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ORIGINAL PAPERS

Silver Salts in Dermatological Pathology

Dragoș-Florentin HUSANU[1], Leonard GURGAȘ[2],
Laurențiu Tony HANGAN[2], Natalia ROȘOIU[1,2,3]

[1] ISD, Doctoral School of Applied Sciences, Ovidius Constanta University
[2] University Ovidius Constanta, Faculty of Medicine, Romania
[3]Academy of Romanian Scientists

* **Corresponding author**: Husanu Dragos mail: dragos_husanu@yahoo.com

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Abstract
This paper is an overview of the beneficial effects of silver salts in medical practice. Silver can be found in nature as a pure element, but occurs more frequently in ores, including argitanite (Ag_2S) and silver chloride (AgCl); it is also found in combination with lead, lead-zinc, copper, gold and copper-nickel

Keywords: silver salts, dermatological patgology, argitanite (Ag_2S), silver chloride (AgCl)

Introduction

The Chaldeans, since 4000 BC, knew the importance of metallic silver. It ranks third among the metals used in ancient history, after gold and copper (1).

And the so-called "father of history", Herodotus, wrote on this subject saying that the Persian kings (Cyrus, for example) drank only water that was preserved in certain silver containers and had the property of keeping it fresh for years. It is easy to intuit the importance of silver in military conflicts when drinking water was not easily found (2). In fact, the Phoenicians, Greeks, Romans, Egyptians used silver to preserve water and food. This happened to including in the Second World War. It is also known in history that in order to heal wounds, or to prevent and treat infections, Macedonians were the first to apply silver plates on them. In this sense, in a pharmacopoeia published in the year 69 BC Rome is talking about using silver nitrate for medical purposes (1).

Properties

Silver has an atomic weight of 107,870 and an atomic number of 47 (3). It can be found in nature as a pure element, but occurs more frequently in ores, including argitanite (Ag_2S) and silver chloride (AgCl); it is also found in combination with lead, lead-zinc, copper, gold and copper-nickel (3). The pure

silver metallic luster is observed a bright white, is slightly harder than gold, but malleable and ductile (3). The melting point of silver is 961.93 ° C, boiling point 2212 ° C and a specific gravity of 10.5 (3).

59 silver isotopes are known. Only 2 isotopes (Ag107 and Ag109) are natural and stable. Silver has three oxidation states Ag [+1], Ag [+2] and Ag [+3] (pure silver is Ag [0]). Of these, only the Ag state [+1] is stable enough to be used as an antibiotic, the other cations being very reactive and of short duration (4), (5). Silver compounds ionize in the presence of water and biological fluids to release Ag (+1) (4).

Silver does not seem to have any physiological role or nutritional value for humans (4), (6), but it appears in the body in low concentrations, by inhalation or ingestion (4), (7), (8), being released into the air and water through natural weather and human activities, including the manufacture of cement and the burning of fossil fuels (7). Silver does not appear to be concentrated in aquatic animals, as is the case with mercury (7). The recommendation of the US Environmental Protection Agency for daily silver intake limits is 0.005 mg / kg / day (8).

Permitted levels of silver in drinking water are 0.1 mg / L (7) or 50 parts per billion (9). For normal individuals these levels include a blood concentration of less than 2,3 μg / L and a urinary excretion of 2 μg / day (5), (10). This is largely due to the ingestion of food and drinking water, the daily consumption of silver from food sources is estimated at 27–88 μg / day (9), (11). Orally ingested silver is absorbed mostly through the small intestine (9), the GI tract being the main route of excretion of ingested silver (9).

Non-ionized silver has no biocides action (4). Pure silver is generally considered non-toxic when used in clinical doses (12), (13). Silver jewelry is also 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 toxicological interest' (5).

In the presence of perspiration, sebum or moisture, silver ions on the intact skin will accumulate on the surface of the skin, with some penetration of the surface layers, leading to precipitation in the stratum corneum in the form of silver sulfide (4). Systemic silver is mostly excreted through the liver and kidneys, but hair and nail growth also provide a minor route of excretion (4). The absorption and metabolism of silver were not sufficiently analyzed, except for silver sulfadiazine and silver nitrate. Silver nitrate has been used as a treatment in topical burns, and silver sulfadiazine has been a major element in burn care (14), (15), (16). Up to 10% of silver sulfadiazine may be absorbed during treatment of partial burns (4), (17) with blood levels measured in blood greater than 300 μg / L (4), (17), (18), (19). The greatest absorption of silver occurs during the phases of inflammation and cell proliferation of wound healing (6), (20), (21).

