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Silver-resistance, allergy, and blue skin: Truth or urban legend?

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ABSTRACT

Medical and non-medical uses of silver are increasing. While the health benefits of silver therapy are widely claimed, few studies address the possible side effects of resistance, allergy, or skin discoloration. In this manuscript, a review of silver absorption, mechanism of action, allergy, microbial resistance and skin changes is presented.

The ideal silver-delivery system is unknown. Most studies of side effects are animal or laboratory studies, which may not correlate with human experience. There is little correlation between serum silver levels, end-organ deposition and cytotoxic effects. The multiple mechanisms of antimicrobial action make true resistance unlikely. In microbes, genotypic resistance does not necessarily confer phenotypic resistance. Most cases of argyria occur from occupational exposure or from ingestion of colloidal silver rather than from topical application.

Although toxicity, resistance and chronic skin changes are a theoretic concern, the lack of reported side effects despite widespread silver use is reassuring.

1. Introduction

Silver containing compounds and materials are the workhorse of burn wound care and are increasingly becoming important in the care of non-thermal wounds. Silver for the use in wounds can be found as a film, foam, alginate, salt, hydrocolloid, hydrogel, solution, cream and nanocrystalline compound to name a few.

Silver containing composites are believed to adequately manage wound bioburden [1–6], decrease wound inflammatory response [7–13], and improve patient comfort [14,15]. However, little is ever discussed regarding allergies, skin discoloration and microbial resistance.

2. Background

A basic understanding of the mechanism of antimicrobial action and pharmacological dynamics must be discussed prior to appreciating potential risks associated with silver compounds.

The antimicrobial properties of silver (Ag) have been known since ancient times. Silver can exist in its metallic or elemental state. This state is usually referred to as Ag^0. However, when exposed to an aqueous environment (for example, water, wound exudates, secretions, etc.), silver in its elemental state becomes oxidized and forms silver cations. These silver cations are typically referred to as ionic silver and abbreviated as Ag^+. Although, silver exhibits three valance or oxidation states (Ag^{+1}, Ag^{+2}, Ag^{+3}), for the purpose of this discussion and simplicity they will all be referred to as Ag^+.

Ionic silver is a highly reactive cation. It is this reactivity that provides the majority of the desired antimicrobial and unwanted toxic properties [16–19]. All silver containing compounds and materials achieve most of the antimicrobial activity by generating ionic silver (Ag^+). As opposed to most

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antimicrobial agents, ionic silver's activity is generally attributed to four separate mechanisms. These mechanisms can be summarized as: cell membrane binding, electron transport chain inhibitor, DNA/RNA replication, and inhibitor of protein functional precursors [20–26].

It is important to mention that elemental silver (Ag^0) has also been associated with some antimicrobial function. Although this mechanism of action has not been elucidated, it is believed to be associated with the reduction of metalloproteinases in wounds [6,17].

As mentioned, the formation of ionic silver and the leaching of metallic silver are important to determine the antimicrobial activity of all silver compounds. The rate of formation is related to the rate of free silver released into the wound [27]. However, the vehicle to which the silver is attached directly affects the total quantity, rate, and amount of active silver per surface area in the wound bed. For example, a solution of 0.5% silver nitrate requires frequent daily applications due to its low reservoir capacity. In comparison, a nanocrystalline silver compound has a longer dissociative coefficient allowing for longer leaching and exposure of the material in the wound. This difference has been clearly demonstrated on in vitro studies of commercially available dressings [28–30]. Although, these differences are largely publicized and described, they have not been demonstrated to be of value in clinical practice. No study has demonstrated a clinical benefit to differences in concentrations, rate of release, and duration of silver discharge in a wound. This is an area that needs to be further researched.

3. Absorption

The toxicity of silver is directly related to the amount absorbed in the body and accumulation at target organs. With the increase use of silver in different medical and non-medical technologies the instances of silver exposure are numerous [31,32]. For the purpose of this paper we will focus on the oral/gastrointestinal and percutaneous exposure and its absorption of silver. It is important to remember that there is little known to the correlation between total serum silver levels, end organ deposition and demonstration of cytotoxic effects. Most of the data is extrapolated from animal studies [18,33].

3.1. *Percutaneous absorption*

As previously stated the silver in the dressing compound will dissolve and become ionized when exposed to aqueous materials. Much of the ionized silver will precipitate in the wound, become protein bound, or deposit in the wounds [19,25,34–36]. Therefore, the absorption of silver is low. Several studies have evaluated the percutaneous absorption of commonly used silver materials.

