CE Course Handout

Silver Diamine Fluoride

Friday, June 10, 2016
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Since its approval in Japan more than 80 years ago,2 more than 2 million containers have been sold. The silver acts as an antimicrobial, the fluoride promotes remineralization and the ammonia stabilizes high concentrations in solution.3 Because silver diamine fluoride is new to American dentistry and dental education, there is a need for a standardized guideline, protocol and consent. The University of California, San Francisco, School of Dentistry paradigm shift committee assembled a subcommittee with the following goals:

- Use available evidence to develop a list of clinical indications.
- Define a protocol that maximized safety and efficacy and minimized inadvertent staining of clinical facilities.

Until now, no option for the treatment of dental caries in the U.S. besides restorative dentistry has shown substantial efficacy.1 Silver diamine fluoride is an inexpensive topical medicament used extensively in other countries to treat dental caries across the age spectrum. No other intervention approaches the ease of application and efficacy. Multiple randomized clinical trials — with hundreds of patients each — support its use for caries treatment, thus substantiating an intervention that addresses an unmet need in American dentistry. In August 2014, the Food and Drug Administration (FDA) cleared the first silver diamine fluoride product for market, and as of April 2015, that product is available.

UCSF Protocol for Caries Arrest Using Silver Diamine Fluoride: Rationale, Indications and Consent

Jeremy A. Horst, DDS, PhD; Hellene Ellenikiotis, DDS; and Peter L. Milgrom, DDS

ABSTRACT The Food and Drug Administration recently cleared silver diamine fluoride for reducing tooth sensitivity. Clinical trials document arrest and prevention of dental caries by silver diamine fluoride. This off-label use is now permissible and appropriate under U.S. law. A CDT code was approved for caries arresting medicaments for 2016 to facilitate documentation and billing. We present a systematic review, clinical indications, clinical protocol and consent procedure to guide application for caries arrest treatment.
Build an informed consent document at the eighth-grade reading level.

We conducted a systematic review, inquired of authors of published clinical and in vitro studies about details and considerations in their protocols and consulted experts in cariology and materials chemistry where evidence was lacking. The work of this committee resulted in the adoption of silver diamine fluoride use in the UCSF student clinics.

Methods

A literature review was designed by a medical librarian to search PubMed and the International Association of Dental Research abstract archive with the following search terms: “33040-28-7” OR “1Z00ZK3E66” OR “silver diamine fluoride” OR “silver fluoride” OR “silver diamine fluoride” OR “diammine silver fluoride” OR “ammonical silver fluoride” OR “ammoniacal silver fluoride”. Differences in nomenclature have led to confusion around this material. Another review was completed with the terms “dental” OR “caries” AND “silver nitrate” AND “clinical.”

Material

Silver diamine fluoride (38% w/v Ag(NH3)2F, 30% w/w) is a colorless topical agent comprised of 24.4-28.8% (w/v) silver and 5.0-5.9% fluoride at pH 10, and marketed as Advantage Arrest by Elevate Oral Care LLC (West Palm Beach, Fla.). Other companies may market silver diamine fluoride in the future following determination of substantial equivalence and FDA clearance.

Mechanisms

Silver diamine fluoride is used for caries arrest and treatment of dentin hypersensitivity. In the treatment of exposed sensitive dentin surfaces, topical application results in the development of a squamous layer on the exposed dentin, partially plugging the dentinal tubules. High concentration aqueous silver has been long known to form this protective layer. Decreased sensitivity in treated patients is consistent with the hydrodynamic theory of dentin hypersensitivity. Dental caries is a complex progression involving dietary sugars, bacterial metabolism, demineralization and organic degradation. The collagenous organic matrix is exposed once a dentin surface is demineralized and destroyed by native and bacterial proteases to enable a lesion to enlarge. Upon application of silver diamine fluoride to a decayed surface, the squamous layer of silver protein conjugates forms, increasing resistance to acid dissolution and enzymatic digestion. Hydroxyapatite and fluorapatite form on the exposed organic matrix, along with the presence of silver chloride and metallic silver. The treated lesion increases in mineral density and hardness while the lesion depth decreases. Meanwhile, silver diamine fluoride specifically inhibits the proteins that break down the exposed dentin organic matrix: matrix metalloproteinases, cathepsins and bacterial collagenases. Silver ions act directly against bacteria in lesions by breaking membranes, denaturing proteins and inhibiting DNA replication. Ionic silver deactivates nearly any macromolecule. Silver diamine fluoride outperforms other anticaries medicaments in killing cariogenic bacteria in dentinal tubules.

