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V. A. Black  
*Southern Arkansas University, vablack@saumag.edu*

G. Njewel  
*American University of Antigua*

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Search for the Next “Silver Bullet”: A Review of Literature

V.A. Black¹ and G.Njewel²

¹Southern Arkansas University, Magnolia, Arkansas
²American University of Antigua, College of Medicine, New York

¹Correspondence: vablack@saumag.edu

Abstract

We present a review on the application of silver-containing compounds that have been incorporated in the surfaces of a large variety of medical devices including vascular, urinary, and peritoneal catheters, endotracheal tubes, sutures, and fracture fixation devices, as well as other materials such as plastics in kitchen appliances and fabrics. We found renewed and rising interest in silver-containing materials due to their antimicrobial, including antiviral and antifungal, properties, their good toxicology and environmental record. Silver-containing compounds could be used against bacterial strains that are known to be resistant to antibiotics. More research is necessary to determine safe levels and particle-size of silver for use in humans.

Keywords: silver; antimicrobial, antibacterial.

Introduction

The search for new antimicrobial agents is an ongoing process. The rising numbers of antibiotic resistant bacterial strains (Rosenblatt-Farrell 2009), immunodeficiency, and an increase in chronic diseases such as diabetes that decrease the natural healing capability of the organism drive the search.

Silver has a long history of use by humans. In ancient times it was used to purify and store water. Alexander the Great (335 BC) drank water from silver-containing vessels (Russel et al. 1994, White 2002). Silver was used aboard the Apollo, the MIR space station, and NASA space shuttles for water purification (Conrand et al. 1999). In 1800, 2% silver nitrate was used for treatment of ophthalmia neonatorum in newborns (Klasen 2000). Since the 1960’s, silver sulfadiazine has been used as a topical antibacterial (Fox 1968). The emergence of resistant strains of bacteria, such as MRSA, provoked the search for new antimicrobials. There is an increasing interest in silver-containing materials due to their antimicrobial properties in applications such as pharmacology, medicine, the food industry and the healthcare environment (Petica et al. 2008).

Advances have been made in the last decade in medical grade silver technology, from the synthesis of safer and bioavailable silver compounds to new delivery techniques and new environmentally friendly “green” silver containing disinfectants.

The purpose of this literature review is to discuss the use of silver-containing compounds in medicine and beyond.

Why does silver work?

Russel et al (1994) found that silver binds to bacterial DNA and affects cell replication. By interfering with replication, silver ions reduce the number of the bacteria, eventually killing the entire population (Russel et al. 1994).

According to the Kong and Jang (2008), there are several possible explanations of bactericidal properties of silver: 1) silver ions inhibit ATP synthesis via binding to the enzyme associated with ATP generation in the cell, 2) silver ions enter the cell, bind to its DNA, leading to DNA denaturation, 3) silver ions block the respiratory chain in the cytochrome oxidase and NADH-succinate dehydrogenase region, inhibiting ATP generation by the microorganism.

Petica et al (2008) believe that the mechanism of the antibacterial effects of the silver ions (Ag⁺) involves their absorption and accumulation by bacterial cells and shrinkage of the cytoplasmic membrane and its detachment from the cell wall. Due to the infiltration of the cell by Ag⁺ ions, DNA molecules become condensed and incapable of replication.

It has been reported that the mode of action of silver nanoparticles is similar to that of silver ions. However, the effective bactericidal concentration of silver nanoparticles is at a nanomolar level as compared to a micromolar level for silver ions (Kong and Jang 2007).

Current Applications

Use of medical devices, such as central venous or urinary catheters, is associated with infection risks due
to the inevitable colonization of the catheter surface by bacteria. With a goal to reduce infection, silver based molecules of different size and concentrations have been incorporated into the surfaces of a large variety of medical devices including bladder catheters, central venous catheters and peritoneal catheters.

