Journal of Nutritional & Environmental Medicine (June 2003) 13(2), 109–118

Taylor & Francis
healthsciences

REVIEW

Viral Pathogens and Severe Acute Respiratory Syndrome: Oligodynamic Ag^+ for Direct Immune Intervention

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Abstract

This retrospective study of silver-based therapeutics briefly reviews their history, and then explores the modern application of charged silver particles, especially as an antiviral agent. The recent outbreak of severe acute respiratory syndrome (SARS) suggests this is timely. Medical literature shows that a variety of viruses have been successfully treated with silver-based drugs. However, 'silver salts' and/or inferior silver preparations lack the bio-availability, active silver content and safety needed to be effective. State-of-the-art, electrolytically produced 'oligodynamic' Ag^+, however, offers distinct advantages and versatility of use over older and cruder formulations. Possessing much smaller, subnanometer-sized particles, greater electrical potential and lower concentrations, it is more bio-available than other formulations. Efficacy against the SARS-related coronavirus, for example, may be enhanced when nebulized Ag^+ is inhaled. This should achieve swift reduction of viral loads, especially in the early stages. Moreover, there is no known toxicity for Oligodynamic Ag^+ in humans. The only known mechanism of resistance also appears to play no role notwithstanding the mutability of the coronavirus. Therefore no functional barrier to the virotoxic effects of oligodynamic Ag^+ may be expected regardless of the rapidity or variety of mutations.

Keywords: oligodynamic colloidal silver, silver speciation, biocompatibility, antiviral spectrum, oligodynamic Ag^+ pharmacokinetics, SARS-related coronavirus, NASA-commissioned studies, protein-based viral envelope, capsid, viral resistance.

INTRODUCTION: HISTORICAL SUCCESSES AGAINST VIRAL INFECTIONS WITH SILVER FORMULATIONS

The pre-dynastic Egyptians started using silver as currency around 3500 BC. Since ancient times, silver has been highly regarded as a premier preservative and antimicrobial agent [1–4]. So esteemed was silver for this purpose that it literally permeated the known world, including ancient Greece, Rome, Phoenicia and Macedonia [5, 6]. Hippocrates (circa 400 BC) taught that the flowers of silver by itself, in the finest powder, would heal non-healing wound ulcerations [7]. In 69 BC, silver nitrate was described in the contemporary pharmacopoeia [8].

A few thousand years later (1897), silver nitrate began to be widely used in America. The result was an enormous alleviation in blindness among newborns, as it still is today [9, 10]. Just prior to this event, a major discovery occurred that was to give lasting purpose and impart definitive meaning to the entire spectrum of silver-based aids. This pivotal discovery

ISSN 1359-0847 print/ISSN 1364-6907 online/03/020109-10 © Taylor & Francis Ltd
DOI: 10.1080/1359084031000159406

was to become known as silver's oligodynamic power. Older medical reports and controlled studies pointing to the efficacy of silver-based drugs in viral conditions were actually dependent upon the formulation's *oligodynamic silver ion* (Ag^+) content. Spanning over 100 years, many versions of these metal-based oligodynamic drugs were tested (*in vitro* and/or *in vivo*), with various degrees of success, against: adenovirus [11, 12], bovine rotavirus [12, 13], cerebrospinal meningitis [14–16], conjunctivitis [17–22], coxsackie virus type B-3 [23], ECHO virus [24], ECHO virus type 6 [25], enteroviruses [23], *Haemophilus influenzae* [26], hepatitis B [27], influenza [16, 24, 28], influenza A [12, 29, 30], measles virus (Nagahata strain) [31], poliovirus 1 (Sabin strain) [13, 30, 32], poliovirus type 1 [33], pseudorabies virus [12, 24], reovirus type 1 [34], rhinovirus type 1A [23], shingles [11, 35], smallpox [21], vaccinia virus (poxviruses) [13, 24], varicella-zoster virus [35] and warts [21, 36].

HISTORICAL VERSATILITY OF SILVER ADMINISTRATION

The older medical literature provided various guidelines and methods of administration for crude silver formulations. Solutions, ointments, sprays, dusting powder, tablets, irrigations, suppositories, and tampons were employed. Direct application of different silver formulations depended upon their caustic or non-caustic attributes, and accordingly were applied to conjunctiva, nose and throat, topical wounds and ulcers, urethra, bladder, vagina and rectum [37].

