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Commentary

'Colloidal Silver': Recommendations to Remove This Misleading Term for Describing Nanoparticulate Silver Antimicrobial Agents

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ABSTRACT

We endeavour to resolve some of the confusion surrounding the (mis) use of the term 'colloidal silver', particularly in a pharmaceutical context. It is proposed that, wherever possible, the term 'colloidal silver' be replaced by a clearer descriptor indicating a silver formulation's composition and function, particularly when used either to help treat infections and/or to stimulate healing (as in restorative medicine).

For discussion, we propose adopting some less ambiguous terms to describe metallic silver formulations; this new terminology being more related to their physical properties and their end use, e.g. bioactive silver dispersion, nano (sized)silver clusters (NSC), reactive atomic clusters, 'quantum meta-silver', etc. Methods for characterising medicinal silver products are also considered – these being needed to adequately certify the chemical composition and physical properties of novel pharmaco-active silver formulations – before submitting them for clinical evaluation.

Key words: *Materia medica*, Silver antimicrobials, Nano silver clusters (NSC), 'quantum silver', 'meta-silver'.

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INTRODUCTION

For at least 80 years, the small part of the scientific community involved in the production and testing of so-called colloidal silver, did not want to know about differences in accessible silver antiseptics. As a consequence, few attempts were made to question the identity of other nano-silver products - irrespective of what they might be, how they were produced and indeed what to call them. Instead of evolving a rational and scientific approach to characterising 'colloidal silver', the ensuing confusion and lack of understanding has kept medicinal silver and its many attributes undeservedly in limbo[1,2]

Clearer understanding of any *materia medica* requires clear description of its origins and its biomedicinal properties: this is classic pharmacognosy. It necessitates not only defining, as unambiguously as possible, what the drug preparation may be, but also indicating what it is not. This is communication (as in the title of this Journal.) Ideally this is summarised by describing not only the source and chemical composition of any *materia medica,* but also by indicating the therapeutic ratio of the effective dose (ED) to the toxic (TD) doses, and therefore its likely suitability for medicinal use.

It is also important to understand that insoluble atomic silver clusters, used as nano- pharmaceuticals might be metastable. Depending on their purity, size and electrical charge in a given medium, these atomic silver clusters may be metastable *ex vivo*, undergoing surface oxidation. When present *in vivo* or applied externally (e.g. to wounds), these clusters may be continually subject to dynamic redox transformation(s) (Figure 1) involving change of valency, electric charge, chemical reactivity and bio efficacy.

This occurs when an outer valency electron (e) is i) removed by oxidants (stage 1) or ii) acquired by (bio) chemical reduction or from exogenous physical sources, e.g. gamma rays or photonic energy absorption <420 nm (stage 2).[1,3,4] [This latter reductive transformation is the basis of the photographic process, within which dispersed ionic silver halides being reduced to black metallic silver after exposure to light.]

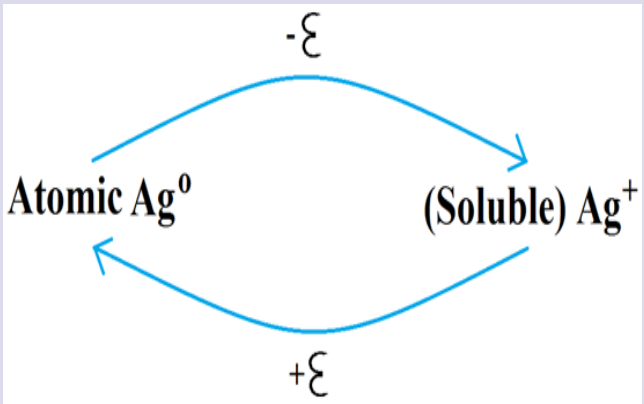

Figure 1: Oxidation of zerovalent atomic silver (Ag^{o}) and reduction of monovalent silver ions (Ag^{+}), with loss or gain of an electron (ε).

Characterising silver medicinals

Questions that must be asked about any silver medicinals being considered as agents with antimicrobial actions, immunoregulatory properties, or agents to promote healing:

1. Exactly what is the constitution of a pharmaco-active formulation whether prepared a) physically from solid silver electro photochemically, by irradiation or by ablation or b) chemically from silver salts using reductants and antioxidants, including those present in plant extracts (so-called 'green medicine').
2. How stable is it *ex vivo?*
3. How effective is it *in vivo* or when applied topically?
4. What is its likely mechanism of action e.g. catalytic, local energy transducer, slow-release molecular poison, selective toxin (such as used for disrupting bacterial biofilms)?

5. How safe is it for different clinical applications: for example as a pro-drug; for intermittent use or for continual/chronic use; or as an (occasional) adjunct to other therapies etc?

Here we are concerned with trying to answer the first two questions. Thus, we need to consider first the reproducible production of bio-active silver formulations, and then their stability and resulting influence on their pharmaceutic properties.[5] Careful attention to these matters will then determine the likely pharmacological value of the product to provide some answers to questions 3, 4 and 5.

