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Silver in medicine: The basic science

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A B S T R A C T

The usage of silver compounds in medicine and everyday life is on the rise. It's not clear if silver compounds are beneficial or harmful. Silver's biology and physiology are discussed, with a focus on its use in wound treatment.

Keywords: Infected Burn Wound Antimicrobial

Introduction

The atomic weight of silver is 107.870, and it has an atomic number of 47 [1]. Although elemental silver may be discovered in the wild, it is often found in ores such as Argentite (Ag2S) and horn silver (AgCl), as well as in alloys with lead, lead-zinc, copper, gold, and copper-nickel [1]. Although it is somewhat harder than gold, pure silver is nevertheless rather malleable and ductile [1]. The melting point of silver is 961.93 °C, whereas its boiling point is 2212.8 °C.

along with a specific gravity of 10.5 [1]. When it comes to electricity and heat transfer, silver is unrivaled [1]. It has the greatest conductivity, lowest contact resistance, and best thermal conductivity of any element or metal. The element silver has 59 recognized isotopes. Only two isotopes of silver are known to be stable in nature (Ag107 and Ag109). There are three oxidation states that silver may take on: [+1], [+2], and [+3]. (pure metallic silver is Ag [0]). While the other cations are extremely reactive and shortlived [2,3], the Ag [+1] state is sufficiently stable for use as an antibiotic. Silver compounds ionize into Ag(+) in the presence of water and biological fluids [2].

Silver's usage as coinage, jewelry, and food-safeware from ancient times has made it a familiar sight in people's everyday lives.

The first written records of human history. As early as 3000 BC [1], people had figured out how to separate silver and lead. Even the first book of the Old Testament [1,4] alludes to the fact that silver was used as payment and in drinking vessels. Silver is employed in a wide variety of modern applications, from dental fillings and photography to water purification and brazing and soldering [5].disinfection, brazing and solder- ing, and electronic equipment [5].

Biochemistry and physiology

There is no evidence that silver has a physiological function in humans or is nutritionally significant [2,6]. As a result of inhalation and ingestion, silver does accumulate to a small degree in the human body [2,5,7]. Natural weathering of rocks (exposure to rain and water) and human activities, such as cement production and the burning of fossil fuels, release silver into the atmosphere and water, respectively [5]. Comparatively, silver does not seem to accumulate in aquatic organisms in the same way as mercury does [5]. Silver consumption should be

Silver limited to 0.005 mg/ kg/day, as recommended by the US Environmental Protection Agency [7]. Recommended silver values for potable water are in addition to 2 mg/day in the urine [3,9]. Taking it in via one's diet and one's water supply are major contributors to this. It is estimated that the average person consumes 27-88 mg of silver per day from food sources [8,10]. When taken orally, silver is mostly absorbed in the ileum [8]. Most of the silver we consume is eliminated via the gastrointestinal tract [8].

Non-ionized silver is harmless to living things [2]. In therapeutic dosages, pure (elemental) silver is typically safe [11,12]. The same holds true for silver jewelry (which is often used for body piercing). In their review, White and Cutting state, "the interaction of metallic silver with undamaged skin does not create any discernible rise in blood levels and is not of considerable toxicologic concern" [3].

Silver is not toxic to humans (US EPA Toxicity Category IV) and does not cause skin sensitization [7]. When it comes to humans, silver has not been linked to any cancers and does not seem to be a mutagen [7].

When silver ions are applied to intact skin, they collect on the skin's surface and, if perspiration, sebum, or moisture is present, some of the ions penetrate the superficial layers and precipitate in the stratum corneum as silver sulfide [2]. Excretion of systemic silver occurs mostly through the liver and kidneys, with some contribution from hair and nail growth [2]. Other than research on burn antimicrobials like silver sulfadiazine and silver nitrate, the absorption and metabolism of silver have not been well investigated. Both silver nitrate and silver sulfadiazine have been used topically for burns since 1965 [13-15]. Silver sulfadiazine may be absorbed by partial thickness burns at a rate of up to 10%.n high quantities of silver (>300 mg/L) in the blood and healthy blood vessels [2,16]. quantitatively [2,1618]. Silver is best absorbed by wounds during the inflammatory and cell proliferation stages of healing [6,19,20]. When silver compounds are utilized for a long time to treat big open wounds (burns), the patient's urinary silver excretion may rise by a factor of one thousand [11,18]. There doesn't seem to be any practical relevance here [11].

