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REMOVAL OF INTERNALLY DEPOSITED GOLD BY 2,3-DIMERCAPTO-PROPANE SODIUM SULPHONATE (DIMAVAL)

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1 Orally administered 2,3-dimercaptopropane sodium sulphonate (DMPS, Dimaval) reduced the concentration of gold in rats treated with Auro-Detoxin and increased the urinary excretion of the metal.

2 In a long-term experiment, DMPS decreased significantly the concentration of gold in the kidneys and in the skin and increased it in plasma.

3 DMPS appears to be of interest as a possible antidote to gold, which could replace the more toxic 2,3-dimercaptopropanol (BAL).

Introduction

The beneficial effect of gold compounds in the treatment of rheumatoid arthritis is well documented (Empire Rheumatism Council, 1960; Eberl, 1974; Schattenkirchner, 1977). However, there is a relatively high rate of toxic side-effects, mainly disturbances of the haemapoietic system, dermatitis and nephrosis (Eberl, 1974; Schattenkirchner, 1977). In severe cases, 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) has been employed to counter the development of these toxic effects (Cohen, Goldman & Dubbs, 1947; Lockie, Norcross & George, 1947; Ragan & Boots, 1947; Meyer, 1963; Witzgall, 1967). More recently, D-penicillamine, which is better tolerated than BAL, has been tried (Bluhm, Sigler, Ensign & Sharp, 1962; Eyring & Engleman, 1963). However, under carefully controlled conditions, D-penicillamine has proved ineffective in removing gold from the body (Dvořák & Ehrig, 1970; Brown & Smith, 1977). In an attempt to replace BAL, the water-soluble and less toxic compound 2,3-dimercaptopropane sodium sulphonate (DMPS, Dimaval) was investigated.

Methods

Male rats of the Heiligenberg strain (weight 170 to 200 g) were injected intravenously with 2.0 mg Au/kg as Auro-Detoxin (Johann A. Wülfing, Neuss) in 0.5 ml distilled water. The Auro-Detoxin had been activated previously by neutron irradiation in the FR-2 reactor of the Kernforschungszentrum Karlsruhe, for 30 s in a flux of 8.0×10^{13} neutrons.$cm^{-2}.s^{-1}$. The activated Auro-Detoxin was dissolved for injection after 5 days' decay. Three types of experiment were carried out:

(1) Thirty minutes after the gold injection, the animals received DMPS (Dimaval, Heyl & Co., Berlin) orally at a dose of 0.15, 0.75 or 3.0 mmol/kg in 0.5 ml distilled water (immediate treatment). They were kept in metabolism cages (Nigrovic & Mohr, 1966) in which urine was absorbed by filter paper. Twenty-four hours after gold administration, the rats were exsanguinated under ether anaesthesia. The γ-radiation in blood, plasma, liver kidneys, spleen, muscle (M. Quadriceps), a femur and skin was measured in a counter (Packard Instruments, Model 5123) at the 410 keV-peak. The counting efficiency for ^{198}Au was 37%. The counts in faeces, paper strips, whole organs or pieces of organs were measured without further treatment in closed polyethylene vials and expressed as a percentage of the injected ^{198}Au-dose, determined by measuring aliquots of the injection solution.

(2) A second group of rats was injected in the same manner with the same radioactive Auro-Detoxin solution. The DMPS was administered 24 h after the gold injection (delayed treatment) and the animals were killed at 48 h.

(3) Male rats of the same strain weighing 100 to 130 g at the begining of the experiment received Auro-Detoxin (2.0 mg Au/kg in 0.5 ml distilled water) intraperitoneally daily for 10 days. From day 11 until day 20, DMPS was given orally at a dose of 0.75

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mmol.kg^{-1}.day^{-1} in 0.5 ml distilled water. The rats were killed on day 21 as described under (1). Gold in the organs was activated by neutron irradiation as described for Auro-Detoxin solutions. The gold content of the irradiated organs was determined after 5 days' decay as described. Eberl & Altmann (1969) have shown that this interval is necessary to eliminate interference due to activation of other elements.

Control animals received 0.9% w/v NaCl solution (saline) intraperitoneally and distilled water orally. Differences between means were considered as statistically significant when Student's t test yielded $P < 0.05$. The gold content of the red blood cells was calculated on the basis of a mean haematocrit of 44.6 ± 0.4% (n = 32).

Results

Table 1 shows the influence of DMPS on the distribution of gold under optimal conditions of chelation (i.e. a high dose of the chelating agent had been administered a short time after the metal (Catsch, 1964)). With increasing dose, DMPS-treatment decreased the gold concentration in all the organs examined except liver and spleen, which did not change. After treatment with the lowest dose of DMPS, the concentration of gold in the kidneys was significantly increased, but that in the other organs was not altered.

