Argentum Medical LLC

SILVERLON®

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Silver Toxicity and Resistance In Wound Care

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Recent articles in the lay press have suggested that medical and non-medical uses of silver pose a threat to human health or the environment. Such articles, which do not include data, at best can represent only the opinion of the author(s) and should not be considered as conclusive scientific studies.

As a manufacturer of silver-containing medical products, Argentum Medical LLC encourages open discussion of the indications and benefits of silver therapies. Proper forums for such discussion include the scientific meetings of reputable medical organizations and manuscripts that are published in peer-reviewed medical journals. To facilitate discussion and exchange of research ideas, Argentum Medical LLC maintains a Medical Advisory Board of physicians and scientists with significant expertise in the fields of microbiology, burn surgery, wound care and reconstructive surgery. Members of the Advisory Board are available to discuss specific medical concerns or proposals for appropriate research studies.

The environmental impact of silver-containing medical devices is vastly overstated. Silver is not a super-toxic disinfectant developed in a chemical laboratory: rather it is a naturally-occurring element that is ubiquitous in nature. Humankind has had significant interaction and exposure to silver since antiquity. Silver has been widely utilized for currency, jewelry, water purification, cooking or serving vessels, plates, utensils, and as an electrical conductor. If silver represented a threat to human health, the use of silverware, silver plates and silver earrings would have ceased long ago.

In terms of global ecology, the medical use of silver for wound dressings represents a tiny fraction of annual total global silver production. The Silver Institute maintains statistics on annual silver supply and demand. Since 1999, annual worldwide silver demand averages approximately 900 million ounces. By comparison, as one of the top five manufacturers of silver based bandages, Argentum used approximately ***7,000 ounces*** of silver in 2009. This represents 0.0008 % (0.000008) of global annual silver consumption.

As a precious metal, industrial silver is often recycled or reclaimed. The one valid environmental question regarding silver-containing medical dressings is whether or not the silver in such products can be recycled. Research into this question is clearly indicated. Finally, it could be argued that the use of a naturally occurring (and potentially recyclable) element as a wound dressing can replace the use of toxic chemicals or late-generation antibiotics presently utilized for these indications: for this reason, the use of silver medical dressings may actually benefit the environment.

The second concern is the potential for silver-containing medical devices to cause microbial resistance. The answer here is both simple and complex: clinically relevant microbial resistance to silver might occur, but we presently lack clinical evidence and appropriate laboratory methodology to measure or quantify such resistance (1). It is reassuring to note that over 100 years of clinical experience with silver-containing products strongly suggests that microbial resistance to silver has little or no clinical impact.

Traditionally, microbial resistance to antibiotics has been measured either in terms of zones of growth inhibition on agar plates or by quantitative antimicrobial assays using serial dilutions to determine a minimal inhibitory concentration (MIC) necessary to achieve appropriate 'kill levels'. Neither assay is useful to assess the efficacy of silver, which exerts an antimicrobial effect largely through release of silver ion (Ag+). The problem is that the microbial growth media utilized for both methodologies contain multiple substances such as chloride ions, sulfate ions, phosphate ions and organic anions that react and bind with ionic silver. When agar diffusion assays are utilized, it is difficult to determine what we are measuring by microbial growth endpoint. Does the zone of inhibition represent dilution of the silver ion beyond that required for a bactericidal effect, the limit of silver inactivation of a component necessary for growth of the test organism, a critical level of silver ion binding to substrates or a combination of all three? When performing serial dilution assays to determine MIC, a similar problem occurs. We are diluting the concentration of silver ion, but not the concentrations of bindable chloride, sulfate and organic ions in the growth medium, leading to a nonlinear and misleading relationship.

To be clinically useful, the minimal inhibitory concentration levels that correlate with categorical breakpoints (susceptible, intermediate or resistant) must be established (1). This is usually done by a professional organization such as the European Committee on Antimicrobial Susceptibility Testing (1). Unfortunately, there is no consensus on what MIC constitutes silver resistance. Tenfold variations in MIC (8-80 mg/L for *Staphylococcus aureus* and 8 – 70 mg/L for *Pseudomonas aeruginosa*) have been reported(1). Because the multiple silver-containing products on the market all differ in rate and level of silver delivery, MIC values determined for one product would not correlate with efficacy in other products (1). Finally, zones of inhibition or MIC values (developed for use of systemic antibiotic therapy) may have little correlation with clinical practice, where a topical wound dressing is typically delivering bactericidal silver ion at very high concentrations directly to the wound bed.

