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### ► To cite this version:

Benedicte Lelievre, Anne-Charlotte Tellier, Gabriel Colonna, Benjamin Cohen, Yoann Cazaubon, et al. High silver concentrations in biological samples following different exposures: Two case reports. *Journal of Trace Elements in Medicine and Biology*, 2021, 67, pp.126775. 10.1016/j.jtemb.2021.126775 . hal-03230635

**HAL Id: hal-03230635**

**<https://univ-angers.hal.science/hal-03230635>**

Submitted on 24 May 2023

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## **High silver concentrations in biological samples following different exposures: two case reports**

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## **Abstract**

**Background:** Silver is used in various industrial applications, but also in confectioneries and for therapeutic use due to its antibiotic properties. Its toxicity is not well documented and most often only in the context of professional exposure.

**Aim:** Here we report two cases of high silver concentrations in biological samples in two women: the first patient presented grey marks around her cuticles, probably due to her consumption of silvered sweets and the second patient presented agranulocytosis and thrombocytopenia occurring within 24 hours after the topical application of a cream containing sulfadiazine and silver to burns over a large surface area.

**Methods:** Silver concentrations were determined in blood and urine samples and sweets using inductively coupled plasma- mass spectrometry (ICP-MS).

**Results:** The silver concentrations were elevated compared to population reference values and confirmed the hypotheses for the patients: the significant consumption of sweets coated with silver nanoparticles and the topical application of a cream containing silver to burns over a large area.

**Discussion-conclusion:** After initial questioning by the dermatologist, Patient 1 explained that she consumed more than 30 bags of the sweets per year. She decreased her consumption of the sweets and the control performed one year later showed a plasma silver concentration of 1.5 µg/L. For Patient 2, the absorption of silver through burns over a large area appeared relatively significant, whereas it is very low through undamaged skin. The haematological cells counts returned to normal levels quickly and no other major effects were highlighted. To apply these findings to a larger population, further investigation to determine sulfadiazine and silver concentrations in plasma and urine have been initiated in a cohort of patients with burns over a large area.

**Running title:** High silver concentrations following different exposures

**Keywords:** silver, burn skin, sweets, ICP-MS

## Introduction

Silver (Ag) is a metal used for industrial applications, but also in food preparation due to its antimicrobial properties such as its effects against *Staphylococcus aureus*. It is therefore present in the composition of some drugs for external use such as silver sulfadiazine. Human exposure to silver originates from two sources: professional exposure by inhalation of dust containing silver or via medical applications such as surgical sutures with silver thread, or topical healing cream. The absorption of silver depends on the speciation, the solubility in biological matrices and the grain size of the compound. The main route of exposure is pulmonary (90%), digestive and to a lesser extent, cutaneous. Silver binds to red blood cells and globulins. The blood half-life is 50 days. It is mainly stored in the liver and brain, as well as in the reticuloendothelial system. The elimination is mostly in faeces (half-lives of 1 and 5 days), with a small proportion in urine and sweat (<8%) [1].

The signs of toxicity fall under the heading of argyria. The main signs are argyria (dermatosis characterized by a grey or blue grey and progressive colouring of gums and skin), shortness of breath, heart palpitations, and oedema. The dose of silver necessary and the delay for occurrence of argyria depends upon the individual. Nevertheless, an estimation is that signs of argyria appear for doses of silver higher than 4-5 g [2]. The population reference values are: less than 0.8 µg/L (95<sup>th</sup> percentile) for plasma [3] and less than 0.029 µg/L for urine [4]. Here we present two cases in females. Because of the occurrence of clinical signs, determination of silver concentrations in plasma and urine were requested. For the first case, a supplementary analysis was performed to confirm the source of this intoxication.

## Case history

### # Case 1

A 47-year-old woman saw her dermatologist as she presented grey marks around her cuticles. No other clinical signs were reported. [A further ophthalmological examination has revealed no corneal deposit.](#) As the suspected cause was silver intoxication, blood and urinary samples were sent for analysis. After discussion with the dermatologist the hypothesis of the main source of silver was silver-coated sweets. The sweets were also sent for analysis. They were grey in appearance due to the silver-coating. [During the initial visit,](#) the patient said she consumed 12 bags of sweets per year and she added that sometimes she consumed one bag during an evening.

