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Oral toxicity of silver ions, silver nanoparticles and colloidal silver – A review

Niels Hadrup [a,*], Henrik R. Lam [b]

[a] Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark, Mørkhøj Bygade 19, DK 2860 Søborg, Denmark
[b] Environment and Toxicology, DHI, Agern Allé 5, DK 2970 Hørsholm, Denmark

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ABSTRACT

Orally administered silver has been described to be absorbed in a range of 0.4–18% in mammals with a human value of 18%. Based on findings in animals, silver seems to be distributed to all of the organs investigated, with the highest levels being observed in the intestine and stomach. In the skin, silver induces a blue–grey discoloration termed argyria. Excretion occurs via the bile and urine. The following dose-dependent animal toxicity findings have been reported: death, weight loss, hypoactivity, altered neurotransmitter levels, altered liver enzymes, altered blood values, enlarged hearts and immunological effects. Substantial evidence exists suggesting that the effects induced by particulate silver are mediated via silver ions that are released from the particle surface. With the current data regarding toxicity and average human dietary exposure, a Margin of Safety calculation indicates at least a factor of five before a level of concern to the general population is reached.

1. Physical formulations and human exposure

Silver (chemical symbol: Ag) has an atomic number of 47 and an atomic mass of 107.868 g/mole. Silver ions (Ag+) are dissociated from different salts and from particulate silver (Kittler et al., 2010; Liu et al., 2010; Locht et al., 2009; Loeschner et al., 2011; van der Zande et al., 2012). Nanoparticles have been defined by the European Union as particles with one or more dimensions on the order of 100 nm or less (EU, 2006). Silver nanoparticulate suspensions can be pure in theory, but in practice, are most likely to be mixtures consisting of silver ions, nanoparticles, sub-nano sized particles and aggregated nanoparticles that are either nano-size or greater (Bouwmeester et al., 2011; Locht et al., 2011; Loeschner et al., 2011; Miura and Shinohara, 2009; van der Zande et al., 2012). A term that can also refer to larger silver particles is colloidal silver. Colloidal particles can be defined as particles microscopically dispersed throughout another substance where the particle size in the dispersed phase is typically 2–500 nm (Levine, 2001).

Silver has not yet been identified as a trace metal, and thus, seems to be non-essential to human physiology (Lansdown, 2007). Therefore, exposure to silver is considered to be unwanted. Silver is bacteriostatic and is included in a range of products for which such an effect is desirable (Alexander, 2009; Holler et al., 2007), including wound dressings, refrigerators, bone cement and socks (Holler et al., 2007; Ohbo et al., 1996; Tamimi et al., 1998). Humans also come into contact with silver via brazing or soldering, coins, tableware, jewellery, anti-smoking remedies, dental fillings, dietary supplements and ingestion of marine organisms (Holler et al., 2007; Mirsattari et al., 2004; Ohbo et al., 1996; Tamimi et al., 1998). Daily human dietary silver intake has been investigated by several groups. In Italian population groups, Clemente et al. found values of less than 0.4 μg/day (Clemente et al., 1977), while Gibson et al. found values of 7 μg/day in Canadian women (Gibson and Scythes, 1984), and values of 27 μg/day were found in a population from the United Kingdom (Hamilton and Minski, 1973). However, accidental or self/parental-inflicted poisonings with ionic or colloidal silver also occur. Such poisonings are often manifested as argyria, a blue–grey discoloration of the skin that is caused by silver deposits (Chang et al., 2006; McIntyre et al., 2001; Ohbo et al., 1996).

2. Absorption distribution metabolism and excretion (ADME)

2.1. Absorption

Absorption following oral administration in humans and other mammals has been described qualitatively in numerous investigations (Chang et al., 2006; Mirsattari et al., 2004; Ohbo

* Corresponding author.
E-mail addresses: nilha@food.dtu.dk (N. Hadrup), hrl@dhigroup.com (H.R. Lam).

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et al., 1996). Only a few studies presenting quantitative data are available. Furchner et al. (1968) used the orally administered 110 radionuclide of silver (as silver nitrate) to investigate silver excretion in several species, and found the following faecal excretion values: 99.6% for mice, 98% for rats, 90% for dogs and 94% for monkeys. Although these values did not take into account the fact that silver could be absorbed and then excreted via the bile, these data indicate that absorption ranges from 0.4% to 10% depending on the species, with 10% and 6% for dogs and monkeys, respectively. East et al. (1980) investigated silver retention in a 47-year-old woman who already suffered from argyria. Using a radioactive tracer, silver retention was found to be 18% of an orally administered dose. When comparing ionic silver and nanoparticulate silver after oral administration, the latter was shown to be less bioavailable based on higher faecal excretion and lower absolute levels in organs following head to head investigations (Loeschner et al., 2011; van der Zande et al., 2012).