Urinary excretion of silver can increase a thousandfold when silver compounds are used to treat large open wounds (burns) over long periods of time (12), (19), without having clinical significance (12). In patients with burns treated with silver sulfadiazine, silver plasma concentrations can reach a level of 50-310 μg / L, and urine excretion can reach a maximum of 400 μg / day (5). Silver sulfadiazine labeled with radioactive Ag110 shows that silver tends to accumulate in the superficial layers of the wound and is completely cleansed within 28 days (5), (22). Elevated blood and urine levels in combination with increased liver enzymes have been reported in patients with "silver nanometer" burns or nanocrystalline burn dressings (5), (23), (24), which have returned to levels normal after treatment has been discontinued.

There is a direct link between bacterial lethality and the free concentration of silver ions in the environment. Pure metallic silver is inert and does not react with human tissue and does not kill microorganisms until it is ionized (6). Silver ion bound, chelated or precipitated in insoluble complexes with tissue exudate or secretions is not available for antimicrobial actions. Ionic silver is highly reactive and will combine with halides (especially chloride), inorganic compounds, organic acids, negatively charged proteins, DNA and RNA (25), (26). Because many of these compounds can be found in wounds, the silver released into a wound dilutes rapidly (25). Chlorine ion seems to be a particular problem, because wound exudate has a high percentage of Cl ions, which bind with Ag + to form the inactive biological precipitate from silver chloride (AgCl) (12). The amount of silver required for efficacy in the case of complex wounds is 80-2000 times less than that required in simple aqueous solution (26) (27) (28) (29). Some experts argue that when excess Cl- is present, it is possible to overcome this precipitation (and restore antimicrobial action) by delivering a relatively large amount of silver (12), (28). Clinical experience shows this, and most commercially available dressings are designed to provide high levels of silver ions that reason. A study testing the antimicrobial effects of a silver dressing in wound fluid showed that the silver-containing dressing may provide a barrier against infection, probably due to the high levels of silver ion delivered (5), (30).

Antimicrobial effects

Dr. Crede, a surgeon, was the first to use colloidal silver to disinfect wounds in 1891 by applying a foil to them to treat infections (1), (2). The application of silver salts quickly became a habit in the therapies of burn wounds, Crusius using silver nitrogen to treat these burns since the 1890s. Vonnaegele observed that the antibacterial results of silver were primarily due to the silver ion, and through repeated studies he finally found that silver is an effective antimicrobial for almost all single-celled organisms (31).

It is now known that the silver ion is responsible for the antimicrobial effects of silver by dissociating ions from the surface of the oxidized metal, but the truth is that the mechanism by which silver destroys bacterial cells has not been established without a doubt. Four potential mechanisms have been discussed that have been proposed for the antimicrobial effects of silver (6), (12).

The first postulated mechanism involves the inhibition of life-supporting enzymes by chemical interaction with the silver ion, capable of blocking the transport of electrons in bacteria (32). It has been observed that at concentrations of 15 μg / ml, ionic silver inhibits the oxidation of glucose, glycerol, fumarate, succinate, d-lactate, l-lactate and other endogenous substances in E. coli (33). Ionic silver inhibits respiratory chain enzymes at the two specific sites: between cytochrome b and cytochrome d and between the entry site of the substrate in the respiratory chain and flavoprotein in the regions of NADH coenzyme and succinate dehydrogenase. At concentrations of up to 2 μg / ml of ionic silver, the absorption of inorganic phosphate was inhibited and the accumulated phosphate efflux occurred (33).

The silver ion interacts with thiol groups in the structure of enzymes. These groups are present in enzymes that contain the amino acid cysteine, and when ionic silver binds to this group, the enzyme is inactivated, leading to the death of bacterial cells. However, a cell can circumvent this mechanism by producing large amounts of reduced glutathione or cysteine in the protoplasm, which has the potential to prevent thiol-silver binding (34).

