A review of the use of silver in wound care: facts and fallacies

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Abstract

This review traces the use of silver in wound care, discussing its merits as an antibacterial agent and constituent of many new dressings, which are increasingly tailored to the treatment of wounds ranging from acute surgical lesions to chronic and diabetic leg ulcers. Misconceptions regarding the biological properties of silver, its possible physiological value in the human body and wound bed, absorption through the skin, and safety factors are addressed. The article aims to present silver and the new range of sustained silver-release dressings as important features in the management of skin wounds, providing effective control of wound infections while ensuring patient comfort and quality of life.

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Silver has made many notable contributions to human health and medicine. In early times, silver coins were used to purify the drinking water of the monarchs of ancient dynasties in the Middle East and South America; since then silver has been employed in prostheses, water purification, surgical needles, catheters, dentistry and wound therapy. Ambrose Paré, the eminent French surgeon (1517–1590), used silver clips in facial reconstruction, and William Halstead (1895), chief surgeon of the Johns Hopkins Medical School, used silver wire sutures in surgery for hernias. Halstead (1895) found that silver foil provided an effective means of dressing surgical wounds and controlling postoperative infection.

Silver nitrate has a history in the treatment of maladies and infectious diseases dating from long before the identification of bacteria, the classic studies of Louis Pasteur and the introduction of Robert Koch's postulates in the 1880s (Evans, 1976; Munch, 2003). Silver nitrate has formed the mainstay of antiseptics used in wound care for more than 150 years, and is still used in burns clinics today.

The antiseptic properties of silver nitrate were appreciated by Credé (1894) who claimed that 0.5–1.0% silver nitrate reduced the incidence of neonatal eye infections in his clinic from 10.8% to about 2%. Early studies indicated that silver nitrate formed 'resistant precipitates' with proteins in skin wounds and that its local antibacterial action could be easily controlled. Lubinsku (1914) remarked that the antiseptic action of silver nitrate extended 'quite deeply' into a wound, with the silver forming soluble double salts of silver albuminate and silver chloride in the tissues.

Silver nitrate is severely caustic at concentrations of 10% or more, but this property is beneficial in the removal of warts, calluses and unsightly granulations (Sollemann, 1942). Nowadays, toughened silver nitrate caustics are licensed by the Medicines Control Agency, but should be used with extreme caution. Surprisingly, Sollemann (1942) remarked that the concentrated solutions of silver nitrate were less painful to patients than the dilute preparations.

Early pharmacologists attempted to overcome the irritancy of silver nitrate by introducing colloidal silver proteins (Sollemann, 1942). They presumed that by precipitating silver in the form of a silver proteinate or colloidal solution, they could overcome the irritancy of free silver ion while preserving its antiseptic action. These colloidal silver proteins achieved some popularity until about 30 years ago, when they were superseded by newer and safer antiseptics, notably penicillins and silver sulphadiazine (sulfadiazine) (Lansdown, 2002a).

The introduction of silver sulphadiazine (sulfadiazine) by Fox (1968) marked a renaissance in the use of silver in wound care. While researching the antibiotic therapies available for controlling *Pseudomonas aeruginosa* in burn wounds, Fox noted that two main agents available at the time, dilute silver nitrate solutions and mafenide-containing ointment, were highly effective but had severe disadvantages. Silver nitrate discoloured everything it came into contact with, and caused electrolyte imbalances in wound fluids, while mafenide inhibited key enzymes (e.g. carbonic anhydrase) and gave rise to hyperpnoea and hyperchloraemic acidosis.

Silver is contained in wound dressings in a variety of forms… from silver metal in microcrystalline form…and silver-impregnated "activated" charcoal …to inorganic silver compounds. Organic complexes include colloidal silver preparations, silver proteinates and silver allantoinate… Nevertheless, to be effective as an antibacterial/ antifungal agent, the silver complex contained in a dressing must release biologically active silver ions.

In introducing silver sulphadiazine (sulfadiazine), Fox combined the antiseptic properties of silver with sulphonamide, providing a broader spectrum and safer antibiotic for use in wound care and surgery. Fox noted that sulphonamides had been used widely in wound therapy during World War II and were relatively safe. Silver sulphadiazine (sulfadiazine) and silver nitrate have been highly successful in controlling burn wound infections for many years, even though the emergence of sulphonamide-resistant bacteria led to a temporary withdrawal of silver sulphadiazine (sulfadiazine) in some hospitals in the mid-1970s (Lowbury, 1972, 1977; Lowbury et al, 1976).