2.2. Distribution

Orally administered ionic and nanoparticulate silver have been described to be deposited in a wide range of organs. The most well described depositional effect is the blue–grey discoloration of the human skin that is observed during argyria (Chang et al., 2006; Ohbo et al., 1996). In addition to skin, silver has been detected in numerous organs following oral administration, including liver, kidneys, brain, skin, pelt, spleen, eyes, muscles, blood, small intestine, stomach, lungs, bladder, prostate, tongue, teeth, salivary glands, thyroid, parathyroid, heart, pancreas and duodenum (Goebel and Muller, 1973; Loeschner et al., 2011; Olcott, 1947, 1948a,b, 1950b; Olcott and Richter, 1958; Pereira, 1977; Rungby, 1986; Rungby and Danscher, 1983; van der Zande et al., 2012; Walker, 1971, 1972). In the kidneys, orally administered silver was found to be deposited in the glomerular basement membrane (Creasey and Moffat, 1973; Ham and Tange, 1972; Walker, 1972). In the brain, Rungby found that silver that was administered in the drinking water localised to glial cells and neurons in such brain regions as the hippocampus and pons. The fact that silver only localised to certain brain regions was explained by the authors to be the result of either local differences in the permeability of the blood–brain barrier or special turnover properties in certain neurons (Rungby and Danscher, 1983). These data suggest that silver does cross the blood–brain barrier to enter the brain extracellular fluid following oral administration. However, other lines of evidence point to silver not actually crossing the blood–brain barrier. Transmission electron microscopy data obtained by Van Breemen and Clemente suggest that orally administered silver does not cross the blood–brain barrier, but rather is deposited in its lining (Vanbreemen and Clemente, 1955). Goebel and Muller found silver in the brain of a 72 year old woman suffering from argyria. However, no silver was observed within the central nervous parenchyma (Goebel and Muller, 1973). Lee et al. (2012) observed the transfer of silver from mothers to offspring following an oral dose of 250 mg/kg of bw/day of 8 nm silver nanoparticles, suggesting that silver can cross the placental barrier.

The list of organs in which silver in its ionic or particulate form is deposited seems limited to the organs that have been studied, suggesting that silver (with the possible exception of the brain extracellular fluid) is deposited in all human tissues. However, a range of investigations have shown that some organs are more prone to silver deposition than others. Loeschner et al. (2011) investigated the oral administration of doses of 9 mg of ionic silver/kg of bw[1]/day (administered as silver acetate) for 28 days and found that the small intestine contained 35 μg of silver/g of tissue, while the concentrations in the stomach, liver and kidneys ranged from 3 to 10 μg/g of tissue, and those in the lungs, muscles, brain and plasma were less than 1 μg/g of tissue. The oral administration of 14 nm silver nanoparticles at an equivalent dose resulted in a similar pattern of distribution, although lower amounts were observed in the lungs, muscle, brain and plasma compared to ionic silver. Van der Zande et al. (2012) compared an oral dose of 9 mg of ionic silver/kg of bw/day (administered as silver nitrate) with an oral dose of 90 mg of nanoparticulate silver/kg of bw/day for 28 days (the nanoparticle sizes were 15 and 20 nm), and found similar results. When normalising to the administered dose, the authors found the majority of the silver in the stomach and small and large intestines, followed by (in descending order) the liver, spleen, testes, kidneys, brain, lungs, blood, bladder and heart. In the same study, less deposition was observed following silver nanoparticle administration than following ionic silver administration. However, the differences were pronounced for all organs. Pelkonen et al. (2003) found that following the administration of the 110 silver tracer at concentrations of 0.03 mg/L of silver ions in the drinking water for 1 or 2 weeks, the highest concentrations were found in the soleus muscle, followed (in descending order) by the cerebellum, spleen, duodenum, myocardial muscles, lungs, cerebrum, the gastrocnemius muscle, liver, kidneys, and blood.

2.3. Metabolism

Following oral exposure to both ionic and nanoparticulate silver suspensions, silver has been reported to be deposited as particles in tissues such as the skin epidermis, the glomeruli and the intestines (Chang et al., 2006; Creasey and Moffat, 1973; Ham and Tange, 1972; Loeschner et al., 2011; Matuk et al., 1981; Olcott, 1947). These particles have been described to be 12 nm in diameter in the rat intestines and to contain sulphur and selenium in addition to silver (Loeschner et al., 2011). In a human with argyria, the particles deposited in the kidney were described to contain selenium (Aaseth et al., 1981). Particle deposition was described to increase both in number and size in rat eyes during the first weeks of silver ion administration. Following continued exposure, only increases in size were described. However, the particles decreased in number and size when silver was withdrawn, although the particles were still present 12 months after the silver was withdrawn (Matuk et al., 1981). It has been suggested that the deposition of particulate silver following the oral administration of nanoparticulate solutions is not due to the whole particle's being deposited, but rather due to the ionic silver contained in the suspension or ionic silver that is released from the particle surface. The reason being the similar composition of the deposited particles regardless of whether ionic or nanoparticulate silver was administered (Loeschner et al., 2011; van der Zande et al., 2012).

2.4. Excretion

2.4.1. Faecal excretion

Furchner et al. (1968) (using the 110 radionuclide of silver in several animal species, as described previously) found the following faecal excretion rates: 99.6% for mice, 98% for rats, 90% for dogs, and 98% for monkeys. Scott and Hamilton showed that when the bile duct is ligated prior to the oral administration of radioactive silver, the excretion of absorbed silver diminished markedly leading to silver accumulation in the liver (Scott and Hamilton, 1950). In addition, Dijkstra et al. (1996) conducted a *non-oral* investigation that revealed that 50% of an infused dose of silver could be recovered in the rat bile. Faecal excretion following oral administration is described to be higher for 14 nm silver nanoparticles than for ionic silver; namely 63% and 49% for nanoparticles

[1] Throughout this review, bw is used as an abbreviation of "body weight" in the context "mg/kg of bw/day".