**Catheters**

A study by Jansen and colleagues (1994) evaluated the *in vitro* biocompatibility and the antimicrobial activity of silver-coated polyurethane catheters. The catheters were designed to be used as an antimicrobial material and to prevent the bacterial colonization associated with use of a catheter. The antimicrobial activity of the catheters was tested using *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. Catheters coated with silver demonstrated antimicrobial capability and performed well in cell toxicity, blood compatibility, and acute toxicity tests in mice. For all test strains, a reduction in the number of adherent cells to the silver-coated catheters was observed, which was more pronounced after an adherence time of 24 h. In a case of *S. epidermidis* (10⁸ cfu/ml) % reduction of adherence in 3 h was 82.7% and 90% in 24 h, 90% in 3 h; 83.7% in 24 h for E. coli and 99.9 % in 3 and 24 h for *P. aeruginosa*. With an inoculum of 10⁵ cfu/ml, *S. epidermidis* demonstrated 94.6 % reduction of adherence in 3 h and 80.0 in 24 h, *E. coli* - 93.3% in 3 h and 99.1 % in 24 h, and *P. aeruginosa* – 99.9% in 3 h and 24 h (Jansen et al. 1994).

According to research from the University of Michigan Health System, 5% of hospitalized patients that undergo urinary catheterization develop bacteriuria. Proper management of the drainage system, including use of the antimicrobial agents and rigorous cleansing, was emphasized, but seem to have only a small benefit. Saint and Lipsky (1999) analyzing results of 8 randomized trials involved silver-coated urinary catheters found, that silver alloy catheters were significantly better in prevention of bacterial infections than noncoated control catheters and it would be reasonable to consider using silver alloy catheters in hospitalized patients (Saint and Lipsky 1999).

Johnson and associates (2006) have also concluded that “antimicrobial urinary catheters can prevent bacteriuria in hospitalized patients”, but the effect depends on the characteristics of the antimicrobial coating, such as the size of the silver particles (Johnson et al. 2006).

Loertzer and colleagues (2006) found evidence that the use of catheters coated with silver reduced the risk of infection in kidney transplant recipients. There is an increased risk of microbial infection in transplant patients due to immunosuppression therapy (Zand 2005). The main cause of the catheter-related infections is microbial colonization of the central venous catheters. Catheters were analyzed microbiologically. Catheters coated with silver demonstrated a significant reduction in associated infections of the blood stream, as well as increased protection against bacteria and fungi during the entire time of catheterization (Loertzer et al. 2006).

**Endotracheal tubes (ETTs).**

Endotracheal tubes are often used in the management of a patient’s airway. Bacterial biofilms may form on the surface of the endotracheal tubes in and around the place of the insertion and may increase risk of the pneumonia being developed by the patient.

Berra et al (2008) developed and tested ETTs coated with silver sulfadiazine (SSD). In the in vitro study SSD-ETTs demonstrated bactericidal properties against *P. aeruginosa*, preventing biofilm formation on ETT lumen in 6, 24 and 72 h, whereas standard ETT (St-ETT) showed heavy *P. aeruginosa* growth and biofilm formation (p<0.01). In 24-h study of young female Dorset sheep, 4 sheep received SDD-ETT and showed no bacterial growth in ETT, while heavy colonization was found in sheep received St-ETT (p<0.01) (Berra et al. 2008).

**Silver-coated megaprosthesis**

Despite the use of antibiotic prophylaxis, infection rates associated with implantation of prostheses remain high. Gosheger et al (2004) evaluated the antimicrobial efficacy and side effects of the silver coated megaprosthesis. 15 rabbits received titanium endoprostheses and 15 – silver coated one. Both groups were infected with *Staphylococcus aureus* (Strain number A 22616-5) isolated from bone specimen of a 34 years-old female with osteomyelitis. After 90 days of observation, group of rabbits with silver coated endoprosthesis demonstrated significantly lower inflammation sigs (p<0.005) including C-reactive-protein and neutrophilic leukocytes measurements in comparison with the group with titanium endoprosthesis. Infection rates were also significantly lower in the group with silver endoprosthesis (7% versus 47%). The silver concentration in the blood and organs of the rabbits were elevated (mean 1.883 and 0.798-86.002 ppb respectively), but did not cause pathological changes in the organs including brain,
heart, kidney and reproductive organs (Gosheger et al. 2004).

**Dental care**

Scientists are in agreement that dental caries caused by Streptococcus mutans is a worldwide, public health concern, especially in patients whose immune system has been compromised.