Silver and fluoride ions penetrate ~25 microns into enamel and 50-200 microns into dentin. Fluoride promotes remineralization, and silver is available for antimicrobial action upon release by re-acidification. Silver diamine fluoride arrested lesions are 150 microns thick. Artificial lesions treated with silver diamine fluoride are resistant to biofilm formation and further cavity formation, presumably due to remnant ionic silver. More silver and fluoride is deposited in demineralized than nondemineralized dentin. Correspondingly, treated demineralized dentin is more resistant to caries bacteria than treated sound dentin. When bacteria killed by silver ions are added to living bacteria, the silver is re-activated so that effectively the dead bacteria kill the living bacteria in a “zombie effect.” This reservoir effect helps explain why silver deposited on bacteria and dentin proteins within a cavity has sustained antimicrobial effects.

Clinical Evidence

Silver Nitrate Plus Fluoride Varnish

Before the FDA cleared silver diamine fluoride, some U.S. dentists sequentially applied silver nitrate then fluoride varnish to dentinal decay as the only available noninvasive option for caries treatment. Duffin rediscovered silver nitrate from the early literature, which had been lost.
to modern cariology. Surprisingly, there is no mention of silver nitrate in either of the American Dental Association Council on Scientific Affairs reports on Nonfluoride Caries-Preventive Agents or Managing Xerostomia and Salivary Gland Hypofunction, and it is not part of standard dental school curricula. Case series of carious lesions arrested by silver nitrate date to the 1800s. For example, in 1891, 87 of 142 treated lesions were arrested. Percy Howe, DDS, then director of the Forsyth Institute in Boston, added ammonia to silver nitrate, making it more stable and effective as an antimicrobial for application to any infected tooth structure from early cavitated lesions to infected root canals. Duffin added the application of fluoride varnish following silver nitrate, simulating silver diamine fluoride. While his clinic doubled in patients, cases needing general anesthesia disappeared. His review of randomly selected charts showed only seven of 578 treated lesions progressed within two and a half years to the point that extractions were needed. 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**Ongoing Trials**

Unpublished reports of clinical studies unanimously confirm better caries arrest and/or prevention by silver diamine fluoride over control or other materials. A one-year report of a study of the elderly demonstrated that the addition of a saturated solution of potassium iodide (SSKI) to decrease discoloration did not significantly alter caries arrest or prevention. This was confirmed in the two-year examinations (personal communication, Edward Lo). A one-year report of a study in children showed that the application once per week for three consecutive weeks, once per year, was more effective than that of single annual application. Other studies have recently begun to evaluate the ability of silver diamine fluoride to arrest interproximal carious lesions, to compare the relative efficacy of silver diamine fluoride to the combination of silver nitrate plus fluoride varnish and to compare the effects on populations with or without access to fluoridated water. Final reports from these studies will follow in the coming years.

**Recommendations From the Literature on Clinical Efficacy**

These studies show that 38% silver diamine fluoride is effective and efficient in arresting and preventing carious lesions. Application only to lesions appears to be similarly effective in preventing cavities in other teeth and surfaces as applying directly. Single application appears insufficient for sustained effects, while annual re-application results in remarkable success, and even greater effects with semi-annual application. From these data, we recommend twice-per-year application, only to carious lesions without excavation, for at least the first two years.

For any patient with active caries, we recommend considering replacement of fluoride varnish as the primary means to prevent new lesions, with application of silver diamine fluoride to the active lesions only. For patients without access to both sealants and monitoring, silver diamine fluoride is the agent of choice for prevention of caries in permanent molars — particularly as there is no margin to leak and thereby facilitate deep caries and it does not stain sound enamel.