Advances in technology have enabled the manufacturers of wound dressing products to develop safer and more effective antibacterial therapies with barriers to reinfection (Morgan, 1999). The introduction of sustained silver-release dressings in the last 20 years marks a second renaissance in the use of silver in wound therapy. Early dressings included silver-impregnated porcine skin xenografts, silver-impregnated nylon fabrics and meshes and synthetic materials containing silver sulphadiazine (sulfadiazine) for sustained release (Deitch et al, 1987; Chu et al, 2000). Kawai et al (2001) described an artificial dermis based on biodegradable collagen sponge capable of releasing silver sulphadiazine (sulfadiazine).

Actisorb was the first of the modern silver-release dressings to emerge (Mulligan et al, 1986; Furr et al, 1994). The dressing consists of a carbonized fabric impregnated with metallic silver. Acticoat was first patented in the USA in 1997 as an antimicrobial coating for medical devices. It was claimed to provide a 'topical, pure silver delivery system' as a burn wound antiseptic (Tredgett et al, 1998; Wright et al, 1998a; Burrell, 2003).

A variety of silver-release dressings are now licensed in Europe and the USA. They differ greatly in composition, presumed mechanism of action and rate of silver release. They are variously tailored, with recommendations for treating acute surgical wounds, burns and chronic or indolent wounds associated with profound exudation, unpleasant odours and severe patient discomfort. All are claimed to be effective against a wide spectrum of bacteria (including methicillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant enterococci) and to provide an effective barrier to wound re-infection.

Review of the recent literature expounding the merits and clinical advantages of silver-release dressings in wound management reveals factual inaccuracies and misinterpretations, which are perpetuated. These can lead to confusion and uncertainty as to the suitability of silver-release dressings. This article attempts to clarify common misconceptions concerning the presumed mechanism of action of silver in the wound bed, its benefits in repair processes, and its relative safety.

OBSERVATIONS ON THE CHEMISTRY OF SILVER

Silver is an inert metal and does not react with human tissues in its non-ionized or 'pure' form. In the presence of moisture, wound fluids and exudates, silver readily ionizes to release Ag^+ or other biologically active ions, which bind with proteins on cell surfaces, including bacteria and fungi. (Silver can form a variety of compounds as Ag^{2+} or Ag^{3+}, but these are rare and unstable.)

Silver is contained in wound dressings in a variety of forms, which vary in their capacity to liberate silver ions. They range from silver metal in microcrystalline form (prepared using nanotechnology, as in Acticoat dressings) and silver-impregnated 'activated' charcoal (Actisorb Silver 220), to inorganic silver compounds such as nitrate, chloride, zirconium lactate, oxide, phosphate, zeolite and sulphadiazine (sulfadiazine). Organic complexes include colloidal silver preparations, silver proteinates and silver allantoinate. Occasionally, the silver content of a dressing is identified as 'ionic silver or Ag^+' with the identity of the silver complex undefined. Nevertheless, to be effective as an antibacterial/antifungal agent, the silver complex contained in a dressing must release biologically active silver ions.

The solubility and ionization of the silver sources used in wound dressings vary greatly (Burrell, 2003). Silver nitrate is freely soluble and ionizes readily, whereas silver chloride is largely insoluble in water at room temperature and releases only about 1.3 µg Ag^+/ml. Gibbons (2003) claimed that an ionic concentration of 1.43 ppm (ppm and µg/ml are equivalent) is sufficient to kill or inhibit a wide range of microorganisms. By comparison, products based on microfine particles of silver metal with a particle size of <20 nm

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release 70–100 ppm silver ion into a wound site within 4 hours (Wright et al, 1998a; Burrell, 2003). In-vitro tests have shown that nanocrystalline silver products can maintain antibacterial activity for at least 7 days.