Hernandez-Sierra et al. (2008) used nanoparticles of silver, zinc oxide, and gold of an average size of 25 nm, 125 nm and 80 nm respectively to demonstrated bacteriostatic and bactericidal effects on S. mutans. Findings showed that nanoparticles of silver, as compared with those of gold and zinc oxide, required a lower concentration (MIC on average 4.86±2.71µg/mL) to inhibit development of the S. mutans strains compared to the zinc oxide (MIC on average 500±306.18µg/mL) and gold (MIC on average 197 µg/mL) leading to consideration that silver particles may be most effective for controlling S. mutans and therefore caries (Hernandez-Sierra et al. 2008).

Three sizes of silver nanoparticles were used to find minimum inhibitory concentration (MIC) for Streptococcus mutans in the study by Espinosa-Cristobal and associates (2009). Nanoparticles with the lowest MIC was 8.4 nm in diameter, followed by 16.1 and 98 nm, suggesting that antibacterial property of silver nanoparticles possibly depend on the size of the particles (Espinosa-Cristobal et al. 2009).

**Eye care**

Antimicrobial medications that are traditionally used on the ocular surface are effective, but they are rapidly cleared through the tear ducts, reducing contact time and drug effectiveness.

Contact lenses containing silver nanoparticles as an antimicrobial measure have been studied. Santoro et al. (2007) investigated silver nanoparticles as a source of silver ions against contact lens-associated bacterium, Pseudomonas aeruginosa strain PA01. BBL™ Prompt™ tube containing 1.5 ×10^8 CFU/ml P. aeruginosa was inoculated to 1 ×10^9 CFU/ml in Erlenmeyer flasks containing 20 ml media with silver nanoparticles. Also, solutions of 20 ml media containing various concentrations (2, 4, 6, 10 µM) of control silver nitrate were inoculated to 1 ×10^9 CFU/ml of bacteria. Flasks were incubated overnight at 37 °C while shaking at 200 rpm. Minimal bactericidal effects were observed for several nanoparticles suspensions (with maximum of 2.6 µM silver ion concentration), which believed to be due to that silver particles themselves at this concentration and size ranging from 20 to 60 nm are not microcidal under conditions tested and substantial increase in silver particle loading in the lens in the future experiments will allow to produce desirable bactericidal effect (Santoro et al. 2007).

**Silver-antibiotic combination**

Shahverdi et al. (2007) demonstrated that combining penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin with silver nanoparticles leads to an increase in antibacterial activity of the antibiotics against Staphylococcus aureus and Escherichia coli. This finding suggests that combining antibiotics with silver nanoparticles increases antibacterial properties of antibiotics (Shahverdi et al. 2007). In addition, according to Patil and coworkers, chloramphenicol loaded with nanoparticles showed substantially enhanced activity against Salmonella typhi (Patil et al. 2009).

**Silver and wound care**

Chronic wounds are more likely to be colonized by normal bacterial microflora such as Staphylococcus aureus and Streptococcus epidermidis that easily become cause of opportunistic infection. Silver containing material could be used to reduce risks and duration of infections associated with opportunistic microorganisms.

Castellano et al. (2007) reported using eight commercially available silver-containing dressings Acticoat™ 7, Acticoat™ Moisture Control, Acticoat™ Absorbent, Silvercel™, Aquacel®, Coutreet®F, Urgotol® SSD, and Actisorb®. Dressings were tested in vitro for antimicrobial effectiveness against Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Streptococcus faecalis (ATCC 29212) and Staphylococcus aureus (ATCC 29213). Zone of bacterial inhibition was measured after 24, 48, and 72 hours. Silver-containing dressings were also compared to efficacy of antimicrobial creams and topical silver containing antimicrobial gel Silvasorb. Results of this study suggested that all silver dressings displayed antimicrobial activity; however, their bactericidal and bacetriostatic properties were secondary to commonly used topical antimicrobial agents such as Sulfamylon® and Gentamicin Sulfate Cream 0.1%.

Ballard and McGregor (2002) described using silver hydropolymer dressing Avance and Avance A for open exuding chronic wounds. In the clinical trials on three patients over a 4-week period Avance demonstrated many of the characteristics of the ideal dressing. It had ability to absorb exudate, had
antimicrobial effect and was easy to use. Silver-containing hydropolymer dressing Avance not only facilitated healing of the wound, but also enhanced quality of life by reducing pain.

