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Silver in Health Care: Antimicrobial Effects and Safety in Use

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Abstract

Silver has a long and intriguing history as an antibiotic in human health care. It has been developed for use in water purification, wound care, bone prostheses, reconstructive orthopaedic surgery, cardiac devices, catheters and surgical appliances. Advancing biotechnology has enabled incorporation of ionizable silver into fabrics for clinical use to reduce the risk of nosocomial infections and for personal hygiene. The antimicrobial action of silver or silver compounds is proportional to the bioactive silver ion (Ag^+) released and its availability to interact with bacterial or fungal cell membranes. Silver metal and inorganic silver compounds ionize in the presence of water, body fluids or tissue exudates. The silver ion is biologically active and readily interacts with proteins, amino acid residues, free anions and receptors on mammalian and eukaryotic cell membranes. Bacterial (and probably fungal) sensitivity to silver is genetically determined and relates to the levels of intracellular silver uptake and its ability to interact and irreversibly denature key enzyme systems. Silver exhibits low toxicity in the human body, and minimal risk is expected due to clinical exposure by inhalation, ingestion, dermal application or through the urological or haematogenous route. Chronic ingestion or inhalation of silver preparations (especially colloidal silver) can lead to deposition of silver metal/silver sulphide particles in the skin (argyria), eye (argyrosis) and other organs. These are not life-threatening conditions but cosmetically undesirable. Silver is absorbed into the human body and enters the systemic circulation as a protein complex to be eliminated by the liver and kidneys. Silver metabolism is modulated by induction and binding to metallothioneins. This complex mitigates the cellular toxicity of silver and contributes to tissue repair. Silver allergy is a known contra-indication for using silver in medical devices or antibiotic textiles.

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Silver is a precious metal found in many parts of the world. The date of its discovery is not documented, but early manuscripts describe its medicinal properties and the value of silver vessels and coins in purifying the drinking water. Since these early days, silver has been used in a wide range of medical devices

including bone prostheses, surgical sutures and needles, cardiac implants, catheters, dentistry, wound therapy and surgical textiles [1]. Whilst much of the early enthusiasm for using silver may have stemmed from its aesthetic value as a precious metal, evidence over the past 200 years increasingly points to its proven ability to protect the human body from infectious diseases. The French surgeon Credé [2] claimed that 0.5–1.0% silver nitrate reduced the incidence of neonatal eye infections in his clinic from 10.8 to about 2%, although details of this work are not available. It is anecdotal that whereas early 19th century surgeons like Credé and William Halstead chose silver foil and silver nitrate to protect wounds against disease, the actual isolation of infectious agents (bacteria) and their sensitivity to silver and other metals derive from the classical studies of Louis Pasteur and the postulates of infectious diseases by Robert Koch several years later [3].

Classical surgical studies demonstrating the antiseptic properties of silver date back to the times of Ambroise Paré (1517–1590), who used silver clips in facial reconstruction, and Halstead [4], chief surgeon of the Johns Hopkins Medical School, who employed silver wire sutures in surgery for hernia and found silver foil an effective means of controlling postoperative infections in surgical wounds. Silver nitrate has a long history in treating infectious diseases and proved an efficacious antiseptic for wound care for more than 150 years. Early clinical observations indicated that silver nitrate complexes with proteins in skin wounds to form ‘resistant precipitates’ and that the local antibacterial action can be easily controlled. This antiseptic action extends ‘quite deeply’ into wounds with silver forming soluble double salts of silver albuminates and silver chloride in the tissues. Its caustic and astringent properties are well documented in early pharmacopoeias when lunar caustic, silver nitrate pencils and strong silver preparations proved beneficial in eliminating calluses, warts and unsightly wound granulations [5]. Silver nitrate is still used in wound care and burns clinics today despite its astringency and ability to discolour the tissues.

Silver metal and silver nitrate formed the mainstay of antibiotics suitable for medicinal use up to the 1920s. Pharmaceutical studies of the 1920–1940 era provided fundamental knowledge on the antimicrobial action of silver. Von Naegeli (1895) is accredited with observing that silver exerts an ‘oligodynamic’ action on bacteria, namely that it exerts a lethal effect at very low concentrations. Later, Clarke [6] reported that bacteria, trypanosomes and yeasts are killed by silver at concentrations from 10^5 to 10^7 ions per cell, this concentration being equivalent to the ‘estimated number of enzyme-protein molecules per cell’. More recent research suggests that most pathogenic organisms are killed *in vitro* at concentrations of 10–40 ppm Ag^+ with particularly sensitive organisms susceptible to 60 ppm [7].

In an attempt to overcome the irritancy of silver nitrate solutions, colloidal silver preparations were introduced into pharmacopoeias about 80 years ago [5]. Pharmacologists presumed that, by precipitating silver in the form of silver proteinate or colloidal solution, they could provide an efficacious antiseptic without undesirable side-effects. Although early colloidal silver products identified as mild or strong silver protein, colloidal silver halides and silver proteins achieved some popularity, they were superseded by newer and safer antiseptics, notably penicillins and silver sulphadiazine [8].

