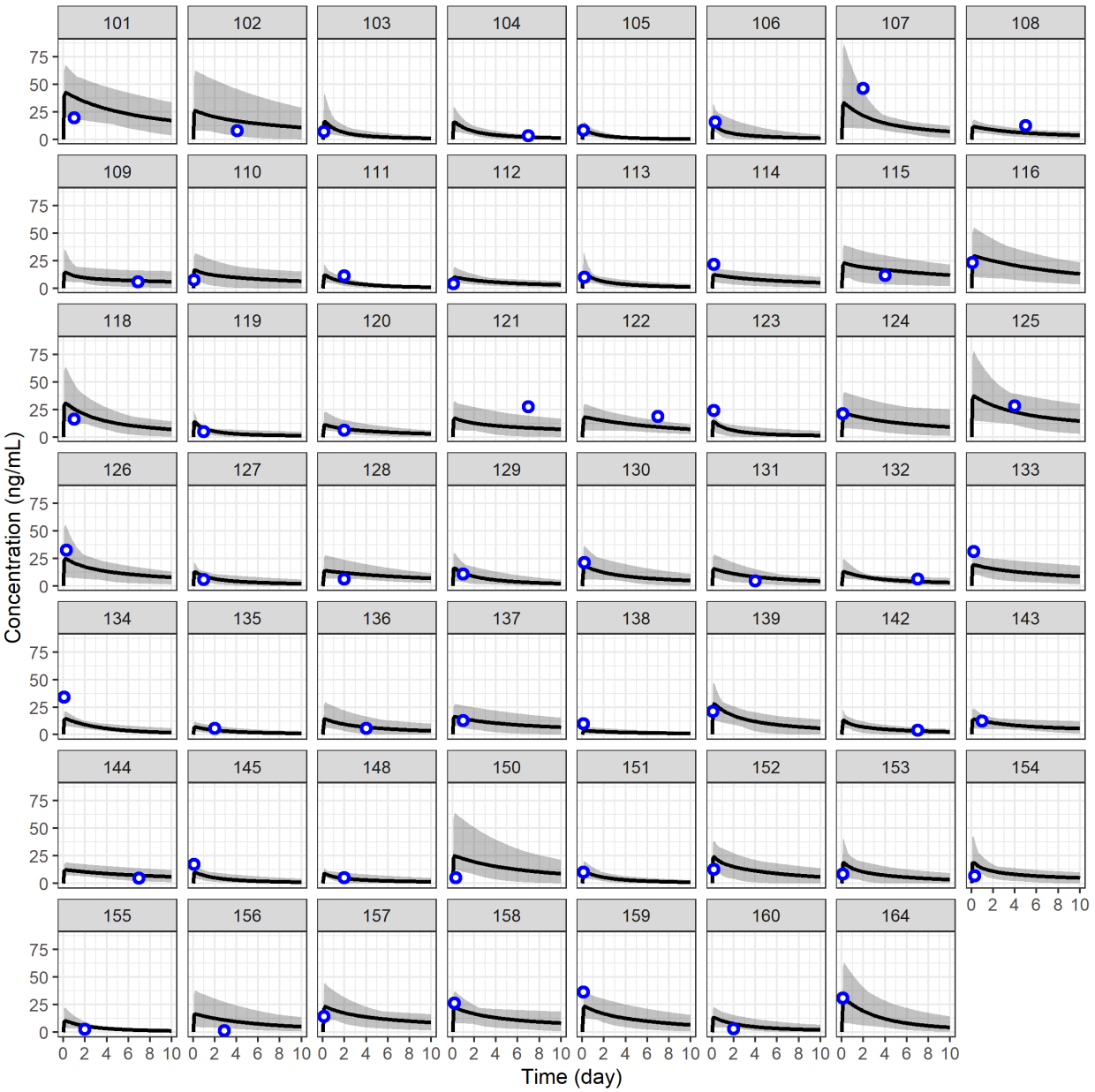
