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The History and Use of Silver Diamine Fluoride in Dentistry: A Review

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ABSTRACT Silver has a long history of use in medicine, even before its antimicrobial properties were fully understood. Dentistry's recent paradigm shift to medical management of oral disease elevates the use of medicaments. After years of use in the developing world, silver diamine fluoride has emerged as a successful alternative to invasive dental treatment in the United States. This medicinal option to bridge primary prevention and surgical treatment holds exciting promise for future development and research.

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Humans have valued silver for thousands of years for its antimicrobial properties. Even before the advent of germ theory, Alexander the Great stored water in silver containers on his campaigns, ancient Romans described placing silver foil in wounds in their first book of medicine and American settlers traveling west to California dropped silver coins in their water barrels to slow the growth of algae and bacteria.[1] As the microbial origin of disease became better understood and antibiotics were developed, silver continued to play an important role in creating successful and safe medical devices such as sutures, catheter parts, cardiac devices and other surgical appliances.[2]

Silver was first used in dentistry as early as the 1840s in the form of "nitrate of silver" (known today as silver nitrate, $AgNO_3$). This salt is extremely caustic and early American dentists used it to instantaneously cauterize carious lesions in order to achieve an effect analogous to the hard, dark crust observed on teeth whose untreated decay had fortuitously arrested naturally over time.[3] Silver nitrate continued to be a popular dental medicament through the era of G.V. Black and his modernization of operative dentistry. In 1917, an ammoniacal silver nitrate solution ($AgNH_3NO_3$) was developed and marketed as an antimicrobial product that purportedly could penetrate even deeper into dentin. Until the 1950s, this "Howe's solution" was used to sterilize lesions after preparation and was even advocated as a disinfectant in root canal therapy.[4]

In the 1970s, the Western Australia School Dental Service used silver fluoride (AgF) as the initial part of a minimally invasive treatment process for a cohort of disadvantaged young children in New South Wales.[5] In order to systematically decrease the large backlog of dental cases in this rural area, AgF was seen as essential to inhibiting the growth of

existing lesions. This step was followed by an application of stannous fluoride (SnF_2) to act both as a reducing agent for AgF and to prevent new lesions from occurring. This two-step "metal fluoride" approach resulted in 74 percent of the existing lesions remaining unchanged and only 35 percent of all lesions requiring additional surgical treatment. Despite this combination's success in decreasing caries, there were few studies after the 1990s investigating this method.[4]

A Brief History of Silver Diamine Fluoride in Dentistry

Silver diamine fluoride (SDF) was first investigated as part of Mizuho Nishino, PhD's thesis at Osaka University in Japan in 1969.[6] She sought to combine the powerful antimicrobial properties of silver with the benefits of a high dose of fluoride. This formulation also resulted in a precipitate that occluded dentinal tubules and reduced hypersensitivity.[7] Soon after, "diammine silver fluoride" was granted approval from the Central Pharmaceutical Council of the Ministry of Health and Welfare of Japan as a cariostatic agent and marketed under the name Saforide (Toyo Seiyaku Kasei Co. Ltd., Osaka, Japan). This compound, $AgF(NH_3)$,[2] is commonly misspelled or misinterpreted as silver diamine fluoride, when in fact the proper terminology is silver diammine fluoride as it contains two ammine groups (NH_3), not two amine groups (NH_2).[4] The use of the term "diamine" is so ubiquitous, however it has become the accepted form both in the scientific and marketing literature.

In vivo and in vitro studies of SDF as an alternative dental treatment initially emerged from dental public health researchers in the developing world, where access to oral health care is extremely limited. Most of these primary population studies came from teams in Argentina, Brazil, China, Cuba, Japan and Nepal.[8,9] The results of these studies are challenging to analyze because of their diverse methodology, inconsistent inclusion criteria, lack of standardized controls and dissimilar outcome criteria, but several key themes emerged. First, a concentration of 38% SDF was found to be superior at arresting caries compared to lower concentrations of 10 or 12%.[10] This was true with or without reducing agents such as potassium iodide or tannic acid found in tea.[11,12] Second, SDF was superior at arresting dental caries and preventing new caries compared to fluoride varnish alone, interim therapeutic restorations (ITR) with fluoride-releasing glass ionomer cement (GIC) or other medicaments and low-cost interventions such as chlorhexidine and oral hygiene instruction.[8,13,14] This however did not hold true when SDF was used as a sealant over noncavitated molar grooves. In these studies, it performed worse than or equal to GIC or resin sealants.[11,15,16] Finally, multiple applications of SDF were found to be more successful at arresting dental caries than one-time placement. There was no consistence evidence for what the optimal frequency and time interval between these applications might be or the variables that could influence these protocols, but most recommend an application every six to 12 months.[8,17]

> In October 2016, the FDA awarded SDF the designation of "breakthrough therapy" based on its arrest of dental decay in children and adults, a first for an oral health therapy.