The absorption of silver from silver nitrate has been described. In a study reported by Lansdow, tracer studies using an isotope of silver in silver nitrated, less than 4% of the silver is absorbed through intact skin [19].

The absorption of silver from silver sulfadiazine has also been evaluated. Maitre et al. described two patients that had elevated levels of serum silver after treatment with silver sulfadiazine [37]. Both of these patients had elevation in serum silver of 38 μg/L and 440 μg/L. Coombs et al. demonstrated that the silver serum level rose in patients with greater than 5% total body surface area (TBSA) burn treated with silver sulfadiazine. As expected, they demonstrated higher levels of silver on patients with greater than 20% TBSA. Also they noted a peak silver serum level at day 4. The maximum plasma silver level was 310 μg/L. Additionally, when two volunteers, without burned skin, were exposed to silver sulfadiazine, they did not demonstrate elevation in serum silver [38]. This relationship of TBSA burn and silver absorption of silver sulfadiazine has been demonstrated by other authors [39].

In vitro studies have demonstrated that the nano particle absorption through injured and intact skin is very low yet detectable [40]. Wang et al. evaluated the serum silver level of 46 pediatric burn patients treated with Acticoat. He demonstrated that 36 patients with a mean of 13.4% TBSA burns had a mean peak serum silver level of 114 μg/L. Interestingly, the remaining 10 patients had a mean total body surface area burn of 1.85% and demonstrated undetectable levels of silver [41]. Vlachou et al. published the evaluation of 30 patients with 0.5–45% TBSA burns. They demonstrated increase absorption of silver on those patients with largest exposure to Acticoat. They found a median maximum serum silver level of 56.8 μg/L [42]. Moiemen et al. recently published the absorption of silver from Acticoat on burn patients with greater than 20% TBSA. They demonstrated transient elevation of serum silver peaking at day 9 similarly to Vlachou et al. The median maximum silver level was 200.3 μg/L [43].

3.2. *Oral/gastrointestinal absorption*

Silver absorption from the gastrointestinal tract is estimated to be around 10% with 2–4% being retained in tissues [18]. On a patient with argyria, East et al. demonstrated that she absorbed about 18% of a single dose of colloidal silver [44]. However, this was not compared to other subjects due to the risk of colloidal silver exposure. Oral mucosal absorption of silver has been reported but not quantified [45].

3.3. *Allergies*

Contact dermatitis to silver containing compounds is rare. The proposed incidence is not known. Most of the reported cases have occurred on previous sensitized population like silver miners, jewelers, photographers, etc. [18,46,47]. However, contact dermatitis has been reported with silver nitrate markings used for allergen testing [48–50]. Although rare, sensitivity to silver from silver sulfadiazine has been reported [51,52]. This sensitivity is typically described as a red rash over areas exposed. As described by Fuller, the hypersensitivity of silver sulfadiazine can be attributed to the toxicity of the sulfadiazine moiety [53] and not necessarily the silver molecules.

3.4. *Resistance*

The extensive and unregulated use of silver in non-medical and medical products has raised concern for the development of silver resistant bacteria [31,32,54]. Despite its extensive use

through history, little resistance has emerged. As previously described, the toxicity of silver is attributed to its corruption of DNA replication, cell wall formation, functional protein precursors and the electron transport chain. Due to this multi-target approach bacterial resistance to silver is rare. In those few instances, genes located in plasmids are attributed with this development. The complex mechanism of silver resistance and clinical implications has been recently reviewed [5,55,56].

There are few reported cases of silver resistant bacteria. These include clinical cases for *Pseudomonas aeruginosa* [57,58], *Escherichia coli* [59], *Enterobacter cloacae* [59,60], *Klebsiella pneumoniae* [59], *Proteus mirabilis* [59], and *Citrobacter freundii* [59]. Also, non-clinical isolation of plasmid-mediated silver resistance has been observed in *Acinetobacter baumannii* [61], *E. coli*[62], *Salmonella enterica* serovar Typhimurium [63], and *Pseudomonas stutzeri* [64]. Although, these bacteria do demonstrate resistance in vitro, it is difficult to extrapolate these results in vivo. As described by Percival et al. genetic resistance (in vitro) does not translate to phenotypic resistance (in vivo) to silver [65].

