# A Scientific Perspective on the Use of Topical Silver Preparations



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T he use of silver as an antimicrobial agent reaches back into antiquity, when people first learned that water stored in silver vessels kept better than water stored in other types of containers. Those who settled the American west placed silver dollars in their wooden water barrels to preserve the water. Such occurrences predate Pasteur's Germ Theory of Disease (published in 1877) and knowledge of the role that micro-organisms play in disease.
In 1884, Crede started using a 1% silver nitrate solution on neonates to prevent ocular infections.1 This was followed by Von Behring's work in 1887, where he showed that 0.25% and 0.01% silver nitrate solutions were effective against typhoid and anthrax bacilli, respectively.1 In 1893, von Nageli coined the term oligodynamic to describe the high level of antibacterial activity that was generated from relatively small amounts of silver and other heavy metals.1 Silver in the form of hammered foils and colloidal silver was used to treat indolent wounds in the early 1900s. During these treatments, a decrease in rubor often was noted, suggesting that the wounds were changing from an inflamed state to a non-inflamed healing state. In the 1920s, the US Food and Drug Administration accepted colloidal silver as a wound treatment.2
In the 1940s, with the advent of antibiotics, research on medical applications of silver declined dramatically. Not until the 1960s when Moyer and Monafo3 and Burke4 started using 0.5% silver nitrate solutions on burn wounds were research interests rekindled. In 1968, Fox5 introduced 1% silver sulfadiazine cream, which has become one of the leading topical agents used to treat burn wounds over the last 35 years.

Characteristics

Antimicrobial activity. Silver is effective against a broad range of aerobic, anaerobic, Gram-negative and Gram-positive bacteria, yeast, filamentous fungi, and viruses.1,6-8 In combination with its broad antimicrobial properties, silver also appears to have other prohealing or anti-inflammatory properties as suggested by the loss of rubor in chronic wounds treated with silver.2

The concentrations of silver that are needed to create a biological effect are dependent upon the local environment. In a pristine aqueous system, concentrations as low as 10 ug/L are effective in controlling bacteria, while in complex organic media, the minimum inhibitory concentration (MIC) increases 2,000-fold to the 20 to 40 ug/mL concentration reported by Ricketts et al.9

Yin et al6 determined MICs for five clinically relevant bacteria in Mueller-Hinton broth, a complex organic growth medium. The MIC values ranged from 5 to 12.5 ug Ag/mL.

Lack of toxicity. Few reported cases of silver toxicity exist in the medical literature. This suggests a low mammalian cell toxicity. Although cases of silver sensitivity (allergic responses) have occurred, no other pathological conditions have been noted despite large exposures to silver in burn wound treatment.

 Silver nitrate is typically applied 12 times per day in the treatment of serious burns. In 1 mL of absorptive capacity of dressing (about 1 square inch depending upon number of plies), the wound is treated (12 mL/day x 3,176 ug Ag+/mL) with 38,112 ug of silver per day or 533,568 ug of silver per 14 days.

 Silver sulfadiazine is typically applied twice daily on serious burns at a thickness of about 4 mm. This translates into about 2.6 grams of SSD per square inch (2.6 g x 3,000 ug Ag+/g SSD) or 7,800 ug of silver applied twice daily for a total of 15,600 ug of silver per day. This equates to 218,400 ug of silver per 14 days - about 41% of the silver applied through silver nitrate treatments. This reduction in silver usage was achieved by using the sulfadiazine moiety to control the release of silver and was considered a significant improvement in silver delivery. Reports in the literature regarding the condition argyria (the development of a bluish hue to the skin as a result of the deposition of silver in the dermis) state that this deposition also occurs in other organs but the condition has not been reported as a result of the use of topical silver. It appears to be a problem associated with the ingestion or inhalation of silver (silver dust) or silver products (colloidal silver) over an extended period of time (see Table 1).2
Drawbacks.

The high level of chemical reactivity is thought to impair penetration of silver ions into the wound bed. This is a concern when the wound bed is considered deeply infected (ie, organisms have penetrated a significant distance into the wound bed) because some organisms may not be affected by the silver. This is probably not an issue for contaminated or critically colonized wounds where the organisms have not penetrated the wound bed.10
Other silver product-based problems are related to the anions or carriers used to deliver the silver. In the case of silver nitrate, the nitrate molecule may be pro-inflammatory while the cream base in silver sulfadiazine products reacts with serous exudates to produce a pseudo-eschar that must be removed before the cream is reapplied.2 This is uncomfortable for the patient, as is the constant need (12 times per day) to replace complexed silver ions in patents treated with silver nitrate.
Although 0.5% silver nitrate and 1% silver sulfadiazine creams have been the principal delivery vehicles for silver over the last 35 years, they are less than ideal because of the need to provide large excesses of silver to compensate for losses to chemical inactivation and the presence of undesirable counter ions and carrier creams. As a result, many new technologies have been developed to improve the controlled release of silver ions.