Products such as Actisorb Silver 220 utilize a different technology. Silver is adsorbed onto activated charcoal in a high-temperature process, but is not released into the wound site from this dressing (White, 2001). Bacteria are absorbed into the activated charcoal, along with exudates, by a form of wicking, to be killed by ionic silver liberated 'within the dressing' (Scanlon and Dowsett, 2001; Leak, 2002). A similar action is seen with Contreet Foam, which is intended for heavily exudating wounds (Karlsmark et al, 2003; Lansdown et al, 2003).

BIOLOGICAL PROPERTIES OF SILVER

Silver is found in minute quantities in the human body (<2.3 µg/litre in blood, urine, liver and kidney) (Wan et al, 1991). Higher concentrations might be expected in people exposed to silver or silver dust occupationally. Contrary to statements in the medical literature that silver is a 'trace element' or a 'normal body component', silver has no recognized value as a trace metal nutrient and performs no physiological role in the human body (Lansdown, 1995).

One California-based company even stated that Americans were suffering from the novel and undefined condition of 'silver deficiency'. As far as we know, silver does not accumulate or form reservoirs in any tissue in the body, although there are numerous reports of argyria (deposition of silver salts in the skin) and argyrosis (deposition of silver in the eye) in the literature (Bleehen et al, 1981; Lee and Lee, 1994; Lansdown and Williams, 2004).

Argyria usually results from the use of silver nitrate solutions or colloidal silver preparations as oral antiseptics, or from inhalation of silver dust (Pariser, 1978; Bleehen et al, 1981). Silver ion absorbed through the intestine or nasal mucosa complexes with blood proteins, to be deposited as silver sulphide or fine granules of silver metal deep in the skin in the region of hair follicles or sweat ducts or in the eye (Bleehen et al, 1981). Rarely are true cases of argyria reported following topical application of silver sulphadiazine (sulfadiazine) or silver-containing dressings for skin wounds (Lansdown 2002b,c). Silver is not usually eliminated through the skin, but the dark discolorations fade gradually during tissue remodelling or following normal wear and tear processes.

Colloidal silver preparations were once popular for treating infections ranging from pneumonia, influenza and venereal diseases to bubonic plague and were phased out of pharmacopoeias and national formularies more than 30 years ago for safety reasons (mainly argyria and excessive levels of silver in the blood) (Fung and Bowen, 1996).

A new range of colloidal silver products has emerged in the clandestine market in recent years, with far-fetched claims on the internet and in journals of alternative medicine as to their efficacy as food additives and treatments for AIDs, cancer, infectious diseases, acne, prostatic enlargement and haemorrhoids. These products are claimed to have no known side-effects, but the available evidence is limited and of dubious scientific value (Lansdown, 2002d). Furthermore, it is unlikely that supportive data on these products would meet the stringent regulatory requirements in the UK. Claims that silver released from colloidal silver products acts as a systemic disinfectant and functions like a 'secondary immune system' are complete fantasy.

SILVER AS AN ANTIMICROBIAL AGENT

Metal ions can be ranked in order of their antimicrobial activity: silver and mercury head the list and are effective at concentrations of <1 ppm in vitro (Sykes, 1965). Both metals show an affinity for sulphydryl groups on bacterial cell membranes, and are absorbed into the organisms where they act as cytoplasmic poisons. Von Nägeli is reputed to have coined the expression 'oligodynamic' to describe the lethal effects of metals on susceptible bacteria at concentrations as low as 10^{-5} to 10^{-7} silver ions per cell (Romans, 1954).

Early studies (mainly in Germany) suggested that 'active metal ions' are absorbed by bacteria/fungi and coagulate intracellular proteins. Pure metal is inactive. Sensitive organisms accumulate silver from low concentrations in their environment. Silver may have antiviral properties (herpes zoster virus, varicella zoster virus, Herpesvirus hominis), but this area is not well documented

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at present (Chang and Weinstein, 1975; Montes et al, 1986).

The bactericidal efficacy of silver ions has been evaluated mainly in in-vitro culture media (Furr et al, 1994; Thomas and McCubbin, 2003a,b). Recent studies using electron microscopy, X-ray microanalysis and enzyme inhibition have provided detailed information on bacterial sensitivity to silver and mechanisms of bactericidal action, and a possible explanation of why certain bacteria are susceptible and others are resistant (Starodub and Trevors, 1989, 1990). Published studies in the past 30 years show that silver absorbed by sensitive strains of organisms such as *Escherichia coli*, *Ps. aeruginosa* and Klebsiella species:

- Impairs bacterial cell wall integrity
- Binds and disrupts subcellular components
- Inhibits respiration
- Impairs essential enzymes and metabolic events modulated by sodium, magnesium, phosphate, etc.
- Inactivates bacterial DNA and RNA.