The introduction of silver sulphadiazine marked a renaissance in the use of silver in wound care. Whilst researching the antibiotic therapies available for controlling *Pseudomonas aeruginosa* in burn wounds, Fox [9] combined the antiseptic properties of silver with sulphonamide to provide a broader spectrum and safer antibiotic for use in burn wounds and surgery. Silver sulphadiazine and silver nitrate have been highly successful in controlling infections for many years even though the emergence of sulphonamide-resistant bacteria led to a temporary withdrawal of silver sulphadiazine in some hospitals in the mid-1970s [10]. Silver sulphadiazine has achieved a wider use in recent years with its inclusion in coatings for indwelling catheters and cardiac devices.

Improved technology permits manufacturers to enhance the delivery of silver ions to wounds to provide a safer and more efficacious antibacterial action (including methicillin-resistant *Staphylococcus aureus*, MRSA, and vancomycin-resistant enterococci) and effective prophylaxis against wound re-infection. The recent development of sustained silver release dressings marks a second renaissance of silver in wound therapy [8, 11]. The variety of silver release dressings now licensed in Europe and the USA differs greatly in composition, mechanism of presumed action and rates of silver release. They are variously tailored with recommendations for treating acute surgical wounds, burns, chronic or indolent wounds with profound exudation, unpleasant odours and severe patient discomfort.

Experience gained in the use of silver in wound care has inevitably led to the development of silver antibiotics in other medical devices. Thus, silver metal or a suitable silver compound is incorporated in polymers and resins used in the construction of medical devices, catheters, prostheses, bone cements etc., or it has been applied as an antibiotic 'coating' to silicone, textiles and other materials. Whilst clinicians have reported some success in reducing bacterial contamination and associated bacteraemias, recurrent problems have been encountered in biofilm transformation. These calcareous colonies of resistant bacterial and fungal infections form as a means of self-preservation. Biofilms are prevalent in indwelling catheters and implants, and are resistant to antibiotics and a host's own immune system. Although silver exhibits some ability to reduce bacterial adhesion as a preliminary step to biofilm formation, its success in eliminating or fully protecting against infections is limited.

The use of silver and silver release compounds in textile technology represents a new and exciting progression in health care [12]. Medicated clothing for nurses working in intensive-care clinics is a potentially beneficial means of controlling life-threatening nosocomial infections including MRSA as well as adding to levels of personal hygiene. The technology is discussed elsewhere in this publication, but antimicrobial efficacy against a range of pathogenic bacteria and fungi has been demonstrated in *in vitro* cultures. A feature of modern technology relevant to silver is compliance with safety standards. At the moment, most safety data and details on the metabolism and elimination of silver derive from occupational exposures complemented by clinical studies with silver sulphadiazine, but this holds clear clinical indications for the use of silver in other products.

Silver in Medical Devices and Textiles

Chemistry of Silver and Compounds Available for Antibiotic Action

Silver occurs naturally as two isotopes – Ag^{107} and Ag^{109} – in approximately similar proportions. It exhibits three oxidation states – $\text{Ag}[1]$, $\text{Ag}[2]$ and $\text{Ag}[3]$ – but only compounds of the $\text{Ag}[1]$ state are sufficiently stable to be of relevance as antibiotics in medical devices and textiles [7]. Like all other metals, silver is an electron-positive element with the Ag^+ cation showing a profound ability to interact with and bind proteins and anions in a medium. Additionally Ag^+ binds receptor groups on the surfaces of adjacent cells, bacteria and fungi/yeasts. Silver metal and the majority of silver compounds ionize in the presence of water, body fluids and tissue exudates to some extent to release Ag^+ or other ‘biologically active silver ions’ for antibiotic action or absorption into adjacent human tissues. The chemistry of silver is not well documented, and accurate data on relative ionization rates for the compounds commonly used in medical devices are not available (table 1).

Occasionally, documents fail to identify the nature of the chemical source of silver in products referring only to ‘silver content’ or ‘ionic silver’. The ionizing capacity of the silver metal or silver compound is critical in comparing their antimicrobial activities and in predicting the possible toxicity or health risk. To be effective in killing pathogenic organisms, each silver source should release silver ions. The expressions ‘activated’ or ‘hydro-activated’ are used colloquially to denote the bioactive state of the silver ion. The silver cation binds strongly to electron donor groups of biological molecules containing sulphur ($-\text{SH}$), oxygen and nitrogen.

Table 1. Silver compounds used in medical devices and textiles

Compound	Ionizing capacity
Metallic silver (incl. nanocrystalline forms and silver coatings)	low (<1 g·ml ⁻¹)
Phosphate	moderate
Nitrate	very high
Chloride	low
Sulphate	moderate
Zeolite	?
Sulphadiazine complex	high
Colloidal silver preparations	moderate to high
Allantoins	?
Oxide (Ag ₂ O)	low

Metallic silver has been used in wound care products over many years even though it ionizes slowly. The development of nanochemistry has facilitated the production of microfine silver particles (<20 nm diameter) with greatly increased 'solubility' and release of silver ions (70–100 ppm). Ionization of silver metal is proportional to the surface area of the particle exposed. Ionization of silver or silver compounds is enhanced also by electric currents which are increasingly used in medical devices for orthopaedic surgery and wound care therapies [13].