**FIGURE 1.** Graphic summary of randomized controlled trials demonstrating caries arrest after topical treatment with 38% silver diamine fluoride (SDF). Studies are arranged vertically by frequency of silver diamine fluoride application. Caries arrest is defined as the fraction of initially active carious lesions that became inactive and firm to a dental explorer. SDF [38% unless noted otherwise], q6mon, every six months; q1year, every year; q3mon, every three months; GIC, glass ionomer cement; NaF, 5% sodium fluoride varnish; + OHI q6mon, SDF every year and oral hygiene instructions every six months.

For 373 6-year-olds, Llodra et al., 2005: 3.2 lesions at start.

For 181 3- to 4-year-olds, Zhi et al., 2012: 3.4 surfaces at start.

For 308 3- to 5-year-olds, Chu et al., 2002: 6 lesions at start.

For 227 60- to 89-year-olds, Zhang et al., 2013: 0.91 lesions at start.

For 624 3- to 9-year-olds, Yee et al., 2009: 6.8 lesions at start.

For 322 5- to 6-year-olds, Santos et al., 2014: 3.8 lesions at start.
Safety

Maximum Dose and Safety Margin

The margin of safety for dosing is of paramount concern. In gaining clearance from the FDA, female and male rat and mouse studies were conducted to determine the lethal dose (LD50) of silver diamine fluoride by oral and subcutaneous administration. Average LD50 by oral administration was 520 mg/kg and by subcutaneous administration was 380 mg/kg. The subcutaneous route is taken here as a worst-case scenario. One drop (25 μL) is ample material to treat five teeth and contains 9.5 mg silver diamine fluoride. Assuming the smallest child with caries would be in the range of 10 kg, the dose would be 0.95 mg/kg child. Thus, the relative safety margin of using an entire drop on a 10 kg child is 380 mg/kg LD50/0.95 mg/kg dose = four-hundredfold safety margin. The actual dose is likely to be much smaller, for example 2.37 mg total for three teeth was the largest dose measured in six patients. The most frequent application monitored in a clinical trial was weekly for three weeks, annually. Thus, we set our recommended limit as one drop (25 μL) per 10 kg per treatment visit, with weekly intervals at most. This dose is commensurate with the Environmental Protection Agency’s (EPA) allowable short-term exposure of 1.142 mg silver per liter of drinking water for one to 10 days (Agency for Toxic Substances and Disease Registry, ATSDR, 1990).

Cumulative exposure from lower-level acute or chronic silver intake has no real physiologic disease importance, but the bluing of skin in argyria should obviously be avoided. The EPA set the lifetime exposure conservatively at 1 gm to safely avoid argyria. The highest applied dose for three teeth measured in the pharmacokinetic study, 2.37 mg, would enable > 400 applications. Silver

Longer studies are needed to determine whether caries arrest and prevention can be maintained with decreased application after two to three years, and whether more frequent use would enhance efficacy. Traditional or nontraditional restorative approaches, such as the atrumatic restorative technique (ART) and Hall crowns, should be performed as dictated by the response of the patient, disease progression and the nature of individual lesions.
nitrilotriacetic acid (neither typically a 25% solution) has been used for more than 100 years in the U.S. without incident, including acceptance by the ADA, and in other countries for arresting dental caries.3

Adverse Effects

Not a single adverse event has been reported to the Japanese authorities since they approved silver diamine fluoride (Saforide, Toyo Seiyaku Kasei Co. Ltd., Osaka, Japan) more than 80 years ago.47 The manufacturer estimates that more than 2 million multi-use containers have been sold, including > 41,000 units in each of the last three reporting years.

In the nine randomized clinical trials in which silver diamine fluoride was applied to multiple teeth to arrest or prevent dental caries, the only side effect noted was for three of 1,493 children or elderly patients monitored for one to three years who experienced “a small, mildly painful white lesion in the mucosa, which disappeared at 48 hours without treatment.”48 The occurrence of reversible localized changes to the oral mucosa was predicted in the first reports of longitudinal studies.49 No adverse pulpal response was observed.