SDF gained clearance from the U.S. Food and Drug Administration (FDA) as a Class II medical device in August 2014. Similar to 5% sodium fluoride varnish, its approval for use to treat dentin hypersensitivity in adults aged 21 and older was grandfathered in because it was in use before 1976. Its physical ability to block dentin tubules allowed it to be classified as a medical device, rather than a drug, paving the way for expedited approval. In October 2016, the FDA awarded SDF the designation of "breakthrough therapy" based on its arrest of dental decay in children and adults, a first for an oral health therapy. This distinction identifies SDF as a drug "to treat a serious or life-threatening disease or condition" and affirms that "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies."[18] This marked the first time that oral disease had been categorized as a serious medical condition and elevated its importance as a significant public health issue. As of this writing, SDF is manufactured by one company in the U.S.

Utilization of SDF

Medical Management of Caries

The resurgence of using silver ion products in dentistry stems from the growing movement to shift the surgical management of dental caries to a medically managed process. In medicine, care exists in three broad levels: primary, secondary and tertiary care. For example, primary care of noninsulin-dependent diabetes mellitus includes preventive measures such as eating a healthy diet, maintaining appropriate body weight and regular exercise. Secondary care for this disease includes intervention with medications such as metformin or sulfonylureas. If the disease continues to

progress, tertiary care in the form of surgery (e.g., bariatric to maintain body weight or limb amputation) may be necessary. From the profession's barber-surgeon origins until the late 20th century, dentistry was concerned primarily with tertiary treatment of oral disease sequelae. As more of the infectious process was understood and with recognition that surgical treatment alone was not a cure, the profession embraced a medical model to manage the disease.

A 2001 consensus statement from the National Institutes of Health affirmed that this paradigm shift involved assessing the caries risk of a patient and providing preventive measures as necessary based on this risk.[19] Primary care, including oral hygiene instruction, dietary counseling and fluoride supplementation was formally included to address specific patient risk factors.[20] Introduction of pharmaceuticals as secondary care was the next logical step in full adoption of this model. Dental chemotherapeutics (e.g., high-concentration fluorides, pellicle-inhibiting drugs such as chlorhexidine and silver ion compounds) act as adjunct options to the surgical treatment of these lesions as caries-inhibiting and caries-arresting medications. Currently, SDF is covered under the Current Dental Terminology code D1354 as set forth by the American Dental Association. This is designated for a caries-arresting medicament to topically treat an existing asymptomatic carious lesion without removal of tooth structure and can be used by all properly trained dental professionals. Future research will hopefully continue to add secondary care adjuncts to the dental arsenal.

Mechanism of SDF

SDF is a uniquely powerful caries-arresting medicament because of the combined antibacterial properties of silver, the resulting precipitated barrier and the high dose of fluoride delivered. The two main components, fluoride and silver, are made soluble in water by the addition of ammonia. While metallic silver is inert, silver ions are a broad-spectrum antimicrobial that has high biocompatibility and low toxicity in humans. These ions act as tiny "silver bullets" that damage and degrade bacterial cell walls, disrupt bacterial DNA synthesis and replication and disrupt intracellular metabolic activity, eventually leading to cell death.[21] These killed bacteria further act as a carrier for silver ions and can kill living bacteria nearby in a process known as the "zombie effect."[22]

Once applied, a physical barrier precipitates out of the clear solution onto the carious lesion. Two major products form — silver phosphate (Ag_3PO_4), which acts a reservoir of phosphate ions, and calcium fluoride (CaF_2), which is a pH-regulated fluoride supply available during cariogenic challenge.[4,6] Minor products such as silver-protein complexes form, but their role is poorly understood. It is hypothesized that silver fills the microtubules, further sealing the tooth from disease.[23] Free silver ions in the lesion or other physical harbors (e.g., demineralized crevices or craze lines) are reduced by environmental oxygen and turn the lesion black, which is the major nonmedical side effect of this medicament (**FIGURE**).[12] A small decrease in discoloration is possible by binding free silver ions with an application of potassium iodide, however the darkened color remains a concern in aesthetic areas. A recent study reported that parent acceptability of the resulting staining was low for anterior teeth (29.7 percent), but acceptance increased if the choice was between SDF application and treatment under general anesthesia (60.3 percent).[24]

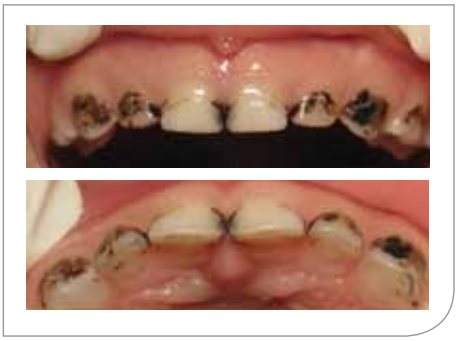

FIGURE. Black staining characteristic of treatment with SDF on a 3-year-old patient. (Courtesy of Daniel G. Raether, DDS, MS, private practice, Plymouth, Minn.)