The application methods included intravenous, intramuscular, subcutaneous, and oral. Historic clinical reports have stated that injected Ag^+ produced dramatic immediate improvement in URT infections [15].

DISCUSSION: PROBING THE STRATEGIC ASPECTS OF THE ANTIMICROBIAL PROPERTIES OF SILVER

Like bacteria and fungi, infectious viral organisms may have multiple susceptibilities when encountering oligodynamic Ag^+. On the other hand, evidence suggests that oligodynamic Ag^+ will not interfere with normal white blood cell (WBC) activity, and may even enhance WBC activity [38, 39]. Feng *et al.* [40] concluded that oligodynamic Ag^+ offered profound immune benefits because of its ability to intervene with select bacteria in three key ways almost simultaneously. Central to all three is the ability of oligodynamic Ag^+ to denature (dose-dependent permanent inactivation) essential microorganisms' protein and DNA:

1. One type of essential protein maintains the integrity of the cell's membranes and boundaries. Once the membranes become unstable, the cell begins to rupture.
2. Simultaneously, the smallest sizes of Ag^+ may more easily penetrate the membrane pores of the bacteria. Once penetration occurs, life-essential enzyme reactions governing cell metabolism go into partial or full arrest.
3. As the silver further penetrates the most interior recesses of the cell, the genetic building blocks (nucleic acids) of the germs are paralyzed, ending the ability of the invaders to replicate.

COLLOIDAL SILVER PRODUCTS GAIN POTENCY BY ORDERS OF MAGNITUDE VIA PARTICLE CONCENTRATION, PARTICLE SIZE, AND PARTICLE CHARGE

Here we will address the main issue surrounding the most important active state of silver-based drugs—their oligodynamics—and relate it to an emerging global threat, severe acute respiratory syndrome (SARS).

The specific means used to create a given silver formula determines its oligodynamic qualities. By 1937, the three factors governing the oligodynamic action of silver were known. These are: (a) particle concentration, (b) particle size and (c) particle charge [41]. The common denominator to the pharmacokinetics of all silver-based drugs is their respective content of Ag^+. The Therapeutic Index of Ag^+ activity depends upon *speciation* of the silver-based drug. Speciation is the term that applies to a specific metal as it occurs over a variety of metal compounds, which differentiates their respective fates, transport systems and toxicities. Reduced or neutral silver has no known medical value. Goetz *et al.* [42] stated that *oligodynamic* Ag^+ cannot be toxic to mammals, and when produced electrolytically, it is the most therapeutic form of Ag^+. Long-term industrial exposure to silver ore and refining compounds only produces irritation [43].

Particle Concentration

In 1893, a Swiss botanist Carl Nägeli (also referred to as K.W. von Naegeli) first identified the oligodynamic effect (from the Greek *oligos* = few, and *dynamis* = power) to best describe how extremely low metal ion concentrations beyond definitive chemical analysis exert potent biocidal actions [44]. *Webster's Dictionary* gives further definition to the biocidal properties of extremely low metal ion concentrations as follows: Ol-i-go-dynamic *adj* [ISV *olig+dynamic,* orig. formed as G oligodynamisch] 1: active in very small quantities <an ~ germicide> 2 a: produced by very small quantities <~ action of finely divided silver in disinfecting water> b: of or relating to the action of such quantities [45].

Nägeli determined that oligodynamic Ag^+ was an effective biocide at concentrations ranging between 0.0000001 and 0.00006% (equivalent to 9.2×10^{-9}–5.5×10^{-6} M or 9.2 ppb to 5.5 ppm) *in vitro* [3].

In 1970, a NASA-sponsored study confirmed in principle Nägeli's findings *in vitro* that oligodynamic Ag^+ was a highly effective biocide in concentrations of 50 ppm over 4 hours or less, and in concentrations of 250 ppb over 2 hours or less [46]. As advances in understanding occurred, it was determined that raising the Ag^+ concentrations to 10 ppm or more reduced the necessary time of exposure to mere minutes [47].

Particle Size—Dissociation Constant vs. Colloidal Surface Area

The key strategic advantage of colloidal drugs over drug compounds is their ability to adsorb and penetrate into the greatest possible biological area in the lowest possible effective dose. One critical characteristic of metal ions, central to their chemical and biological activity, is size, an important factor in determining whether one metal can replace another in a given environment [48]. As a result, it can be concluded that the smaller the *colloidal* silver particle, the more biologically active it becomes. Colloidal silver particles in commercial products of the last century were thought to be 0.014–0.026 mm (14–26 nm) [49]. The standard was Collargol®, which was measured to have an average colloidal particle size of 20 nm [50].

