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REVIEW

Silver Products for Medical Indications: Risk-Benefit Assessment

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ABSTRACT

Background: Legitimate medicinal use of silver-containing products has dramatically diminished over the last several decades. Recently, however, some manufacturers have begun to enthusiastically promote oral colloidal silver proteins as mineral supplements and for prevention and treatment of many diseases. Indiscriminate use of silver products can lead to toxicity such as argyria. Objective: To assist health care professionals in a risk versus benefit assessment of over-the-counter silver-containing products, we herein examine the following issues: historical uses, chemistry, pharmacology, clinical toxicology, case reports of adverse events in the literature, and the recent promotion of over-the-counter silver products. Other sources of silver exposure (including environmental and dietary) and EPA exposure standards are discussed. A list of currently available silver products is provided for easy reference and screening. Conclusions: We emphasize the lack of established effectiveness and potential toxicity of these products.

INTRODUCTION

Silver medicinals have been used in the past for many ailments.[1-7] During the Middle Ages, Lunar Caustic (silver nitrate) was given for patients with nervous disorders. Epilepsy was also treated by silver nitrate until the late 19th century, and syphilis was treated with silver arsphenamine in the early 20th century. Colloidal silver proteins (CSP) were used in cold remedies until the middle of this century. With the development of many newer and more effective alternatives, the legitimate use of silver products has dwindled so only a few prescription silver-containing drug products remain available.

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However, manufacturers of some health food products have recently begun promoting CSP to the public as an essential mineral supplement and cure-all.[8] In order to provide further information to health-care professionals and consumers, presented herein are a review of the basic chemistry, pharmacokinetics, pharmacology, clinical toxicology, case reports of adverse events, and an evaluation of the validity of current claims for colloidal silver proteins and other silver products. Also included are summary data for available products, as well as environmental and dietary sources of silver.

Physical and Chemical Properties

CSP are prepared by mixing silver nitrate, sodium hydroxide, and gelatin and diluting this mixture with water to the desired concentration.[1,7] These ingredients react together, forming a complex colloidal aggregate. Historically, many colloidal silver suspensions have been marketed.[5,7] Commonly used CSP are Mild Silver Protein (19-23% silver) and Strong Silver Protein (7.5-8.5% silver). Mild Silver Protein contains a higher silver concentration which is less ionizable, causes minimal irritation, and is bacteriostatic. Conversely, Strong Silver Protein contains less silver which is more ionizable, irritating, and is purported to be bactericidal. The currently promoted health food store products appear to be further dilutions of these two forms of CSP.

Inorganic silver compounds are germicidal.[2,3,5] Silver readily denatures proteins by binding to the reactive groups of the proteins, causing precipitation. Silver compounds inactivate enzymes by forming hemisilver sulfides with sulfhydryl groups. Silver can also bind amino, carboxyl, phosphate, and imidazole groups. Shinogi and Maeizumi demonstrated that silver deposits in rat liver and binds with high affinity to the sulfhydryl groups in cellular components and basal membranes.[9] They also found that silver can diminish the activities of lactate dehydrogenase and glutathione peroxidase and peroxidation of membrane lipids.

Historical Uses[1-7]

Since the late 19th century, CSP have been promoted for numerous medical indications. Although CSP have been used to treat (or prevent) gonorrhea and gonorrheal conjunctivitis due to purported bacteriocidal properties, such treatment has been largely replaced by less toxic antimicrobials with substantiated effectiveness. In the past, such products were also promoted as topicals for direct application to mucous membranes in the nose, throat, urethra, and colon. However, there is no evidence that CSP are effective at these other sites and toxicity has been reported. Although silver products were infrequently promoted for oral use, benefits have been even more questionable. The 1960 Edition of the US Dispensary states that "there is no justification for this (internal) use either theoretically or practically".[7]

