Silver I: its antibacterial properties and mechanism of action

Silver products have two key advantages: they are broad-spectrum antibiotics and are not yet associated with drug resistance. This article, the first in a two-part series, describes the main mechanism of action of this metallic element

infections; percutaneous absorption; silver; trace metals

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Metals and metal ions are an essential feature of the human environment. At least 15 metals are vital nutrients for the human body — as components of metalloprotein complexes, enzyme systems or extracellular matrices.

Xenobiotic metals with no known nutrient value may enter the body through diet, inhalation or by skin absorption, and are toxic to some extent.[1] Historically, several, including lead, bismuth, cadmium, arsenic, antimony, mercury and silver, have proved highly effective in the treatment of human infections including venereal diseases, fungal and protozoal diseases, and dysentery.[2,3]

Early pharmacologists coined the term 'oligodynamic action' to refer to the relative efficacy of metal compounds as antibacterial agents at very low concentrations. Mercury (as chloride) and silver (nitrate) have been identified as the most efficacious.[4,5] They inhibited growth of a wide range of Gram-positive and Gram-negative organisms at concentrations of less than one part per million.

Following the development of modern antibacterial chemotherapy and the introduction of sulphonamides and penicillins, most metal-based anti-infective preparations were superseded by safer and more efficacious agents. However, silver compounds continued to be attractive as antibacterials due to their proven efficacy against wound infection, their relatively low toxicity and the introduction of silver sulphadiazine,[6] which controls delivery of silver ion to skin wounds (notably burns).

History of silver in wound care

Although silver and related compounds have always been used to treat maladies and disease, their function as antibacterial agents was not recognised until the late nineteenth century (Table I).

Before 1800 silver nitrate was used for a variety of conditions including epilepsy, venereal infections, acne and leg ulcers.[3,7,8] Silver foil applied to surgical wounds improved healing and reduced postoperative infections,[9] while silver and 'lunar caustic' (pencils containing silver nitrate mitigated with potassium nitrate) were used for wart removal and ulcer debridement.[2]

It is unclear when the true antibacterial properties of silver were first recognised. In the latter half of the nineteenth century Ehrlich developed antibacterial Salvarsan (an arsenical compound), silver-salvarsan and neo-silver-salvarsan for the treatment of venereal diseases.[3] Towards the end of the century Credé[10] claimed that installation of 1% silver nitrate into the conjunctival sac reduced postpartum eye infections from 10.8% to 0.2%, although the reliability of these figures has been questioned.[2] In 1914 Lubinsku[11] found that silver nitrate could release silver ion to form soluble silver albuminates.

In the early twentieth century silver proteins and colloidal silver preparations became popular antiseptics for the treatment of mucus membrane

Table 1. Development of understanding of the antibacterial properties of silver compounds

Period	Advances in bacteriology	Silver-based antibiotics
Up to 1800	Minimal or limited knowledge of the causes of disease or the spread of infection	Metallic silver
1800-1930	Jenner's studies on vaccination and the development of the microscope. Discovery of microbiological infection as a cause of disease. Research by Pasteur, Koch and Ehrlich on the pathogenicity of infectious diseases. Silver used in the purification of water	Metallic silver, colloidal silver (argyrol and protargol-type agents), lunar caustic (as an escharotic agent) and silver salt of arsphenamine (an arsenical compound)
1930-1970	The birth of modern antimicrobial chemotherapy. Research by Fleming, Chain and Florey led to the development of sulphonamides and penicillin	Metallic silver, colloidal silver, silver protein and silver sulphadiazine
1970 to the present day	New techniques in the identification, culture and typing of bacteria. Antimicrobial sensitivity testing. New technology in the production of wound dressings	Metallic silver, silver sulphadiazine, Acticoat, Arglaes, Contreet-H, Avance etc., silver-coated catheters and needles for surgery

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infections.[12,13] These hygroscopic products, prepared from silver oxide, nitrate and other salts, were less irritant than silver nitrate. However, their antibacterial potency was closely related to the amount and rate of free silver ion released. Therefore, mild silver protein preparations like cargentos and silvol, where only a small fraction of the 19–30% silver was present in the ionised form, were appreciably less irritant than strong silver protein preparations (protargol) containing 7.0–8.5% highly ionised silver.[2] Silver iodide and chloride were also available as colloidal solutions for topical or intravenous injection during this period but were later superseded by safer products.