Stephen-Haynes and Toner (2007) emphasized importance of accurate wound assessment and holistic choice of the silver-containing material for facilitation of wound healing and wound healing success. Multilaminate high density polyethylene dressing containing nano-crystalline silver Acticoat/Acticoat 7 demonstrated effectiveness in healing of pressure ulcers, venous ulcers and diabetic ulcers. Actisorb Silver 220 containing hydrocolloid fibers with silver was effective against heavy odorous and infected chronic wounds and ulcers. Hydroalginate with silver Silvercel was effective against MRSA.

Benbow (2005) described improvement in wound healing using SILVERHEALING wound pad containing metallic silver under a polyethylene net from which silver ions are released when it comes into contact with exudates. Reportedly, the effect of this material that has been tested against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Candida albicans is immediate, inhibitive, and hypoallergenic.

Jain et al (2009) concluded that silver nanoparticles could have successful therapeutic use as a part of the antimicrobial gel for topical use. A standard antimicrobial sensitivity tests carried out in Muller-Hinton agar plates were used to evaluate the antimicrobial activity of the silver nanoparticles containing gel against bacterial cultures of Escherichia coli (ATCC 117), Pseudomonas aeruginosa (ATCC 9027), Staphylococcus aureus (ATCC 6538), and Streptococcus epidermidis (ATCC 12228). Gram-negative bacteria were killed more effectively (3 log decrease in 5-9 h) than Gram-positive bacteria (3 log decrease in 12 h). Gel also exhibited good antifungal activity (50% inhibition at 75 µg/mL with antifungal index 55.5% against Aspergillus niger and MIC of 25 µg/mL against Candida albicans). Acute dermal toxicity studies on gel formulation (S-gel) in Sprague-Dawley rats showed complete safety for topical application.

Silver in tumor treatment

Maaskant et al (2009) examined the effectiveness of chlorhexidine-silver sulfadiazine impregnated central venous catheters (CVCs) in patients that received high-dose chemotherapy followed by peripheral stem cell transplantation. Patients were treated for different diagnoses including breast cancer, Non-Hodgkin lymphoma, testicular cancer, Hodgkin’s disease, Kahler’s diseases, Ewing sarcoma, and other cancers. Study evaluated 139 patients of whom 69 were provided with impregnated CVCs and 70 patients with non-impregnated CVCs. The median number of day a CVC has been used was 16 days in impregnated group and 18 days in non-impregnated group. Less catheter colonization was found in the patients with chlorhexidine-silver sulfadiazine CVCs (RR 0.63, 95% CI 0.41-0.96; P=0.03). These results were clinically significant, because colonized CVCs could be a source of systemic infections. Catheter-related blood stream infections were also less frequent, but the results did not meet statistical significance (RR 0.15, 95% CI 0.02-1.15; P=0.06).

Silver nanoparticles have demonstrated inhibition of the formation of new blood vessels (angiogenesis) in mice with tumors, possibly due to inactivation of PI3K signaling pathways. Because angiogenesis is an important part of normal and pathological growth, this research is a significant finding for future treatment of the malignant, ocular, and inflammatory diseases (Gurunathan et al. 2009).

Silver in fabrics

Use of silver-containing nanoparticles in fabrics was studied by several scientists. The goal of the study was to examine the antimicrobial activity in cotton fabrics loaded with colloidal silver nanoparticles. Also studied were the antimicrobial affects of silver deposited onto fabric surfaces against Escherichia coli, Staphylococcus aureus, and the fungus Candida albicans. Cotton fabrics loaded with silver nanoparticles exhibited good antimicrobial activity (Ilic et al. 2009).

Textile fibers and fabrics have a wide variety of biomedical applications. According to Russo and Maffezzoli (2009), there are not too many fabrics with a good degree of biocompatibility, resistance to autoclaving, and antibacterial properties. To fill this void, the silver-coated fibers were developed and demonstrated good coating stability together with antimicrobial efficacy (Russo and Maffezzoli 2009).

Hipler et al (2005) presented a study that was intended to test whether silver-covered seaweed-based fibers Sea Cell® Active exert antibacterial and antifungal properties. Colonies of pure culture of Staphylococcus aureus (ATCC 22926) and Escherichia coli (ATCC 35218) were inoculated in 5 mL Mueller-Hinton broth and incubated at 37 °C until the turbidity of suspension was equal to that of 0.5 McFarland. Sea Cell® Active was then placed in the center of Muller-
Hinton agar plates that had been inoculated with test bacteria and incubated at 37°C for 24 h. Fibers demonstrated excellent antibacterial properties with highest activity with Sea Cell®. Active fibers with 100% of the active silver load. Sea Cell® Active also demonstrated reduction of the cell proliferation of the Candida species (DSM 11225, ATCC 1169, ATCC 6258) down to 10-20% compared with control.