Gingival responses have been minimal. In a pharmacokinetic study of silver diamine fluoride application to three teeth in each of six 48- to 82-year-olds, no erythema, bleeding, white changes, ulceration or pigmentation was found after 24 hours. Serum fluoride hardly went up from baseline, while serum silver increased about tenfold and stayed high past the four hours of measurement.40 In a two-site hypersensitivity trial of 126 patients in Peru, at baseline 9 percent of patients presented redness scores of 2 (1 being normal, 2 being mild to moderate redness and 3 being severe); and after one day, 13 percent in silver diamine fluoride treated patients versus 4 percent in controls. All redness was gone at seven days. Meanwhile, gingival index improved slightly in silver diamine fluoride treated patients.51 Nonetheless, gingival contact should be minimized. In our experience, it has been adequate to coat the nearby gingiva with petroleum jelly, use the smallest available microsponge and dab the side of the dappen dish to remove excess liquid before application.

Concerns for fluoride safety are most relevant to chronic exposure,52 whereas this is an acute exposure. Chronically high systemic fluoride results in dental fluorosis. The ubiquitous use of fluoride-based gas in general anesthetics has shown that the first acute response is transient renal holding, and is rare.53 Concerns have been raised about poorly controlled silver diamine fluoride concentrations52 and fluorosis appearing in treated rats.54 However, silver and fluoride levels are closely monitored for the U.S. product, and the Health Department of Western Australia conducted a study that found no evidence of fluorosis resulting from long-term proper use of silver diamine fluoride.55 Therefore, we have concluded that the development of fluorosis after application of the U.S.-approved product is not a clinically significant risk.

Silver allergy is a contraindication. Relative contraindications include any significant desquamative gingivitis or mucositis that disrupts the protective barrier formed by stratified squamous epithelium. Increased absorption and pain would be expected with contact. Heightened caution and use of a protective gingival coating may suffice.

A saturated solution of potassium iodide (SSKI) is contraindicated in pregnant women and during the first six months of breastfeeding because of the concern of overloading the developing thyroid with iodide; thyroid specialists suggested a pregnancy test prior to use in women of childbearing age uncertain of their status.

Nonmedical Side Effects

Silver diamine fluoride darkens carious lesions. At least for children, many parents have seen the color changes as a positive indication that the treatment was effective.29 Application of an SSKI immediately following silver diamine fluoride treatment is thought to decrease staining (patent US6461161). This is an off-label use; potassium iodide is approved as an over-the-counter drug to facilitate mucus release to breathe more easily with chronic lung problems and to protect the thyroid from radioactive iodine in radiation emergencies. In our clinical experience, SSKI helps but does not dramatically effect stain; arrested lesions normally darken. Most stain remains at the dentin-enamel or cementum-enamel junction. However, SSKI maintains resistance to biofilm formation or activity in laboratory studies.20 Also, SSKI maintained caries arrest efficacy in the early results of an ongoing clinical trial.42 Meanwhile, silver diamine fluoride-treated lesions can also be covered with GIC or composite (see below for discussion on bonding).

Patients note a transient metallic or bitter taste. In our experience, with judicious use, the taste and texture...
response is more favorable than the response to fluoride varnish.

Even a small amount of silver diamine fluoride can cause a “temporary tattoo” to the skin (on the patient or provider), like a silver nitrate stain or henna tattoo, and does no harm. Stain on the skin resolves with the natural exfoliation of skin in two to 14 days. Universal precautions prevent most exposures. Long-term mucosal stain, local argyria akin to an amalgam tattoo, has been observed when applying silver nitrate to intraoral wounds; we anticipate similar stains with submucosal exposure to silver diamine fluoride.

Silver diamine fluoride stains clinic surfaces and clothes. The stain does not come out once it sets. Spills should be cleaned up immediately with copious water, ethanol or bleach. High pH solvents such as ammonia may be more successful. Secondary containers and plastic liners for surfaces are adequate preventives.

**Effects on Bonding**

Using a contemporary bonding system, silver diamine fluoride had no effect on composite bonding to noncarious dentin using either self-etch or full-etch systems. In one study, simply rinsing after silver diamine fluoride application avoided a 50 percent decrease in bond strength for GIC. In another study, increased dentin bond strength to GIC was observed. Silver diamine fluoride decreased dentin bonding strength of resin-based crown cement by approximately one-third. Thus, rinsing will suffice for direct restorations, while excitation of the silver diamine fluoride-treated superficial dentin is appropriate for cementing crowns.

