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Subchronic Treatment with Sodium 2,3-Dimercaptopropane-1-sulfonate in Methylmercury Poisoning

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In the past methylmercury has been involved in mass poisonings in humans. In order to develop therapeutic measures in several studies the effects of chelating agents on the excretion of methylmercury (MAGOS & CLARKSON 1978, AASETH & FRIEDHEIM 1978) has been examined. In most cases treatment lasted only for short times of 1 or 2 weeks. This holds true also for DMPS (GABARD 1976a, b) although the toxicity of this water soluble derivative of the well known 2,3-dimercaptopropane-1-ol (BAL) was reported to be very low (PLANAS-BOHNE 1977). Because of the rather long biological half-life of methylmercury (65 days in humans, BAKIR et al. 1973) it was decided to study the effect of subchronic DMPS treatment for 4 weeks upon the decorporation of ^{203}Hg-methylmercury with urine and feces as well as its organ distribution.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats of about 270 g body weight (Versuchstierzucht WIGA, Sulzfeld, FRG) were housed in metabolism cages in an animal room (temperature 21°C, humidity 55%, 12 hours light/day). The rats had free access to food and drinking water. A finely ground diet (Altromin 1321, Altrogge, Lage, FRG) was used throughout the experiment.

Chemicals. CH_3-^{203}HgCl with a spec.act.of 0.71 mCi/mg (NEN, Dreieich, FRG) was dissolved in aqueous sodium carbonate (2.938%) together with 24 times the amount of CH_3HgCl (Merck, Darmstadt,FRG) to give a final concentration of 0.5 mg/ml (12.2 µCi/ml). Sodium 2,3-dimercaptopropane-1-sulfonate (DMPS), a gift from Heyl&Co. (Berlin,FRG) was added to the diet at 1 g/kg. All other chemicals were of analytical grade and commercially available.

Experimental design. The rats were randomized into two groups of 7 animals each. After adaption to the metabolism cages for one week the rats were injected i.p. with 0.2 ml/100 g b.w. (1 mg/kg) of the CH_3-^{203}HgCl containing solution. Subsequently whole body radioactivity was measured and taken as 100% value of body burden. On the following day one group received the DMPS fortified diet, the other group served as control. Body weights and food consumption were measured daily as well as radioactivity in whole bodies, urine and feces. After 28 days the animals were killed by bleeding from the aorta abdominalis. 14 different tissues were removed for determination of radioactivity.

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Analytical procedure. Radioactivity in urine, feces and whole body as well as in tissues was measured in a whole body counter for small animals (Gammaspectrometer type Armac, Packard, Frankfurt, FRG). Decay of radioactivity was corrected by aid of a 250 ml glass bottle approximating the size of a rat and containing a known amount of ^{203}Hg.

Data evaluation. The excretion of ^{203}Hg during the 24 h sampling periods with urine and feces are expressed as percent of the 100% value measured immediatly after i.p. administration. Radioactivity in tissues was calculated as mg CH_3-$^{203}HgCl$/kg tissue (wet weight) and given as mean±SEM. Differences between the group means were assessed by Student's t-test. For the calculation of elimination half lives mono- or biexponential equations were fitted to the data as described previously (RICHTER et al. 1982).

RESULTS

Body weight increased continuously throughout the experimental period in all animals from 270±6 g up to 351±11 g. The experimental diet did not influence body weight gain and food consumption.

Figure 1 illustrates the influence of DMPS on the body mercury administered as CH_3-$^{203}HgCl$ on the basis of an one compartment model. During 28 days the control rats eliminated 48.2±10.9 percent of the dose administered, DMPS treated rats 82.4±18.2%. Although the elimination data correlated highly to the one compartment model leading to half lives of 28.8 days (r=0.9994) in controls and 10.8 days (r=0.9973) in DMPS-treated rats an uneven distribution of the data points around the regression line can be observed. Therefore the data were fitted also to a two compartment model (Table 1) giving a very high correlation. The main effects of DMPS are the shortening of the half lives of the second compartment by a factor of 2.4 and the increase of constant A giving the first compartment a greater importance.