The latest high-tech commercially available silver hydrosol product has achieved a 0.8 nm average particle size. This makes it picoscalar in diameter. Particle size creates particle *surface area,* which is of utmost therapeutic importance. The activity of biocatalysts like colloidal silver is directly proportional to the adsorption power upon a biological surface, which totally depends upon the surface area of the metal [51]. Bechhold [52], Alexander [53], Jirgensons and Straumanis [54] and Hartman [55] all adapted tables from Wolfgang Oswald, who demonstrated the geometric progression to the surface area of silver particles by assuming a starting point of 1 cm^3 of silver. Reducing incrementally into smaller and smaller cubes, the silver particles eventually approach a 6 km^2 surface area:

$1.0\,cm = 6\,cm^2$
$1.0\,\mu m = 6\,m^2$
$1.0\,nm = 6\,km^2$.

In summary, Kopaczewski [56] concluded as early as 1928 that the *net* colloidal particle size meant a great deal to the oligodynamic effectiveness of any colloidal silver preparation, because the smaller the particle, the greater its effective surface area, the better its ability to penetrate and disperse within tissue and the larger the electrical mass it can provide for reactivity. He wrote that only the finest dispersed colloidal particles had the desired antiseptic effects.

Particle Charge

The term oligodynamic is only applicable to extremely low concentrations of metal ions (Ag^+). Acél [57] was perhaps the first to observe that the oligodynamic action of silver was due to liberated Ag^+ as opposed to metallic (neutral) Ag. Eichorn *et al.* [48] emphasized that the charge significantly facilitates electron displacement. The oligodynamic metal charge effectively yanks electrons away from a molecule, in essence weakening the molecular bond and rendering it susceptible to cleavage. Goetz [58] observed that silver is microcidal only *if* it is in the ionic state, and this was later characterized further by Rochart and Uzdins [59] who observed that cells selectively bond only with Ag^+.

SUMMARY OF PHARMACOKINETICS OF OLIGODYNAMIC AG^+

Due to its vicious triple denaturing actions associated with oligodynamic Ag^+ coupled to the triad of physical attributes that perfect its therapeusis, oligodynamic Ag^+ is generating enormous excitement among research into virology. As stated above, delivery of active Ag^+ is the key to success. Providing that delivery of oligodynamic Ag^+ to the viral foci is accomplished, the effective dosage level of pure oligodynamic Ag^+ is essentially medically benign to human cells [60]. As Berger *et al.* [61] concluded, oligodynamic Ag^+ generated electrically at a target tissue area is observed to be a very effective immune intervention at low concentrations, yet appears to cause no harm to normal mammalian cells.

THE ANTIVIRAL PROPERTIES OF SILVER POTENTIALLY APPLICABLE TO SARS

Emerging medical studies confirm the antiviral immune intervention of oligodynamic Ag^+ *in vitro* and *in vivo* against some of the most formidable viral organisms such as HIV [31, 62–69] and herpesvirus hominis [3, 12, 70–74].

THE EMERGENCE OF HIGH-TECH SILVER FORMULATIONS

Previous studies generated much success against viral agents, but depending upon the type of silver formulation used, outcomes varied widely. Silver nitrate, silver sulfadiazine and electrolytically produced Ag^+ all had different antiviral properties.

Due to the advances in modern technology allowing for the production of high medical grade oligodynamic Ag^+ formulations, it may be worthwhile to review earlier research [75–78]. For example, studies completed for NASA in 1970 concluded that there was a slight advantage to electrolytically produced oligodynamic Ag^+ over Ag^+ derived from silver salts [79]. Their follow-up data in 1971 appeared to support this finding at the 3-hour testing mark [80]. However, their overall conclusions indicated that the difference was too small to offer anything definitive. It is interesting to note that the reliability of their ion

generator was lacking, and this difference may have offset their ability to make definitive conclusions on the Ag^+ source at that time [81]. Comparative information on a silver salt such as silver sulfadiazine vs. anodally produced Ag^+ (electrolytically produced oligodynamic Ag^+) has been studied. Under a specific set of circumstances, Berger *et al.* [61] have shown that the minimal lethal dose for both Gram-positive and Gram-negative pathogens with oligodynamic Ag^+ is 10–100 times greater than silver sulfadiazine. More recently, Simonetti *et al.* [82] confirmed these findings.