Silver foil continued to be popular among some plastic surgeons in Europe in the 1980s, although it was noted[14] that diffusion of silver ions from solid surfaces (including foil) is limited, even though free silver ion is extremely reactive and combines readily with any proteinaceous material.

Silver sulphadiazine cream, developed in the 1960s, has always been widely accepted as a burn wound therapy.[15,16] It is relatively inexpensive, easy to apply and well tolerated by most patients, and has good antibacterial action against most pathogens found in burn wounds.[17]

Use of silver metal or silver oxide-coated catheters has had varying success in controlling urinary tract infections.[18-21]

Research into burn wound antibiotics led to the introduction of non-toxic and sustained silver ion-release preparations for *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* infections,[8] as well as a variety of creams, impregnated dressings and hydrocolloids containing silver sulphadiazine.[22-25] Deitch[23] noted that the theoretical advantage of these products is their ability to continuously release silver ions into the burn wound for 'as long as the material is in contact [with it]'.

Other innovations that are designed to enhance silver ion release, antibacterial potency and wound healing include:

- Liposomal delivery of silver from silver sulphadiazine[26]
- Silver sulphadiazine plus chlorhexidine, zinc sulphadiazine or another antibiotic, to provide broad-spectrum bactericidal potency[27-31]
- Silver sulphadiazine plus cerium nitrate, as a topical burn wound dressing (Flammacerium [Duphar])[32,33]
- Silver sulphadiazine in combination with growth factors, to provide the dual effect of antibacterial efficacy and promotion of wound healing.[34,35]

Antibiotic action of silver

Mechanism of action

Discussion on the presumed mechanism(s) of silver and related compounds should acknowledge that:

- Silver is a broad-spectrum antibiotic[36]
- Organisms (especially bacteria) show a low propensity to develop resistance to silver-based products.[37,38]

From the earliest reliable studies, the microbicidal action of silver products has been directly related to the amount and rate of silver released and its ability to inactivate target bacterial and fungal cells.[39] The oligodynamic microbicidal action of silver compounds at low concentrations probably does not reflect any remarkable effect of a comparatively small number of ions on the cell, but rather the ability of bacteria, trypanosomes and yeasts to take up and concentrate silver from very dilute solutions.[4,5,40] Therefore, bacteria killed by silver may contain 10^5–10^7 Ag+ per cell, the same order of magnitude as the estimated number of enzyme-protein molecules per cell.[41]

In culture media, uptake and toxicity of silver ions in *Pseudomonas stutzeri* is influenced by sodium chloride, which results in precipitation of relatively insoluble silver chloride.[42] Kuschner found variations in the sensitivity of mutant strains of *Salmonella typhimurium* to the biocidal action of metals such as copper, cobalt, nickel and chromium, whereas both parent and mutant strains of the bacterium remained equally sensitive to silver (and mercury).[43]

Chemically, metallic silver is relatively inert but its interaction with moisture on the skin surface and with wound fluids leads to the release of silver ion and its biocidal properties. Silver ion is a highly reactive moiety and avidly binds to tissue proteins, causing structural changes in bacterial cell walls and intracellular and nuclear membranes.[44] These lead to cellular distortion and loss of viability.[45,46] Silver binds to and denatures bacterial DNA and RNA, thereby inhibiting replication.[47,48]

A recent study demonstrated the inhibitory action of silver on two strains of Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. It found that silver-nitrate exposure lead to the formation of electron-light regions in their cytoplasm and condensation of DNA molecules.[49] Granules of silver were observed in the cytoplasm, but RNA and DNA damage and protein inactivation seemed to be the principal mechanisms for bacteriostasis. Intracellular protective mechanisms against silver differed in the Gram-positive and Gram-negative bacteria.