To date, this medicament has the highest concentration of fluoride ions available on the market. The 5% SDF solution contains 44,800 fluoride parts per million (ppm), almost twice that of 5% sodium fluoride varnish containing 22,600 ppm. In this concentration, SDF reacts with calcium and phosphate ions to produce fluorohydroxyapatite crystals, which are less susceptible to solubility and crucial to tooth remineralization.[25] Despite the high concentration, the small amount required to be effective suggests that SDF is well within the margin of safety for use.[26]

Indications for Use

As medicament options for the treatment of dental caries expand, their potential uses will become further defined and perhaps more specialized. SDF is currently only approved in the U.S. to treat dentin hypersensitivity and is a conservative alternative to restorative treatment for individuals who experience sensitivity from gastroesophageal reflux disease (GERD) or severe bruxism. It is also a clinically acceptable treatment alternative for individuals with challenging behavior or whose safe dental treatment is precluded by other medical management complexities. Its ease of application allows it to be applied in office without need for sedation or other invasive measures. This makes it ideal for individuals who are uncooperative, either because of age or special health care disability. When

dental care cannot be completed because of a more urgent medical complexity, such as the need for an organ transplant, SDF can buy time until more definitive treatment can be accomplished.[27]

Contraindications to the use of SDF include use in individuals with a silver allergy, those with open oral sores and teeth that require pulpal therapy (i.e., irreversible pulpitis or necrosis). The exact prevalence of individuals with a silver allergy, most commonly a Type IV reaction, is unknown but believed to be rare. Individuals at risk for developing a silver allergy include those who have been previously sensitized to the metal either from medical (e.g., burn treatment with silver sulphadiazine) or industrial (e.g., metallurgical processing) exposure.[28] SDF can irritate already sensitive open mouth sores (e.g., herpetic gingivastomatitis, ulcerative gingivitis) and should be used with caution until those symptoms subside. Coverage of the irritated mucosa with petroleum jelly to protect it during application is an option.

For teeth with large carious lesions approximating the pulp, adjunctive treatments to SDF should be considered to maximize its effectiveness, as it does not restore form and function. Placement of GIC over an SDF-treated lesion using the silver modified atraumatic restorative technique (SMART) is an option.[29] This placement should be done several hours or days after initial SDF placement, as the ammonia in the wet medicament can be corrosive to glass. SDF placed as an indirect pulp cap in deep lesions approximating the pulp have shown similar remineralizing efficacy as GIC and calcium hydroxide ($Ca(OH)_2$) in one in vivo study, but the opposite was seen in an in vitro investigation.[30] Further research into the indications of using SDF is needed and, given its popularity, is anticipated soon.

Conclusion

Silver diamine fluoride represents the application of a familiar medicine to a modern medical control of dental caries. Its meteoric rise to popularity in the U.S. is reflective of the quick adoption of this "medical model" for the management of oral disease. Future research into it and other potential medicaments is needed to continue to support this shift. ■