Silver Technologies
The following is a summary of silver technologies available. Table 2 lists the silver species, the concentrations they release, and their bactericidal properties as determined using a 30-minute log reduction test with Pseudomonas aeruginosa.

Silver salts. Various salts have been used as wound treatments over the years, including silver nitrate, silver sulfadiazine, silver chloride, silver-calcium-sodium phosphate, and silver-sodium carboxymethylcellulose.

Silver nitrate. A highly soluble salt of silver, silver nitrate's medical use dates to 1884 when Crede used a 1% solution to treat eyes of neonates to prevent ocular infections.1 It is currently used as a 0.5% solution in wound treatment in a small number of burn units in North America. Although easy to use, it causes staining of the patient and environment and can lead to electrolyte imbalances in patients. In vitro tests have shown that silver nitrate has a negative impact on fibroblasts,11 hepatocytes,12 and lymphocytes,13 but studies on anodically generated silver ions show no impact on mammalian cells in culture.14 Similarly, Bador15 and Cooms et al16 noted no tissue toxicity in clinical evaluations, and Demling and DeSanti2 report no evidence that links the silver ion to toxicity.
Silver sulfadiazine. Fox developed this moderately soluble silver salt in 1968.5 Usually formulated with a cream base for easy application, this delivery system has been extensively studied due to its wide use in the clinic. In vitro studies have shown that silver sulfadiazine is cytotoxic17 and that this cytotoxicity can be reduced by controlling the delivery of the active agent.18 Other in vivo studies have provided evidence that silver sulfadiazine may not be cytotoxic.29 Hollinger20 reviewed topical silver pharmaceuticals and concluded that products such as silver sulfadiazine require more study. After 35 years of clinical use, the evidence is still confusing but the product remains the main topical used in burn units.

Silver chloride. Silver chloride-based technology recently has been introduced to the market. Silver chloride is a sparingly soluble salt of silver with a Ksp( of 1.77 x 10-10.21 This limits the silver in solution to 1.3 ug Ag+/mL as a maximum value. The actual concentration in wound fluids is probably less, given the high concentration of chloride ion in the wound.

Silver-calcium-sodium phosphates. These moderately soluble salts are formed as glasses that are co-extruded in a polymer matrix. Dissolution tests in water have shown that polymer films of this material release up to 140 ug of silver per square inch in 2 hours.22 This represents all of the silver in the dressing, as shown through chemical analysis.22 Biological testing on a growth medium shows that residual antimicrobial activity lasts from less than 24 hours for Staphylococcus aureus up to 4 days for P. aeruginosa, as measured in zone of inhibition tests. Bactericidal measurements (log reduction) show that this material has limited efficacy against a broad range of bacteria.22 The differences between the zone of inhibition tests and the bactericidal log reduction tests suggest that this material is bacteriostatic.

Silver-sodium carboxymethylcellulose dressings. These dressings contain 1.2% ionic silver (750 ug of silver per square inch). The material is produced via an ion-exchange process where sodium is replaced by silver. When this material is used in wound care, sodium in the wound exudate binds to the dressing, causing a release of silver from the dressing fibers. This salt is sparingly soluble and releases less than a microgram/mL of silver in fluid.23 This technology has limited residual antimicrobial activity as shown in biological testing in a simulated wound fluid. Tests have shown that for P. aeruginosa and S. aureus, the measured antimicrobial activity at time 0 is approximately a 5.8 bacterial log reduction, which dwindles to a 1 log bacterial reduction after days 1 and 2, respectively.24

Adsorbed or trapped ionic silver. Ionic silver can be adsorbed or trapped into or onto materials. Two forms of these technologies are currently in the market - silver charcoal and silver zeolite products.

Silver charcoal. This technology utilizes silver adsorbed on organic matter that is converted to charcoal through a high temperature process. These materials do not release silver into the medium, but are intended to kill organisms that are adsorbed onto the charcoal.