TABLE 1. Elimination constants and half lives of CH_3-$^{203}HgCl$ elimination from rats (N=7).[a]

Treatment group	A	B	k_1	k_2	$\frac{\ln 2}{k_1}$	$\frac{\ln 2}{k_2}$	SS[b]
Control	6.88	97.69	0.237	0.023	2.95	30.4	0.86
DMPS	35.29	81.48	0.249	0.056	2.82	12.5	18.4

[a]A biexponential equation of the type $C = A\, e^{-k_1} + B\, e^{-k_2}$ was fitted to the experimental data excluding day 1 (27 data points). C represents the amount of CH_3-$^{203}HgCl$ in the body at day t in percent of the dose administered. A,B(%) and k_1,k_2(day^{-1}) are elimination constants. $\ln 2/k_1$ and $\ln 2/k_2$ (days) represent the half lives of the first and second compartment.
[b]SS = sum of squares.

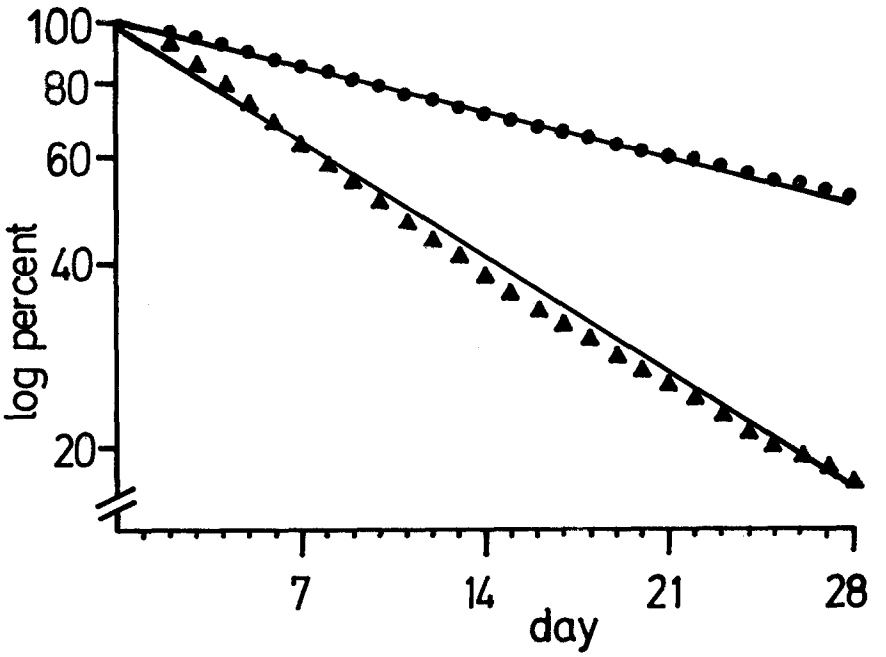


FIGURE 1. The effect of 0.1% DMPS in the diet upon the elimination of CH_3-$^{203}HgCl$ from rat body. Values represent ^{203}Hg derived radioactivity in the rat body in percent of the amount administered (mean of 7 rats). ● , Control; ▲ , DMPS.

TABLE 2. Concentration of CH_3-$^{203}HgCl$ in tissues of rats.[a]

Tissue	Control	DMPS[b]
Kidneys	4565 ± 872	739 ± 165
Blood	1880 ± 373	413 ± 59
Skin	1084 ± 431	774 ± 293
Liver	677 ± 132	217 ± 105
Spleen	546 ± 89	81 ± 41
Lung	406 ± 147	115 ± 52
Muscle	319 ± 73	98 ± 44
Jejunum	212 ± 53	46 ± 18
Brain	175 ± 65	52 ± 40
Stomach	143 ± 70	21 ± 7
Colon	142 ± 46	45 ± 24
Testes	112 ± 17	31 ± 14
Abdominal fat	36 ± 15	7.9 ± 6.3

[a]Values represent mg methylmercury/kg tissue; mean±SEM (N=7).
[b]Significantly different from control values with the exception of skin ($p<0.05$).

