Establishing Pharmacokinetic Modeling of 38 percent Silver Diamine Fluoride in Children

Dillon Kampp, DDS[1], Travis Nelson, DDS, MSD, MPH[1], Marilynn Rothen, RDH, MS[1], Claudia Mariella Vera Reyes, DDS[1], Yvonne Lin, PhD[1], Peter Milgrom, DDS, PhD[1]

University of Washington School of Dentistry, Department of Pediatric Dentistry[1]

BACKGROUND

Over the last ~15 years silver diamine fluoride (SDF) has been utilized in the United States as an efficacious, low cost, and atraumatic treatment for caries management and desensitization. Currently approved by the FDA as a dentin desensitizer, one of the most common utilizations has been off-label as a caries treatment for pediatric patients who may not tolerate restorative dentistry due to behavior.

Despite its long history of use, with no side affects apart from the black staining of caries after application, the literature on absorption and elimination after SDF application is limited. Additionally, data on the pharmacokinetics of silver and fluoride after SDF application have only been available recently, primarily in adult subjects. Even less literature exists for pediatric populations.

PURPOSE

The purpose of this study was to further characterize basic pharmacokinetic (PK) parameters of SDF in healthy children. This study was designed to contribute to the ongoing effort to have SDF FDA approved for the management of caries.

METHODS

- This study recruited children between the ages of 2-13 at the University of Washington Center for Pediatric Dentistry.
- All participants were healthy and had caries lesions eligible for treatment with SDF.
- Participants were randomly assigned to different blood draw sampling times depending on age.
- Samples were analyzed to determine serum concentrations of both silver and fluoride at various timepoints. These measurements were utilized to generate models showing absorption and subsequent elimination of silver and fluoride.
- SDF was applied to lesions with dosage determined by weight of microbrush before and after application. Patients then waited on site until their respective sampling time. Additional samples were gathered when patients returned for their respective secondary sampling times.

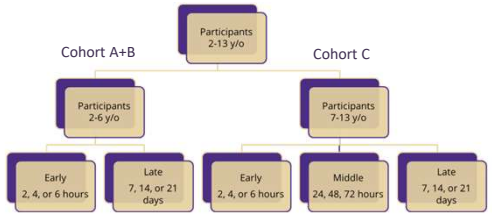

Figure 1. Randomization scheme

RESULTS

- 32 participants were recruited for this study, and 23 completed all blood draw sampling.
- The mean age in years was 7.1±3.1. The average amount of SDF applied was 19±23 mg. Due to the paucity and variability in the silver concentrations at early timepoints, the absorption rate constant for silver was fixed at 23.7. Population pharmacokinetic parameter estimates values for volume of distribution of silver (V) and clearance of silver (CL) were generated from our data.
- Bootstrap analysis was used to verify the reproducibility and/or robustness of the final population PK model for silver. Population PK parameters and interindividual variability estimates were used to generate simulated cohorts of patients of varying weights after application of 19mg of SDF (Figure 3).
- After SDF treatment, participant serum fluoride concentrations (<5-36 ng/mL) fluctuated around previously reported baseline levels in teenagers (3.04-15.4 ng/mL).
- Peak observed silver concentrations (range: 0.5-26.1 ng/mL) overlapped with the range of observed to adult peak concentrations (4-hr adult PK: 3-29 ng/mL; 24-hr adult PK: 0.13-2.2 ng/mL) observed a similar study Silver was eliminated with a half-life of approximately 7.2 days (95% CI: 6.2 - 8.2 days).

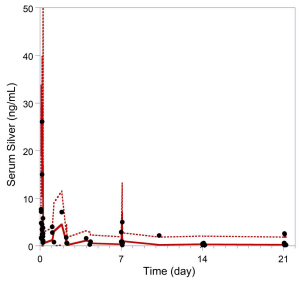

Figure 2. Observed serum fluoride concentrations following application of 38% SDF to children. The solid red line is the simulated concentration-time curve.

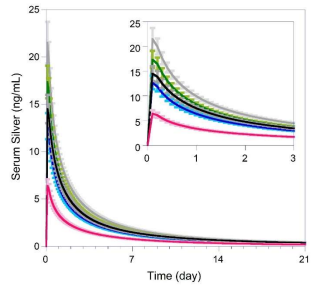

Figure 3. Average simulated serum silver concentration vs. time curves in cohorts of children following application of 19 mg of SDF. Cohorts: 12 kg (gray), 15 kg (green), 20 kg (blue), and 30 kg (black), and 40 kg (pink).

DISCUSSION

- 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.
- In this study no fluoride or silver concentrations exceeded the EPA limits.

CONCLUSION

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.