The action of silver on bacterial infections in water supplies has also increased our understanding of its microbicidal action. Cell penetration of silver is considered the principal objective in the development of copper/silver ionisation techniques.[50] Positively charged copper ions form electrostatic bonds at negatively charged sites on bacterial cell walls, and the resulting damage permits the uptake

and release of silver ions. Silver-related degenerative changes in bacterial RNA and DNA, mitochondrial respiration and cytosolic protein lead to cell death. Silver filters and metal used in the control of Legionella suggest that silver and copper ion concentrations are 40:400µg/l respectively.[51]

The action of silver ion on cell walls is illustrated by reference to the yeast *Candida albicans*. Silver has been shown to inhibit the enzyme phosphomannose isomerase (PIM) by binding cysteine residues.[52] This enzyme plays an essential role in the synthesis of the yeast cell wall, and defects lead to the release of phosphate, glutamine and other vital nutrients.[53] Silver ion did not inhibit PIM in *Escherichia coli* cultures.[53]

Recent literature suggests that the microbicidal action of silver products is partly related to the inhibitory action of silver ion on cellular respiration and cellular function, although the contribution made by 'other' silver radicals generated is also acknowledged.[54] The exact nature of these silver radicals is not clear but Ovington[44] noted that nanocrystalline silver products (Acticoat, Smith and Nephew) can release a cluster of highly reactive silver cations and radicals, which provide a high antibacterial potency on account of unpaired electrons in outer orbitals. Silver and silver radicals released from Acticoat also cause impaired electron transport, bacterial DNA inactivation, cell membrane damage, and binding and precipitation of insoluble complexes with cytosolic anions, proteins and sulphydryl moieties.[5,50,55]

Skin infections and wounds

Open wounds and burns are notoriously prone to infection with antibiotic-resistant bacteria, particularly staphylococci, streptococci and Gram-negative rods.[36] The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterobacteria represent a further major problem.[56,57] The type and prevalence of infections vary according to the location and circumstances of the patient, the extent of the skin wound and local levels of sterility and wound care.[58,59]

Burns are frequently colonised by *Staphylococcus aureus*, but the most dangerous pathogens are *Pseudomonas aeruginosa* and *Streptococcus pyogenes*.[56] The introduction of silver nitrate and other forms of topical prophylaxis was partly responsible for the successful control of pseudomonas infections.[60,61] Moyer et al. found that application of 0.5% silver nitrate to large burn wounds delayed sepsis and reduced mortality from 81% to 33%.[60] During the 1950s and 1960s, 0.5–2.0% silver nitrate solutions and compresses were widely available and perceived as safe, broad-spectrum antibiotics with specific action against *Pseudomonas aeruginosa* in burn wounds and wounds caused by ulcer surgery.[62,63]

Silver nitrate (0.5%) is cheap and effective against many organisms and is not associated with drug resistance.[60,62] However, it stains everything black and causes some electrolyte leakage and manifestations of sodium and potassium concentration imbalances.[64] Use of silver nitrate in burn wound therapy is contraindicated if argyria is present. Argyria (grey colour of skin and conjunctiva) results from the deposition of minute granules of silver sulphide in the dermis around the basement membrane and sweat ducts. Silver bound to proteins in wound sites or deposited as silver sulphide in wound debris can be expected to slough away,[65] whereas argyria tends to be long-lasting and even possibly permanent.

Silver sulphadiazine has been readily accepted as a barrier treatment for burn wounds, and for many years seemed the best antiseptic available.[6,15,66-69] It has proven activity against many Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as well as against some relevant Gram-positive organisms, and does not have several of the complications associated with silver nitrate.[48,70-72] It can be applied liberally to wounds, where it combines the oligodynamic action of silver ions with the specific antibacterial action of sulphonamide.[67] When 1% cream is used, silver is rapidly absorbed through membranes into wound sites, leading to elevated serum silver as well as deposition of silver in the liver and kidneys.[73-76] Sensitive atomic absorption methods show that it is not readily absorbed through intact skin.[75]