Administration of DMPS 24 h after the injection of Auro-Detoxin led to similar changes in the distribution of gold (Table 2). Concentrations were reduced in all organs except liver and spleen. Unlike immediate treatment, delayed treatment with the lowest DMPS-dose significantly decreased the gold concentration in the red blood cells, plasma, femur, muscle and skin.

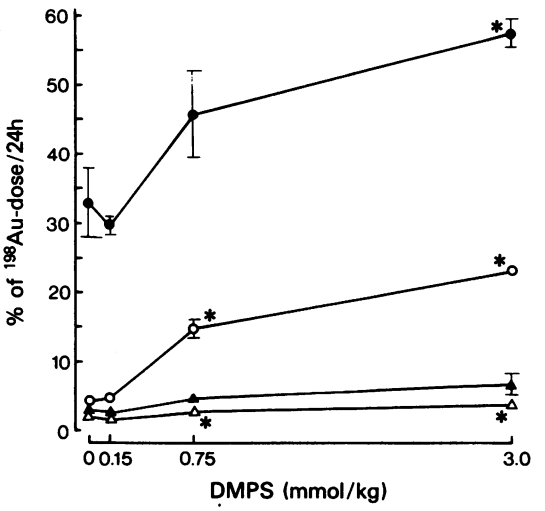

Figure 1 Urinary (circles) and faecal (triangles) excretion of gold 24 h after oral treatment with different doses of 2,3-dimercaptopropane sodium sulphonate (DMPS). In immediate treatment (solid symbols) DMPS was administered 30 min, and in delayed treatment (open symbols) 24 h after the injection of gold (2.0 mg Au/kg).

* Significantly different from the control value: $P < 0.05$.

However, the concentration in the kidneys was significantly higher than than the control value.

The excretion of gold in urine and faeces in the 24 h following immediate or delayed treatment with DMPS (Figure 1) reflected the influence of the chelating agent on the distribution of the metal in the organs, and was increased in a dose-related fashion

Table 1. Concentrations of ^{198}Au in organs as % of the injected dose/g or ml (fresh weight): oral treatment (immediate) with 2,3-dimercaptopropane sodium sulphonate (DMPS) 30 min after the injection of gold (2 mg Au/kg)

	DMPS-dose (mmol/kg)			
Organs	*0 (Control)*	*0.15*	*0.75*	*3.0*
Red blood cells	0.263 ± 0.045	0.294 ± 0.012	0.060 ± 0.010*	0.045 ± 0.004*
Plasma	0.636 ± 0.101	0.613 ± 0.018	0.115 ± 0.016*	0.049 ± 0.005*
Liver	0.341 ± 0.040	0.267 ± 0.007	0.322 ± 0.016	0.259 ± 0.033
Kidneys	13.06 ± 1.37	17.34 ± 0.57*	12.19 ± 0.35	4.77 ± 0.26*
Spleen	0.471 ± 0.056	0.373 ± 0.017	0.426 ± 0.028	0.529 ± 0.129
Femur	0.225 ± 0.024	0.217 ± 0.004	0.104 ± 0.004*	0.056 ± 0.004*
Muscles	0.093 ± 0.016	0.083 ± 0.003	0.019 ± 0.002*	0.012 ± 0.001*
Skin	0.322 ± 0.032	0.263 ± 0.014	0.178 ± 0.019*	0.112 ± 0.007*

Number of animals per dose: 5. Values are mean ± s.e. mean.
* Significantly different from the control value: $P < 0.05$.

except by the lowest dose of DMPS. The faecal excretion of gold was significantly increased only after delayed DMPS-treatment.

Long-term treatment with DMPS (Table 3) lowered the gold-content in the kidneys and in the skin whilst increasing it in plasma. The other organs did not show any changes.

Discussion

In agreement with earlier observations (Dvorak & Ehrig, 1970), the relative distribution of gold after repeated treatment and after a single injection was similar. Although the gold content in organs at the end of the long-term treatment is low in comparison with the administered quantity, clinical data indicate that in liver and some other tissues, gold may be retained over long periods (Parr & Taylor, 1963; Harvey, 1970).

Oral administration of DMPS mobilized gold from the tissues (Tables 1 and 2). The chelated gold was mainly excreted in the urine confirming that 30 to 40% of an oral dose of DMPS is absorbed from the gastro-intestinal tract (Gabard, 1978). The slight increases in faecal gold excretion after DMPS treatment probably result from excretion through the bile and/or the intestine of a fraction of the DMPS-gold complex. Biliary excretion of such complexes has been shown to occur for example with Pu and Ce after treatment with Ca-DTPA (calcium chelate of diethylenetriaminepenta-acetic acid; Ballou & Hess, 1972; Planas-Bohne, 1974; Guhl, 1976).