Reports of clinical failures due to silver resistance have not been documented. Silver-resistance genes have rarely been found, however unlike many of the past and present parenteral agents, a silver "resistance" gene linkage to multiply antibiotic resistance transfer mechanisms has *not* been reported as a clinical reality. At this time clinical observation of wound condition, as unscientific as this may be, is the only practical evaluation for the effectiveness of specific silver dressings. It is unreasonable to conclude that clinically significant silver resistance cannot occur; *the fact is that it simply has not been demonstrated.*

Discussion points concerning the clinical utilization of silver:

- In 1881, it was discovered that application of silver nitrate solutions to the eyes of newborns would prevent ophthalmia neonatorium, an infection that can lead to serious eye damage or blindness. This practice quickly became a standard of care and was mandated by state law in most US jurisdictions by the early 1900's. As recently as 1978, the US Centers for Disease Control and the American Academy of Pediatrics advocated silver nitrate eye drops as one of three antibiotic choices for newborn eye prophylaxis (2,3), and as recently as 1981, 11 states allowed only silver nitrate drops to be utilized for this purpose (2,3). One hundred and twenty nine years after the initial discovery, silver nitrate eye drops are still used by some clinicians in the United States.

- Burn patients are an immunosuppressed population with large open wounds. With loss of the protective skin barrier, it would be expected that any topical agent applied to burn patients would also have systemic effects. Silver-containing solutions have been utilized as topical burn therapy for over 75 years with little adverse effect:

- Ten percent solutions of silver nitrate were applied as escharotics over burn wounds as early as 1935 (2,4)

- In 1965, Moyer et al described the use of 0.5 % silver nitrate solution as a topical therapy for patients with large burns (5). The choice of silver nitrate was influenced by the experiences of one of his coauthors, who had been utilizing silver nitrate solution in the management of necrotizing fasciitis and other contaminated wounds since 1941 (5). Sixty-five years after the first case reports, silver nitrate continues to be utilized as the primary topical antimicrobial in some burn centers (4).

- In 1968, Fox introduced silver sulfadiazine cream for the management of burn wounds (6). For forty-two years, this combination of sulfa drug and silver ion has been utilized as the primary topical antimicrobial agent in burn centers around the world.

- Since 2003, Silverlon® dressings have been extensively utilized by the US Military. US Service members and Coalition Partners burned in the war zone are frequently treated in Silverlon® dressings. Silverlon® dressings are also considered a standard of care for long-range aeromedical transportation of burn patients (8), including transcontinental flights.

- 1% silver sulphadiazene cream ($C_{10}H_9AgN_4O_2S$) that is 30% silver by weight, would provide 950 µg/cm² *per application* assuming a coating thickness of .125". If applied twice per day over 7 days, the total silver load would be 13,300 µg.

- By comparison, the silver bio-burden to the patient is much lower when using Silverlon®. The *total* amount of silver coating contained in Silverlon® wound dressings is approximately 5,799 µg / cm² . As measured by Atomic Absorption Spectrometry, *only 6.5% (50-60 ug/mL) of silver is actually measured in the test medium (tryptic soy broth) after seven days of immersion.*

- Reported microbial resistance to silver is exceptionally uncommon. A recent literature search covering the medical literature from 1950 to April 2010 combining the search terms 'silver compounds/ or silver' and drug resistance, microbial' yielded only 56 references. All were either in-vitro (bench) studies, literature reviews or letters to the editor***. There were no studies demonstrating any clinical significance of silver microbial resistance.***

- Genes that confer silver resistance to bacteria have been documented but are probably of little clinical significance. At least one study suggests that silver-containing wound dressings are effective in killing methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria that possess silver-resistance genes (7).

- Dressings that deliver low (or even sub lethal) levels of silver ion may play a role in increasing bacterial resistance to silver (1). Products such as Silverlon®, which deliver consistent and high levels of silver ion, may have an advantage in this regard.

- One article in the popular (nonmedical) press states that “silver threatens the use of antibiotics”. In reality, the opposite is more likely to be true in that *silver can reduce the need for systemic antibiotics*. Topical silver dressings are frequently utilized for patients with chronic wounds colonized with multiple drug-resistant (MDR) organisms as a result of long-term antibiotic therapy. Dressings that release ionic silver are ideal in this application, because the high silver levels achieved are usually lethal to MDR organisms. Chronic non-healing wounds frequently are associated with poor blood circulation, limiting the availability of systemic antibiotics to the wound itself. Topical silver therapy does not have this limitation.

- Topical silver dressings are beneficial to the patient. The ability to leave a dressing intact for several days decreases the number of painful dressings that a patient must undergo and is cost-effective in terms of saving time for the nursing staff. Topical silver dressings frequently allow management of chronic wounds in the outpatient rather than inpatient setting. This limits exposure of the hospital environment to the MDR organisms frequently found in chronic wounds and limits patient exposure to multiple drug-resistant hospital flora.

In summary, extensive medical use of silver ion for over one hundred years has shown that this mode of therapy is both highly effective and well tolerated. While microbial resistance to silver is a theoretic possibility, to date, the clinical significance of silver resistance is minimal to absent. In an era where antibiotic over-use has resulted in the development of multiple drug-resistant flora, it makes sense to utilize topical silver dressings instead of systemic antibiotics whenever possible.

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