Using a rat model, Constable et al. [21] studied the systemic uptake of Ag111-tagged silver nitrate solutions. The liver was found to have absorbed a

disproportionate amount of silver isotopes, whereas the kidneys absorbed far less. Approximately 40% of the isotope was still present

in the liver after one week, and 25% after two weeks, after treatment with silver nitrate was discontinued.

Maximum daily urinary excretion of 400 mg of silver has been reported in patients receiving silver sulfadiazine for the treatment of burns [3]. Plasma silver levels in these individuals might reach 50–310 mg/L. Radioactive silver sulfadiazine (Ag110) shows that silver concentrates in the top layers of wounds and is gone after 28 days [3,22]. Patients with burns who were treated with 'nanometer silver' or nanocrystalline burn dressings had elevated silver levels in their blood and urine, as well as elevated liver enzymes [3,23,24]. As soon as therapy was stopped, symptoms went away.

Once ionized, however, pure metallic silver becomes reactive and may destroy microbes and react with human flesh [6]. Free silver ion concentration in the media is inversely proportional to bacterial toxicity. If silver ion is insolublely linked to tissue exudates or secretions, it cannot kill microbes.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 silvercontaining 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

Antimicrobial Properties 2.1

The silver ion (Ag+) attaches to the cell surface receptors of bacteria, yeasts, and fungi with the same avidity as it binds to anions and proteins in biological systems [2]. Strong binding also occurs between silver cation and the electron donor groups of biological molecules containing sulfur, oxygen, and nitrogen [2]. Antimicrobial activity seems to depend on silver ion binding to sulfhydryl groups and proteins on cell membranes [2]. Antimicrobial activity comparisons rely heavily on the ionizing capability of the different silver compounds [2]. The amount of silver ionized is proportional to how much of the dressing is in contact with the wound. Ionization is boosted by an electrical current [2]. Multiple animal models [32–43] and some human research [44,45] have looked at the use of silver-nylon dressings in conjunction with weak direct current. Ionic silver, formed by the dissociation of ions from the oxidized metal surface, is responsible for silver's antibacterial properties, although the precise process by which ionic silver kills bacterial cells remains unknown. It has been hypothesized that silver's antibacterial properties occur through four distinct pathways [6,11,4650]. The sensitive bacteria accumulate silver against a concentration gradient until mortality is attained [2,18], and this binding of silver to the cell membrane with intra- cellular absorption is a required initial step regardless of the intra-cellular mechanism.

The first hypothesized mechanism includes the chemical interaction between silver ion and enzymes necessary for life. Bacterial electron transport may be inhibited by silver ion [51,52]. The oxidation of glucose, glycerol, fumarate, succinate, D-lactate, L-lactate, and other endogenous compounds in E. coli is inhibited by ionic silver at concentrations of 15 mg/mL [53]. There are two places in the respiratory chain where ionic silver has been demonstrated to limit enzyme activity: between the b cytochromes and cytochrome d, and between the site of substrate entrance and flavoprotein in the NADH and ubiquinone oxidoreductases.

components of the enzyme that breaks down succinate. The absorption of inorganic phosphate was prevented, and accumulated phosphate was effluxed, by ionic silver at concentrations as low as 2 mg/mL [53]. An enzyme's thiol group may react with silver ion. Enzymes containing the amino acid cysteine have thiol groups; when ionic silver attaches to these groups, the enzyme is inactivated, leading to the death of the bacterial cell. In order to avoid this process, cells may generate substantial levels of glutathione or reduced cysteine in the protoplasm, which may block thiol-silver binding [54].

