Review Article

Capsula Eburnea

A SYSTEMATIC REVIEW OF SILVER- RELEASING DRESSINGS IN THE TREATMENT OF BURNS

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SUMMARY

Silver-releasing materials used for wound dressing have anti-inflammatory, re-epithelizing and antihaemorrhagic properties. Commonly used in topical burn management, silver sulfadiazine (Ag-SD) is a useful antibacterial agent for treating burn wound. The action of silver sulphadiazine has been extensively studied. Since silver sulphadiazine alone was found to be insufficient in preventing or retarding the growth of gram-negative bacteria in patients with burns covering more than 50% of body surface, the use of cerium nitrate in combination with the former was introduced by Monafo and colleagues in 1976. In recent years, a range of wound dressings have been marketed containing slow-release Ag compounds. The application of nanotechology in burn injury treatment is gaining considerable impetus in the century due to its metal nanosizing potential. Metallic silver, in the form of nanoparticles, has made a remarkable comeback as a potential antimicrobial agent.

Introduction

Silver has a long history of use in human healthcare and medicine. The human body contains minute amounts (< 2.3 pg/l) of silver, with higher concentrations found in subjects exposed to silver for long periods [1,2]. In ancient times, metallic silver was used as a disinfectant to store and purify water. It is reported that Alexander the Great (335 BC) drank from, and stored water in silver vessels during his many campaigns [3,4]. Silver has been used for storing and purifying water aboard the Apollo spacecraft [5], the MIR space station [6] and NASA space shuttles. Pure metallic silver is inert, and does not react with human tissue or kill microorganisms until it is ionized. It readily ionizes into silver ions in the presence of aqueous media. It is well documented that the bioactive form of silver is the Ag^+ ions. Recent studies have shown that the presence of higher halide concentration with fewer Ag^+ ions results in the formation of anionic silver complexes (AgX2, where X = Cl^-), which are soluble in aqueous media and bio-active [7]. The bio-activity of anionic silver complexes has been found to increase its toxicity to both sensitive and resistant strain bacteria [7]. The bioavailability of silver ions depends on the delivery technique, silver sources, ionization and solubility [8], as well as on the concentration of the biological ligands it binds to, such as proteins (STIE in genes), peptides and halide ions (Cl^-).

It has been reported that when medical grade silver is used for prophylaxis and wound management, silver is absorbed into the systemic circulation and excreted [1,9]. The absorption of silver is greatest during the inflammation and cell proliferation phases [10,11]. There are no reports of silver accumulation in any body tissues following topical application [12]. The toxic effect of silver in humans is low, and can be attributed to the complexes or the salt

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used to deliver the silver [13]. The toxic effect of silver is well documented with *in vitro* studies on skin cells [14-15], whose results contradict the positive effect of silver in wound treatment [16]. The use of silver in wound management can be traced back to the 18th century, during which silver nitrate ($AgNO_3$) was used in the treatment of ulcers [17]. The antimicrobial activity of silver ions was first identified in the 19th century, and colloidal silver was declared to be effective in wound management in the 1920s by the US Food and Drug Administration (FDA) [18]. However, after the introduction of penicillin in the 1940s, antibiotics became the standard treatment for bacterial infection, with the use of silver consequently diminishing. Silver made a comeback in the management of burn patients in the 1960s, this time in the form of a 0.5% $AgNO_3$ solution [19,20]. $AgNO_3$ was combined with a sulphonamide antibiotic in 1968 to produce silver sulphadiazine (SSD) cream, thus creating a broader spectrum silver-based antibacterial, prescribed mostly for burn wound management [21,22]. More recently, clinicians have again turned to wound dressings that incorporate varying levels of silver, since the emergence and increase of antibiotic-resistant bacteria have resulted in efforts to reduce antibiotics prescribing [23].

Silver-releasing dressing in the treatment of burn injuries

For many years, silver sulphadiazine cream has been considered effective in the treatment of burn wounds, and has been the standard method of wound care in the author's hospital for a decade. More recently, different types of silver dressings have been developed for topical use in acute and chronic wound care. While the development of antibiotic resistance is an alarming concern in clinical practice, the advantage of silver is that it has a minimal bacterial resistance.Therefore, several types of silver-coated dressings with a broad range of components and characteristics have been developed for therapeutic use.