Controlled clinical trials of 0.5% silver nitrate compresses and 1% silver sulphadiazine have shown that both protect burns against infection. The former was highly effective, especially against *Pseudomonas aeruginosa*. Resistant strains have not emerged,[60,62] although this may become a problem in the future. Lowbury concluded that while 0.5% silver nitrate compresses reduced burn wound infections by about 70% in his unit, silver sulphadiazine was an outstanding alternative, except in the presence of sulphonamide-resistant Gram-positive bacilli.[57,77] A retrospective analysis of silver sulphadiazine therapy in 342 patients substantiated its value in reducing wound flora and sepsis. It accelerated deep dermal wound healing and reduced the conversion rate of deep dermal wounds to full-thickness skin wounds. Eschar separation also was delayed, enhancing re-epithelialisation and repair.[32]

A silver nitrate/chlorhexidine cream containing 0.5% silver nitrate and 0.2% chlorhexidine has been developed as a suitable alternative to silver sulphadiazine for use against Gram-negative bacilli.[27,28] Chlorhexidine diphosphanilate is an effective broad-spectrum antibiotic but preliminary trials showed it is painful on application, while concentrations greater than 0.5% were contraindicated.[78]

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Table 2. Overview of silver products developed over the past 40 years that provide sustained release of silver ion to the wound site for up to seven days

Product	Structure	Reference
Arglaes	Controlled-release polymer containing calcium, sodium and silver phosphates	99, 100
Acticoat	High-density polyethylene dressing containing nanocrystalline silver	44, 54, 101, 102
Actisorb/Actisorb Silver 200/Actisorb Plus/SIAX	Activated charcoal cloth impregnated with silver and enclosed within porous nylon sleeve	89, 103
Contreet-H	Hydrocolloid containing ionised silver	85-88, 90
Avance/Avance A	Silver incorporated into a hydrophilic polyurethane foam dressing	104, 105
Sildimac*	Silver sulphadiazine-based sustained silver-release preparation	106
Hydron*	Polyethylene glycol, poly 2-OH-ethylm ethacrylate and silver sulphadiazine (1–3%)	107
Catadinic metal silver*	Micronised catadinic silver with benzoyl peroxide	108, 109

*These products are not available in the UK. Their use elsewhere is unknown

A combination of 0.2% chlorhexidine (digluconate) and 1% silver sulphadiazine cream resulted in a significant reduction in *Staphylococcus aureus* infections compared with silver sulphadiazine alone, but no significant differences were evident for *Enterococcus faecalis*, *Pseudomonas aeruginosa* or *Enterobacter cloacae* infections.[28]

The addition of zinc sulphadiazine or other antibiotics has been examined experimentally and clinically in the treatment of burn wound sepsis and variously claimed to be effective. In most cases, the researchers preferred it to silver sulphadiazine alone.[29-31] However, their current value is debatable in the light of newer and safer silver products.

New silver technology: is there an improved antibacterial effect?

Over the past decade advanced wound dressings have been developed primarily for difficult-to-heal wounds, chronic ulcers and extensive burns.[79,80] The focus has been on convenience of application, patient comfort and reduction of high bacterial burdens, wound exudate and odour.

Falanga has emphasised the value of using silver-based products in wound-bed preparation to advance wound healing.[79] Table 2 lists silver dressings that provide a slow but sustained release of silver ion to the wound site for up to seven days. The other dressing components probably have little or no influence on the bacterial burden but enhance the wound environment and promote conditions favouring re-epithelialisation and repair.

Odour-absorbing dressings (such as Acticoat) developed since 1976 tend to absorb bacteria along with wound fluid through the action of charcoal, with silver providing a bactericidal effect.[81] Although wound fluids can vary greatly and contain different amounts of trace and xenobiotic metals, proteins and wound debris,[82] there is as yet no evidence that they impair the bactericidal or prophylactic efficacy of the dressings or interact with them. In the case of silver nitrate, silver sulphadiazine and silver nitrate chlorhexidine, some free silver ion can be expected to bind to cysteine residues in the wound site, although this has not been demonstrated.

