The safety and efficacy of dressings with silver – addressing clinical concerns

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Cutting K, White R, Edmonds M. The safety and efficacy of dressings with silver – addressing clinical concerns. Int Wound J 2007;4:177–184.

ABSTRACT

With the increasing use of silver as a topical application in wound care, concerns focussing on its role are bound to arise. These concerns, which centre on issues such as resistance and toxicity, clinical efficacy and cost-effectiveness, need to be addressed and openly discussed so that they are viewed from a rational perspective. While clinical efficacy and safety, along with cost–benefit, are of obvious interest, the origin of some of these concerns is a matter of debate. The silver-containing dressing segment of the medical device market is of huge commercial importance, and, consequently, marketing and promotional issues occasionally obscure the evidence that clinicians need to have in order that they may provide appropriate treatment for their patients. The impact of silver application on the wound bioburden needs to be examined carefully to heighten our awareness of any deleterious effects on the healing process, without inducing any unfounded anxieties.

Key words: Resistance • Silver • Toxicity • Wound Dressings

INTRODUCTION

Antiseptics have a long history in the management and prevention of infection, not least silver and its compounds (1). It is the ionic form of silver (Ag^+) that is antimicrobial, being cidal to bacteria and yeasts (2).

With the emergence of silver-impregnated dressings as an increasingly popular approach in the topical control of wound bioburden, any associated concerns accompanying this expanding use of silver should be recognised and addressed. Personal observation indicates that these areas of disquiet tend to relate to issues such as bacterial resistance, toxicity relative to dosing, clinical efficacy and cost.

Silver is described as oligodynamic owing to its bactericidal effects at minute concentrations (3,4). A solution containing only one part per 100 million of elemental silver is sufficient to be used as an effective antimicrobial agent (5). This has contributed to the interest in applying silver to health care products such as silver-coated catheters and wound dressings. Wounds healing by secondary intention host mixed bacterial populations and thus (often but not always) require broad spectrum antimicrobial agents (6). This has, in part, contributed to the popularity of silver impregnated dressings.

Silver is therefore ideally suited to its role as a topical antibacterial and antifungal agent. This, together with the recent advances made in dressing technology, provides opportunities for the topical management of infection and at-risk wounds, often avoiding the need for systemic antibiotic therapy.

Some of the early concerns relating to silver were associated with silver nitrate ($AgNO_3$). This possibly emanates from the fact that silver nitrate possesses a propensity for inducing pain on application and staining of the skin, wounds and the clothing it comes in contact with, together with a potential for

Key Points

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- silver is ideally suited to its role as a topical antibacterial and antifungal agent

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Key Points

- it is important that issues related to the wider use of silver are confronted so that they can be articulated and addressed in the proper context
- although the emergence of antibiotic resistance is regarded with grave concern, resistance to antiseptics such as silver is rarely encountered
- while antiseptic resistance is not yet a real threat, good clinical practice dictates that practitioners should avoid indiscriminate and unjustified use of silver, as with all topical antimicrobials
- this includes avoiding sustained use when a wound has not responded to topical silver therapy within approximately 10–15 days, that is three to five dressing changes

toxicity (7). Silver nitrate solution is not so widely used today for the above reasons and because of the difficulties encountered in its application.

Silver sulphadiazine (SSD), a combination of silver with the sulphonamide antibiotic sulphadiazine (8), is a popular topical antimicrobial available in cream formulation that has a strong legacy of use in wound care stretching back over 40 years. Despite the acknowledged shortcomings of silver nitrate (mentioned above), the pedigree that SSD has acquired through clinical use should rule out any substantial anxieties over use of silver in modern burn wound care. Its use on chronic wounds is less well supported by clinical evidence. The subsequent introduction of an activated carbon dressing, later to become impregnated with metallic silver to the range of dressings in the 1980s provided additional opportunities for the use of silver in wound care. During this period and up to the mid-1990s, challenges relating to silver in the management of wounds were largely unheard of. Why have anxieties associated with use of silver in wound care occurred in recent years? Are these concerns a result of the competitive interests within commerce following the addition of numerous silver products to the market place, or, is this scientifically and clinically driven resulting from the need for clear indications of use?

It is important that issues related to the wider use of silver are confronted so that they can be articulated and addressed in the proper context. One attempt that has been made to spell out concerns in relation to silver in wound care (9) prompted vigorous retorts to the published viewpoints (10,11). It is, therefore, evident that unresolved issues persist and this necessitates continuing debate.