Biological Properties of Silver

Silver is not a recognized trace metal but occurs in the human body at low concentrations (<2.3 µg·l⁻¹) due to ingestion with food or drinking water, inhalation and occupational exposures [7, 14]. Blood silver (argyraemia) is a measure of silver exposure from all sources. Clearly, occupational exposure or medicinal use of silver as an antibiotic in wound dressings, indwelling catheters, cardiac devices and in orthopaedic surgery will be associated with higher than normal blood levels and may be a safety concern [14]. Uptake of silver through mucous membranes (urethra) or by the haematogenous route from indwelling catheters is not well documented.

The percutaneous uptake of silver from medicated textiles like Sea Cell[®] [12] is not known. Medicated fabrics like cellulose fibres, rayon etc. will be in contact with the human skin for prolonged periods. Silver ions released in the presence of sweat, sebum and any moisture accumulate on the skin surface, and some will penetrate the superficial layers of the skin to precipitate as silver sulphide in the stratum corneum. Some will be bound by chloride ions in sweat but a minute proportion can be expected to penetrate into the circulation bound to

albumins and other proteins [15, 16]. Hair and nail growth provides a route for the excretion of silver from the human body, but most will be eliminated via the liver and kidneys [14]. Hot weather and high humidities leading to hyperhydration will promote silver uptake through the skin and mucous membranes, but toxic risks are predictably low, except in individuals sensitized to silver.

Silver in Wound Care

Since early reports of clinicians using silver wire sutures, silver foil protection and silver nitrate in soft tissue surgery, silver has been the antibiotic of choice as a prophylactic or therapeutic against pathogenic infections in skin wounds, burns and transplant surgery [1, 7, 8]. As newer technology has come to hand, manufacturers of wound dressings have increasingly been able to tailor their products to suit wound type, infectious status and clinical features (pain, exudates, granulation tissue etc.). The amount of silver released can be controlled over the expected period of use of the dressings. Present approaches in wound dressings are towards safer and more efficacious dressings, cost-effectiveness and ease of use [17]. Basic principles of silver technology learned in the early days are equally relevant now.

Wound therapies employing silver as antibiotic range from silver metal, silver nitrate and silver sulphadiazine to the new generation of sustained silver release dressings. Emphasis in the silver release dressings is placed upon the nature of the silver source and patterns of release of silver ion. Even now there is a hot debate as to the clinical benefits of the fast high-concentration (bolus-like) silver ion release compared to the gentle, more sustained approach. Either way, wound care embracing silver antibiotic necessarily involves either (a) prophylaxis – to provide a barrier function in protecting acute skin damage (as in postoperative surgery) from nosocomial and idiopathic infections – or (b) therapeutics – to alleviate the microbiological burden in acute and chronic wounds.

The therapeutic management of chronic wounds increasingly observes principles of wound bed preparation [18], which can be critical in advancing the repair of chronic indolent wounds and ulcers. Wound bed preparation involves controlling the balance between commensal bacteria and pathogenic organisms.

Silver Nitrate

Silver nitrate is caustic and irritant at concentrations exceeding 1%; in contact with living tissue it can cause leakage of cellular electrolytes including sodium and potassium. However, it is an excellent antibacterial agent and at 0.5% is particularly effective in inhibiting *P. aeruginosa* which can prove fatal in burn wounds. Silver nitrate is claimed to be superior to many other antibiotics including chlorhexidine and silver sulphadiazine, especially in eliminating more resistant strains of *Streptococcus pyogenes*, *S. aureus* and *P. aeruginosa*

[10]. Silver nitrate compresses are claimed to reduce levels of infection in severe burns by up to 70% and significantly reduce mortality. It exhibits haemostatic properties and may be useful during minor surgery.

Silver Sulphadiazine

Silver sulphadiazine represents a second generation of silver antibiotics. Developed by Charles Fox in 1968, this complex combines the antibiotic properties of silver with a sulphonamide that proved invaluable in controlling wound infections in World War II [9]. It avoids many of the disadvantages of silver nitrate and at 1% in a cream base provides suitable prophylaxis for burns, chronic leg ulcers and pressure sores. Although silver sulphadiazine is sparingly soluble in water, it ionizes readily in body fluids to release silver ions. The amphiphilic (fat- and water-soluble) cream base enhances the penetration of silver sulphadiazine through intact skin and skin wounds allowing up to 10% to reach the systemic circulation [19]. Depending on the severity and depth of wounds, systemic silver sulphadiazine concentrations may reach up to $300 \mu\text{g}\cdot\text{l}^{-1}$, absorption being higher where application is made to partial-thickness wounds with greater vascularity than full-thickness lesions. At concentrations of up to $50 \text{mg}\cdot\text{l}^{-1}$, silver sulphadiazine is claimed to be effective against up to 95% of bacteria commonly found in skin wounds.