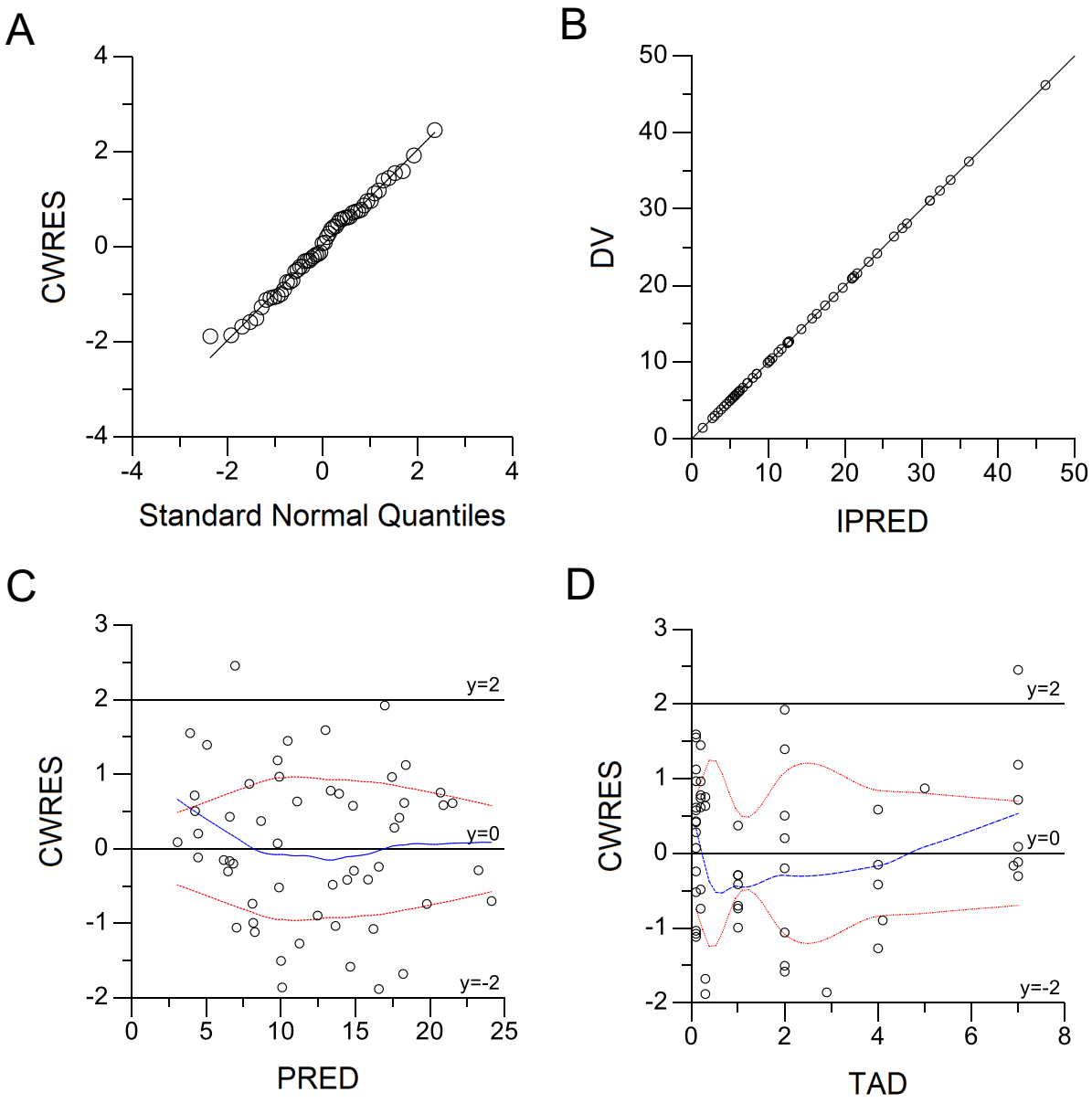