The enigma of pharmaco-active nano-sized silver clusters ('nano-silver')

Some, perhaps many, of the pharmacological attributes of nano-silver depend on its 'apartness'/differences from other antimicrobial preparations. Bioactive nano-silver clusters (particles) will obey the laws of classical physics, especially when the atomic clusters exceed 10 nm in diameter, e.g. their propensity for sedimentation. However below this size they have other properties, some of which may determine their exceptional promise for future therapeutics. These include the (quantum) confinement of its outer valency electrons and the very large ratio of reactive surface to cluster/particle mass. Such attributes belong more in the realm of 'Quantum Science', rather than Classical Physics.

For successful pharmaceutics, it may be important to conserve this quantal character, particularly by minimising transformation of very small atomic clusters to less reactive, larger particles – with their much diminished surface area, relative to mass.

Considering some objectives of Nano-silver cluster (NSC) therapies

Ultimately, this has to be brought into any discussion of how best to describe a particular silver-based antimicrobial agent. Traditional antibiotics are conveniently classified by their prime mode of action, e.g. how they inhibit the synthesis of bacterial cell walls (penicillins), nucleic acids (quinolones) or proteins (tetracyclines). But a silver antimicrobial agent may be multifunctional and exert its actions through multiple pathways. This is why its particular value in any pathophysiological context should be clearly indicated/ 'flagged' in its name, preferably by using an agreed nomenclature.

Historically, silver therapies have been poorly defined. This 'one-size fits all' approach is problematic because older particulate (colloidal) silver preparations were typically a variable mixture of free silver ions, (reactive?) counter ions(e.g. nitrate), and silver clusters of varying size/reactivities, together with various impurities. [They were in fact a pharmaceutical 'stew'.]

Silver-based antimicrobials may employ a range of different strategies, according to the nature and habitat of the targeted pathogen and the characteristics of its life cycle. These antimicrobials may have to be fabricated to optimise particular properties such as:

- bonding to external functional parts of bacteria essential for their motion (flagellae), adhesion (fimbriae), or sexual conjugation (pili);
- bonding to acidic cell wall components such as the teichoic acids of gram-positive bacteria;
- adhesion to hydrophobic lipid-rich cell walls of gram-negative bacteria;
- interacting with sub-mural bacterial DNA;
- ingestion by phagocytic parasites such as protozoa;
- disrupting bacterial assemblage within protective biofilms (an extremely important target that eludes many systemic antibiotics); and
- Other cytostatic or cytotoxic mechanisms.

This means that a product when specifically designed/engineered to achieve any of the above functions may not be as useful in another context.

Paradoxically, the most efficient antimicrobial strategies may sometimes be the slowest acting, for example cluster ingestion by micro-organisms leading to endocellular oxidation, which releases toxic silver ions, as a Trojan horse strategy.

The range of potential anti-microbial actions of silver products is considerably broader than that of most patented antibiotics.

What a particular silver preparation does best as an antimicrobial agent can only be understood by first knowing how it is reproducibly derived, characterised and then appropriately named. Ideally its end-use should also be designated, e.g. antibacterial, antifungal, anti-protozoal, for ingestion or restricted to topical applications.

A particular challenge will be describing yet newer antibacterial formulations; for example, those containing nanometer-sized atomic clusters presented by quantum-confined water within carbon nanotubes. These new drug delivery systems have now entered the realm of preventive medicine.[6] Quantities of silver as low as 30 μg/ml are providing antibacterial activities with minimal cytotoxicity to the host's cells ie optimal biocompatibility.

Therefore we should urgently clarify, or even amplify, the nomenclature of silver antimicrobial agents. This is long overdue, and will guide more incisive thinking and further experimentation.

OTHER COMMENTS

1. If inorganic silver preparations were considered seriously as pharmaceutical adjuncts for controlling microbial pathogens, then quality controls for defining their composition and efficacy would already be in place. Within the pharmaceutical industry, there is a lack of knowledge of the pharmacology of silver products.
2. Another problem is a lack of understanding by governmental regulators of these products, their physical and chemical properties, and possible applications. Currently their attitude seems to be to be to pass these by, on purported safety grounds. Meanwhile they actively discourage (even penalise) any claims for silver-based products having any medicinal activity (as is presently the case in the USA and Australia.) This is a severe impediment to obtaining financial support for independent critical experimentation, particularly that in the area of product optimization which must precede clinical studies.
3. Resolving these problems and other negative aspects outlined in this article may hasten further evaluation of the potential uses of silver-based products in medicine. This is particularly timely in the context of the tremendous challenge presented by ever-increasing antibiotic resistance.[7]
4. If the problems of "super bugs" demand that we need "super drugs", then why not consider silver-based products in this context? The answer to this may lie in the history of these, with poorly described or controlled processes of manufacture, a lack of standards for quality, insufficient efforts towards proper characterisation, and an inadequate and imprecise nomenclature. Improving the latter seems a good place to start, especially if it helps rid the scientific community of sloppy thinking, wild scientific claims and dubious salesmanship.