Bacterial resistance to silver was documented by Lowbury (Lowbury et al, 1976; Lowbury, 1977) in clinical trials with silver nitrate and silver sulphadiazine (sulfadiazine) in burns patients at the Birmingham Accident Hospital. Silver sulphadiazine (sulfadiazine) (1%) and a cream containing silver nitrate (0.5%) and 2% chlorhexidine were comparably effective in protecting burns from infection, but silver nitrate compresses were less effective against Gram-negative bacilli. The emergence of sulphonamide-resistant bacilli in extensive burns treated with silver sulphadiazine (sulfadiazine) led to a temporary abandonment of the product. Silver nitrate solution was favoured for treating wounds infected with *Ps. aeruginosa*.

Resistance to silver has been studied in laboratory strains of *E. coli* and Pseudomonas species. Starodub and Trevors (1989, 1990) found that silver accumulation by a sensitive strain of *E. coli* was more than five times higher than that seen in resistant strains. (Sensitive strains of Klebsiella accumulated 3–4 times more silver than did resistant strains.) Silver-sensitive bacteria produced 33% less hydrogen sulphide. Cytochemical and genetic studies (Starodub and Trevors, 1989, 1990) suggest that resistance to silver may be attributable to the formation of silver–sulphide complexes within the cell and intracellular 'protective systems' involving cytoplasmic particles or plasmids. Resistant strains contained two large plasmids (identified as pJT1 and pJT2).

Modern investigative techniques have enabled the molecular and genetic basis for bacterial resistance to silver to be unravelled. Silver and Phung Le (1996) and Gupta et al (2001) have cloned and studied the 'determinants' involved in silver resistance in bacteria isolated from burns. They have identified the gene sequences signalling the synthesis of key proteins involved in silver binding or metal uptake in Salmonella species. Further research aims to study environmental and biological causes of bacterial mutagenesis and silver resistance in wounds.

SILVER IN THE WOUND ENVIRONMENT

When a silver-containing dressing is applied to a skin wound, silver ion is released. However, only minute quantities of this free ion penetrate intact human skin because of the effective epidermal barrier function (Coombs et al, 1992). When the natural barrier function of the skin is impaired through cuts, lacerations, surgical incisions, burns or ulceration, it can be anticipated that the silver ion liberated from dressings will (Coombs et al, 1992):

- Be absorbed by bacteria, fungi and inflammatory cells in superficial aspects of the wound
- Bind to free sulphydryl groups on/in wound debris
- Be absorbed into cells at the wound margin
- Penetrate the wound bed
- Be absorbed into the systemic circulation.

Although silver can be detected in tissues at concentrations as low as 1 ng/L using atomic absorption spectrometry, few clinical or experimental studies are available to illustrate the partition of silver in the different wound compartments (listed above). Even in the most severely infected wounds, only a small proportion of silver entering a wound site will be absorbed by bacteria and be involved in disinfecting the tissues; the remainder will bind with sulphydryl groups and proteins in the wound bed or tissues peripheral to the wound. Studies with silver sulphadiazine (sulfadiazine) suggest that most of the silver absorbed into the body will be excreted via the liver or kidneys (Boosalis et al, 1987; Lansdown and

Williams, 2004). Measurement of silver in urine or faeces may provide a useful guide to how much silver is absorbed from silver-containing dressings (Boosalis et al, 1987). However, the few studies published are inconclusive, either because the concentrations of silver present are very low or because patients exhibit higher than normal background levels of blood silver (argyraemia) as a result of previous medications, silver in food, environmental exposure, etc. (Karlsmark et al, 2003).

When a wound is treated with silver nitrate, most silver ion precipitates as black silver sulphide on the surface of wound debris, to be lost as the wound heals. Only minute amounts penetrate the systemic circulation. In contrast, percutaneous uptake of silver sulphadiazine (sulfadiazine) through burns may reach 10%, but uptake tends to be higher in partial-thickness wounds where exposure to severed blood vessels is greater (Coombs et al, 1992).