The amounts of ^{203}Hg excreted with urine and feces in percent of the dose administered are demonstrated in figures 2a and 2b. In control animals most of the mercury is excreted with feces (41.6±9.7% after 28 days) and urinary excretion is rather low (6.7±1.6%). DMPS treatment changed the excretion pattern. Mercury excretion was predominantly accelerated with urine (37.3±11.8% after 28 days) whereas fecal excretion was only slightly influenced (45.2±8.4%).

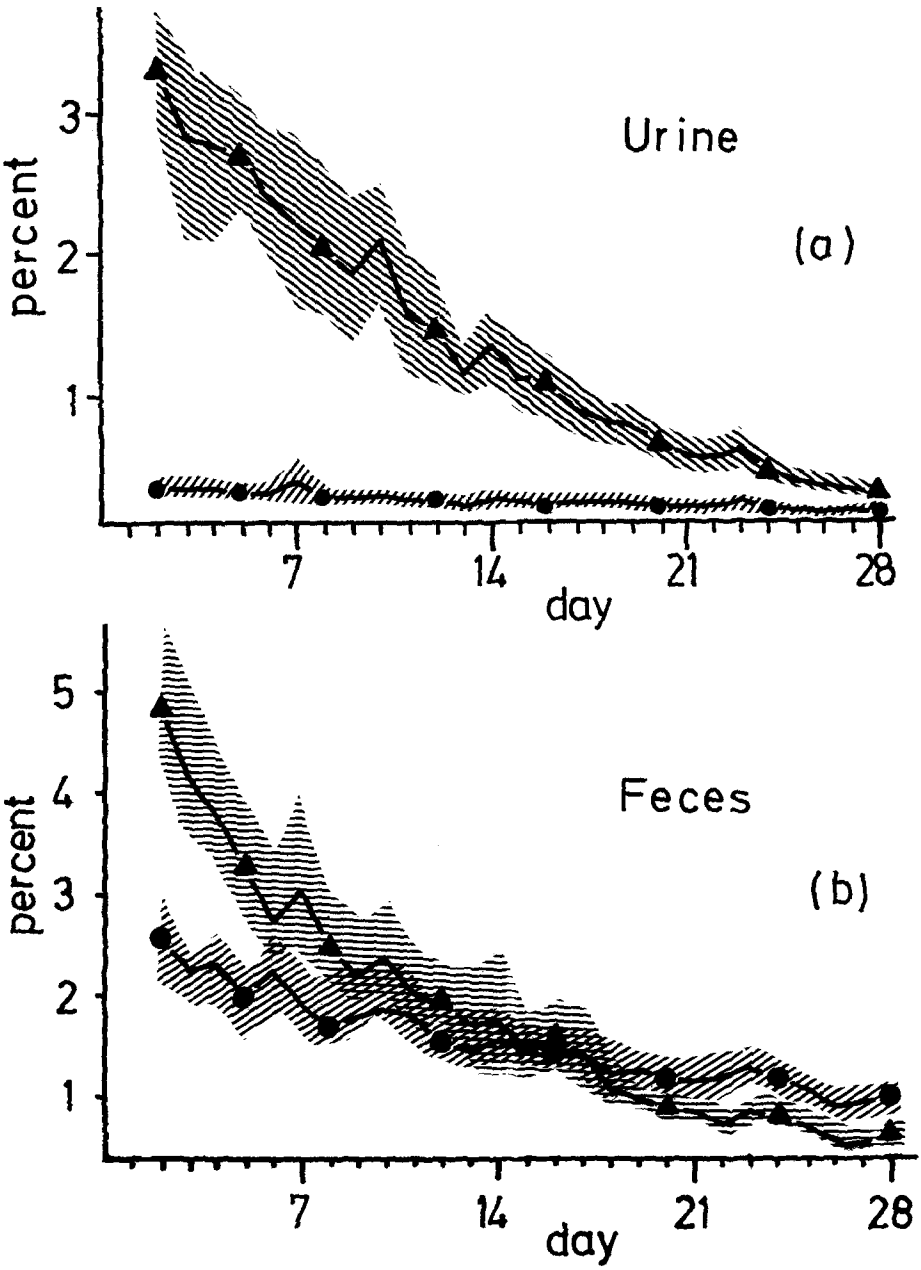
28 days after i.p. administration of methylmercury the organ distribution (Table 2) showed an enrichment of ^{203}Hg as compared to the whole body in the kidneys, blood and skin in both, control and DMPS treated rats. Mercury concentrations were significantly lowered to about 15-30% of control values in all tissues with the exception of skin (70%).