Silver Exposure

Silver is the 47th element in the periodic table. Due to wide industrial applications, a historically high incidence of silver toxicity has been reported but new occupational safety regulations have dramatically decreased this reported toxicity. Besides drug or industrial exposures, silver can be ingested with food and water. The EPA publishes a Reference Dose (Rfd) which is an estimate of daily exposure to the entire population (including sensitive subgroups) that is unlikely to be associated with an appreciable risk of deleterious effects during a lifetime.[10] It is based on a presumption that some threshold may exist for certain toxic effects of a chemical such as cellular necrosis independent of carcinogenicity. The current Rfd for oral silver exposure is 5 μg/kg/d with a critical dose estimated at 14 μg/kg/d for the average person. The EPA also publishes safety guidelines for silver in drinking water. The Maximum Contaminant Level Goal proposed by the EPA for silver in the drinking water is < 0.1 mg/L.[11]

Based on the current Rfd, for a 5 kg infant to a 70 kg adult, the maximal daily silver exposure should be less than 25-350 μg/d. If the silver in drinking water sources meets EPA guidelines, an average person who drinks 2 L/d is exposed to less than 200 μg of silver. However, a regular daily diet may contain up to about 90 μg of silver as a background level of exposure.[2,12,13] For example, wheat flour contains 0.3 μg/g, bran contains 0.9 μg/g, and mushrooms contain up to several hundred μg/g of silver. Milk which contains about 27-54 μg/L is also a major contributor to daily silver intake.[13] For most food sources, local soil correlates highly with measured silver concentrations.

Currently available CSP products promoted for medicinal or mineral supplement purposes are reported to have an active silver ion concentration of about 1-6 ppm (5-30 μg) per dose[8] (Table 1). Although the active ionizable silver concentration is in the few ppm range, the total silver content of individual products may be much higher. For example, the previously available Argyrol 10% SS Ophthalmic (Mild Silver Protein) has about 20 mg/mL of silver. In case of accidental ingestion by a child, a 15 mL bottle would give a total of 300 mg silver exposure. The highly variable silver concentrations in promoted drug products may add to unnecessary silver exposure for consumers.

Current Promotion

Currently available CSP formulations in the health food stores include oral suspensions, aerosols and douches (Table 1A). These products are being promoted as essential mineral supplements and advertised for use in diseases such as cancer, diabetes, AIDS, and herpes. Their manufacturers have also advanced an unsubstantiated hypothesis that silver deficiency leads to impaired immunity which results in cancer.[8]

Regulatory History: Efficacy

Mild Silver Protein was once listed as an ingredient under review by the FDA as a potential antiseptic. However, an FDA Advisory Expert Panel noted a lack of human efficacy data and recommended that sponsors conduct further studies to substantiate effectiveness. Since the agency received no further data, this ingredient was removed from the over-the-counter (OTC) monograph in 1992. Thus, no approved CSP products are available OTC.

A higher concentration (20% Argyrol SS) Mild Silver Protein ophthalmic and other topical silver nitrate and silver sulfadiazine preparations remain available only by prescription (Table 1B). Silver nitrate has been occasionally used as prophylaxis for ophthalmia neonatorum in newborns and as a cauterizing agent for uncontrolled epistaxis and some skin conditions (warts and corns). However, these silver products are not without adverse effects.[14-18] For example, burn treatment with silver nitrate can cause methemoglobinemia, hypochloridemia, hyponatremia, and eschars that adhere to dressings. Due to these effects, silver sulfadiazine has largely replaced silver nitrate, although silver sulfadiazine may cause leukopenia and nephrotic syndrome rarely.

Clinical Toxicology: Safety

In animals, research has demonstrated that silver accumulates widely in the body. Although it was originally believed not to penetrate the blood-brain barrier, Rungby and Danscher showed that parenterally administered silver salts can accumulate in neurons and in protoplasmic glia cells of the brain and spinal cord.[19] In a subsequent experiment, the same authors found that mice exposed to either peroral or parenteral administration of silver salts became hypoactive compared to the untreated controls, suggesting that silver intoxication could have an influence on CNS function.[20] Rungby also demonstrated that silver can induce a decrease in the total volume of developing hippocampal pyramidal cells in fetal rats.[21]