3.5. *Skin changes*

There are several conditions that are typically associated with skin discoloration and silver products. These conditions are methemoglobinemia, localized argyria, and systemic argyria.

Typically the color change associated with methemoglobinemia is described as pale, gray, and blue. Methemoglobin is the oxidized state of hemoglobin. The heme groups in hemoglobin contain an iron molecule in the reduced or ferrous form (Fe^{2+}). In this form, iron can combine with oxygen and provides for the majority of oxygen carrying capacity of blood. Hemoglobin can accept and transport oxygen only when the iron atom is in its ferrous form. When hemoglobin loses an electron and becomes oxidized, it is converted to the ferric state (Fe^{3+}) or methemoglobin. In this state, heme is incapable of binding to oxygen leading to a decrease in oxygen transport [66]. The development of methemoglobinemia is classically described with the use of silver nitrate [66–70]. The use of silver sulfadiazine and cerium nitrate in burn wounds has been associated with the formation of methemoglobinemia [71]. However, the cerium nitrate is the most likely culprit in forming the ferric state of heme [71–73].

Argyria occurs from the prolonged contact and absorption of silver. Argyria can be subcategorized into local and systemic argyria. The incidence of systemic and localized argyria is unknown. It is characterized by a blue-gray, gray-black staining of skin or mucous membranes. The discoloring is likely to be caused by the photoreduction of silver chloride and/or silver phosphate in the skin.

Local argyria occurs in the skin and mucosa after prolonged local exposure to silver containing compounds (for example, earrings, acupuncture needles, dental fillings). Conversely, systemic argyria is characterized by complete skin and mucosa discoloration. This discoloration is most evident on the sun-exposed areas.

Localized argyria has also been reported with the use of silver sulfadiazine [74–76]. These cases are noted for the discoloration of chronically treated wounds. Most of the reported cases of systemic argyria occur from occupational exposure to silver [18]. However, systemic argyria has also been reported from the use of colloidal silver for medicinal treatment for cold and allergies, dietary supplements, silver nitrate in the treatment of intestinal ulcers and gingival bleeding, silver containing eye drops, nasal sprays, silver containing anti-smoking treatments, and silver foil coated breath freshener [18]. Few random cases of silver sulfadiane induced systemic argyria have been reported. Payne et al. reported on a patient that applied silver sulfadiazine cream to chronic leg ulcers for 5 months [77]. Flohr et al. reported on a 25-year-old woman with severe generalized dystrophic epidermolysis bullosa using silver sulfadiazine cream since early childhood [78]. Over the course of many years her skin turned slate-gray and metallic. There is one reported case of argyria like symptoms from nanocrystalline silver. Trop et al. report on a 17 year old male with 30% TBSA burn. This patient was treated for 1 week with Acticoat, then developing grayish discoloration [79]. After removal of the Acticoat the argyria like symptoms subsided.

4. Discussion

The amount of silver containing compounds and materials are drastically increasing. Continuously we are being exposed to an increase number of products with silver not only in medical technology but also on materials for everyday use. The antimicrobial properties of silver are without doubt. However, the best delivery vehicle is unknown. New compounds incorporating nanocrystalloid silver bring another dimension of ambiguity to the delivery of silver. There is little evidence as to the effect of their molecular kinetics, molecular size, wound silver concentration, duration of action, peak silver concentration and effect on the wound and microbes. It is difficult to compare one product with another, when the critical standards have not been defined. These areas required more clinical evaluation.

We do know that silver is absorbed from the wounds. Yet, we do not know what is a cytotoxic concentration. The EPA reference dose (RfD) of 0.005 mg/kg/day for subchronic and chronic exposure of silver was calculated from a lowest-observed-adverse-effect level (LOAEL) of 0.014 mg/kg/day for observed argyria reported by Gaul et al. in 1935 [80,81]. It appears from review of the literature that it is not the maximal single dose concentration but the chronic accumulated dose that are more toxic. However, this limited information is extrapolated form animal studies yet not validated from known human exposure. Millions of people that have been treated with these materials, yet, there are little reported data of toxicity and detrimental effects from these exposures. If the incidence of these complications would be high, you would expect more reported cases to be available. Therefore, complications like argyria are rare and unlikely to occur. Inasmuch, few silver resistant bacteria have been identified despite the high levels of silver exposure. Although, resistance and silver toxicity are a theoretical risk the lack of evidence despite extensive population exposure decreases its clinical concern.

Conflict of Interest

There is no conflict of interest.

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