Ionic silver's contact with and disruption of the cell membrane or wall is the second way it kills bacteria. Both cationic and anionic charges may be found on the outer surface of a bacterial cell membrane. The silver ions in solution will attract the membrane's anionic components due to electrostatic repulsion. As a result, the membrane may get damaged and begin to leak, preventing the creature from moving freely. Mannitol, succinate, glutamine, and proline have all been shown to leak out of bacterial cell membranes when exposed to ionic silver [53]. To add insult to injury, silver's binding to a membrane may block nutrient transport across it and/or disrupt the usual concentration gradients between the inside and outside of the cell, all of which can result in cell death.

Ionic silver's interplay with bacterial cell DNA represents a third process. Prokaryotic cells, such as bacteria, have DNA in the cytoplasm but are not impacted by this process since DNA is housed in the nucleus of eukaryotic cells. Guanine– cytosine and adenine–thymine base pairs have been found to be able to interact with ionic silver. Ionic silver binds to the N [7] atom of guanine during its contact with guaninecytosine, whereas adenine-thymine pairs undergo thymine dimerization when exposed to ultraviolet light during their association with silver.

antibacterial substance that obviously slows down microbial development. The minimum inhibitory concentration (MIC) for silver has varied greatly across research. Bacterial growth is inhibited at bacterial concentrations of 105-107 colony-forming units (CFU)/mL with MIC values ranging from 8 to 80 mg silver/mL for Staphylococcus aureus and 8 to 70 mg silver/mL for Pseudomonas aeruginosa [57]. The oligodynamic effect explains why even trace amounts of metal ions are effective against such large quantities of bacteria.

In 1895, von Nageli, the pioneer in the study of metals' antibacterial properties, coined the term "oligodynamic effect" (Greek:, oligos; dynamis; power). Since a deadly impact on bacteria is seen at extremely

low concentrations of silver and other metals, the term 'oligodynamic' was coined to describe this phenomenon [2]. In 1809, Thiele and Wolf used silver on an infected agar plate to show the oligodynamic phenomena. They found spots surrounding the silver metal where no bacteria grew during incubation. The primary takeaway from these tests was the realization that the silver's antibacterial efficacy was lost after being removed by chemical or mechanical cleaning of the metal surface. Because of this, it was concluded that silver with a purity of >99% lacked any kind of activity, whereas the oxidation of silver surfaces produced ionic silver, which was responsible for the oligodynamic effect. Antimicrobial activity of silver ions is shown against most bacteria at concentrations as low as one part per million [2,11,48,59].

The stated MIC data above suggests that even at the low light [54]. Both of these interactions will result in mutation of the DNA and ultimately in the death of a
bacterial cell.
A fourth interaction involves the destruction of a bacterial cell by silver free-radicals. These free-radicals possess end of the MIC range, 8 mg/mL of ionic silver paired with 107 CFU/mL (the high end of the bacterial levels utilized in MIC testing) would still generate a very high silver ion: proportion of bacterium cells as follows: Total amount of silver ions per milliliter of solution:

light [54]. In any case, the bacterial cell's DNA will mutate, leading to its eventual demise.

The death of a bacterial cell at the hands of free-radical silver is the subject of our fourth encounter. The presence of unpaired electrons gives these free radicals a high antibacterial efficacy.antimicrobial agent that will visibly inhibit the growth of a microorganism. In different studies,

In conclusion, some people are worried about the safety of leaving silver

(and other metal-based) dressings in place during MRI scans. Tattoos used for cosmetic or ornamental purposes may include ferromagnetic particles, which may increase process temperatures or cause image distortion if MRI is used [94–97]. Most wound dressing manufacturers advise their products be removed before any imaging treatment, but MRIs in particular [94]. In most cases, these suggestions lack a solid empirical foundation [94].
Common silver burn dressings were studied by Chaudhry et al. [94] using an MRI to see how it affected them. No money from the industry was used to conduct the research. Image and skin temperature quality were analyzed. To my knowledge, none of the silver-based treatments produced any appreciable rises in temperature or noticeable distortions in visual clarity. The authors found that the three silver-based wound dressings they tested were safe for patients and could be used in an MRI [94], therefore there's no need to remove silver-containing dressings before MRI examinations. In conclusion, the intake of colloidal silver or silver salts for unproven purposes accounts for many of the reported problems of silver-based treatments. Wound dressings containing silver tend to have minimal side effects when used for short periods of time. Most doctors still take off these bandages before MRI scans, despite the fact that it may not be required.