Although Coombs et al did not find a clear correlation between silver absorption and burn depth, they noted that serum silver levels were higher in patients with burns extending over larger body areas. At least 50% of the silver absorbed is eliminated within 10–12 hours, but as much as 45% forms complexes with proteins in wound exudates or the wound bed (Baxter, 1971). It is conceivable that this 'reservoir' of silver will provide a sustained antibacterial action, but little is known about the stability of the complexes or how readily silver is released from them (Dollery, 1991).

Rarely, black discolorations resembling argyria have been reported following the use of silver sulphadiazine (sulfadiazine) or some of the newer dressings releasing high concentrations of silver into the wound site, but the true nature of these deposits awaits analysis (Lansdown and Williams, 2004). A large part of the silver released from silver sulphadiazine (sulfadiazine) and silver-containing dressings that do not leave dark stains in the wound will probably be precipitated as colourless protein complexes in the wound bed. The silver sulphadiazine (sulfadiazine) complex dissociates within the wound, with the sulphonamide moiety being eliminated more rapidly than silver in the urine (Boosalis et al, 1987). Silver uptake from wound dressings is not well documented, but is an important area of research that should be addressed as new and highly efficacious silver-containing dressings are accepted into wound care.

DOES SILVER AID WOUND HEALING?

Numerous clinical and experimental studies claim that silver released from dressings promotes or kick-starts wound healing by promoting haemostasis, reducing inflammation, and enhancing re-epithelialization and neovascularization, but these claims are still the subject of debate (Kjolseth et al, 1994; Lansdown et al, 1997; Sibbald et al, 2000; Karlsmark et al, 2003). While acute wounds with low levels of infection and minimal systemic or other complications do seem to heal better in the presence of silver, some chronic or indolent wounds exposed to silver sulphadiazine (sulfadiazine) (Flamazine cream) or silver-containing dressings may persist for many months with questionable signs of improvement (Ballard and McGregor, 2002).

Innes et al (2001) do not recommend the use of Acticoat as a dressing for skin graft donor sites. In a recent presentation (Harding, 2003) to the European Tissue Repair Society, Professor Harding remarked on the very high incidence of complications that might impair healing (e.g. vascular disease, systemic infections, diabetes, arthritis) in patients with chronic ulcers.

In order to identify ways in which silver might aid wound healing, it may be useful to examine its known action at constituent steps in the so-called wound-healing cascade.

Haemostasis

There do not appear to be any studies which demonstrate that silver released from any product influences haemostasis in acute or chronic skin wounds, even though experimental studies suggest that local calcium concentrations may be raised (calcium is factor IV in blood coagulation) (Lansdown et al, 1997). Aquacel Ag is recommended for the treatment of 'wounds that are prone to bleeding' (ConvaTec, 2003), presumably because of the haemostatic properties of the hydrofibre component.

Alginates have been used to aid haemostasis since the 1800s (Blair et al, 1990). Avance was claimed to reduce bleeding in a chronic wound in an elderly patient, but the mechanism is not known (Morgan et al, 2001).

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Inflammation

Equivocal evidence exists to show that silver ion may influence inflammation or granulation tissue formation in skin wounds by a mechanism other than its antibacterial effect. Although clinical trials and case reports frequently note that treatments with Avance, Actisorb Silver 220, Acticoat, Contreet, etc. reduce patient pain and discomfort, this is mostly attributed to the antibacterial effects of the silver and neutralization of the toxins produced by the bacteria, rather than any effects it may have on the infiltration of inflammatory cells into the wound bed.

Demling and DeSanti (2002) claim that meshed autografts promote re-epithelialization in clinical wounds, and refer to the ‘pro-healing’ effects of silver. They attribute this effect to the ability of silver to inhibit the formation of matrix metalloproteinases (MMPs). MMPs tend to be higher in some chronic wounds and may hinder healing. MMPs are mostly zinc-based enzymes involved in the degradation of collagen and wound debris. However, it seems likely that since silver (from Acticoat) encouraged deep burns and ulcers with excessive MMPs to heal, silver can have only a limited propensity to shut off inflammatory changes in a wound site (Demling and DeSanti, 2001, 2002). Experimental studies have demonstrated that suppression of MMPs by topical application of synthetic inhibitors delays healing (Agren et al, 2001).