Recall that the length of the ionic bond is due to the dissociation constant of the solvent governing the separation between the salt's cation and anion content. To paraphrase Goetz, as far as the purely chemical oligodynamic activation is concerned, it appears certain that only the solubility of the compound formed at the metal surface determines its activity [83]. For example, a silver surface activated by means of a sulfadiazine (SD) or nitrate (NO_3) anion will obtain an oligodynamic activity equivalent to an Ag concentration that corresponds to the *solubility* of the AgSD or $AgNO_3$ in a given solvent (e.g. water, plasma or serum). In general, silver salts have difficulty achieving biologically meaningful concentrations of Ag^+. For example, a list of over 16 silver salt speciations revealed that with the exception of silver nitrate ($AgNO_3$), none could exceed $1.82\,mg\,l^{-1}$ Ag^+ concentrations (the specific solubility product of these salts)! [83]. On the other hand, Goetz remarked that Ag^+ concentrations could be produced vastly exceeding any known silver compound if made by electrolytic technology [83].

As early as 1929, Voigt [84] proved that Ag^+ could be concentrated into electrolytic suspensions (called silver hydrosols) as opposed to exclusively neutral Ag. Crocker and Grier [85] have confirmed this work, which suggested that silver cations could be stabilized without a counterpart anion. This is a sensational finding because nanometer scale (nanoscalar) metal solutions that have undergone partial oxidation are a speciation of enhanced catalysts for free radical processes [86]. As virologists and immunologists are well aware, WBCs defeat viruses by their ability to act as catalysts to free radical processes [39]. With today's technology, one high-end commercially available *picoscalar* colloidal silver hydrosol product actually achieves levels of Ag^+ that exceed $21\,mg\,l^{-1}$, the highest ever documented [87].

Therapeutic Index

As Goetz [42] stated so plainly,

> In view of practical applications it appears that silver is best suited as an oligodynamic material because of the extremely slight solubility of most of its salts, which fact renders it almost impossible for large concentrations of silver ions to occur in higher organisms. This particular property singles out silver from the host of other oligodynamic metals which may have the same activity, and renders it practically harmless to animals and humans.

Due to modern technology, a high concentration picoscalar oligodynamic Ag^+ hydrosol becomes possible, and due to the absence of anions, results in a formulation as gentle as water.

HIGH-TECH MEETS SARS

Some generalizations can be made regarding the recent outbreak of SARS. If a mutant human coronavirus is found to be the etiological agent as suspected, this apparent ssRNA, positive polarity, enveloped, coronaviridae pleomorphic virion, is comprised of a 'layered envelope–capsid complex' predominantly composed of proteins and glycoproteins

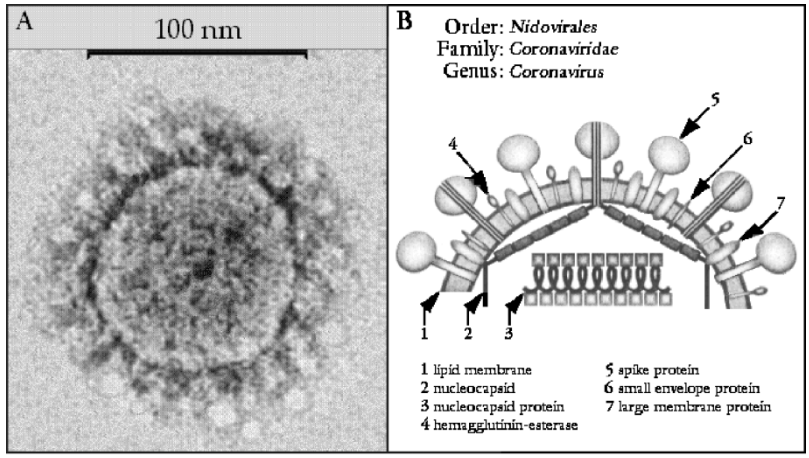

FIG. 1. Coronavirus. (A) A cryoelectron microscopic photograph. (B) A schematic diagram of the virus and virion surface structure.