Metallic silver. A variety of metallic silver-containing products are on the market today. Metallic silver deposition technologies include electroless plating, vacuum deposition, and ion implantation processes.

Nanocrystalline silver. Nanocrystalline silver coatings are a recent innovation in metallic silver processing. From a materials perspective, a nanocrystalline material has a crystal size less than 20 nm.25 This is a functional definition related to the changes that occur in the physical and chemical properties as the crystal or grain size drops below 20 nm. These changes are due, in part, to the increase in the volume of the crystal or grain boundary relative to the crystal bodies. Birringer25 suggested that the grain boundary region may represent a new state of solid matter. The traditional states of solid matter are amorphous and crystalline states. Amorphous matter, where the atoms and molecules interact with their nearest neighbor, and crystalline matter, where atoms and molecules interact with the atoms and molecules of the crystal lattice, have short-range and long-range order, respectively. Atoms and molecules that reside in grain boundaries are influenced by the adjacent grains, but because they are not part of the crystal structure, they have no long-range order. Further, they are unable to interact with neighbor atoms or molecules because of the effects of the adjacent grains and, therefore, may have no order at all.25 This would make these atoms unique and may contribute to the unusual dissolution products of nanocrystalline silver - Ag+ and Ag0.26 The dissolution process reaches a steady state condition (see Figure 1), dependent upon temperature, when the silver concentration in solution is between 70 and 100 ug/ml.22 In in vitro tests, antimicrobial levels of silver are demonstrated in the dressing for at least 7 days.22

Nanocrystalline silver technology has been extensively reported in the literature. The chemical/physical structure gives rise to unique biological activity. The nanocrystalline-derived silver is bactericidal to a wide range of bacteria, antibiotic resistant bacteria (see Figure 2) and fungi.6-8

Anti-Inflammatory Properties of Silver

In the early 1900s when indolent wounds were treated with colloidal silver, reports noted an observed decrease in rubor - perhaps the first observation of an anti-inflammatory effect of a noble metal. Colloidal silver will release low levels of Ag+ as it oxidizes in water with OH- as the counter ion, so what form of the silver might have provided the anti-inflammatory effect is unclear. Since then, other noble metals have been used clinically for their anti-inflammatory or anti-inflammatory like properties. Gold chloride is used as an intra-articular injectable for the treatment of rheumatoid arthritis because of its potent anti-inflammatory properties.
Silver technologies in the last half of the 20th century were designed to deliver Ag+; in many cases, the carrier creams and counter ions were at best neutral and perhaps pro-inflammatory. The nanocrystalline form of silver has increased the ways in which silver is released. Two species of silver (Ag+ and Ag0)27 are released from these materials - one of which (Ag0) is not likely to react with chloride as quickly as Ag+ and does not require a carrier.

 A recent paper evaluated matrix metalloproteinases (MMP), cell apoptosis, and healing in a porcine model where wounds were dressed with nanocrystalline silver dressing, silver nitrate, and saline soaks.28

 Preliminary clinical data suggest that MMP modulation also may occur in wounds where the nanocrystalline silver dressing had been applied (see Figures 3 and 4a and 4b). A recent pilot clinical study29 examined the composition of venous ulcer wound fluids in wounds treated with the nanocrystalline silver dressing and a control. The authors report that, in this 10-patient study (five treated with the nanocrystalline silver dressing and five control), MMP-9 and TNF-alpha levels were suppressed relative to the controls. Demling and DeSanti30 have shown that meshed autografts in the clinic re-epithelialize faster when treated with nanocrystalline silver dressings than when treated with a petrolatum-impregnated gauze with moist neomycin compresses. This finding was supported by Olson's31 earlier work on porcine donor sites. Voigt and Paul32 have used nanocrystalline silver dressings extensively and are currently studying re-epithelialization of donor sites as well as a variety of other applications.

No other forms of silver have generated the types of wound responses observed in preclinical and clinical studies with nanocrystalline silver dressings. This is consistent with Demling and DeSanti's2 position that the form of silver and the choice of carriers are important.

Conclusion
Silver is a powerful antimicrobial agent that is susceptible to inactivation through chemical complexation. Past treatment protocols compensated for large losses of silver ions by providing large excesses of replacement silver at frequent intervals which, while efficacious, also created problems for healthcare providers and patients. New materials such as nanocrystalline silver are opening new research areas on silver and all of its biological properties. Not only will silver provide excellent antimicrobial protection, but it also may enhance wound closure. Only more research will provide the answers.

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