## # Case 2

A 33-year-old woman was admitted to the Emergency Department for skin burns affecting a body surface area of 62%. To prevent infection due to *Staphylococcus aureus*, antimicrobial cream (silver sulfadiazine, Flammazine®) was applied once a day. But 24 hours after the treatment initiation, agranulocytosis (neutrophils concentration: 0.28 G/L) and thrombocytopenia (platelets concentration: 91.5 G/L) occurred. As an iatrogenic origin was suspected, blood and urinary samples were sent to determine silver concentration in plasma and urinary samples. No analysis was presently available. [No ophthalmological examination has been performed.](#)

## Material and Methods

The analysis was performed using ICP-MS (7800, Agilent, Les Ulis, France). The main instrumental parameters were as follows: plasma power of 1550 W, plasmagen flow (Ar): 15L/min, nickel sampler and skimmer, quartz Scott nebulization chamber, micromist meinhard nebulizer (flow rate: 1.05 ml/min), helium flow rate of 3.8 ml/min, analysis in three replicates. The silver calibration ( $^{107}\text{Ag}$ , first ionization energy: 7.58 eV) was performed in Milli Q water (Millipore Reference A+, Merck, Molsheim, France) and ranged from 0.5 to 20  $\mu\text{g/L}$ . The calibrates, controls or samples were 1/20 diluted using hydrochloric acid 2% (Merck, Darmstadt, Germany) solution containing the internal standard ( $^{103}\text{Rh}$ , first ionization energy: 7.46 eV) at concentration of 10  $\mu\text{g/L}$  before analysis. Internal quality controls used were Clincheck plasma and serum trace elements (Recipe, Munich, Germany) and QM-U-Q1815, QM-U-Q1823, QM-U-Q1906, QM-U-Q1924 (INSPQ, Sainte Foy, Quebec). The method was validated according to Cofrac organism's recommendations (ISO 15189 norm), using the parameters of accuracy, precision, linearity, and limit of quantitation. The intra-day and inter-day testing was evaluated as follows: three internal quality controls (1.91; 4.98 and 19.70  $\mu\text{g/L}$  for plasma and 1.48; 3.90 and 6.03  $\mu\text{g/L}$  for urine) were analysed four times per day over four days. The coefficient of variation (CV) should be less than 20%, 15%, and 10% for low, medium, and high levels, respectively. The linearity was evaluated by analysing the calibration performed three times; the correlation coefficient ( $r^2$ ) should be higher than 0.999. The plasma and urine low level internal quality controls were analysed ten times for the validation of the limit of quantitation; the CV should not exceed 20%. Thus, the intra- and

inter-day precisions (CV < 7 %), the linearity ( $r^2 > 0.999$ ) and the limit of quantitation (CV < 7%) were within an acceptance range of the above-mentioned bioanalytical method validation guidelines. The laboratory also subscribes to the external quality controls program QMEQAS (INSPQ, Sainte Foy, Quebec). The CVs of the plasma silver external quality controls were 8.8% (level 1 :  $\leq 2.5 \mu\text{g/L}$ ), 0.5% (level 2:  $2.5\text{-}10 \mu\text{g/L}$ ) and no control was included in the third level ( $> 10 \mu\text{g/L}$ ). The CVs of the urine silver external quality controls were 8.7% (level 1:  $\leq 2.5 \mu\text{g/L}$ ), 4.9% (level 2:  $2.5\text{-}5 \mu\text{g/L}$ ) and 3.3% (level 3:  $> 5 \mu\text{g/L}$ ). For the sweets, two were weighted in duplicate. The silver coating was recovered after addition of 500  $\mu\text{L}$  of hot Milli Q water ((Millipore Reference A+, Merck, Molsheim, France). Then they were mineralized using 250  $\mu\text{L}$  of nitric acid (Suprapur, Merck, Darmstadt, Germany), at 70°C for 1 hour. The samples were then analysed using the same method as previously described.

## Results

The silver concentrations in biological samples were high in comparison with population reference values of  $< 0.8 \mu\text{g/L}$  for plasma and  $< 0.029 \mu\text{g/L}$  for urine. The silver concentrations were of  $88.7 \mu\text{g/L}$  in plasma and less than  $0.5 \mu\text{g/L}$  in urine for Patient 1 and  $1403 \mu\text{g/L}$  in plasma and  $106.1 \mu\text{g/L}$  (or  $51.8 \mu\text{g/g}$  creatinine) for Patient 2, respectively. The silver concentration on the sweets was  $30.5 \mu\text{g/g}$  dry weight (CV: 0,2%).