the MIC for silver has shown wide variation. Ten-fold variations in MIC (8–80 mg silver/mL for *Staphylococcus aureus* and 8–70 mg silver/mL for *Pseudomonas aeruginosa*) have been reported to inhibit bacterial

growth at bacterial concentrations of 10^5–10^7 colony-forming units (CFU)/mL [57]. The effectiveness of very low levels of metal ions against these high bacterial concentrations is explained by the oligodynamic effect.

The ‘‘oligodynamic effect’’ (Gr. *Oligos* meaning few, *dynamis* meaning power) was described in the 1895 by von Nageli, who performed the first systematic studies of the antibacterial effects of metals [58]. The term ‘oligodynamic’ comes from the observation that the lethal effect on bacteria is observed at very low concentrations of silver and other metals [2]. Thiele and Wolf first demonstrated the oligodynamic phenomenon in 1809 by placing silver on an agar plate that had been inoculated with bacteria. After incubation, they noted regions around the silver metal where no growth of bacteria occurred. A fundamental observation was noted during the course of these experiments was that if the metal surface was rigorously cleaned, either chemically or mechanically, the silver lost its antimicrobial effectiveness. This led to the general conclusionthat

high-purity silver (>99%) was devoid of

activity, while oxidized silver surfaces released ionic silver, which was responsible for the observed oligodynamic effect. For most microorganisms, an antimicrobial effect is seen at silver ion levels of one part-per-million or lower [2,11,48,59].

Using the worst case scenario with the reported MIC data above, 8 mg/mL of ionic silver (the low side of the reported MIC range) combined with 10^7 CFU/mL (the high side of the bacterial levels used in MIC testing) would still yield an incredibly high silver ion:
bacterial cell ratio as follows:
Number of silver ions in each milliliter of solution:

high antimicrobial potency due to the presence of unpairedelectrons

2.2. Clinical Considerations: Diagnostic Tools

When it comes to determining how effective silver is against bacteria and other microorganisms, opinions are divided. Studies on the effectiveness of new silver products are often industry-funded [26,55], and these studies are biased toward the product's supposed advantages. The majority of these research have been conducted in a laboratory using culture plates and inhibitory zones [26]. It is generally agreed that inhibitory zones are the least trustworthy and relevant to real clinical wound situations [26]. Also, there seems to be little relationship between log-reduction tests and zone of inhibition data [25]. Due to a lack of correlation between zone size and silver release [25,98-100], the zone of inhibition test should not be used to determine silver's presence or absence.
Because this strategy is more favorable to products that give big boluses of silver, several producers highlight 30-minute death rates [26,28]. Minimum inhibitory concentrations (MIC), minimum bacteriocidal concentrations (MBC), and log reductions [25,26] are also alternatives to the zone of inhibition test. The minimum inhibitory concentration (MIC) assay may

reveal which organisms are susceptible to silver, but it cannot provide the optimal amount for therapy [25]. To prevent resistance from developing, the treatment dosage must be higher than the mutant prevention concentration (MPC), which is higher than the minimal inhibitory concentration (MIC) [25]. Killing efficiency may be tested for using the MBC or the log-reduction test [25]. A bacteriocidal decline is defined as a three-log or more decrease in viable bacteria from the starting population [25]. Studies recommend administering a silver ion (Ag+) concentration of at least 1 ppm to provide a broad-spectrum bacteriocidal impact, or a 3-log decrease.

at concentrations of 30-40 mg/L or higher in organic-chloride complex fluids [25,61,101,102].