Some researchers have suggested that Vitamin E or selenium deficiency may increase susceptibility to systemic silver toxicity. Wagner *et al.* and Bunyan *et al.* have shown that hepatic necrosis can be induced by administering silver preparations to Vitamin E/selenium deficient rats.[22-23] They hypothesized that toxicity was due to a silver-induced selenium deficiency that inhibits the synthesis of the seleno-enzyme glutathione peroxidase. Further, Bunyan *et al.* showed that if rat diets were supplemented with selenium or Vitamin E, exposure to silver as high as 140 mg/kg/d was still well tolerated.[23]

When absorption is limited, systemic silver toxicity occurs infrequently. However, after ingestion, up to 10% of silver salts may be absorbed.[3] Moreover, absorption is increased from disrupted mucous membranes or skin wounds such as burns. Also, ingested soluble silver salts may corrode the gastrointestinal mucosa. Occasionally, death may result from local trauma, hemorrhagic gastroenteritis, and shock.[5]

Upon systemic absorption, the highest concentrations of silver are found in the skin, liver, spleen, and adrenals with lesser deposits in the muscle and brain.[2,3] Depending on the silver salt, the route of administration, and the animal studied, the biologic half-life is reported to range from days to months.[2,3] However, absorbed silver deposited in skin has a much longer half-life. Excretion of silver is

Table 1

List of Currently Promoted Silver Products

Unapproved Products

Market	Product Name	Manufacturer	Ingredients	Promoted Uses
health food	Colloidal Silver Golden Silver OxyGold Silver Cidal Advanced Colloidal	various manufacturers	1-6 ppm CSP per dose	mineral supplement "antibiotic"

Prescription Only Drug Products

Market	Product Name	Manufacturer	Ingredients	Promoted Uses
Rx	Argyrol SS 20%	Iolab	20% mild silver protein	ophthalmic antiseptic
Rx	Silver Nitrate	Lilly	1% silver nitrate	prevention of gonorrheal ophthalmia neonatorum
	Silver Nitrate	Gordon Labs	10%, 25%, 50% silver nitrate	wart/corn
	Silver Nitrate	Graham-Field	75% silver nitrate	wart/corn
Rx	Silvadene	Marion Merrell Dow	10 mg/g silver sulfadiazine	burn wounds
	SSD Cream	Boots	10 mg/g silver sulfadiazine	burn wounds
	SSD AF	Boots	1% silver sulfadiazine	burn wounds
	Thermazene	Sherwood	10 mg/g silver sulfadiazine	burn wounds

Information provided by the Nontraditional Drug Compliance Branch, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration and the 1995 edition of Drug Facts and Comparisons (Publisher: Wolters Kluwer Company, St. Louis).

primarily via fecal elimination with active biliary excretion. Previous studies have confirmed that even inhaled silver is eliminated primarily in the feces.[2,3]

In humans, even trace amounts of silver may accumulate in the body and may reach an appreciable amount in later life depending on dietary preferences and local environmental levels.[5] Additional sources include industrial exposure and indiscriminate use of silver-containing medicinals. Absorbed silver is widely distributed in the body and large amounts accumulate in the subepithelial portions of the skin causing argyria (Figure 1). The first sign of argyria is in the gingiva, a slate-blue silver line from the deposition of metallic silver and silver sulfide pigments.[24-25]

In addition to these direct silver deposits, pigmentation results from silver stimulation of melanocytes, increasing melanin production. Further, discoloration is more pronounced in sunexposed areas because photoactivation reduces silver. Argyria is effectively irreversible and an important cosmetic concern. Chelation therapy with British Antilewisite