## Discussion

Cases of silver toxicity occur rarely. For Patient 1, additional questioning by the dermatologist revealed a higher consumption of sweets (more than 30 bags per year) than her first declaration. The composition of the sweets contained the colorant E174, which corresponds to silver nanoparticles. The dermatologist invited her patient to decrease drastically her consumption of sweets and to come back to evaluate the evolution of the marks around her nails and of the silver concentration in biological samples. The control performed one year later showed a decrease of plasma silver concentration ( $1.5 \mu\text{g/L}$ ). Hanada *et al* reported the case of a 79-year-old male who had consumed sweets coated with silver particles over a period of 20 years [5]. The concentration of silver measurement was performed using proton-induced X-ray emission and was about 0.1 mg per particle. The minimal oral dose to induce general argyria was estimated about 25-60 g over 6 months.

E174 is used in sugar confectionery (coating sugar pearls, almonds or even chocolates) [6]. The use of silver as food additive has been evaluated by the SCF in 1975 [7], JECFA in 1977 [8] and 1978 [9]. JECFA concluded that “in view of the rare use of this metal and in the absence of the knowledge of the exact nature of silver used on or in foods, specifications were not prepared. The data available suggest that this substance might accumulate in certain tissues following long-term exposure. There were, however, insufficient data to evaluate this point fully, nor were any adequate long-term studies available. Thus, no evaluation could be made”. The scientific Committee on medicinal products and medical devices proposed to prohibit the use of silver E174 in medicinal products (2000). Based on the potential effects on consumer health and on the precautionary principle, the Bundesinstitut für Risicobewertung recommended avoiding the use of silver nanoparticles in foods until the availability of more data about their effect on health [10]. The French Agency for Food, Environmental and occupational health and safety (ANSES) reviewed toxicological studies related to silver nanoparticles [11]. Further clarifications about the causal link between observed effects and silver nanoparticles (effects of silver ions, of silver nanoparticles or additional effects of ions and nanoparticles) are needed. Based on an occasional consumption (10 times per year) and the use at low level (below 1%) as a coating compound in the confectioneries, silver (in E174) is still allowed. [Our case highlighted the potential toxicity of sweets containing E174 in case of excessive consumption in terms of quantity and duration.](#)

For Patient 2, the use of silver sulfadiazine is crucial to prevent bacterial infections in patients with important burns. The medical staff has decided to reduce the thickness of the layer of cream applied topically. The control of the complete blood count revealed the resolution of the agranulocytosis and the thrombocytopenia. This side effect of silver sulfadiazine is known but its occurrence is estimated to be uncommon [12]. Cases of transient leukopenia have been reported in patients treated with silver sulfadiazine [13]-[16]. According to published data, a decrease of neutrophil count is followed by a decrease in white blood cells which is major within 2 to 4 days of initiation of therapy. The concentration of leukocytes returned to a normal level within [a further] 2 to 3 days, regardless of whether silver sulfadiazine application was interrupted or not [17]. Eldad *et al* reported the case of a 20-year old male with burns to 35% of body surface area [18]. After four days of twice daily application of silver sulfadiazine 1%, he presented acute haemolytic anaemia (hemoglobinemia at 10.5 g/dl (versus 16.5 g/dl three days before), whole blood cell count at 4,800/mm<sup>3</sup> (versus 16,300/mm<sup>3</sup>

three days before) and platelet count at 140,000/mm<sup>3</sup> versus 297,000/mm<sup>3</sup> three days before)). After replacement of silver sulfadiazine by povidone iodide (Betadine®) and administration of 2 units of packed cells, the haemoglobin concentration increased.

Trop [et al](#) reported the case of a 17-year old male with burns to 30% of body surface area [19]. After one week of local treatment with Acticoat™ (a silver-coated wound dressing), he presented a hepatotoxicity and a greyish discoloration of the face. The silver concentrations were of 107 µg/L in plasma and 28 µg/L in urine. After the arrest of the use of Acticoat™, the [transaminases concentrations](#) returned to normal level and the coloration faded.