**Indications**

Countless patients would benefit from conservative treatment of nonsymptomatic active carious lesions. We discuss the following indications.

First, extreme caries risk is defined as patients with salivary dysfunction, usually secondary to cancer treatment, Sjogren’s syndrome, polypharmacy, aging or methamphetamine abuse. For these patients, frequent prevention visits and traditional restorations fail to stop disease progression. Similar disease recurrence occurs in severe early childhood caries.

Second, some patients cannot tolerate standard treatment for medical or psychological reasons. These include the precooperative child, the frail elderly, those with severe cognitive or physical disabilities and those with dental phobias. Various forms of immunocompromise mean that these same patients have a much higher risk of systemic infection arising from untreated dental caries. Many only receive restorative care with general anesthesia or sedation and others are not good candidates for general anesthesia due to frailty or another medical complexity. The Centers for Disease Control and Prevention (CDC) estimates 1.4 million people in the U.S. live in nursing homes and 1.2 million live in hospice. These individuals tend to have medical, behavioral, physical and financial limitations that beg a reasonable option.

Third, some patients have more lesions than can be treated in one visit, such that new lesions arise or existing lesions become symptomatic while awaiting completion of treatment. This is particularly relevant to the dental school setting where treatment is slow. American dentistry has been desperately lacking an efficient instrument to be used at the diagnostic visit to provide a step toward controlling the disease.

Fourth, some lesions are just difficult to treat. Recurrent caries at a crown margin, root caries in a furcation or the occlusal of a partially erupted wisdom tooth pose a challenge to access, isolation and cleansability necessary for restorative success.

Following the above considerations, we developed four indications for treatment of dental caries with silver diamine fluoride:

1. Extreme caries risk (xerostomia or severe early childhood caries).
2. Treatment challenged by behavioral or medical management.
3. Patients with carious lesions that may not all be treated in one visit.
4. Difficult to treat dental carious lesions.

Finally, these indications are for our school clinics. They do not address access to care. The U.S. Department of Health and Human Services estimates 108 million Americans are without dental insurance, and there are 4,230 shortage areas with 49 million people without access to a dental health professional. Unlike fillings, failure of silver diamine fluoride treatment does not appear to create an environment that promotes caries, and thus needs to be monitored. Thus, a final important indication is:

5. Patients without access to dental care.

**Clinical Application**

We considered practical strategies to maximize safety and effectiveness in the design of a clinical protocol for the UCSF dental clinics (FIGURE 3). The key factor is repeat application...
over multiple years. We believe that dryness of the lesion during application is also important. Isolation with gauze and/or cotton rolls is sufficient, while air drying prior to application is thought to improve effectiveness. Allowing one to three minutes for the silver diamine fluoride to soak into and react with a lesion is thought to effect success.

Allowing only a few seconds to soak in due to the cooperation limits of very young patients commonly results in arrest. Application time in clinical studies does not correlate to outcome. However, our committee decided to be cautious in our recommendations for initial use. Longer absorption time also decreases concerns about removing silver diamine fluoride with a posttreatment rinse. Removing any excess material with the same cotton used to isolate is routine to minimize systemic absorption.

Many clinicians place silver diamine fluoride at the diagnostic visit, then at one and/or three-month follow ups, then at semiannual recall visits (six, 12, 18, 24 months). Whether application needs
to continue after two or three years to maintain caries arrest is not known. Another approach is simply to substitute silver diamine fluoride for any application of fluoride varnish to a patient with untreated carious lesions. Increased frequency with higher disease burden follows the caries management by risk assessment (CAMBRA) principles. It is relevant to take photographs to track lesions over time.

Efforts to improve the penetration of silver diamine fluoride into affected dentin by chemical cavity preparation have not been studied but are being explored clinically. Pretreatment with ethylenediaminetetraacetic acid (EDTA) to remove superficial hydroxyapatite in affected dentin may open the dentinal tubules to further silver diamine fluoride penetration. Pretreatment with hypochlorite (bleach) may help breakdown bacteria and exposed dentin proteins, but this may be redundant to the action of the silver. Hypochlorite to decrease discoloration after silver diamine fluoride treatment is not recommended, as the color comes from silver that cannot be broken down like organic chromophores and might break down dentin proteins stabilized against the effects of bacteria and acid by interactions with silver.

