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Silver in medicine: The basic science☆

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ABSTRACT

Silver compounds are increasingly used in medical applications and consumer products. Confusion exists over the benefits and hazards associated with silver compounds. In this article, the biochemistry and physiology of silver are reviewed with emphasis on the use of silver for wound care.

1. Introduction

Silver is a naturally occurring element with an atomic weight of 107.870 and an atomic number of 47 [1]. Silver may be found in nature as the pure element, but more commonly occurs in ores, including Argentite (Ag_2S), and horn silver (AgCl); and in combination with lead, lead–zinc, copper, gold, and copper–nickel [1]. Pure silver has a brilliant white metallic luster and is slightly harder than gold but highly malleable and ductile [1]. Silver has a melting point of 961.93 °C, a boiling point of 2212 °C and a specific gravity of 10.5 [1]. Silver has the highest electrical conductivity and lowest contact resistance of any element and the highest thermal conductivity of any metal [1].

There are 59 known isotopes of silver. Only 2 isotopes (Ag^{107} and Ag^{109}) are naturally occurring and stable. Silver exhibits three oxidation states Ag [+1], Ag [+2] and Ag [+3] (pure metallic silver is Ag [0]). Of these, only the Ag [+1] state is sufficiently stable for use as an antibiotic as the other cations are highly reactive and short-lived [2,3]. Silver compounds ionize in the presence of water and biologic fluids to release Ag (+1) [2].

Human experience with silver is ubiquitous, with the metal used for currency, jewelry, and food handling from the beginning of recorded history. There is evidence that humans learned to separate silver from lead as early as 3000 BC [1]. The use of silver for currency and for drinking cups is mentioned in the first book of the Old Testament [1,4]. In addition to jewelry and silverware, silver in contemporary life is used in dental fillings, photography, water disinfection, brazing and soldering, and electronic equipment [5].

2. Biochemistry and physiology

Silver is not a recognized trace metal in humans and appears to have no known physiological role or nutritional value [2,6]. Silver does occur in the body at low concentrations secondary to natural exposure via inhalation or ingestion [2,5,7]. Silver is released into the air and water through the natural weathering of rocks (rain and water exposure) and by human activities including cement manufacture and the burning of fossil fuels [5]. Unlike mercury, silver does not appear to concentrate in aquatic animals [5]. The US Environmental Protection Agency recommendation for daily intake limits of silver is 0.005 mg/kg/day [7]. The allowable levels of silver in drinking water are 0.1 mg/L [5] or 50 parts per billion [8]. Typical silver levels in normal individuals include a blood concentration of <2.3 μg/L

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and a urinary excretion of 2 μg/day [3,9]. This is largely from ingestion in food and drinking water. The daily oral intake of silver from dietary sources is estimated to be 27–88 μg/day [8,10]. Orally ingested silver is mostly absorbed through the small intestine [8]. The GI tract is the main avenue of excretion for ingested silver [8].

Silver in the non-ionized state has no biocidal action [2]. Pure (elemental) silver is generally considered nontoxic when used at clinical doses [11,12]. Silver jewelry (often used for body piercing), likewise is inert. White and Cutting note that "the interaction of metallic silver with intact skin does not cause any detectable increase in blood levels and is not of great toxicologic interest" [3].

Silver is not an eye or skin irritant (US EPA Toxicity Category IV), and is not a skin sensitizer [7]. Silver is not known to have human carcinogenic potential, and does not appear to be a mutagen [7].

In the presence of sweat, sebum or moisture, silver ions placed on intact skin will accumulate on the skin surface, with some penetration of the superficial layers resulting in precipitation in the stratum corneum as silver sulfide [2]. Systemic silver is mostly excreted through the liver and kidneys but hair and nail growth also provides a minor avenue of excretion [2]. The uptake and metabolism of silver have not been well studied with exception of some work with burn antimicrobials such as silver sulfadiazine and silver nitrate. Silver nitrate has been utilized as a topical burn treatment since 1965 and silver sulfadiazine has been a mainstay of burn care since 1968 [13–15]. As much as 10% of silver sulfadiazine may be absorbed through partial thickness burns that have good vascularity [2,16] with blood silver levels of >300 μg/L measured [2,16–18]. The absorption of silver is greatest during the inflammation and cell proliferation phases of wound healing [6,19,20]. Urinary silver excretion may increase a thousand-fold when silver compounds are used to treat large open wounds (burns) for prolonged periods of times [11,18]. This appears to have no clinical significance [11].