Figure 2. Average simulated serum silver concentration vs. time curves in cohorts of children following application of 33 mg of SDF (100 simulations per cohort). Cohorts: 15 kg (gray solid line), 20 kg (dotted line), 30 kg (dashed line), and 50 kg (black solid line).



Supplemental Figure 1. Visual predictive check (VPC) of the final model for silver for individual study participants. Observed concentrations are depicted by the dots. The predicted concentrations are represented by the lines. The 95% confidence interval (CI) is represented by the shaded region.



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

TABLES

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

Characteristic[a]	**Healthy Child Participants (N = 55)**
Age (years)	7.7 ± 2.9
3-6	26 (47%)
7-10	21 (38%)
11-13	8 (15%)
Weight (kg)[b]	32.6 ± 16.5 (15.0-73.6)
Gender	
Male	30 (55%)
Female	25 (45%)
Race	
White	11 (20%)
Asian	11 (20%)
African American	8 (15%)
Unknown or not reported	25 (45%)
Ethnicity	
Hispanic or Latino	24 (44%)
Not Hispanic or Latino	25 (45%)
Unknown or not reported	6 (11%)
Amount of SDF applied (mg)	33 ± 8 (10-55)
Number of teeth treated	7.3 ± 2.6 (2-15)

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

[b] Weight was missing for 1 participant (n = 54)

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

Parameters	Model Parameter Estimates (RSE%)
ka (day^{-1})	23.7 FIXED
V/F (L)	2279 (6.8%)
CL/F (L/day)	387 (16%)
Interindividual variability	
V/F BSV (%)	61 (13%)
CL/F BSV (%)	89 (28%)
dVdWeight	0.37 (17%)
dCLdWeight	1.66 (7.9%)
Residual error	0.074 (2.6%)

ka: absorption rate constant
V/F: apparent volume of distribution
CL/F: apparent oral clearance
BSV: between subject variability of the indicated parameter
dVdWeight: weight covariate on V/F
dCLdWeight: weight covariate on CL/F
RSE: relative standard error

Table 3. Estimated pharmacokinetic parameters of silver based on simulated silver concentration vs. time profiles for cohorts of children ranging from 15 to 50 kg (100 simulations per cohort).

	Simulated Pediatric Cohort			
Parameter	**15 kg**	**20 kg**	**30 kg**	**50 kg**
SDF Applied (mg)	33	33	33	33
T_{max} (hr)	5.9 (5.7 – 6.1)	5.6 (5.4 – 5.8)	4.9 (4.7 – 5.2)	4.4 (4.2 – 4.7)
C_{max} (ng/mL)	22.0 (19.4 – 24.6)	21.7 (18.4 – 24.9)	16.9 (14.6 – 19.1)	12.8 (11.3 – 14.3)
V/F (L/kg)	136 (117 – 155)	122 (103 – 142)	89 (77 – 101)	73 (61 – 86)
CL/F (L/hr/kg)	0.52 (0.41 – 0.63)	0.63 (0.51 – 0.74)	0.88 (0.71 – 1.05)	1.32 (0.93 – 1.72)
AUC (ng·day/mL)	382 (317 – 447)	260 (188 – 333)	106 (84 – 128)	51 (38 – 63)
$t_{1/2}$ (day)	15.5 (12.5 – 18.5)	12.1 (8.8 – 15.4)	5.9 (4.6 – 7.2)	4.0 (2.7 – 5.3)

Reported as average (95% confidence interval)
C_{max}: peak concentration
T_{max}: time of peak concentration
V/F: apparent volume of distribution
CL/F: apparent oral clearance
AUC: area under the curve
$t_{1/2}$: elimination half-life

REFERENCES

Chapron BD, Chapron A, Leeder JS. 2021. Recent advances in the ontogeny of drug disposition. Br J Clin Pharmacol. doi:10.1111/bcp.14821.

Chen KF, Milgrom P, Lin YS. 2020. Silver Diamine Fluoride in Children Using Physiologically Based PK Modeling. J Dent Res. 99(8):907–913. doi:10.1177/0022034520917368.