Several silver-incorporating products have been introduced for use as a topical antibacterial agent, such as silver nitrate, silver sulphadiazine (SSD) (Flammazine™, Smith & Nephew Healthcare Limited, Hull, Canada) [24], silver sulphadiazine/chlorhexidine (Silverex®, Motiff Laboratories Pvt. Ltd. Kare Health specialties, Verna, Goa), SSD with cerium nitrate (Flammacerium®, Solvay, Brussels, Belgium), and silver sulphadiazine-impregnated lipidocolloid wound dressing Urgotul SSD® (Laboratories Urgo, Chenove, France) [25,26-28]. In contrast with these silver agents, newly developed products such as Acticoat™ (Westaim Biomedical Inc., Fort Saskatchewan, Alberta, Canada) and Silverlon® (Argentum Medical, L.L.C., Lakemont, Georgia) have a more controlled and prolonged release of nanocrystalline silver to the wound area. This silver delivery method allows the dressings to be changed less frequently, thereby reducing the cost of care, and, more importantly, the risk of a nosocomial infection, further tissue damage and patient discomfort [29-31].

Silver products for clinical use

<u>Silver sulphadiazine</u>

With an excellent spectrum of activity, low toxicity, and ease of application with minimal pain, silver sulphadiazine is still the most frequently used topical agent.

Mechanism of action. Silver sulphadiazine is thought to act via the inhibition of DNA replication and modifications of the cell membrane and wall.

Spectrum of antimicrobial activity. This agent is bactericidal against species of both Gram-positive and Gram-negative organisms, but resistance has occasionally been reported.

Clinical use. Silver sulphadiazine is used as an adjunct in the prevention and treatment of infection in second- and third-degree burns. However, this treatment method is likely to fail with continued use in large burns (> 50qc TBSA). Concomitant administration of appropriated systemic anti-infective agents may be necessary if infection is present or suspected. The use of silver sulphadiazine is frequently associated with the development of a "pseudo-eschar" within two to four days from the initial application, owing to an interaction between the drug and the proteinaceous exudate within the wound, which can lead to errors in the evaluation of burn depth by inexperienced observer.

Adverse-effects. Local skin reactions, such as pain, burning, or itching and hypersensitivity, are occasionally reported. Transient leukopenia occurs in 5-15% of patients, but there is no increased incidence of infectious complications. This may be due to an intrinsic response to the burn injury, and therefore unrelated to the use of silver sulphadiazine. Systemic absorption may produce reactions characteristic of sulphonamides, including crystalluria or methaemoglobinaemia.

Cerium nitrate-silver sulphadiazine

Treatment with a compound of cerium nitrate and sulphadiazine results in enhanced clinical efficacy in patients with large burns.

Mechanism of action. Cerium nitrate has an antimicrobial effect *in vitro,* and reverses post-burn cell-mediated immunosuppression.

Spectrum of antimicrobial activity. The addition of cerium nitrate to silver sulphadiazine has been shown to render the product effective against Gram-positive and Gram-negative organisms, as well as fungal pathogens.

Clinical use. The clinical application of cerium nitrate-silver sulphadiazine is identical to that of silver sulphadiazine alone. This drug combination produces an adherent eschar that provides satisfactory wound coverage until tangential excision can be carried out. Clinical trials have showed no difference in mortality in patients treated with silver sulphadiazine alone compared to those treated with a silver sulphadiazine-cerium nitrate compound.

Adverse effects. The adverse effects of cerium nitrate-silver sulphadiazine are similar to those seen with silver sulphadiazine alone.

Mafenide

Although its antimicrobial and eschar penetration qualities are excellent, mafenide was dropped from general clinical use because of its severe side effects, especially when applied in large areas.

Mechanism of action. Mafenide is believed to interfere bacterial cellular metabolism.

Spectrum of antimicrobial activity. In topical application, mafenide is bacteriostatic against Gram-positive and Gram-negative bacteria. However, it has limited action against *S. aureus* and fungus. Development of organisms resistant to mafenide has not been reported.

Clinical use. Mafenide is used as an adjunct in the treatment of bacterial invasion in second- and third-degree burns to prevent septicemia caused by susceptible organisms. It also efficiently penetrates cartilage, which makes it a good choice in burn wound located in ears and noses.

Adverse effect. Local pain or a burning sensation following mafenide application is the most frequently reported adverse effect. Mafenide is a strong carbonic anhydrase inhibitor and its use leads to alkaline diuresis, which can cause acid-base abnormalities. It also inhibits epithelial regeneration.