Experience with the combination of silver nitrate plus fluoride varnish (see above) has many practitioners asking about a topical varnish after silver diamine fluoride placement to prevent silver diamine fluoride taste and keep the silver diamine fluoride in the lesion. We see no evidence that varnish would help achieve either goal. Varnish does not seal. Rather, allowing more time for residence and diffusion of silver diamine fluoride to react with and dry into the lesion is more likely to improve effectiveness. Also, in our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

Decreased darkening of lesions in the esthetic zone improves acceptance. SSKI is an option if the patient is not pregnant, though significant darkening should still be expected. SSKI and silver diamine fluoride are not to be combined prior to application — SSKI can be placed after drying the silver diamine fluoride-treated tooth. Silver diamine fluoride does not prevent restoration of a lesion, thus it does not prevent esthetic options. While silver diamine fluoride has been shown to be more effective than ART or interim restorative treatment (IRT), the two are compatible and can be combined across one or more visits.

The California Business and Professions Code permits dental hygienists and assistants to apply silver diamine fluoride for the control of caries because they are topical fluorides (Section 1910,(b)). Physicians, nurses and their assistants are permitted to apply fluorides in California and in many other states and federal programs. The recent decision of the Oregon Dental Board to allow dental hygienists and assistants to place silver diamine fluoride under existing rules for topical fluoride medicaments sets a precedent. Dental hygienists and assistants in Oregon were barred from providing silver nitrate in a previous decision. All providers need to be trained. Applications should be tracked if applied to the same patient by multiple clinics.

In our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

**Documentation and Billing**

A new code, D1354, for “interim caries arresting medication application” was approved by the Code on Dental Procedures and Nomenclature (CDT) Code Maintenance Commission for 2016. The code definition is “Conservative treatment of an active, nonsymptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without mechanical removal of sound tooth structure.” The CDT Code is the U.S. HIPAA standard code set and is required for billing. The Commission includes representatives from the major insurers, Medicaid, ADA, AGD and specialty organizations. Insurers are in the process of evaluating coverage for this treatment.

**Legal Considerations**

Silver diamine fluoride is cleared by the FDA for marketing as a Class II medical device to treat tooth sensitivity. We are discussing off-label use as a drug to treat and prevent dental caries. This is a parallel situation to fluoride varnish, which has the same device clearance but is ubiquitously used off label by dentists and physicians as a drug to prevent caries. The same public health dentists who achieved the FDA device clearance are now applying for a dental caries indication. However, this is a more complicated process, normally only carried out by large pharmaceutical companies, and is likely to take longer.

**Consent**

Because silver diamine fluoride is new in the U.S., it is important to communicate effectively. In the UCSF clinics, we are using a special consent form (FIGURE 4) as a way to inform patients, parents and caregivers, and...
to standardize procedures because we have so many inexperienced student clinicians. All practices have established procedures for consent and an extra form may not be needed in the community. The normal elements of informed consent apply. We sought to ensure awareness of the expected change in color of the dentin as the decay arrests, likelihood of reapplication and contraindications in the presence of silver allergy and stomatitis. Note the importance of distinguishing between allergy to nickel and other trace metals rather than silver allergy, which is rare. We used readability measurements to guide intelligibility and included a progressively discoloring lesion to show stain of a lesion but not healthy enamel.
The UCSF paradigm shift committee subcommittee on silver caries arrest included Sean Mong, DDS, ED; Spomenka Djojarovic, DDS, MS; Paul Atkinson, DDS, PhD; George Taylor, DMD, MPH, DrPH; Natalie Heavilin, DDS; Ling Zhan, DDS, PhD; John Featherstone, PhD; Helleine Ellenikisots, DDS; and Jeremy Horst, DDS, PhD. Thanks to Linda Milgrom for designing the PubMed search. Thanks to Chad Zillich, DDS, for help with the literature review. Thanks to study authors, particularly Edward Lo, BDS, MDS, PhD; Chun Hung Chu, BDS, MDS, PhD; and Geoff Knight, BDSc, MSc, MBA, for helpful discussions.

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