The low toxicity and antibacterial efficacy of sulphadiazine have been developed in a number of wound dressings using different vehicles and polymers (polyethylene glycol + poly-2-hydroxyethyl methacrylate, liposomes, poly-*L*-leucine and cadaver skin). Many have not progressed past the early laboratory stages, but a new lipocolloid formulation containing 3.75% silver sulphadiazine (Urgotul[®] SSD, Urgo-Parema Medical) is currently available and efficacious in treating acute and chronic wounds infected with a wide range of infections including MRSA [20]. Silver sulphadiazine cream 1% (Flamazine[®]) is still widely used either alone or in combination with other silver dressings. It is well tolerated by most patients and is preferred in burn clinics. A further development of particular benefit in burn wound therapy is Flammacerium[®] cream comprising 1% silver sulphadiazine with 2.2% cerium nitrate [21]. Both substances exhibit antibacterial properties, but the cerium ion actively reduces inflammatory changes, provides transitory immunosuppression against toxic factors released in tissue destruction and reduces mortality. Flammacerium is recommended in the treatment of severe burn wounds where excision is impractical and where infection is a serious health risk [21].

Sustained Silver Release Wound Dressings

Sustained silver release dressings presently available vary greatly in their technology, silver content, patterns of silver ion release and recommendations

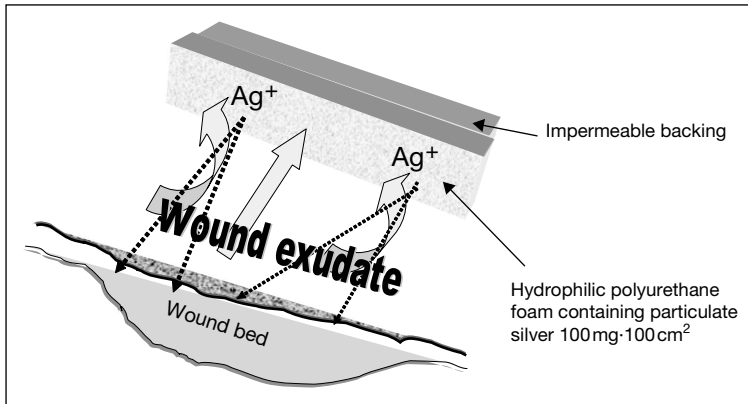


Fig. 1. Contreet® Foam Wound Dressing (Coloplast a/s, Humlebaek, Denmark). This dressing absorbs wound exudates into the hydrophilic matrix. Silver ions released within this matrix kill bacteria and fungal infections and inactivate toxins.

for clinical application [14, 20]. In each case, wound fluids and tissue exudates trigger the release of free silver ions for antimicrobial action or for absorption into tissues of the wound bed. Ideally, silver ion release will be sustained for the expected life-span of the dressing (up to 7 days). Three main forms of dressing are currently available:

- (1) those releasing high levels of silver for rapid antimicrobial action;
- (2) dressings that absorb wound exudates and where silver ions released provide sustained antimicrobial action (fig. 1);
- (3) dressings that release silver sulphadiazine (Urgotul SSD).

Some dressings embody features of the first two of these considerations but all release more silver than the 10–40 ppm deemed necessary for appropriate antimicrobial action [14]. The excess silver compensates for that bound by scavenger anions or proteins in the wound bed (including wound debris) and which is unavailable for killing bacteria and fungi [20].

The silver content of dressings currently available varies from $<10 \text{ mg} \cdot 100 \text{ cm}^{-2}$ to more than $100 \text{ mg} \cdot 100 \text{ cm}^{-2}$. Several dressings provide a twofold objective of liberating silver as an antimicrobial agent and incorporating a material such as hydrocolloid, synthetic fabric or organic fibres to absorb exudates, odours and wound debris. These additional features are consistent with present clinical approaches to wound care, including wound bed preparation [18]. In each case, dressing materials or additives used are of low toxic risk and selected to absorb wound exudates, control pain and remove distasteful odours [7, 8, 17].

Nanotechnology has been used beneficially in the production of the high silver release dressing Acticoat (Smith & Nephew). Minute particles of silver

contained within a 3-ply dressing of absorbent rayon polyester provide release of up to 70 ppm silver ions and antibacterial action lasting up to 3 days [14, 20]. This dressing is claimed to be effective against 150 wound pathogens including MRSA and more efficacious than silver nitrate or silver sulphadiazine. A further development of a wound dressing based on metallic silver employs activated-charcoal-impregnated cloth as a specific means of controlling wound odour attributable to pathogenic bacteria. The dressing (Actisorb Silver, Johnson & Johnson) is claimed to clear infections with the charcoal absorbing odours and bacterial toxins.

A third form of technology seen in wound dressings involves silver glass chemistry, similar to that developed for use in bone surgery and in orthopaedic prostheses. The polyurethane film dressings containing inorganic silver oxide, phosphate and polyphosphates have achieved notable success in the prophylaxis of acute wound therapy including open heart surgery. They protect wounds from nosocomial and other pathogenic flora whilst being entirely safe. The thin laminate slowly dissolves in wound fluids to release silver, calcium and phosphate ions for antibacterial action and wound repair.