The second mechanism by which ionic silver destroys bacterial cells is by the interaction and rupture of the cell membrane or cell wall. The bacterial cell membrane contains both cationic and anionic charges on its surface, and in solution the ionic silver will electrostatically bind to the anionic portions of the membrane. This can cause the membrane to rupture or efflux. Ionic silver is known to induce the leakage of mannitol, succinate, glutamine and proline from bacterial cell membranes (33). Moreover, the binding of silver to a membrane can inhibit the passage of nutrients through the membrane and / or interfere with gradients of normal concentration between the cell and the environment, leading to cell death.

A third mechanism involves the interaction of ionic silver with the DNA of bacterial cells. Eukaryotic cells are not affected by this mechanism (because DNA is contained in the nucleus), prokaryotic cells such as bacteria do not have a nucleus and have DNA present in the cytoplasm. Ionic silver has been shown to interact with the basic pairs guanine-cytosine and adenine-thymine. The interaction of ionic silver with guanine-cytosine involves the N (8) atom binding guanine to silver, while the interaction with the adenine-thymine pair determines the dimerization of thymine in the presence of UV light (34). Both interactions will result in DNA mutation and ultimately the death of a bacterial cell.

A fourth theory involves the destruction of a bacterial cell by silver free radicals. These free radicals have a high antimicrobial potency due to the presence of unpaired electrons in the silver atom. Ionic silver can bind to many amino acids in a bacterial cell, including arginine and glutamic acid. When silver binds to amino acids, an organometallic complex is formed. If the silver-containing bond of the complex subsequently breaks, a silver free radical can be generated inside the cell. Free silver radicals that accumulate in the cell can affect the electron transport chain, inactivate bacterial DNA and RNA, and damage the cell membrane and precipitate proteins with cysteine and thiol groups causing cell death (20).

The healing role of silver salts

At the level of the tissues on which they are applied, the solutions of inorganic silver salts exert an immediate germicidal effect which continues to release small amounts of silver ions from the forms of protein silver thus maintaining a sustained bacteriostatic action.

Silver and its salts are absorbed very slowly and therefore do not give toxic concentrations to the body. Contact with sodium chloride in the body's secretions and plasma leads to the formation of silver chloride, an insoluble salt that precipitates very quickly, blocking the continuation of the action in depth. Silver nitrate (silver nitrate) works by releasing active silver ions. Concentrated solutions initially have a bactericidal effect, but lead to the precipitation of superficial albumin forming a membrane from which silver ions with bacteriostatic action are gradually released (35). The intensity of its action depends on the concentration and the time it is left to act. It is also used as a cauterizing agent for the oral mucosa, in local applications, by punctiform touches in case of canker sores, umbilical granuloma (in the form of 30% silver nitrate solution) (36).

Colloidal silver is a liquid in which very small particles are suspended in solution. Inhibits oxygen-carrying enzymes used in the metabolism of bacteria, viruses and fungi, speeding up wound healing. Colloidal suspensions 1-5% to 10% of organic silver salts are used as mucosal antiseptics, especially in coconut infections (37).

Silver ions are antimicrobial in very low concentrations. The antimicrobial efficacy of silver was determined by using the test of the minimum inhibitory concentration, a method that evaluates the lowest concentration of an antimicrobial agent that will be able to visibly inhibit the growth of a microorganism.

The 'oligodynamic effect' (Gr. Oligos = little, dynamis = power) was shown in 1895 by von Nageli, who carried out the first systematic studies of the antibacterial effects of metals (38). The term 'oligodynamic' comes from the

observation that the lethal effect on bacteria is observed at very low concentrations of silver and other metals (4). Thiele and Wolf first demonstrated the oligodynamic phenomenon in 1809 by placing silver on a plate on which bacteria were inoculated. After an incubation period, regions around the silver metal were observed, where the bacteria did not proliferate. It has been observed during these experiments that when the metal surface is rigorously cleaned the silver loses its antimicrobial efficacy. This led to the general conclusion that high purity silver (> 99%) was inactive, while oxidized silver surfaces released ionic silver, responsible for the observed oligodynamic effect (4), (34).

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