It is of interest to note that the Nucryst Pharmaceuticals division of the Westaim Corporation is currently using nanotechnology to develop a topical silver preparation for the treatment of atopic dermatitis and inflammatory conditions of the skin. Initial preclinical studies suggest that the product (NPI32101) has anti-inflammatory properties and broad-spectrum antibacterial activity. Clinical trials are ongoing.

Wound re-epithelialization

More tangible evidence exists to show that, in acute wounds at least, silver can promote cell proliferation and wound healing. Electron microscopy and chemical analysis have shown that silver penetrates living cells at the wound margin, binds to intracellular proteins (including zinc- and copper-binding metallothioneins), and can activate processes that are dependent on metalloenzymes (Lansdown et al, 1997; Lansdown, 2002a). Further research is necessary to determine how much silver ion is required to enhance trace metal metabolism in human skin wounds to activate repair processes.

Zinc levels in human skin are six times higher in the epidermis than in the dermis and range from 3–10 µg/g (weight analysis) to about 14–20 µg/g in normally healing wounds and 7–15 µg/g in chronic wounds (Henzel et al, 1970). It is conceivable that dressings which release 100 ppm silver into the wound within 8–10 hours (Wright et al, 1998a,b) will significantly enhance zinc or copper levels to trigger or kick-start wound repair, as claimed in product information documents, but clinical evidence is urgently required.

It will be interesting to see whether silver influences other features in the wound environment to advance chemotactic pathways, cell migration patterns and maturation, which are critical during the later stages of wound reorganization and normalization.

PRECLINICAL EVALUATION OF SILVER PRODUCTS IN WOUND CARE

Laboratory studies form an essential preclinical step in the development of any medicine or healthcare product. A sequence of meticulously controlled tests are conducted under defined conditions to assess the physicochemical characteristics of a product, its stability, release of bioactive constituents, pharmacological properties and potential toxicity.

In the case of silver, microbiological tests are a major component of the preclinical evaluation (Furr et al, 1994; Bowler et al, 1998). Tests will be conducted in vitro to identify the minimum concentrations necessary to kill or inhibit 50% of named organisms (including bacteria or fungi isolated from human wounds) and other features of their bactericidal profile (Furr et al, 1994; Thomas and McCubbin, 2003a,b). Preclinical studies provide a cost-effective means of determining which products are suitable for clinical trials and which should be abandoned.

Tissue and cell culture techniques are now sufficiently advanced to allow any cell type in the human body to be cultured under defined conditions of culture medium, temperature, oxygen, etc. Keratinocytes, fibroblasts, neutrophils and macrophages can be shown to respond to growth factors, nutrients,

cytokines, hormones and other factors that influence proliferation, migration and maturation in an intact tissue. Cells can be cultured to provide multilaminate structures resembling the epidermis, with evidence of cell and biochemical gradients representing in-vivo tissue physiology.

Cell culture techniques have been used to examine the toxicity of silver and to identify the minimum toxic dose (Hidalgo et al, 1998; Gibbons, 2003). However, none of these systems can adequately reproduce the complex environment present in any repairing or regenerating tissue in situ. The skin exists naturally in a state of dynamic equilibrium with its environment and exhibits a defined and genetically determined programme of cell death and regeneration in response to normal wear and tear and injury.

Modulation of the processes involved is highly complex and incompletely understood. Only limited success has been achieved so far in understanding the complex chemical and nutrient gradients involved in cell migration and maturation, the nutritional requirements, and the role of hormones, growth factors and conditions in the microenvironment.

Cultured cells are to all intents 'naked cells'. They are highly vulnerable to physical and chemical conditions in the local environment. Hidalgo et al (1998) demonstrated that cultured fibroblasts are sensitive to silver nitrate concentrations 100–700 times lower than those required to disinfect skin wounds in clinical practice. It is unrealistic to predict that a concentration of silver capable of killing 50% of cells in culture (IC_{50}) will produce evidence of skin toxicity when applied to a wound. If the results of titrating silver against mammalian cell cultures showing an IC_{50} of 50 ppm in 24 hours were to be extrapolated to a chronic wound situation, dressings releasing 100 ppm silver would clearly be unacceptable. Experience has shown that Acticoat 7 and Contreet Foam are effective products for wound care and are without toxic risk (Demling and DeSanti, 2001; Karlsmark et al, 2003). The results of in-vitro tests should always be viewed with extreme caution (Lansdown and Williams, 2004).