REFERENCES

1. Barillo DJ, Marx DE. Silver in medicine: A brief history BC 335 to present. *Burns* 2014;40 Suppl 1:S3–8.
2. Lansdown ABG. Silver in health care: Antimicrobial effects and safety in use. *Curr Probl Dermatol* 2006;33:17–34.
3. Stebbens E. What value has argenti nitras as a therapeutic in dentistry? *Int Dent J* 1891;12(10):661–671.
4. Peng JJY, Botelho MG, Matinlinna JP. Silver compounds used in dentistry for caries management: A review. *J Dent* 2012;40(7):531–541.
5. Craig GG, Powell KR, Cooper MH. Caries progression in primary molars: 24-month results from a minimal treatment programme. *Community Dent Oral Epidemiol* 1981;9(6):260–265.
6. Nishino M, Yoshida S, Sobue S, Kato J, Nishida M. Effect of topically applied ammoniacal silver fluoride on dental caries in children. *J Osaka Univ Dent Sch* 1969;9:149–155.
7. Yamaga R, Nishino M, Yoshida S, Yokomizo I. Diammine silver fluoride and its clinical application. *J Osaka Univ Dent Sch* 1972;12:1–20.
8. Gao SS, Zhang S, Mei ML, Lo EC-M, Chu CH. Caries remineralisation and arresting effect in children by professionally applied fluoride treatment – a systematic review. *BMC Oral Health* 2016;16(1):12.
9. Llodra JC, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M. Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of schoolchildren: 36-month clinical trial. *Practitioner* 2005;249(1675):721–724.
10. Dos Santos VE, De Vasconcelos FMN, Ribeiro AG, Rosenblatt A. Paradigm shift in the effective treatment of caries in schoolchildren at risk. *Int Dent J* 2012;62(1):47–51.
11. Monse B, Heinrich-Weltzien R, Mulder J, Holmgren C, van Palenstein Helderman WH. Caries preventive efficacy of silver diamine fluoride (SDF) and ART sealants in a school-based daily fluoride toothbrushing program in the Philippines. *BMC Oral Health* 2012;12(1):52.
12. Yee R, Holmgren C, Mulder J, Lama D, Walker D, van Palenstein Helderman W. Efficacy of Silver Diamine Fluoride for Arresting Caries Treatment. *J Dent Res* 2009;88(7):644–647.
13. Tan HP, Lo ECM, Dyson JE, Luo Y, Corbet EF. A Randomized Trial on Root Caries Prevention in Elders. *J Dent Res* 2010;89(10):1086–1090.
14. Nantanee R, Santiwong B, Trairatvorakul C, Hamba H, Tagami J. Silver diamine fluoride and glass ionomer differentially remineralize early caries lesions, in situ. *Clin Oral Investig* 2016;20(6):1151–1157.
15. Braga MM, Mendes FM, De Benedetto MS, Imparato JCP. Effect of silver diamine fluoride on incipient caries lesions in erupting permanent first molars: A pilot study. *J Dent Child (Chic)* 2009;76(1):28–33.
16. Liu BY, Lo ECM, Chu CH, Lin HC. Randomized Trial on Fluorides and Sealants for Fissure Caries Prevention. *J Dent Res* 2012;91(8):753–758.
17. Zhi QH, Lo ECM, Lin HC. Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children. *J Dent* 2012;40(11):962–967.
18. FDA. Fact Sheet: Breakthrough Therapies. www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm. Accessed May 1, 2017.
19. Horowitz AM. A report on the NIH Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life. *J Dent Res* 2004;83 Spec No:C15–7.
20. Fontana M, Zero DT. Assessing patients' caries risk. *J Am Dent Assoc* 2006;137(9):1231–1239.
21. Jung WK, Koo HC, Kim KW, Shin S, Kim SH, Park YH. Antibacterial Activity and Mechanism of Action of the Silver Ion in *Staphylococcus aureus* and *Escherichia coli*. *Appl Environ Microbiol* 2008;74(7):2171–2178.
22. Wakshlak RB-K, Pedahzur R, Avnir D. Antibacterial activity of silver-killed bacteria: The "zombies" effect. *Sci Rep* 2015;5(1):9555.
23. Seto J, Horst JA, Parkinson DY, Frachella JC, DeRisi JL. Silver microwires from treating tooth decay with silver diamine fluoride. *bioRxiv* Epub ahead of print. June 2017.
24. Crystal YO, Janal MN, Hamilton DS, Niederman R. Parental perceptions and acceptance of silver diamine fluoride staining. *J Am Dent Assoc* 2017 Jul;148(7):510-518.e4. doi: 10.1016/j.adaj.2017.03.013. Epub 2017 Apr 27.
25. Mei ML, Nudelman F, Marzec B, et al. Formation of Fluorohydroxyapatite With Silver Diamine Fluoride. *J Dent Res* 2017 Sep;96(10):1122-1128. doi: 10.1177/0022034517709738. Epub 2017 May 18.
26. Horst JA, Ellenikiotis H, Milgrom PL. UCSF Protocol for Caries Arrest Using Silver Diamine Fluoride: Rationale, Indications and Consent. *J Calif Dent Assoc* 2016;44(1):16–28.
27. Chu CH, Lee AHC, Zheng L, Mei ML, Chan GC. Arresting rampant dental caries with silver diamine fluoride in a young teenager suffering from chronic oral graft versus host disease post-bone marrow transplantation: A case report. *BMC Res Notes* 2014;7:3.
28. Group A, Lea A. Contact dermatitis with a highlight on silver: A review. *Wounds* 2010;22(12):311–315.
29. Alvear Fa B, Arron J, Wong A, Young D. Silver Modified Atraumatic Restorative Technique (SMART): An alternative caries prevention tool. *StomaEduJ* 2016;3(2):18–24.
30. Shah N, Gupta A, Sinha N, Logani A. Remineralizing efficacy of silver diamine fluoride and glass ionomer type VII for their proposed use as indirect pulp capping materials – Part II (a clinical study). *J Conserv Dent* 2011;14(3):233.

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