Assessment of the relative antimicrobial efficacy of the various products emanating from new silver technology is difficult. In theory, silver-impregnated fabrics that continuously release silver ion into the wound have the greatest antibacterial effect.[23,54,83,84] However, many studies on these dressings are sponsored by the manufacturer, and have promoted the relative benefits of the principal product under investigation. Nevertheless, several preliminary clinical reports provide commendable evidence of their efficacy in microbial control and wound healing.[54,81,83]

Many of the claims for antimicrobial effects made for the new silver preparations are based on *in vitro* studies, where the effects on specific bacteria, especially *Staphylococcus aureus* and *Pseudomonas aeruginosa*, are evaluated in culture media on in zonal-inhibition plates.[85-92] Therefore, the manufacturers of the nanocrystalline silver product Acticoat-7 claim that it provides an effective barrier against over 150 pathogenic organisms including MRSA and vancomycin-resistant Enterococci. It is suggested that the product releases 30 times less silver than other topical silver preparations but has a longer acting time, with the nanocrystalline structure allowing a 'greater surface area for silver release' and antibacterial potency.[54]

Other products, including Arglaes (Maersk), Contreet-H (Coloplast), Avance (SSL) and Actisorb (Johnson and Johnson), are also claimed as effective against MRSA in culture media but confirmatory data are awaited from large-scale clinical trials.

Bacterial resistance to silver antibiotics

The clinical problem of drug resistance is complex. While infections like syphilis do not readily appear to develop drug resistance, acquired resistance in *Staphylococcus aureus* and certain Gram-positive bacilli has created difficulties.[56] Certain Gram-positive bacilli also have intrinsic or acquired resistance to antibiotics, although infections with Klebsiella,

Proteus and Serratia are of less concern than *Pseudomonas aeruginosa* or *Streptococcus pyogenes*.

Silver nitrate has proved an effective prophylactic[60] but, contrary to many published reports, there are silver-resistant strains.[56,57,62] An *in vitro* study that exposed antibiotic-resistant bacteria to silver nitrate, silver sulphadiazine and a silver-coated dressing found that the latter was the more effective antibacterial, having a broader range of activity and rate of effect than the other two.[93] A hospital burns unit reported that silver sulphadiazine was a consistently better prophylactic than silver nitrate, especially against coliform bacteria,[36] although the emergence of sulphonamide-resistant strains has limited its use. A silver nitrate chlorhexidine complex, incorporating silver nitrate in a chlorhexidine dressing, has partly overcome this problem, but chlorhexidine is toxic and can cause sensitisation.[94-96] Chlorhexidine has been incorporated into silver sulphadiazine for use in sterilising intravenous catheters.[97]

Sodium chloride excreted by the skin may also influence the responsiveness of resistant strains of *Escherichia coli* to applied silver. Low concentrations of sodium chloride tended to increase differences in cellular inhibition between resistant and non-resistant strains, whereas higher concentrations exaggerated the sensitivities of both strain types.[98]

Available evidence suggests that most, if not all, of the sustained silver ion-release products are effective against methicillin- and vancomycin-resistant strains and that no resistant strains have been encountered. Nevertheless, vigilance is necessary in the light of experiences gained in the use of silver and silver-oxide cuffing of urethral and intravenous catheters. Although initial studies claimed that coating catheters provided an effective barrier against most types of bacteria,[18] later work has shown the effect to be marginal or irrelevant.[19-21]

Box 1. Summary of the main findings

The microbicidal action of silver has been recognised for over 100 years. When metallic silver interacts with moisture on the skin surface or with wound fluids, silver ions are released which damage bacterial RNA and DNA, inhibiting replication

Silver is a broad-spectrum antibiotic. Silver nitrate is cheap and effective against many organisms, but can have adverse effects. Silver sulphadiazine does not have several of the complications associated with silver nitrate, and has proven activity against many Gram-negative and some relevant Gram-positive organisms

Silver dressings are not associated with drug resistance, although this may become a problem in the future

Many studies on the efficacy of new silver products are sponsored by the manufacturer and tend to promote the benefits of the principal product under investigation. Additionally, many claims for silver's antimicrobial effects are based on *in vitro* studies, although preliminary studies have found good evidence

Conclusion

Current interest in the value of silver in wound care and the development of new dressings that combine antisepsis with wound management reflects advances in experimental surgery and therapeutic evaluation.

This article has focused on the history of silver in wound care, antimicrobial efficacy and mechanisms of antimicrobial action. A follow-up article, to be published in the next issue, will discuss the toxicity of silver dressings. ■

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