Silver nitrate solution 0.5 %

Mechanism of action. The effects of silver nitrate appear to result from silver ions readily combining with sulphydryl-, carboxyl-, phosphate-, amino-, and other biologically important chemical groups.

Spectrum of antimicrobial activity. Silver nitrate is a broad-spectrum agent, showing bacteriostatic activies at a concentration of 0.5%; development of resistance to this agent is uncommon.

Clinical use. Silver nitrate is effective in prophylactic use in second- and third-degree burns; however, it does not penetrate burn eschar, and requires bulky dressing which need to be frequently changed, limiting its clinical use.

Adverse effects. Silver nitrate is prepared with distilled water resulting in an extremely hypotonic solution, leading to electrolyte imbalance. Methaemoglobinaemia is another potential complication, owing to the reduction of nitrate to nitrite by bacteria.

Sustained silver-releasing dressings-nanocrystalline silver

Various silver-based dressings have been introduced in the past few years, whose use has become the latest and most popular novel approach to wound care. The innovation entailed in these new types of dressings is the fact that silver is incorporated within the dressing itself, rather than being applied as a separate salt, compound, or solution. The basic issues in choosing a silver-containing dressing can be broadly conceptualized in terms of: (1) the characteristics of the ''carrier'' dressing and (2) the delivery method of silver by the dressing to the wound. Keeping these basic issues in mind can help make sense of some of the marketing hype associated with these products [31]. The following list of available dressings is not intended to be exhaustive, as the number of products available with similar characteristics is growing rapidly. Rather, it should be considered to illustrate different carrier dressing materials used in conjunction with various silver-delivery ''reservoirs''[31].

- *Acticoat-7* (Smith & Nephew, Hull, United Kingdom) dressing consists of three layer of polyethylene mesh coated with nanocrystalline (<20 nm diameter) silver and two layers of rayon polyester. The nanocrystalline silver provides an initial large bolus of silver to the wound followed by a subsequent, more sustained release.
- *Actisorb Silver 220* (Johnson & Johnson, New Brunswick, N.J.) is an activated charcoal dressing to which silver is bound. Actisorb works by absorbing bacteria into the charcoal component,where silver destroys them. The ''odor- eating'' nature of the charcoal is used as a marketing focus.
- *Aquacel-Ag Hydrofiber* (Convatec, Skillman, N.J.; 70:30 sodium: silver carboxymethylcellulose hydrofiber) is an absorptive dressing. Silver ions are released from the carboxymethylcellulose carrier as it is hydrated, thereby achieving a gradual, sustained release.
- *Arglaes* (Medline, Mundelein, Il1.) is a silver-impregnated polymer film. The silver reservoir is Ag/CaPo4, formed as glass particles co-extruded in a polymer matrix.
- *Contreet-H* (Coloplast, Marietta, Ga.) is a dense, silver-incorporating hydrocolloid dressing.
- *SilvaSorb* (Medline) is a polyacrylate matrix with a silver halide reservoir.
- *Silverlon* (Argentum LLC, Willowbrook, Ill.) is a polymeric fabric coated with metallic silver by autocatalytic electroless chemical plating. Marketing is focused on the three-dimensional fabric, which has a large surface area and is flexible.

Conclusion and future prospects

In summary, it can be concluded that among the different antimicrobial agents, silver has certainly been studied the most, as well as being the most common means to combat infection and prevent spoilage since ancient times. The antibacterial, antifungal and antiviral properties of silver ions, compounds and nanoparticles have been comprehensively studied.

Silver is non-toxic to humans in minute concentrations. Different micro-organisms are more likely to develop resistance to antibiotics rather than to silver, due to the broad-range antimicrobial effects of the latter. With their unique chemical and physical properties, silver nanoparticles are proving to play a key role in the development of new antibacterial agents. Silver nanoparticles have also found diverse uses, varying from application to wound dressings, to coating medical devices or, impregnating medical textiles, etc.

The advantage of using silver nanoparticles for impregnation is that they provide a continuous release of silver ions, and, additionally, devices can be coated on both the outer and the inner side, thus, enhancing the antimicrobial efficacy. Treatment of burn injures with silver nanoparticles results in improved cosmetic appearance and a higher probability of scarless healing.

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