SILVER RESISTANCE IN MICROORGANISMS

Many metals are essential for normal cell function; and all cells, whether prokaryotic or eukaryotic, must establish metal homeostasis for survival. The requirements for any particular metal, for example as an enzyme co-factor, must be balanced with the possible toxicity of excess quantities of that metal. Excess metals are either exported from cells or detoxified by a variety of mechanisms (12). Silver has no known biological function in living cells and is rarely encountered (by them); thus, there has been little evolutionary pressure to develop a specific mechanism of homeostatic control.

In many bacterial species 'heavy metals' in general, such as silver and copper, nickel and zinc, can be 'exported' by an efflux pump mechanism; these are often membrane adenosine triphosphatase (ATPases) (13), which also act to eliminate antibiotics (14). The Gram-negative bacterium *Pseudomonas aeruginosa*, for example, has such an efflux pump, which has been shown to lead to multidrug resistance (15). Similarly, *Escherichia coli* exports both copper and silver by the CopA ATPase efflux pump (16).

There is evidence of silver resistance genes transcribed on plasmids in a number of bacterial species (17,18). This mechanism was, to our knowledge, first reported in 1979 (19) although silver resistance had been reported in *E. coli* in 1969 (20) and resistance to SSD reported in 1974 (21). Silver resistance genes, denoted *sil* A, C, E, P and R, have been described, and their plasmids were sequenced (22). Thus, the literature is abundantly clear, resistance to silver is a feature in some bacteria (6), in particular enterobacteriaceae, for example *Enterobacter cloacae* (23,24). The links between silver resistance and the use of silver in medicine have been described (24,25).

The first report on the genetic and molecular basis of silver resistance of bacteria was published in 1999 by Gupta et al. based on the silver-resistant determinant found in *Salmonella* species, which caused septicaemia, killing three patients and subsequently closing the burn unit at Massachusetts General Hospital (22). The silver-resistant plasmid isolated also confers resistance against other antibiotics (54).

Although the emergence of antibiotic resistance is regarded with grave concern, resistance to antiseptics such as silver is rarely encountered (6).

RECENT REPORTS OF CLINICALLY OBSERVED BACTERIAL RESISTANCE TO SILVER

Resistance to silver in the form of SSD has been reported by numerous authors including Gayle

et al. (26). While antiseptic resistance is not yet a real threat (27,28), good clinical practice dictates that practitioners should avoid indiscriminate and unjustified use of silver, as with all topical antimicrobials. In general terms, this includes avoiding sustained use when a wound has not responded to topical silver therapy within approximately 10–15 days, that is three to five dressing changes. The dressing change interval will depend to a great extent on the ancillary performance features of the dressing. Thus, a dressing with exudate absorbency will tend to have longer wear time than a non or low-absorbent silver dressing. The issues relating to silver resistance have been addressed by (3,22,25). While some bacterial species have shown evidence of genes within the *sil* operon, this appears to be rarely expressed in the phenotype.

SILVER TOXICITY

The terms toxicity and cytotoxicity are often encountered in the literature in relation to antimicrobials, including silver (55). In essence, they mean the same – the ability to cause harm to cells/health. The term cytotoxicity tends to be used more in the laboratory, that is as an in vitro phenomenon, whereas toxicity is more commonly used in the clinical setting. Additionally, some may use the term cytotoxicity as indicative of a localised effect and toxicity as having the propensity to have systemic impact. The question that demands answering is at what level, and under which circumstances, is silver (cyto)toxic in vivo? A satisfactory answer to this will assist clinicians in the appropriate selection and optimal use of silver dressings.

Several factors influence the capacity of a metal to produce either local or systemic toxic effects; these include the degree of absorption as influenced by solubility of the metal or its compounds; the ability to bind to biological sites and the degree to which the metal complexes so formed are sequestered, metabolised and ultimately excreted.