Silver and MRSA

An article in Medical Technology and Devices Week reported on the potential use of the silver in preventing the spread of bacterial strains, including meticillin-resistant Staphylococcus aureus (MRSA). It described the capability of silver to kill strains of bacteria that were resistant to current treatments using antibiotics (Ford et al 2007).

O’Hanlon and Enright (2008) evaluated the antistaphylococcal activity of commercially available silver containing textile treatment Clineweave® (CW). Testing included 49 meticillin-resistant genetically diverse Staphylococcus aureus strains (MRSA) Antimicrobial activity of CW-treated polyester was compared to three other commercially available silver-containing antimicrobial fabrics. In this study only CW-treated fabric demonstrated any significant antibacterial activity and reduction of bacterial numbers within 1 h. Time-kill study of liquid CW in culture showed 2 log reduction of MRSA within 30 min and 3 log reduction of MRSA within 240 min. Silver containing textile Clineweave® proved to be biocidal and useful for reduction of MRSA burden.

Other areas of silver use

Silver-containing compounds have reportedly been used in material that is used to make binders, markers and staplers. In Europe antibacterial silver-based polymers include hospital equipment, medical packaging, and door handles. Silver based antimicrobial Makrolon polycarbonate is used in medical devices like intravenous (IV) systems, urological devices, and housing for diagnostic and hospital equipment (Markarian 2009).

Samsung Electronics manufactures new appliances that use a silver-based antibacterial material termed “silver nano health systems” (SNHS). Samsung washing machines contain nano silver particles coating, refrigerators that use silver trays and that are coated with silver water-filters, tubes, and air conditioner surfaces. LG Electronics produces refrigerators with a silver-containing coating in the internal food storage compartment.

Jo and colleagues examined the use of silver in the control of plant diseases caused by pathogenic fungi Bipolaris Sorokiniana and Magnaporthe grisea. Results indicated that silver ions and nanoparticles affected disease progress and spore formation in plant pathogenic fungi, reducing the progress of the disease (Jo et al. 2009).

What about toxicity?

In view of silver’s potential toxicity, extensive and in depth research is needed.

Despite the opinion that there is no silver accumulation in tissue after topical application, autopsy study of two patients treated for 1 and 6 month respectively for burns with 0.5% AgNO3, revealed significant silver deposition in multiple organs. Autopsy study on a burned child treated with silver sulfadiazine cream (AgSD) for 3 months showed silver deposition in liver and kidney with concentration of the silver in liver tissue 1600 times that of normal liver specimen (Fuller 2009).

Coombs et al (1992) in a study of 22 patients with burns treated with AgSD demonstrated rise in serum silver levels up to 20 times the normal level within 6 hours after the initial application. Thus, silver deposition in the tissue could occur whenever serum silver levels rises and remains above normal.

The most common condition described in the literature associated with prolong silver exposure is argyria, which characterized by a blue-gray discoloration of the skin and total silver concentration in the blood up to 4-6 g (Lee and Lee 1994, Lansdown 2002, Gosheger et al. 2004).

The latest technologies used for production of silver-containing compounds appear to be safe and effective (Lansdown 2002).

Conclusions

Silver has been used for centuries in the form of silver nitrate, silver sulfadiazine and metallic silver. Its use has somewhat declined because of the development and increased use of antibiotics. Today, new technologies are bringing silver back in the form of nanoparticles with potential antimicrobial effects.

The results of many studies have demonstrated that silver nanoparticles inhibit the growth of bacteria including Staphylococcus aureus, Streptococcus epidermidis, Enterococcus, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli and fungi such as Candida albicans. Studies suggest that silver nanoparticles can be used as effective microbial growth
inhibitors, making silver applicable to diverse medical devices and antimicrobial control systems.

Despite promising in vitro results, more research is needed to determine the concentration and size of silver particles that does not cause toxic silver levels in serum and/or damage to human organs, but that still provide bacteriostatic and bactericidal effect in humans.

Literature Cited