Researches have a hard time comparing log reduction data because of the wide variety of incubation durations, medium, and organisms used by each researcher [25]. By comparing the log-reduction data from other investigations of silver products, Warriner and Burrell discovered that at silver concentrations above 36 mg/L, 67.9% of the test sites exhibited reductions of more than three logs [25]. While the quantity of silver released from various commercial dressings varies widely (from below 10 mg/100 cm2 to well over 100 mg/cm2), all of them release more silver than the 1040 ppm considered sufficient for antibacterial activity [2,103].

In conclusion, producers use a variety of conventional microbiological tests to prove the efficacy of silvercontaining dressings against microorganisms. These tests don't adequately reflect real-world scenarios in medicine. Few log-reduction data from real wounds in animal research or human clinical trials have been published. To create a therapeutically accurate antimicrobial test, it is necessary to account for the presence of ions (Cl—) and organic compounds known to bind silver ion, both of which may be detected in wound fluids.

Research on silver-based dressings in clinical settings

It is challenging to conduct and evaluate clinical studies of silver-containing wound products with any degree of significance. Study outcomes, silver delivery claims, carrier dressing types, and silver sources (metallic silver vs. ionic compounds) all differ widely. Small sample size (burn patients), disagreement on end-point, lengthy healing times, multiple co-morbidities common to the chronic-wound population, and an inability to blind clinical investigators to the dressings used are all barriers to conducting proper prospective, double-blind randomized clinical trials. The effectiveness of the biologically active substance is affected by the kind of dressing utilized [11,104]. It is not simple to extrapolate data from one form of dressing containing silver to another [11]. Silver may come from ionic compounds like silver calcium phosphate and silver chloride, or it may come from metallic compounds like nanocrystalline silver [25,28].

Commercially available nanocrys- talline silver dressings in the US and Europe vary in composition, silver release rate, mode of action, and purported oxidation state of the bioactive silver moiety [6].

Since "silver effectiveness itself is not at risk," [26] the primary concerns while evaluating various dressings are the properties of the carrier dressing and the distribution of silver to the wound. The silver content of a dressing is probably less essential than the dressing's ability to fit snugly over the wound [3]. Dead space and gaps in the dressing provide ideal conditions for bacterial growth [3].

When conducting a clinical study, the end-point or success determinant is crucial. Although a 30% reduction in wound size could be statistically significant, if a 20 cm decubitus ulcer is reduced to a 13 cm still-open deep lesion, the improvement is clinically useless. Full wound healing is the only validated outcome measure of success so far [105]. Many

There is minimal evidence of a difference in full wound healing between the treatment and control arms in the published wound care studies that last just 4-8 weeks [105]. Wounds may heal rapidly or slowly, as proven by the research of Robson et al., with the latter group expected to need at least 9 months to fully heal [105,106]. Dropout rates more than 20% are problematic for randomized clinical trials of this duration, and many evidence-based medicine grading methods reduce the value of such research [105].

Most people who suffer from chronic wounds are elderly, and many of them have diabetes, other chronic health conditions, and dietary or other difficulties that prevent their wounds from healing. Extremely high rates of wound infection and recurrence are seen in this population [105]. Wounds don't always heal properly unless underlying problems are addressed [105]. The average length of a wound treated in a clinical setting is a year or more [105]. It is common practice to treat these patients in stages, with each stage requiring a unique wound therapy. It is difficult to assess the effectiveness of various dressings in promoting wound closure since silver dressings (and other modalities) are seldom utilized for the whole length of the wound course [105].