Silver is applied clinically to open, dermal wounds in the form of dressings impregnated with silver salts (e.g. silver nitrate) and metallic silver or as organic compounds such as SSD cream (8) and as a coating for catheters (29). It is generally a safe and effective antimicrobial agent. However, it is important to appreciate that topically applied silver may penetrate breached skin (30,31) and be available to the systemic circulation; under such circumstances, toxicity is a risk. The chemical nature and formulation of the applied silver will influence its absorption, distribution and metabolism. Studies on 'background' or environmental silver levels in human tissues indicate that the normal concentration of silver is very low (32). There is evidence of systemic toxicity after topical application of silver-containing treatments: for example, renal toxicity from silver has been reported after application of SSD cream, leading Chaby et al. to conclude that this should not be used for long periods on extensive wounds (33). Similarly, Lansdown and Williams (34) acknowledge that the use of topical silver in burns and chronic ulcers can lead to systemic absorption and subsequent deposits in the organs. There are few reported data on systemic absorption of silver from sources other than topical SSD. In a clinical case report Trop et al. reported silver toxicity in a 17-year-old male with 30% mixed depth burns. Following 1 week of topical management with a silver-coated, high-density polyethylene mesh dressing (Ag polyethylene mesh), hepatotoxicity and argyria-like symptoms were recorded. Elevated plasma and urine silver levels of 107 μg/kg and 28 μg/kg, respectively, were measured, as were elevated liver enzymes (aspartate aminotransferase, alanine aminotransferase and gamma glutamic transpeptidase). The symptoms disappeared when the dressing was discontinued. The authors conclude that potential silver toxicity should be borne in mind by clinicians when treating burn patients with silver-coated dressings. Empirical clinical evidence suggests that silver dressings are safe when used on chronic wounds for limited periods, for example up to 4 weeks (eight to ten dressing changes). It is only when large body surface areas (approximately 30% body surface area or greater) (35) or smaller wounds for extensive periods (more than 30 days) are treated that toxicity can occur.

HYPERPIGMENTATION (ARGYRIA) AND SKIN STAINING

Long-term exposure by ingestion, inhalation or dermal exposure of silver or silver compounds in humans may cause argyria. The word argyria comes from the Greek word 'arguros', which means silver; it is a grey dyschromia (discolouration) of the skin, conjunctiva and

Key Points

- cytotoxicity tends to be used more in the laboratory, that is as an *in vitro* phenomenon, whereas toxicity is more commonly used in the clinical setting
- silver is generally a safe and effective antimicrobial, however, it is important to appreciate that topically applied silver may penetrate breached skin and be available to the systemic circulation; under such circumstances, toxicity is a risk
- it is only when large body surface areas (approximately 30% body surface area or greater) or smaller wounds for extensive periods (more than 30 days) are treated that toxicity can occur
- long-term exposure by ingestion, inhalation or dermal exposure of silver or silver compounds in humans may cause argyria, which is a grey dyschromia (discolouration) of the skin

Key Points

- true argyria is an irreversible staining of the skin that does not diminish over time
- *in vivo* studies indicate that silver can exert a beneficial effect on wound healing in a variety of wounds

internal organs. Once deposited, silver particles remain immobile and can accumulate during the ageing process because of its insignificant rate of excretion (36). Generally, it is accepted that argyria has become a rare dermatosis, mainly because of the avoidance of silver-containing compounds as medicines and a decrease in occupational exposure in the silver industry (37). True argyria is an irreversible staining of the skin that does not diminish over time.

Hyperpigmentation (argyria) of skin following application of topical silver has been reported by Dupuis (38) in relation to SSD. In a brief case report by a letter, Dupuis states that the case in question supports previous work where the silver component of SSD may be absorbed to cause staining of the skin.

Lansdown (2) reported in a literature review that discolouration of tissue had not been recorded in relation to a range of modern silver products; more recent work indicates otherwise (30,31). To examine potential skin staining as a result of application of modern silver dressings (30,31) Walker et al. applied two commercially available products a sodium carboxymethylcellulose dressing containing ionic silver (AgNaCMC) and an Ag polyethylene mesh, for a maximum of 96 hours, to human skin samples where the epidermis had been removed. Tissue samples were then evaluated for silver deposition to the de-epidermalised dermis. The authors conclude that deposition of silver was evident following the application of the Ag polyethylene mesh dressing but not with application of Ag-NaCMC dressing. This was local deposition and cannot be termed argyria. It is important to remember however the relevance of in vitro findings to the clinical situation. We were unable to find in vivo evidence of argyria associated with modern silver dressings.

In the clinical case report (35) reported above, it is important to note that the disappearance of the argyria-like symptoms on withdrawal of the silver-coated dressing suggests that the observed skin staining was not true argyria as this phenomena is not reversible. Transient staining of the wound bed with silver may hamper accurate assessment and is therefore best avoided; this is best achieved by avoiding those dressings that are known to cause staining (31).

ANTIMICROBIAL CLINICAL EFFICACY OF SILVER

When examining modern silver products, the important point has been made that because silver efficacy is not in dispute, the choice of dressing rests on the characteristics of the carrier dressing and the delivery of silver to the wound (39,40). The importance of the dressing technology will be reviewed in a subsequent article.