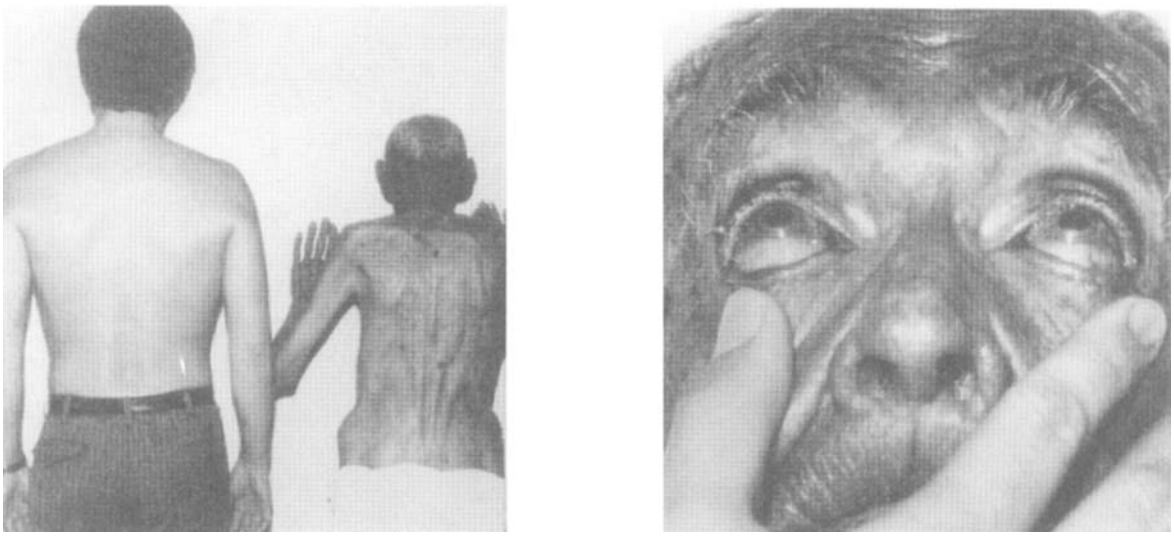

Figure 1. This is a photograph of a 92-year-old Caucasian man who developed generalized argyria by applying silver-containing nose drops daily for years. Diagnosis is confirmed by skin biopsy. The bluish-gray discoloration is more pronounced in the sun-exposed areas such as face, neck, and nails but also involves the conjunctiva, sclera, and mucous membranes. (Reproduced with permission from *Hospital Practice*, October 15, 1994.)

(BAL) or D-penicillamine has been ineffective.[16,26] Successful local reversals have rarely been reported by intradermal injection with 6% sodium thiosulfate or 1% potassium ferrocyanide although repeated injections for large areas remains impractical.[5]

According to a 1973 submission to the FDA, 365 cases of argyria from 1802 to 1951 were reported in the medical literature.[1] However, argyria continues to be reported. Lee and Lee reported a recent case of generalized argyria in a 33-year-old woman who self-treated her recurrent oral ulcers for six years with a silver-containing product.[27] The patient developed skin discoloration after one year and biopsies of oral mucosa and the forearm revealed small silver granules scattered in the dermis, blood vessels (most numerous in the basal laminae), and hair follicles.

Steininger *et al.* reported generalized argyrosis secondary to systemic use of silver in a 52-year-old patient who had treated duodenal ulcer with 35 g of a silver preparation for more than 18 years.[28] The patient subsequently died of cardiac failure and autopsy showed generalized argyrosis. Besides skin involvement, dense silver deposits were found in the walls of most blood vessels, renal glomeruli, choroid plexus, seminiferous tubules, and liver portal fields.

Internal silver deposition has also been reported to cause neurologic deficits. Westhofen and Schafer reported a 55-year-old woman who developed progressive hypogeusia, hyposmia, vertigo, gait disturbance, skin hypesthesia, and weakness after self-treating for oral mycosis with a silver product for nine years.[29] Chemosensory tests and electrophysiologic studies confirmed the clinical findings. X ray microanalysis of the affected tissues revealed silver sulfide deposits. Upon further examination by electronic microscopy, silver deposits were found in basal membranes, macrophages, elastic and collagenous fibers, perineurium of peripheral nerves, and in necrotic cells of the oral submucosa. The authors suggested deposition of the insoluble silver sulfide over basal membranes and neuronal structures as the cause of these conditions.

Generalized argyrosis can develop more quickly if sufficient amounts are ingested. Jurecka reported a 58-year-old patient who used silver-containing tablets (exact amount unknown) for pharyngitis over only a 18-month period and developed generalized argyria.[26] Diagnosis was confirmed by histology, X ray micro-analysis, and electron microscopy. Chelation therapy with D-penicillamine failed to reverse this patient's condition.