It is unfortunate that although notable antibacterial and antifungal activity has been reported for all the sustained silver release dressings in in vitro experiments, clinical verification of their action is not generally available. Preliminary clinical trials in the Charing Cross Hospital have shown that patients treated with a range of dressings still show residual infections. It is unclear whether these bacteria are pathogenic or whether they are silver resistant [20]. So far, we have identified only 1 incidence of silver-resistant bacteria in a wound treated with a sustained silver release dressing (the coliform organism *Acinetobacter cloacae*) [Lansdown and Philip, unpubl.]. Further studies are now required to confirm whether this phenotypic silver resistance is a reflection of genetically determined changes.

Silver in Catheters

Clinical catheters for central vascular insertion or for urethral drainage are notoriously prone to infection with nosocomial organisms leading to biofilm formation. Indwelling central venous catheters are a major source of bacteraemias and candidaemias. Biofilm formation and accumulation of mineralized aggregates is a recurrent cause of catheter obstruction. New technology has been directed to engineer out risks of infection using silver as a component of catheter polymers or in the form of a hydrophilic coating to inhibit adhesion and colonization by pathogenic bacteria and yeasts with varying levels of success (fig. 2) [22, 23]. Catheters treated with silver metal (including nanocrystalline forms), silver oxide, silver sulphadiazine and other ionizable silver complexes have been evaluated in vitro, in animal experiments and in clinical

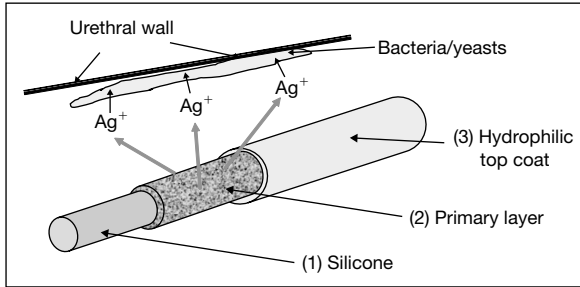


Fig. 2. Diagram of a silver-coated catheter (Dover[®]; Tyco Healthcare) showing a silicone core catheter with a primary coating of silver compound within a hydrophilic outer layer.

trials. Occasionally, other antibiotics including gentamycin, chlorhexidine gluconate or rifampicin have been included to complement the action of silver. Silver sulphadiazine and chlorhexidine gluconate act in a form of ‘synergy’ whereby the chlorhexidine gluconate serves to denature the bacterial cell membrane allowing improved ingress of silver ions. The copper ion exhibits a similar effect in medical catheters. Copper:silver filters are widely used in the purification of hospital water systems against *Legionella* sp. [8].

Silver-coated and silver-impregnated catheters have been evaluated for their antimicrobial action and capacity to prevent biofilm formation in a variety of in vitro systems, some simulating conditions of expected catheter use in clinical practice [23, 24]. Although laboratory experiments have substantiated the antimicrobial efficacy of silvered catheters, the observations have not been substantiated in live animal models or in clinical practice.

Silver has occasionally been employed to control infections associated with intraperitoneal catheters. Thus, silver as impregnate in cuffs, coatings or as ion-beam-assisted deposition has been applied as a coating for Silastic or other catheters but antibacterial protection has not been routinely confirmed [23].

Silver in Devices for Orthopaedic Surgery

Infection is a recurrent problem in association with external fixation pins and screws, prostheses, cements used in orthopaedic surgery and dental cavity fillings. Nosocomial organisms are documented causes of inflammatory changes, degenerative conditions, impaired healing and tissue function leading to lowered patient survival. Prophylactic concentrations of ionizable silver compounds have been included in these devices or applied in the form of a coating on the expectation that ions are released to control pathogenic infections

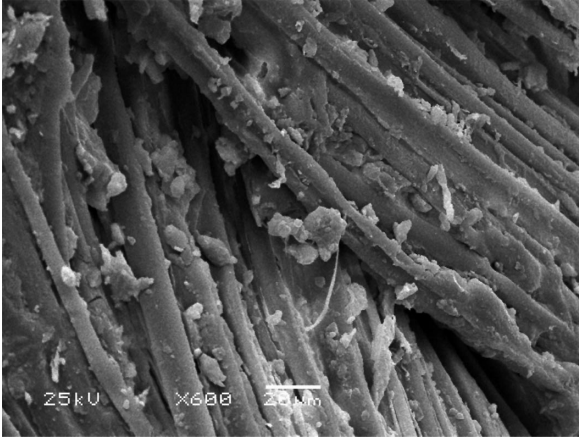


Fig. 3. Mersilk® (Ethicon) suture fibres following immersion in a slurry of silver-oxide-treated Bioglass granules. High-resolution SEM $\times 600$.

without influencing repair mechanisms. At the moment, insufficient experimental or clinical evidence is available to justify the use of colloidal silver or other silver coating in fixation pins. Polymethacrylate bone cements laced with silver have proved effective in controlling *P. aeruginosa*, *S. aureus* and *Escherichia coli* in experimental studies but this has yet to be validated in clinical trials. The same is true where silver is used in bone prostheses.