(peplomer protein E1, peplomer protein E2 JHM, gpE1, etc...), and a long flexible coiled helix [88] (Fig. 1).

If indeed the SARS strain of human coronavirus is enveloped with a minimal fatty wrapper or without a fatty wrapper, which is likely, then oligodynamic Ag^+ should readily denature: (1) its envelope, (2) its capsid, (3) its protein constituents, and (4) its entire genome, as suggested by the work of Feng *et al.* [40]. Zhang *et al.* [89] have shown that Ag^+ is a first-order inhibitor of both rennin and protease in HIV.

Also, it is a member of the largest genome of RNA virions, an envelope averaging 80–160 nm in diameter, thus making it a large target for oligodynamic Ag^+ adsorption when presented in picoscalar colloidal form. In the case of SARS, a picoscalar (8 Å) oligodynamic Ag^+ formula is capable of impregnating up to 30,000 particles into the outer envelope of a single coronavirus 100 nm in diameter. Metal chelators have been shown to form metal-linked dimers. As dimerization could be important for viral replication, Ag^+ may offer an important intervention at this juncture in the virus's lifecycle [69].

Thus, oligodynamic Ag^+ may be highly effective against this new mutant strain of human coronavirus, especially if delivered in small frequent amounts during the early stages of SARS in a nebulized form. SARS probably has the following multiple protein-related targets vulnerable to the denaturing action of oligodynamic Ag^+ with none of the known mechanisms of viral resistance to oligodynamic Ag^+: protein gene, nucleocapsid protein, integral membrane matrix protein, club-shaped peplomer, hemagglutinin/esterase, RNA-dependent RNA polymerase, and protein kinase.

In the earlier historical section on the antiviral actions of oligodynamic Ag^+ formulations, a list was provided of specific viruses and viral groups. This list represents a significant number of subgroup virions vulnerable to oligodynamic Ag^+ under the same classification pertaining to the coronavirus associated with SARS, namely the ssRNA group, which are characterized as being negatively or positively polarized, and possess an outer protective envelope.

OVERCOMING POTENTIAL VIRAL RESISTANCE TO OLIGODYNAMIC AG^+

One interesting side note pertaining to virology is that when virus species are enveloped with thick fatty wrappers (i.e. vaccinia virus and influenza A), a partial resistance to Ag^+

has been observed [90]. Therefore, silver speciation is of utmost importance in counteracting this type of virus. To obtain success, practitioners should consider using: (1) a much higher level (concentration) dose than otherwise required; (2) direct delivery methodologies, including nebulizers; and (3) techniques that enhance the permeability of the capsid to Ag^+, such as therapeutic hyperthermia, localized diathermy, and/or local, regional or systemic electroporation [91, 92].

As previously stated, in the case of SARS, a picoscalar (8 Å) oligodynamic Ag^+ formula is capable of impregnating up to 30,000 particles into the outer envelope of a single coronavirus 100 nm in diameter. However, in general, coronaviruses possess no such fatty wrapper. Pore sizes associated with viruses containing fatty wrapper envelopes are apparently more restrictive. Therefore, such 8 Å oligodynamic Ag^+ aggregates are several orders of magnitude superior as candidates to readily diffuse in sufficient quantities to denature the constituent proteins, enzymes and nucleic acids. A lack of Ångstrom particle size has been perhaps the major roadblock to additional interest in investigating silver drugs against HIV and hepatitis.

Also, in addition to therapeutic electroporation or hyperthermia, attacking and weakening the fatty wrapper directly with lipid oxidation techniques may be of use. Hyperbaric oxygen (HBO) chambers may not only accomplish this [93, 94], but the author postulates that HBO may also re-engage inactive silver into active Ag^+ [39, 95]. Furthermore, even though the coronavirus is not associated with a thick fatty wrapper engulfing its capsid, HBO may still be of great value in SARS protein-based envelope and in relieving the respiratory distress of SARS [96–99], a time-buying life-saving measure that may potentiate the therapeutic window for oligodynamic Ag^+ treatment to gain the upper hand.

CONCLUSIONS

Several promising delivery methods associated with at least one formulation of electrolytically produced picoscalar oligodynamic Ag^+ in pure hydrosol form is generating considerable excitement as a highly strategic and tactical antimicrobial agent. It is an exceptional discovery that a single product, oligodynamic Ag^+, possesses 'multifunctional' viral interventions making it a promising broad-spectrum antiviral agent.

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