Marshall and Schneider reported a 46-year-old patient who used a topical silver product about three times per week to control recurrent gingival bleeding caused by poorly fitting dentures.[30] After about two and a half years, the patient developed generalized argyria. Argyria persisted despite discontinued use of silver and the patient developed chronic abdominal pain. The patient underwent gastroscopy with biopsy where silver deposition in the connective tissues of the stomach was found. During a subsequent abdominal operation, diffuse argyria was documented in multiple internal organs including liver, spleen, intestines, and the peritoneum with the highest pigmentation in the pancreas.

Besides systemic involvement, topical silver use on mucous membranes has been reported to cause argyrosis in tissues other than the skin. For example, Timmins and Morgan reported a 68-year-old patient who used a 1% Mild Silver Protein with ephedrine nasal drops every night at bedtime for nasal congestion for 35 years and developed local argyrosis in the gingival margin of the mouth.[31] Stammberger reported two cases of nasal argyrosis after use of nasal silver products; one patient had been using inhaled silver products for at least six years.[32]

Ocular argyrosis is quite common. The involved eye turns bluish-gray or brownish-black. Loeffler and Lee reported silver deposition in the wall of the lacrimal sac of an 80-year-old patient who had used CSP eyedrops to prevent eye soreness while gardening.[33] Deposition of silver selenide was found in the extracellular matrix on elastic fibers and within cells forming conglomerates in secondary lysosomes.

Besides the use of CSP, other cases of argyrosis have been reported secondary to industrial exposure. Rosenman *et al.* reported ocular argyrosis in 20 out of 30 New York factory workers manufacturing silver nitrate and silver oxide products.[34] Among these subjects, 12 also had measurable silver blood levels and six had generalized argyrosis. A direct correlation was noted between the deposit levels and the duration of employment. Many of these workers also had other systemic complaints such as nausea, headache, tiredness, and nervousness. Among the ten workers with abdominal pain, there was a statistically significant association of the blood silver levels with this complaint.

Other reported cases of argyrosis are referenced for interested readers.[35-43] Besides argyria, silver toxicity is rarely reported. However, industrial exposure at high concentrations is associated with systemic toxicity.[15,16,44] Excessive use of silver causes glomerular damage and proteinuria. Topical use of silver nitrate in burns causes methemoglobinemia. Inhaled silver may cause metal fume fever and chemical pneumonitis. The average amount of exposure required to develop argyria is reported to be 3.8 g of elemental silver.[2,6] An average fatal dose is about 10 g although some subjects have apparently survived even after exposure to 30 g. There is no specific antidote for silver. Treatment is supportive.

There is a potential risk for the developing fetus when pregnant women use silver products. A case-control epidemiology study was conducted by Aschengrau *et al.* among women who delivered infants from 1977 to 1980 in a Massachusetts hospital.[45] Trace element levels of public water were analyzed from the communities in which the women resided during pregnancy. The relationship between community drinking water quality and the occurrence of late adverse pregnancy outcomes was examined. After adjustment for confounding factors, the results suggested some association between maternal exposures to 0.001 mg/L of silver in the drinking water (1/100 of the EPA standard) and some increase in fetal developmental anomalies (ear, face, and neck). As the authors recognized, there are inferential limitations to epidemiologic studies. Further research is needed to explore these findings.

CONCLUSION

In this article, we have reviewed the basic chemistry, pharmacokinetics, pharmacology, clinical toxicology, case reports of adverse events, and have outlined the regulatory history of OTC silver-containing medicinal products, including colloidal silver proteins. Environmental and dietary sources of silver exposure have been presented along with EPA safety guidelines. For easy reference, a table of currently available silver products has been provided. We have outlined what is known about the safety and efficacy of available OTC silver-containing products and have concluded that silver has no known physiologic function and should not be

promoted as an essential mineral supplement. Recent promotional assertions made about the effectiveness of these products in numerous diseases remain unsubstantiated.

Moreover, indiscriminate use of silver can lead to irreversible toxicity and silver in drug products can add to silver exposure from environmental sources such as food and water. Silver is deposited in many organs including neurons. Argyria, the most commonly reported adverse event, results from accumulation of silver deposits in the skin below the epidermis. We conclude that the risk exceeds the unsubstantiated benefit for OTC silver-containing products. Consequently, there are no FDA approved CSP products available OTC.

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