The development of Bioglass® and its applications in bone surgery and in antiseptic sutures holds current interest in orthopaedic medicine. Bioglass biodegrades in the presence of tissue fluids and macrophages to release calcium, silicon and phosphate for bone repair and has clinical applications in hard and soft tissue repair. Silver oxide added to this bone cement has shown excellent antimicrobial potential in preclinical studies but approval for clinical studies is pending. In the same way, where medical silk sutures were ‘doped’ with silver oxide (fig. 3), antibacterial action as demonstrated in vitro and in experimental studies [Lansdown, Blaker and Boccaccini, unpubl.], clinical work is still pending.

Silver in Cardiovascular Surgery

Limited success has been achieved in using silver to control infections associated with cardiovascular devices including heart valve sewing rings, stents and prostheses. Although infections associated with prosthetic valve prostheses may lead to 80% fatality in clinical practice, devices such as the St. Jude Medical Silzone® sewing cuff, polyester-woven fabrics or knitted prostheses are not clinically acceptable or efficacious in controlling infections.

Darouiche [23] concluded that the validation of silver as an antimicrobial in cardiovascular devices was based on insufficient investigation and inadequate preclinical studies.

Silver in Textiles

The use of silver in medical textiles is at an early stage at present but holds many possible advantages in controlling clothing-borne nosocomial infections in hospitals and in personal hygiene products. It is expected to offer special advantages in protecting those people with acquired or inherited immunodeficiency conditions who are at greatest risk from even mildest infections. We have experience of silk sutures dipped in a slurry containing a Bioglass-silver oxide complex which have been developed at Imperial College (London) to be compatible with human cell lines in vitro. Electron microscopy has demonstrated distribution of the silvered granules on the surface of these silk sutures in a sufficiently robust form to withstand clinical incision at surgery (fig. 3).

In contrast, an antifungal and antibacterial cellulose fibre fabric (Sea Cell) has been developed at the Friedrich Schiller University in Jena (Germany) [12]. The natural cellulose fibres containing algal extracts provide a functional carrier for an ionizable silver compound which has shown commendable antimicrobial action against a range of pathogenic organisms in vitro at least. Clinical confirmation of this efficacy is urgently awaited.

Antibiotic Action of Silver

In his *Manual of Pharmacology* (1942) Sollemann [5] remarked that inorganic silver salts (especially nitrate) are astringent, caustic and antibiotic, that their action was readily controlled and their toxicity low. Since the 1940s when strong concentrations of silver nitrate as 'lunar caustic' or silver pencils were used to remove warts, unsightly granulations and skin calluses, silver has been a choice antibiotic (0.1–0.5%) for treating skin infections and bacterial and fungal infections associated with respiratory disease, bone and joint surgery, prostheses, cardiac devices, eye lesions and transplant surgery. Research has led to a greatly improved understanding of the mechanisms of antimicrobial action of silver and the molecular and genetic basis for silver resistance in bacteria and fungi [8, 20].

In its metallic form, silver is inert and exhibits no biocidal action. However, it ionizes in the presence of water or tissue fluids to release Ag^+ or other biologically active ions. This 'activated' ion shows a strong affinity for sulphhydryl groups and protein residues on cell membranes. Importantly, silver exerts its antimicrobial action at low concentrations (1 ppm) and exhibits the so-called oligodynamic effect coined by von Naegeli in 1895. The lethal effect

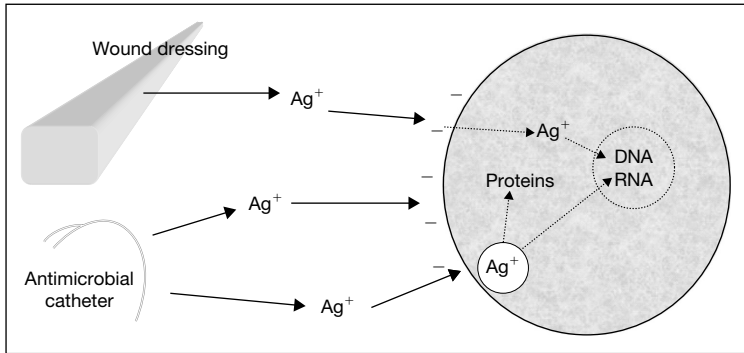


Fig. 4. Antimicrobial action of silver: (1) attachment to the bacterial cell membrane; (2) absorption/diffusion into the cell; (3) coagulation with bacterial proteins/enzymes.

in sensitive microflora was estimated to be equivalent to the number of intracellular enzyme systems to be inactivated, possibly in the range from 10^{-5} to 10^{-7} . Sensitive bacteria accumulate silver against a concentration gradient until lethality is reached [6].

More recently, microbiologists and molecular scientists have sought to unravel the genetic basis for resistance of bacteria to silver. Scanning and transmission electron microscopy has been used to examine:

- the action of silver on cell membranes;
- intracellular uptake and intracellular distribution of silver;
- interaction between silver and subcellular cytoplasmic components (enzymes, metal ion pathways etc.);
- the genetic and morphological basis for bacterial silver resistance.

Available evidence points to a direct correlation between bacterial lethality and 'available' concentrations of free silver in the medium. The silver ion that is chelated, bound or precipitated in insoluble complexes in tissue exudates or secretions is not available for antimicrobial action.

