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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