In a non comparative study, the performance and safety of a silver-containing polyurethane foam dressing (Ag polyurethane foam) in the treatment of 27 diabetic foot ulcers were examined (41). The findings of this study indicate that no harmful effects of silver were observed. Four wounds healed within the study period of 4 weeks, the mean reduction in ulcer size was 56% with the median reduction being 86%. The dressing was also considered to be an effective barrier to infection.

In a prospective, randomised study (42), Caruso et al. compared SSD with AgNaCMC dressing in the management of partial-thickness burns. The findings include less pain and anxiety during dressing changes, less burning and stinging during wear, fewer dressing changes, less nursing time, fewer procedural medications, lower total treatment costs, greater rate of epithelialisation and greater cost-effectiveness when using the silver fibrous dressing. The SSD dressing was associated with greater flexibility and ease of movement.

In a clinical study focussing on 86 patients with traumatic and non healing wounds (43), Ziegler et al. found that a silver-coated polyamide textile dressing (Ag polyamide textile) 'has a superior profile of antimicrobial activity over cellular toxicity'. In addition, the silver dressing reduced the volume of slough and increased granulation tissue and rate of epithelialisation, observed over three dressing changes.

Sibbald et al. (44) used a Ag polyethylene mesh dressing on 29 patients who had a variety of chronic wounds. Following the use of the dressing, there was a decrease in the surface flora of the wound. There was also a reduction in the production of exudate, and some patients achieved a reduction in pain. There was no change in the quantity or quality of the microorganisms that were isolated from the

deep tissue. The significant microorganisms required systemic antibiotic treatment.

The in vivo studies above indicate that silver can exert a beneficial effect on wound healing in a variety of wounds. The studies used a variety of carrier dressings that all delivered ionic silver to the wound in doses that did not appear to cause any toxic effects by impeding the progress of the wound.

EFFICACY AND COST

The bulk of the published literature on the clinical efficacy of silver relates to SSD [reviewed by White and Cooper (8)]. Few dressings have published clinical evidence to support their use in the wider range of wound types. Health economic data on the use of silver dressings is currently sparse (42,45). To address this shortcoming, the VULCAN trial (46,47) is in the process of examining cost-effectiveness in the treatment of venous leg ulcers across a range of silver products.

Currently, evidence exists to support dressings such as Actisorb Silver 220 (48), AQUACEL Ag (42) and Contreet (45). Silver dressings are being used widely on a variety of wounds, both acute and chronic, without clear instructions on criteria for initiation and cessation of treatment.

Silver dressings, as antimicrobial therapies, are generally not indicated for long-term use, unless the patient is at such high risk as to justify this approach or where they contribute to improvements in quality of life such as in patients with fungating tumours. There will therefore be a finite period for silver dressing use. This must be dictated by clear criteria justifying the initiation of treatment, for example critical colonisation (3,4), signs of local infection, or, as an adjunct to systemic antibiotics in spreading infection. The value of topical adjunctive therapy has not yet been established by rigorous clinical evidence. Thereafter, regular wound assessment should guide the further use of the dressing. Duration of treatment should be according to clinical needs and be guided by treatment targets and measured by defined criteria. Long-term, unjustified treatment is wholly inappropriate if a wound does not respond positively.

SILVER AND DIABETIC FOOT ULCERS

One of the greatest problems in the management of diabetic foot ulceration is the diagnosis and treatment of infection. The presence of infection in a diabetic ulcer is a highly significant staging post on the road to amputation.

The classic presentation of infection is cellulitis. However, this is a late stage and covers a spectrum of presentations, ranging from spreading cellulitis, sloughing of soft tissue and, finally, vascular compromise of the skin, seen as a blue discolouration when there is an inadequate supply of oxygen to the soft tissues. By this stage, there may be considerable tissue destruction. The foot can usually be saved from amputation but may need extensive debridement with loss of tissue.

Thus, it is important to diagnose and treat infection early, so as to halt the development of a severe destructive infective process and second to accelerate the healing of ulcers.

Signs of inflammation depend on both an intact peripheral nervous system and an undamaged peripheral vascular system, both of which can be severely impaired in diabetic patients, especially those with foot ulcers. Pain and tenderness may be absent because of neuropathy. Erythema or redness may be absent in the diabetic foot because of the inability of the foot to increase its blood supply in response to infection. Up to 50% of patients with deep foot infections will not have leucocytosis or fever. Thus, lack of clinical signs alone can lead to a failure of early diagnosis of the initial stages of infection.