Silver is now known to inhibit a wide range of laboratory strains and type cultures of Gram-positive and Gram-negative strains. Broad extrapolations are made in predicting the responses of infections in the human body to silver. It is conceivable that where silver has been used in the components of materials used in medical devices or coatings, and where limited antimicrobial efficacy has been noted, a large proportion of silver ions released has been mopped up by chelating or binding agents in the micro-environment.

Mechanisms of antibacterial action by silver in sensitive organisms are complex and equivocal (fig. 4). Binding of silver to cell membranes and intracellular absorption is an obligatory first step; silver binds to electron donor

receptors, notably disulphide, amino, imidazole, carbonyl and phosphate residues on membranes leading to intracellular absorption by endocytic vacuoles and phagocytosis. Inactivation of membrane-related enzymes like phosphomannose isomerase results in denaturation of the bacterial cell envelope and its functional capacity to regulate the inward diffusion of nutrients (e.g. phosphates, succinates) and limits the effusion of essential electrolytes and metabolites. Membrane damage has been identified by pitting and increased permeability as a prelude to lethality. The predominant intracellular effect of silver probably lies in its ability to impair key intracellular enzyme systems by impairing trace metals and electrolytes leading to defective respiratory pathways and RNA and DNA replication [7].

Silver resistance in bacteria at least has a molecular, morphological and genetic basis [8]. A silver-resistant strain of *E. coli* isolated from a burn wound containing two large plasmids failed to absorb or retain silver, whereas in a sensitive strain silver accumulation was fivefold higher. Genetic manipulation of these plasmids can dramatically alter silver uptake and hence the silver sensitivity/resistance of an organism. Electron microscopy and molecular techniques have shown that silver resistance encodes in a pericytoplasmic protein – *SilE* – and that this is expressed in the presence of metallothionein (a silver-induced, cystine-rich metal-binding protein). Cytoplasmic changes in a sensitive strain of *S. aureus* have been identified as electron-light regions in the cytoplasm associated with denatured DNA. Resistance (or R factor) can be transmitted through natural gene transfer mechanisms in bacteria, possibly similar to that seen in biofilm formation. Continued exposure of pathogenic infections in burns or other situations were associated with the clinical emergence of resistant strains in patients in the Birmingham Accident Hospital in the 1970s [10]. Experience suggests that emerging resistance among nosocomial and commensal bacteria may in part be controlled by restricting the use of antibiotics, changing practice in antibiotic therapies and using mixed antibiotics (e.g. silver + chlorhexidine) [22].

Biofilm formation is a major problem in the continued use of indwelling catheters and in orthopaedic materials [23, 24]. A wide variety of bacteria (and possibly yeasts and fungi) are known to adhere to surfaces of these devices, migrating along inner and outer surfaces to establish antibiotic-resistant colonies embedded in calcareous matrices. *Proteus mirabilis* has shown a remarkable ability to creep along such surfaces and develop biofilms. Offending bacteria undergo morphological and genetic changes in transforming from their natural ‘pelagic’ existence to the static way of life. Silver antibiotics in device coatings or materials have shown limited success so far in reducing the initial bacterial adhesion or in penetrating the biofilm matrix to achieve lethality. The reasons for this limited success are not immediately clear but may be related to the insufficiency of free silver ions released for antibacterial action in the devices. Much

research is still needed to understand the mechanisms of bacterial resistance to silver in biofilm formation, why silver fails to penetrate the calcareous matrix and how silver interacts to influence natural human protective mechanisms. It is also unclear whether biofilms are likely to be a problem in the use of medicated textiles in nurses' uniforms or other hygiene products.

Metabolism and Toxicity of Silver in the Human Body

Silver is not a trace metal and serves no physiological role in the human body [7]. Silver absorbed into human tissues from antiseptic respiratory sprays, implanted medical devices, wound dressings or indwelling catheters can be expected to reach the systemic circulation, mostly as a protein complex. Argyraemias are more frequent in people exposed to silver occupationally or by environmental exposures including food and drinking water. Theoretically, silver can be deposited in any tissue in the human body but the skin, brain, liver, kidneys, eyes and bone marrow have received greatest attention [14]. Current information shows that the uptake and metabolism of silver are not well documented and are largely limited to a few clinical studies with silver sulphadiazine, where blood silver levels of $>300 \mu\text{g}\cdot\text{l}^{-1}$ have been recorded [15, 16, 19]. Although silver released from intraurethral catheters is available for absorption through urinary tract membranes, the extent to which this occurs is not known. In these cases, primary attention is given to the influence of silver on bacteraemias and biofilm formation [24]. It is expected that as international regulatory requirements become more stringent, silver absorption data from a wide variety of products including textiles will become mandatory.

The silver ion is absorbed through the gastro-intestinal tract and through the lungs following inhalation of silver dust and vapour possibly by passive diffusion of a silver-protein complex or by protein transfer in a form of endocytosis [14]. Absorption through intact skin is low ($<1 \text{ ppm?}$) since much of the free ion is precipitated as silver sulphide in outer parts of the stratum corneum. As much as 10% of silver sulphadiazine is absorbed through partial-thickness burns with exposure to high vasculature [19].