Long-term therapy with DMPS increased the plasma concentration of gold by 25% (Table 3). This is at variance with the results shown in Tables 1 and 2, where DMPS reduced the gold concentration in plasma by a larger factor than in other organs. Brown & Smith (1977) have shown with D-penicillamine that the oxidation state of the gold plays an important role

Table 2 Concentration of ^{198}Au in organs as % of the injected dose/g or ml (fresh weight): Oral treatment (delayed) with 2,3-dimercaptopropane sodium sulphonate (DMPS) 24 h after the injection of gold (2 mg Au/kg)

Organs	*DMPS-dose (mmol/kg)*			
	0 (Control)	*0.15*	*0.75*	*3.0*
Red blood cells	0.167 ± 0.020	0.113 ± 0.007*	0.112 ± 0.010*	0.067 ± 0.004*
Plasma	0.318 ± 0.036	0.187 ± 0.010*	0.150 ± 0.019*	0.039 ± 0.0009*
Liver	0.452 ± 0.027	0.399 ± 0.025	0.422 ± 0.037	0.401 ± 0.037
Kidneys	10.88 ± 0.48	12.71 ± 0.35*	8.45 ± 0.148*	7.09 ± 0.36*
Spleen	0.698 ± 0.108	0.758 ± 0.185	0.608 ± 0.070	0.573 ± 0.111
Femur	0.218 ± 0.014	0.173 ± 0.008*	0.170 ± 0.015*	0.112 ± 0.0006*
Muscles	0.070 ± 0.006	0.048 ± 0.003*	0.050 ± 0.007*	0.022 ± 0.0006*
Skin	0.248 ± 0.020	0.191 ± 0.012*	0.168 ± 0.021*	0.089 ± 0.002*

Number of animals per dose: 5. Values are mean ± s.e. mean.
* Significantly different from the control value: $P < 0.05$.

Table 3 Concentrations of ^{198}Au in organs in μg/g or ml (fresh weight): 2 mg Au/kg was injected daily for 10 days. 2,3-Dimercaptopropane sodium sulphonate (DMPS, 0.75 mmol/kg) was given orally daily from day 11 until day 20

Organs	*Controls* (n = *12*)	*DMPS-treated* (n = *10*)
Red blood cells	0.364 ± 0.012	0.394 ± 0.022
Plasma	0.678 ± 0.029	0.858 ± 0.020*
Liver	4.99 ± 0.48	4.29 ± 0.32
Kidneys	146.16 ± 14.56	95.86 ± 7.96*
Spleen	7.76 ± 0.92	7.94 ± 0.80
Femur	4.87 ± 0.31	4.44 ± 0.24
Muscles	1.48 ± 0.24	1.28 ± 0.14
Skin	4.55 ± 0.44	3.30 ± 0.31*

Rats were killed on day 21.
Values are given ± s.e. mean. *n* = number of animals.
* Significantly different from the control value: $P < 0.05$.

in the formation or decomposition of the gold-penicillamine chelate. If the ratio of the chelating agent to the metal is low, the D-penicillamine-gold(III) complex decomposes, going through an unstable gold(I) complex. *In vivo*, the result is that some metal may be removed a gold(III)-penicillamine, but mostly a redistribution within the body occurs, in spite of a high association constant of this complex ($\log K_1.K_2 = 24.8$, Eyring & Engleman, 1963). Although the corresponding constants for DMPS-gold complexes are not known, the increased plasma concentration may result from such a redistribution at low DMPS levels, whilst higher levels mobilize gold. This possiblity is supported by the results in Tables 1 and 2: after low DMPS doses, the concentration of gold in the kidneys was increased.

Plasma levels of gold often do not correlate with clinical responses (Schattenkirchner & Grobenski, 1976; Kamel, Brown, Ottaway, Smith, Cottney & Lewis, 1978). The observed reduction by 30% of the gold concentration in kidneys and skin, two organs particularly subject to toxic reactions in cases of increased sensitivity to chrysotherapy (Eberl, 1974) may be of greater importance.

In conclusion, the water-soluble DMPS is a potential antidote for gold poisoning. Its administration, particularly by mouth, is convenient and its toxicity low: The acute LD_{50} in the rat is 5.02 mmol/kg i.p., which is about 10 times the LD_{50} of BAL (Planas-Bohne, Gabard & Schäffer, 1979).

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