Constable et al. [21] investigated systemic absorption of Ag^{111} tagged silver nitrate solutions applied to open wounds in a rat model. They found significant silver isotope uptake in the liver with lower levels present in the kidneys. After cessation of silver nitrate treatment, the isotope rapidly cleared from the liver with 40% remaining after one week and 25% after two weeks.

In burn patients being treated with silver sulfadiazine, plasma silver levels can reach a level of 50–310 μg/L and urine excretion may reach a maximum of 400 μg/day [3]. Silver sulfadiazine tagged with radioactive Ag^{110} demonstrates that silver tends to accumulate in superficial wound layers and is completely cleared in 28 days [3,22]. Elevated blood and urine silver levels in conjunction with increased liver enzymes have been documented in burn patients treated with 'nanometer silver' or nanocrystalline burn dressings [3,23,24]. These resolved after treatment was discontinued.

Pure metallic silver is inert and does not react with human tissue or kill microorganisms until it is ionized [6]. There is a direct correlation between bacterial lethality and free silver ion concentration in the medium. Silver ion that is bound, chelated or precipitated into insoluble complexes with tissue exudate or secretions is not available for antimicrobial action. Ionic silver is highly reactive and will combine with halides (particularly chloride), inorganic compounds, organic acids, negatively charged proteins, DNA and RNA [25,26]. Because many of these compounds can be found in wounds, topical silver released into a wound "can be rapidly consumed" [25]. Chloride ion seems to be a particular problem as wound exudate has a high percentage of Cl^- ions, which bind with Ag^+ to form the biologically inactive precipitate silver chloride (AgCl) [11]. The amount of silver required for efficacy in complex wound broth models is 80–2000 times higher than requirements in simple aqueous solutions [26–29]. Some experts argue that when excess Cl^- is present, it is possible to overcome this precipitation (and to restore antimicrobial action) with the delivery of relatively massive amount of silver [11,28,30]. Clinical experience bears this out, and most commercially available silver dressings purport to deliver high silver ion levels for this reason. One study testing the antimicrobial effects of a silver dressing in simulated wound fluid concluded that the silver-containing dressing is still likely to provide a barrier against infection presumably because of large levels of delivered silver ion [3,31].

2.1. *Antimicrobial effects*

In addition to binding anions and proteins in biologic systems, silver ion (Ag^+) avidly binds to cell surface receptors of bacteria, yeasts and fungi [2]. Silver cation also strongly binds to electron donor groups of biologic molecules containing sulfur, oxygen and nitrogen [2]. The binding of silver ion to sulfhydryl groups and proteins on cell membranes appears to be critical to antimicrobial action [2]. The ionizing capacity of various silver compounds is critical in comparing the antimicrobial activities [2]. Ionization of silver is also proportional to the surface area of dressing that is exposed to the wound. Applied electrical current increases ionization [2]. The combination of silver-nylon dressings and weak direct current has been extensively studied in a number of animal models [32–43] and in limited human studies [44,45].

While it is generally recognized that ionic silver is responsible for the antimicrobial activity of silver due to the dissociation of ions from the oxidized metal surface, the actual mechanism by which ionic silver kills bacterial cells has not been established unequivocally. There are four plausible mechanisms that have been postulated for the antimicrobial effects of silver [6,11,46–50]. Regardless of the intra-cellular mechanism, binding of silver to the cell membrane with intracellular absorption is an obligatory first step and sensitive bacteria accumulate silver against a concentration gradient until lethality is reached [2,18].

The first proposed mechanism involves the inhibition of life-sustaining enzymes by chemical interaction with silver ion. Silver ion is capable of blocking the electron transport system in bacteria [51,52]. Concentrations of 15 μg/mL of ionic silver have been found to inhibit the oxidation of glucose, glycerol, fumarate, succinate, D-lactate, L-Lactate, and other endogenous substances in *E. coli* [53]. Ionic silver has been shown to inhibit the enzymes of the respiratory chain at two specific sites: between the b cytochromes and cytochrome d, and between the site of substrate entry into the respiratory chain and flavoprotein in the NADH and