The intracellular metabolism of silver within human tissues is illustrated with reference to cells of a wound margin exposed to silver sulphadiazine. The silver ion absorbed into epidermal cells induces synthesis of the cystine-rich metal-binding proteins metallothionein 1 and 2. Silver avidly binds these proteins to form stable complexes [14, 20]. Increased cellular metallothionein favours the uptake of the key trace elements zinc and copper which in turn promote RNA and DNA synthesis, cell proliferation and tissue repair. Metallothionein thus provides a double action, it protects tissues against the potential toxic effects of a xenobiotic metal

and promotes healing. It is expected that irrespective of the route of exposure, silver will bind to proteins in tissue fluids and exudates, particularly the albumins and globulins. These will be absorbed into the systemic circulation for distribution to soft and hard tissues. The rate of silver absorption is not known accurately for any route of exposure but silver in urine may provide a useful monitor for clinical or occupational exposure and absorption.

Silver absorbed into the human body accumulates in a transitory fashion in the liver, kidney, brain, lung and bone marrow with minimal or no toxic risk. Silver uptake by bone/teeth is low. On the other hand, silver absorbed intestinally or from antiseptic sprays does accumulate in the cornea of the eye (argyrosis) and in the dermis of the skin (argyria), especially tissues exposed to solar radiation. Argyrosis and argyria attributable to fine deposits of silver metal or silver sulphide tend to be long lasting or permanent but not life threatening. Argyria-like symptoms have been seen in patients subject to chronic silver sulphadiazine therapy or long-term exposure to dressings releasing high levels of silver [14]. These black silver sulphide deposits in wound debris are not in my opinion a true argyria; they are rarely permanent, not present in living tissues and are normally lost as wounds heal.

Silver or silver sulphide deposits in living tissues are rarely a cause for toxicological or physiological concern. In the liver and kidney which form the principal routes for silver excretion, silver granules accumulate in the cytoplasm of phagocytic cells, hepatocytes and renal tubular epithelium bound mostly in lysosomal vesicles. Silver is released into bile ducts and urinary ducts for excretion in the faeces and urine, respectively. Greater concern relates to the influence of chronic silver ingestion or silver sulphadiazine therapy on the bone marrow and circulating neutrophils [14]. Reports of neutropenia and erythema multiforme in burned children treated with silver sulphadiazine are now believed to be a self-limiting and transient change of no toxic significance. Leukopenia regressed when treatment was withheld. However, silver is known to sensitize predisposed individuals; this is a permanent effect and a contra-indication for using silver products for any infection. The incidence of silver allergy is not known (silver sensitivity tests are not routinely conducted except for diagnostic purposes). Clearly, evidence of silver allergy is a contra-indication for using any silver products therapeutically and avoiding silver-containing textiles which come into direct contact with the body.

Neurotoxic changes have been documented but not substantiated following the use of silver antibiotic in medical devices. Deposits of silver sulphide in the eye tend to be long lasting but pathological changes have not been identified in the tissues at concentrations as high as $970 \mu\text{g Ag}\cdot\text{g}^{-1}$ tissue weight. Rarely, these silver sulphide deposits have been found to impair night vision but not optic function [14].

Inherent risks of using silver in wound care, medical devices or in textiles are predictably low. On the other hand, workers exposed to fine silver dust, silver vapours and ion beam technology in manufacturing processes are expected to be at greater risk to silver. The inherent risks of occupational silver exposure will be minimized by close adherence to standard procedures in good manufacturing practice, use of appropriate protective clothing and observation of stringent regulations such as Control of Substances Hazardous to Health (UK) which embodies a 'scientific assessment of risk'. Consumers exposed to silver in textiles are expected to be at minimal risk. Silver is not absorbed through intact skin, even in moist areas, to any great extent. It will be considerably lower than seen in patients exposed to 1% silver sulphadiazine cream (30% Ag) or wound dressings releasing at least $100 \text{ mg Ag}\cdot\text{cm}^{-2}$.

Discussion

Metallic silver and silver compounds are used widely in medical devices and health care products to provide antibacterial and antifungal action. Experience has shown that they are generally safe in use and effective in controlling pathogenic organisms. They do not achieve a 'germ-free' state in wounds, device-related infections or biofilm formation however. Biofilms are silver resistant, and silver-resistant bacteria have been isolated from burn wounds, chronic ulcers and nosocomial isolates [20]. It is expected that where silver has been unsuccessful in limiting infections, much of the free silver ion released for antimicrobial purposes has been mopped up by albumins, globulins, free anions and protein residues on cell membranes. At the moment, we do not know the minimal levels of silver ion necessary in any situation to clear infections, although recent research suggests that concentrations of free ion equivalent to 0.5–1.0 M silver nitrate will be adequate [Lansdown and Philip, unpubl.]. Manufacturers of new products should envisage providing a balance between the silver ion released for antibacterial purposes and the minimal toxic threshold. Although much initial research is still conducted in the laboratory with types of bacterial/fungal strains, further clinical and pharmacological studies are urgently required to examine the safety and efficacy of silver in human patients and volunteers with close attention to ethical considerations.

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