Early intervention may stop the progress of infection. Furthermore, it may help healing of the ulcer. Many wounds are colonised with a stable bacterial population, and bacterial growth in ulcers may impede the wound healing rate. In a recent study, 3-mm tissue biopsies of the ulcer base were taken from eight patients with diabetic foot ulcers >1 cm^2 in area for quantitative bacteriology. Quantitative bacterial counts and organism identification were determined after 36- to 48-hour incubation. In this study, six out of eight patients had $\geq 10^5$ cells/g, despite the absence of clinical signs of infection. Those ulcers with increasing bacterial load had slower healing (49).

How can we clinically recognise the early stages of infection and how can we intervene? If the bacterial burden in an ulcer alters unfavourably, there will be a bacterial imbalance or so-called critical colonisation (4) that may show itself as increased exudate before frank infection develops. The base of the ulcer

Key Points

- silver dressings are being used widely on a variety of wounds, both acute and chronic, without clear instructions on criteria for initiation and cessation of treatment
- one of the greatest problems in the management of diabetic foot ulceration is the diagnosis and treatment of infection
- lack of clinical signs alone can lead to a failure of early diagnosis of the initial stages of infection
- with early recognition of this key stage of infection, it is important to make an appropriate intervention

Key Points

- silver compounds may have a role in treating the early stages of, or preventing, infection in the diabetic foot ulcer
- as these dressings have a valuable antimicrobial function, it is vital that they be used appropriately and not abused
- it is important to remember that silver dressings do not 'cure' infections but have a broad spectrum of activity and when used wisely effectively inhibit bacterial penetration
- there are still numerous questions to be answered in respect of silver in wound care many of which have been articulated in this article
- it is now the responsibility of the Industry and independent clinicians and scientists to address these questions to the satisfaction of all involved in wound management

may change from healthy pink granulation to yellowish or grey tissue (50) and the ulcer may stop healing.

With early recognition of this key stage of infection, it is important to make an appropriate intervention. This may take the form of oral antibiotics. However, recent guidelines support their use only in cases of frank infection. Thus, topical antimicrobials should be considered in this situation.

Ionic silver has broad spectrum of antimicrobial action against Gram-negative and Gram-positive organisms. In vitro, they are effective in killing *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas* species. Silver has been impregnated into dressings and may be useful in the treatment of diabetic foot ulcers (51).

Silver compounds are widely used in antibacterial prophylaxis. In a recent study of sustained silver-releasing dressing in the treatment of diabetic foot ulcers, there was good exudate management and good wound progress of clinically un-infected diabetic foot ulcers with only 2 infections occurring in 27 ulcers (41).

Although, a recent Cochrane review (52) of silver-based wound dressings and topical agents for treating diabetic foot ulcers found no suitable randomised trials or controlled clinical trials to evaluate their clinical effectiveness, a recent prospective, randomised controlled study of non ischaemic diabetic foot ulcers compared AgNaCMC with calcium alginate dressings (53). Subjects who received silver experienced more overall ulcer improvement, $P = 0{\cdot}06$, which was most marked in patients taking antibiotics, $P = 0{\cdot}02$. Ulcers treated with silver reduced in depth nearly twice as much as did those treated with alginate (2·5 versus 1·3 mm, $P = 0{\cdot}04$). Thus, silver compounds may have a role in treating the early stages of, or preventing, infection in the diabetic foot ulcer.

CONCLUSIONS

In the past 5 years, silver-containing wound dressings have become very popular and are now widely used in clinical practice. The evidence supporting their use is still, as yet, sparse and is predominantly in vitro. However, this does not appear to have deterred clinicians from the widespread use of silver dressings, much of which is prophylactic. As these dressings have a valuable antimicrobial function, it is vital that they be used appropriately and not abused. Choices should be based on sound clinical reasons and prophylactic use justified on the basis of patient risk status. It is important to remember that silver dressings do not 'cure' infections but have a broad spectrum of activity and when used wisely effectively inhibit bacterial penetration. There is much benefit to be achieved in their ultilisation. There are still numerous questions to be answered in respect of silver in wound care. We have articulated many in this article. It is now the responsibility of the Industry and independent clinicians and scientists to address these questions to the satisfaction of all involved in wound management. Only through doing this, will we achieve 'best practice' in the use of silver dressings.

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