Laboratory animal studies have a part to play in investigating the possible benefits of silver-containing products on wound repair and regeneration, and their possible mechanisms of action. Although they can provide a satisfactory means of predicting the toxicity of drugs, medicaments and devices used in human medicine, they should also be extrapolated with care (Lansdown, 1978, 1995; Meyer et al, 1978).

Human skin is unique in the animal kingdom and has no exact counterpart, even among higher primates (Kligman, 1978). No animal model can provide other than preliminary information that a product is potentially useful and safe for use in wound care, or that product A is better than B or worse than C. While cell proliferation patterns, migratory pathways and maturation are likely to be similar in experimental and human wounds, it is important to recognize that there are fundamental interspecies differences (*Table 1*).

Table 1. Interspecies differences in relation to wounds

All wounds induced in the skin of experimental animals are of the acute type; chronic wounds cannot be induced in non-human species
Animal skin wounds are usually induced in genetically defined animals maintained under critically controlled laboratory conditions
The natural flora of animal skin differs from that of human skin
The immunological reactivity of animal skin differs from that of human skin (Marzulli et al, 1968; Kligman, 1978)
No non-human species can accurately reproduce the wide diversity of human skin types, which vary according to race, sex, genotype, diet and geographical area
The constitution of epidermal lipids, sweat gland secretions and epidermal barrier are species specific
It is difficult or impossible to reproduce clinical symptoms of human diseases that influence wound healing in human patients, e.g. diabetes mellitus

TOXICITY OF SILVER IN MEDICINE

Accurate information on the toxicity of silver is hard to find. What does exist is frequently fragmentary, occasionally misleading or incompletely evaluated.

Silver is absorbed into the human body through the intestinal mucosa, by inhalation and through skin wounds. The silver ion is highly reactive and shows an affinity for sulphydryl (SH) groups on cell membranes and proteins in a wound or in the circulation. Silver protein complexes are formed in the systemic

circulation and can be mobilized to and deposited in any organ or tissue in the body — particularly the skin, liver, kidneys, bone marrow and eyes. The available evidence shows that although silver can cause transitory changes, including leucopenia, the risk of lasting damage or persistent functional disorder in any tissue is very low (Lansdown and Williams, 2004). Silver is eliminated in the urine and faeces, but little is currently known about the patterns of silver metabolism from deposits in any organ. It is not known to what extent silver accumulates in bone or hard tissue.

Allergy to silver is associated with occupational exposure (e.g. silver worker's finger) and silver in jewellery (Fisher, 1987). The extent to which silver allergy arises in the use of silver-containing wound dressings is not known, but manufacturers normally warn customers of this potential risk.

Patients with chronic wounds do occasionally experience discomfort with silver-containing dressings. Although silver allergy might be diagnosed, the possibility that the patient is sensitive to other materials in the dressing or the environment should not be discounted. Some patients have particularly sensitive skin contraindicating the use of all but the blandest of dressings. Lanolin, paraffin wax, antibiotics (other than silver), antihistamines, latex gloves, and glove powder are all well known causes of skin reactions and delayed hypersensitivity (Fisher, 1987). Hyperthermia, excessive dehydration and reduced gas permeability of a dressing may be contributory factors.

CONCLUSION

The ability of silver ion to kill or otherwise inhibit a wide range of Gram-positive and Gram-negative bacteria, filamentous fungi and some viruses found in skin wounds is unequivocal. Silver is effective at low concentrations and, with the exception of occasional incidences of contact allergy (delayed hypersensitivity), is without appreciable toxic risk.

Modern technology and improved understanding of the pathology and cytological behaviour of the wound bed have led to the introduction of a new generation of silver-containing dressings for wound care. These dressings are realistically tailored to the treatment of specific wound types, ranging from acute surgical lesions to burns, chronic leg ulcers and diabetic ulcers, some of which are notoriously prone to infection.