Case reports and clinical observation series are the most common types of published clinical research [26]. Few randomized prospective clinical trials (RCT) have been well planned or powered, and in certain wound patient groups, RCTs may be inappropriate or even difficult to conduct. Evidencebased medicine proponents are sometimes disappointed to find that doubleblind clinical trials, which would be required to do the grade A research they want, are just not feasible in the field of wound care [11]. In their review of clinical trials using nanocrystalline silver, Gravante et al. [51] discovered only 5 prospective randomized studies that directly compared nanocrystalline silver to either silver nitrate (1 study) or silver sulfadiazine (4 studies). Five investigations were conducted, with a total of 105 patients assigned to the nanocrystalline group and 180 assigned to the SSD or silver nitrate groups [51]. Twenty-six randomized controlled clinical trials with a total of 2066 individuals were discovered in a Cochrane review of the use of topical silver for reducing wound infection [107]. According to the authors, "most investigations were tiny and of low quality" [107]. Metaanalysis could not be performed due to the variability in interventions and outcomes. Three randomized clinical trials involving a total of 847 patients revealed the same findings in a Cochrane evaluation of the impact of silvercontaining wound dressings and topical treatments for the treatment (rather than prevention) of infected wounds [108].

There isn't enough of a burn population for reliable scientific studies to be conducted. Less than one thousand people each year are admitted to U.S. burn centers with burns covering more than half of their bodies' total surface areas (TBSA) [109]. The American Burn Association compiled recommendations for treating burns based on a synthesis of the available research and the opinions of specialists in the field and released these guidelines in 2001 [110]. None of the 12 issues studied had adequate data to establish evidencebased treatment criteria [110]. Consensus statements have been produced on some of the evaluated issues since then,

but there is still not enough evidence to

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Until large-scale randomized trials can be conducted on a suitable study population, expert judgment, rather than data from such studies, will have to serve as the foundation of medical practice.

3. Summary

Humans have been interacting with silver for quite some time, despite the fact that the use of silver ion in burn and wound dressings is relatively new. Silver has been used as coinage, as jewelry, in food preparation, and in the preservation and purifying of water without any ill effects being noted. Although silver is not required for human health and plays no important physiological function, it is present in the body at trace amounts due to inhalation and ingestion from natural sources. There is no evidence that silver may cause allergies, cancer, or mutations. An actual sensitivity to silver is unusual.

Antimicrobial activity of ionic silver is widespread. Nearly 50 years ago, silver-containing compounds became the standard for treating burn wounds. Since there are several antimicrobial mechanisms and locations of action, the reported prevalence of antimicrobial resistance is quite low, and resistance is highly improbable to emerge. Even in bacteria that have genes that confer silver resistance, high quantities of silver ion will overcome resistance.

Silver-based dressings have found a useful use in the therapy of chronic wounds. True chronic wound healing time is

measured in months, if not years. The wound's microbial ecology develops resistance to numerous drugs over time. Antibiotics given intravenously may not be able to reach a site with a poor blood flow. Antibiotic resistance increases when only subtherapeutic doses are used. Direct delivery of the antimicrobial drug to the site of colonization or infection and the absence of systemic complications make topical antimicrobial treatment an attractive option. Wound dressings containing silver ions may be made to release a steady stream of antimicrobial agents into the wound, and these agents have a wide range of activity that is unlikely to breed resistance in the microbes that inhabit the wound.

Unfortunately, there is currently insufficient evidence to warrant widespread use of silver-based dressings. There is a lack of agreement on how to evaluate the efficacy of silverbased dressings. The effectiveness of antimicrobials in treating acute or chronic wounds is not easily extrapolated from the findings of conventional in vitro studies. It is important to consider the silver-binding ability of chloride ion and other species present in wound fluid when planning bench or clinical experiments. Burn and wound care products containing silver should be developed to deliver high and sustained quantities of silver ion over extended periods of time to prevent binding and resistance.

Although prospective, blinded, randomized trials are considered the "gold standard" of clinical research, they are more accurately described as "silver standards" when applied to burns or chronic wounds for a number of reasons. Prospective studies of burn patients on a wide scale are probably not feasible due to the limited size of the patient group. Most patients have complicating systemic conditions like vascular insufficiency or diabetic mellitus, and most wounds will undergo a range of topical therapies over a protracted healing process, making the chronic wound population big enough for such studies yet endlessly variable.

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