EDITOR'S COMMENT

The authors admit they may have failed to offer an instantly recognisable alternative to the imprecise term 'colloidal silver' which they sug-

gest should now be discarded. It is hoped that this article will open a conversation that might lead to a new consensus, particularly about what (brief) forms of nomenclature for bio-active nanosilver clusters would a) be more appropriate and b) provide a clearer description of these novel (and also ancient) pharmaca. Responses from readers would be very welcome. [Please address these to the Editor].

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None

CONFLICT OF INTEREST

None

ABBREVIATIONS USED

ICMS : inductively coupled mass spectrometry; AA: atomic absorption (subject to 'field effects'); TEM: transmission electronic microscopy of dried particles (? →artefacts after dehydration); FTIR: fourier transform infrared spectroscopy.

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TABLE: Characterising Medicinal Nano particulate Silver Cluster (NSC) Preparations by Physical or Chemical Procedures.

Appropriate descriptors for these must identify their chemical composition, particularly the content of atomic silver clusters (particles); soluble or insoluble ionic silver (Ag+) and any additives or impurities. Physical properties should also be delineated, namely the size, shape, polarity and other physical characteristics of the atomic clusters.[8]

• **Methods should be used that determine:**
• The concentration and/or total silver, e.g. by ICMS.
• The content of ionic silver (Ag+), e.g. by precipitation with thiocyanate or phosphate anions
• The content of soluble silver, after removing silver particles by centrifugation or filtration through selected absorbents.
• The content of anions, using precipitation with La+++ or other polybasic cations.
• The content of residual silver remaining after removing soluble silver ions with natural or synthetic anionic polymers such as Na zeolites, or Dowex ion exchange resins.
• **Methods used that may be less specific*, depending on the presence of impurities.**
• Ion electrode measurements for soluble Ag by determining the p[Ag+], cf. pH; but constrained by their low sensitivity.
• Colorimetrically, using fairly specific silver ligands e.g. sodium diethyldithiocarbamate (Ditiocarb).
• Concentration of total silver by AA.
• (Intrinsic) colour density with a spectrophotometer, scanning over the wavelength range from 200-800 nm.
• Cluster size and shape by TEM (often generating dehydration artefacts).
• Zeta potential (in mV), as a measure of the negative charge on a silver cluster repelling other small clusters, thereby minimising their aggregation.
• Particle-induced fluorescence e.g. with methyl orange indicator.
• Light scattering over a range of wavelengths e.g. using red, green, blue lasers.
• X-ray diffraction.
• **The following methods are unspecific for general use, since they are affected by soluble impurities or by the presence of non-silver particles.**
• Conductivity (ohm)/electrical resistance (mho)
• Refractive index.
• Voltammetry for measuring Ag+, especially with an Hg-dropping electrode (that may be 'poisoned' by impurities in Ag preparations).
• **Methods that must be used to detect/quantify likely contaminants such as:**
• unsuitable water supplies, such as those containing chloride ions,
• impurities in the source of silver metal e.g. arsenic, cadmium, or lead
• by-products remaining after using chemical reductants to prepare an NSC product,
• Sorption from the atmosphere, including carbon monoxide (CO),carbon dioxide (CO2),volatile sulphides (e.g.H2S), ammonia, etc.
• Anions of silver salts e.g. nitrate and its (possible) reduction products such as nitrite and NO.
• Extraneous organic components such as added stabilisers or residual impurities from manufacture, detected by FTIR spectroscopy.
(End of Table)

*Appropriate in some contexts, not others – due to interfering factors eg quenching of EM radiation at higher NSC concentrations.

APPENDIX: Understanding some definitions[9]

Colloidal: A historic term to describe a stable mixture of one finely divided material in another medium, such as (1) fog = water suspended in air; (2) smoke = small particles suspended in air; (3) gel = solids forming a stable dispersion in a liquid,such as cream, glue, or paint.

- **Dispersion:** a system in which finely divided droplets, particles or bubbles are distributed in another phase,
- **Suspension:** a system containing solid particles dispersed in a liquid.
- **Meta (material):** based on the Greek work meaning 'beyond'
- **Meta (-) silver:** a term suggested for describing nano size clusters of zero valent metal (Ag°) (0.6–10nm) with some unique properties beyond those of larger silver particles. [This is certainly true for silver, and possibly also for other metallic clusters such as those of gold.] A loose definition would be 'reactive' atomic silver, i.e. 'not normal' silver, that exhibits some of the properties of larger silver particles or even solid silver, but also possesses other distinctive, size-related properties that may contribute to its medicinal potential.
- **Nano silver clusters (NSC) is an abbreviation for the fuller description:** nanometre-sized atomic silver clusters in a stable (aqueous) suspension. [Individual clusters are kept isolated from each other by electro-repulsive forces including the Zeta potential. The larger the negative value of this potential, the greater the stability of the NSC suspension: below minus 25 mV, the Zeta potential may not be sufficient to prevent cluster aggregation, promoted by Van der Waals and other forces.]