There is good evidence that infections are a major cause of chronicity and failure in wound healing, but clinical observations show that chronic wounds are frequently complicated by vascular disease, arthritis, diabetes mellitus and systemic infections. Although silver is frequently able to control wound infections or provide an effective barrier to re-infection, drugs or other therapy given to treat these other conditions may counteract any beneficial influence of silver on or in the wound bed.

The silver-release dressings introduced in recent years use metallic silver, inorganic silver compounds and organic complexes as their source of silver, and components such as polyurethane, alginates, carboxymethylcellulose, knitted fabrics and activated charcoal provide the structure of the dressing. The dressings vary greatly in their total silver content (from 1.6 to 546 mg/100 cm^2), capacity to release free silver ion, and presumed depth of silver penetration into the wound.

Dressings are designed in different ways to modulate silver-release patterns. Selection of an appropriate dressing will invariably be a subjective decision based on the personal judgment and experience of clinicians or tissue viability nurses, aided by advice from manufacturers. Questions do arise for which there are no ready answers. A common question is how much silver is sufficient to treat a wound without producing undesirable side-effects. Answers to these and other questions, with explanations, may become available as more experience is gained and research studies are completed.

Laboratory tests are an essential first step in the development of any medicament, but however meticulously they are conducted in a test tube, tissue culture system or laboratory animal model, they cannot realistically represent conditions in the human wound. Routine microbiological tests have a place in identifying the susceptibility of infectious agents (type cultures or wound isolates) to ionized silver released from a dressing, and may prove useful in comparing the antimicrobial efficacy of different dressings (Wright et al, 1998a,b; Thomas and McCubbin, 2003a,b). Preclinical research studies are designed to predict how a medicament or dressing might

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Although the value of silver in wound care has been appreciated for many years, research still has a major place in providing answers to the questions that regularly arise in clinical and manufacturing practice. We need to use appropriate hospital resources... to investigate how a wound responds to a particular silver dressing, where the silver goes...and rates of elimination of silver from the wound site.

behave in a clinical situation, but they can at best only provide an approximate guide to nurses or clinicians.

Although the value of silver in wound care has been appreciated for many years, research still has a major place in providing answers to the questions that regularly arise in clinical and manufacturing practice. We need to use appropriate hospital resources (e.g. clinical chemistry, biopsy pathology, haematology and sonography) to investigate how a wound responds to a particular silver dressing, where the silver goes (i.e. its distribution between wound infections, wound exudate proteins, wound bed, etc.) and rates of elimination of silver from the wound site.

Despite earlier reports indicating hazards with silver nitrate, colloidal silver and metallic silver (Rungby, 1990; Fung and Bowen, 1996; Humphries and Routledge, 1998), minimal evidence has been found to suggest that silver is toxic when released into the wound, even at high concentrations (Hollinger, 1996; Lansdown and Williams, 2004).

Argyria is a possible side-effect of the use of silver or silver-containing dressings, but this is cosmetic, usually only temporary and not life-threatening. Research is necessary to investigate the condition colloquially known as 'silver dumping'. Chemical analysis may prove useful in identifying the nature of the dark-coloured deposits seen occasionally in patients with heavily exudating wounds treated with high-silver dressings.

It is to be hoped that careful analysis and thoughtful information from laboratory and clinical research will provide a clearer understanding of the importance of silver in wound care, and help to distinguish the facts from the fiction. BJN

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KEY POINTS

- Silver is a broad-spectrum antibacterial and antifungal agent with limited antiviral properties. It has no role in the body as a trace metal nutrient.
- Silver is available as a topical antiseptic (silver nitrate or silver sulphadiazine) and as an anti-infective agent in wound dressings at concentrations ranging from 1.6 to 500 mg/100 cm^2, with widely varying patterns of silver ion release.
- Silver-containing dressings are tailored to the treatment of wounds ranging from acute surgical lesions with low-grade infections to chronic indolent and diabetic wounds and ulcers with recurrent infections, exudation and odour.
- Silver-containing dressings are designed for easy application, maximal patient comfort and safety in use. They provide a barrier to common pathogens.
- Further research and clinical observation is needed to establish how much silver is necessary to eliminate infections in chronic wounds and provide an effective barrier function.