Contreras V, Toro MJ, Eliás-Boneta AR, Encarnación-Burgos A. 2017. Effectiveness of silver diamine fluoride in caries prevention and arrest: A systematic literature review. Gen Dent. 65(3):22–29.

Crystal YO, Marghalani AA, Ureles SD, Wright JT, Sulyanto R, Divaris K, Fontana M, Graham L. 2017. Use of silver diamine fluoride for dental caries management in children and adolescents, including those with special health care needs. Ped Dent. 39(5), 135E-145E.

Crystal YO, Niederman R. 2019. Evidence-Based Dentistry Update on Silver Diamine Fluoride. Dent Clin North Am. 63(1):45–68. doi:10.1016/j.cden.2018.08.011.

Duangthip D, Fung MHT, Wong MCM, Chu CH, Lo ECM. 2018. Adverse Effects of Silver Diamine Fluoride Treatment among Preschool Children. J Dent Res. 97(4):395–401. doi:10.1177/0022034517746678.

Ekstrand J, Koch G, Petersson LG. 1980. Plasma fluoride concentration and urinary fluoride excretion in children following application of the fluoride-containing varnish Duraphat®. Caries Res. 14(4):185–189. doi:10.1159/000260452.

Ekstrand J, Koch G, Lindgren LE, Petersson LG. 1981. Pharmacokinetics of fluoride gels in children and adults. Caries Res. 15(3):213–220. doi:10.1159/000260517.

Horst, JA., & Heima M. 2019. Prevention of dental caries by silver diamine fluoride. Compend Contin Educ Dent, 40(3), 158-163.

IRIS: U.S. Environmental Protection Agency, Integrated Risk Information System: Fluorine (soluble fluoride) (CASRN 7782-41-4); 1987. https://iris.epa.gov/static/pdfs/0053_summary.pdf. Accessed May 10, 2021.

IRIS: U.S. Environmental Protection Agency, Integrated Risk Information System: Silver (CASRN 7440-22-4); 1989. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0099_summary.pdf. Accessed May 10, 2021.

Johnson TN, Rostami-Hodjegan A, Tucker GT. 2006. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet. 45(9):931–956. doi:10.2165/00003088-200645090-00005.

Klaassen CD. 1979. Biliary excretion of silver in the rat, rabbit, and dog. Toxicol Appl Pharmacol. 50(1):49–55. doi:10.1016/0041-008X(79)90491-5.

Lin YS, Rothen ML, Milgrom P. 2019. Pharmacokinetics of 38% topical silver diamine fluoride in healthy adult volunteers. J Am Dent Assoc. 150(3):186–192. doi:10.1016/j.adaj.2018.10.018.

Milgrom P, Horst JA, Ludwig S, Rothen M, Chaffee BW, Lyalina S, Pollard KS, DeRisi JL, Mancl L. 2018. Topical silver diamine fluoride for dental caries arrest in preschool children: A randomized controlled trial and microbiological analysis of

caries associated microbes and resistance gene expression. J Dent. 68:72–78. doi:10.1016/j.jdent.2017.08.015.

Oliveira BH, Rajendra A, Veitz-Keenan A, Niederman R. 2019. The effect of silver diamine fluoride in preventing caries in the primary dentition: A systematic review and meta-analysis. Caries Res. 53(1):24–32. doi:10.1159/000488686.

U.S. 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. ICH. December 2000.

Vasquez E, Zegarra G, Chirinos E, Castillo JL, Taves DR, Watson GE, Dills R, Mancl LL, Milgrom P. 2012. Short term serum pharmacokinetics of diammine silver fluoride after oral application. BMC Oral Health. 12(1):1–7. doi:10.1186/1472-6831-12-60.

Yeung SST, Argaez C. 2017. CADTH rapid response reports: silver diamine fluoride for the prevention and arresting of dental caries or hypersensitivity: a review of clinical effectiveness, cost-effectiveness and guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health.

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