DISCUSSION

Since methylmercury undergoes metabolic transformation (NORSETH&CLARKSON 1970) the elimination process observed in the present study by the aid of $CH_3-^{203}HgCl$ represents only an uncharacterized summation of the parent compound and metabolites, especially inorganic Hg.

The results of our control group showing feces to be the main pathway of methylmercury excretion agree with that of NORSETH& CLARKSON (1971). With regard to the total methylmercury excretion after DMPS treatment the data of GABARD (1976b) compare favorably well with the present study. During 7 days after methylmercury administration rats fed 0.1 or 0.5 mmol DMPS/kg b.w. excreted 26.3 and 44.8% in the study of GABARD compared to 37.3% in the present study (0.3 mmol DMPS/kg). However, fecal excretion was only influenced at higher doses (GABARD 1976a) whereas a 1.55 fold increase was observed after 7 days in the present study. Earlier investigations showed that after methylmercury administration fecal mercury derives from protein-bound methylmercury and inorganic mercury excreted with bile as well as from intestinal exfoliation (REFSVIK&NORSETH 1975) and from the movement of mercury across the intestinal epithelium (SCHÄFER&FORTH 1980). Since only about 40% of orally administered DMPS is absorbed from the intestine (GABARD 1978) the data presented here suggest that not absorbed DMPS may trap parts of the usually reabsorbed fraction of mercury resulting in an increased fecal elimination, provided the DMPS-mercury or -methylmercury complex is not absorbed. Similar results were obtained after oral administration of a non-absorbable resin (CLARKSON et al. 1973, MAGOS&CLARKSON 1976).

In controls urinary excretion of mercury is of secondary importance. Orally administered DMPS enhanced mercury excretion via the kidneys by a factor of 5.6 as compared to control values. Taking into account that methylmercury is partially degraded to inorganic mercury (NORSETH 1971) the high efficacy of this water soluble and partially absorbable derivative of BAL for enhancing



FIGURES 2a and 2b. Effect of 0.1% DMPS in the diet upon the daily excretion of CH_3-$^{203}HgCl$ with urine (a) and feces (b) of rats. Values represent ^{203}Hg derived radioactivity in percent of the amount administered (mean±95% confidence limits of 7 rats). ● , Control; ▲ , DMPS; shaded area: 95% confidence limits.

urinary mercury excretion is may be due to its ability to remove inorganic mercury (GABARD 1976a). An increased urinary elimination of inorganic mercury after DMPS treatment has been shown to reduce the toxic effects of mercury upon the kidneys (PLANAS-BOHNE 1977).

Both effects, increased fecal and urinary excretion, lead to the markedly decreased half life of methylmercury in the rat body A two compartment model for the elimination of methylmercury was also suggested by THOMAS et al.(1982). As a result of the increased methylmercury elimination the concentrations of ^{203}Hg decreased markedly in all tissues of DMPS with the exception of skin. This may be explained by the fact that skin was measured together with hairs. In methylmercury exposure newly formed hair reflects recent blood concentrations of ^{203}Hg (PHELPS et al. 1980). Since hair is not vascularized a removal of deposited methylmercury or inorganic mercury by DMPS seems to be unlikely.

The data presented show that subchronic oral treatment of methylmercury incorporation with DMPS is effective in rats even some weeks after administration. In the rats no visible side effects induced by DMPS could be observed.

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