Fung [et al](#) reported three types of mechanism action explaining the toxicity of silver [20]. Silver ions inhibit enzymatic activities by binding to electron-donating groups resulting in protein denaturation and precipitation. Silver deposition on the subepithelial skin layer could induce the stimulation of melanocytes [and an increased activity of melanocyte tyrosinase](#) [2]. The consequence is the production of melanin and the skin pigmentation. This phenomenon is more pronounced on areas exposed to sunlight, as photoactivation induces the reduction of silver ions. Silver can also intercalate in DNA strands, which can be of interest in antifungal and antibacterial properties. Indeed, it could induce loss of protons through bacterial cell membrane, and dysfunction of oxidative phosphorylation.

As for acute toxicity, silver salts are more toxic than colloidal silver or protein-bound silver. Two databases (Poisindex and Toxinz) have been requested in order to review all recorded cases of silver intoxications [21-22]. The Poisindex database recorded five cases of intoxication orally, one case through inhalation, two cutaneously and one following use of eye drops ([table 1](#)) [21]. Three cases are documented with silver plasma concentrations ranging from 12 to 154.4 µg/L. The Toxinz database reported five cases via oral or gingival mucosa absorption ([table 2](#)) [22].

## Conclusion

The occurrence of argyria remains rare. The two cases illustrate two possible and uncommon routes of exposure. In the first case, an excessive consumption of sweets coated with silver nanoparticles (E174) has been traduced by grey marks to the cuticles. [It highlighted the potential toxicity of sweets containing E174 in case of excessive consumption](#)



in terms of quantity and duration. It also underlined the role of the dermatologist to detect argyrisms. The second case is more common: the loss of dermal integrity with burns over a large surface area favour the absorption of silver. The monitoring of silver concentration (plasma, urine) is seldom carried out for these patients. The possible contribution of sulfadiazine in the occurrence of agranulocytosis and thrombocytopenia cannot be excluded. To investigate this, a study has been initiated in a cohort of patients with burns over a large surface area.

### **Acknowledgements**

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### **Conflict of interest**

The authors declare they have no conflict of interest.

**Funding:** none

## **FIGURES AND TABLES LEGENDS**

Table 1. Poisindex database: cases of argyrisms

Table 2. Toxinz database: cases of argyrisms (chronic intoxication)

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Table 1.

Exposure route	Description of the cases	Reference
Oral route	14-year-old, overuse of mouthwash containing silver to treat a sore throat	[23]
	60-year-old with schizophrenia disorder. Ingestion of colloidal silver over more than 10 years and auto-injection of silver nitrate to prevent infection => argyria	[24]
	Adult, ingestion of a dose higher than 20 mg/day over 40 years => argyria, generalized epilepsy. High plasma silver concentration	[25]
	A 79-year-old male consumed sweets coated with silver particles over 15 years => argyria	[5]
	Schizophrenic adult, ingestion of 20 mg/day of silver over 40 years => epilepsy, (Ag)plasma: 12 µg/L. No epilepsy episode overcame after the arrest of silver consumption	[26]
Inhalation	Professional exposure: a 27-year-old male used silver aerosol and didn't wear protection mask => occurrence of a blue-grey coloration at his face after 4 months. Silver concentrations were of 154.4 µg/L in plasma	[27]

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and 243.2 µg/L in urine. Biopsy of skin revealed the presence of granules containing silver in epiderma

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Cutaneous 75-year old albino male who used silver in his work (jewelleryjewellery smithing) without protection Biopsy of skin revealed the presence of granules containing silver [28]

Use of silver nitrate (10% AgNO<sub>3</sub>), silver sulfadiazine (0,2% Ag, 1%, sulfadiazine micronized silver)

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Eyes Use of eye drops containing silver [26]

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Table 2.

Patient	Context
58-year-old female	oral ingestion of pills containing silver => general argyrisms Use of D-penicillamin but partial recovery
55-year-old female	oral ingestion of silver for the treatment of buccal mycosis since 9 years => hypoguesia, smell disorder, dizziness, skin damage
52-year-old adult	oral ingestion of a silver preparation over 18 years (supposed ingested dose estimated at 35 g)=> general argyrisms, associated with renal, hepatic impairments, metal deposition in blood vessels
46-year-old female	Local application thrice a day of a solution containing silver to treat gingival bleedings over 2.5 years => general argyrisms
33-year-old female	Local application of a solution containing silver to treat oral ulcers over 1 year => argyrisms

The table presents the cases of argyrisms (chronic intoxication) listed in Toxinz database [22]. No silver concentration in biological sample has been precised.