13. *Meso-* AND *racemic*-DMSA AS ANTIDOTES IN HEAVY METAL POISONING

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Lead, cadmium and mercury, well-known toxic metals, could be used in a chemical terrorist attack. Chelating agents are the only antidotes that promote toxic metals elimination from the body (1). At present *meso*-1,3-dimercaptosuccinic acid (*meso*-DMSA) is the optimal officially accepted antidote in lead or mercury poisoning that can be used orally (2). However, a racemic form of DMSA (*rac*-DMSA) seems to have higher stability constants with toxic metals than *meso*-DMSA but has not been yet thoroughly studied *in vivo* (3) and is not in human use. The results of our investigations presented in this paper have been obtained in experimental animal models *in vivo* to compare the efficacy of the mobilising potency of these two chelating agents in reducing toxic metal body retention (3-6).

The efficiency of these two DMSA isomers was tested after lead, mercury or cadmium poisoning in laboratory rats (female Wistar rats). Chelating therapy was started either immediately after or 3 to 5 days following metal application and lasted 2-4 days. Toxic metals were given either as a stable elements (Pb) or as radioactive isotopes (^{203}Hg or ^{109}Cd). At the end of the experiment stable lead was analysed by atomic absorption spectrometry (in tissues) and radioactive isotopes by measuring radioactivity in scintillation counters (separately in whole body and internal organs). Number of animals per group in each experiment was 8 to 11. The results were statistically evaluated by one-way ANOVA followed by *post hoc* Duncan's multiple range test (at $P<0.05$).

Lead

First experiment was carried out on 8-week-old female rats by Pb loading (in the form of acetate) during five consecutive days with 5 mg Pb/kg body weight per day (3). Oral treatment with *meso*-DMSA (Aldrich Chemical Co., Milwaukee, WI, USA) or *rac*-DMSA (synthesis described in ref. 7) was administered for four days at the dose of 0.5 mmol/kg per day. At the end of the experiment lead concentrations were analysed in tissues of control (lead-exposed and untreated) and treated groups administered one of the two DMSA isoforms (Figure 1). Femur lead concentrations (reflecting whole body burden of lead) were significantly reduced. This effect was significantly greater after *rac*- than after *meso*-DMSA treatment. Lead concentrations in the kidneys were markedly reduced by treatment with both isoforms of DMSA and the effect was greater after *rac*-DMSA. Neither compound was efficient in reducing liver lead concentrations. Brain lead levels were reduced by both chelators with no difference between *rac*- and *meso*-DMSA treated groups.

Lead mobilization was further tested in 7-day-old suckling rats (4). Very young are at a higher risk than adults for health effects of lead. Five mg Pb/kg body weight was given as a single intraperitoneal injection. *Meso*- and *rac*-DMSA were administered twice at the dose of 0.5 mmol/kg body weight, 24 and 48 hours after Pb. At the end of the experiment lead was determined in carcass (skeleton without organs and fur), kidneys, liver and brain (Figure 2). The results showed again that *rac*-DMSA causes a greater effect in reducing tissue Pb concentrations (kidneys) than treatment with *meso*-DMSA.

Mercury

Mercury mobilisation was tested in 7-week-old rats by giving a single intraperitoneal injection of 0.5 mg/kg of $HgCl_2$ labelled with radioactive ^{203}Hg (5). Chelators *meso-* or *rac-*DMSA were administered by gastric intubation during four days at the dose of 1 mmol/kg body weight per day. Results of whole body (Figure 3) and tissue retentions (Figure 4) showed that the lowest retention of ^{203}Hg was obtained after *rac*-DMSA treatment in the whole body, liver and kidneys.

Cadmium

In an experiment on 4-week-old rats cadmium chloride was administered intraperitoneally with 0.03 mg $CdCl_2$ x H_2O labelled with radioactive ^{109}Cd (6). Intraperitoneal treatment with chelators started immediately and was repeated 24 hours later at the dose of 1 mmol/kg. After 6 days both DMSA isomer treatments caused a decrease of whole body ^{109}Cd retention with *rac*-DMSA being more efficient (Figure 5). The same reduction of ^{109}Cd was obtained in the liver, but in the kidneys only *rac*-DMSA was effective (Figure 6). This reduction of cadmium in the body was modest by both isoforms of DMSA being slightly more efficient with *rac-* than *meso*-DMSA.

In conclusion, results of our investigations show that the racemic isoform of DMSA is more efficient in reducing the body burden and target organ retention of toxic metals - lead, mercury and cadmium - than *meso*-DMSA. The efficiency of metal body burden reduction with *rac*-DMSA was ordered: mercury > lead > cadmium. These studies will be continued to assess whether *rac*-DMSA could be applied clinically.

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KEYWORDS

Lead, cadmium, mercury, chelation therapy, 2,3-dimercaptosuccinic acid isoforms

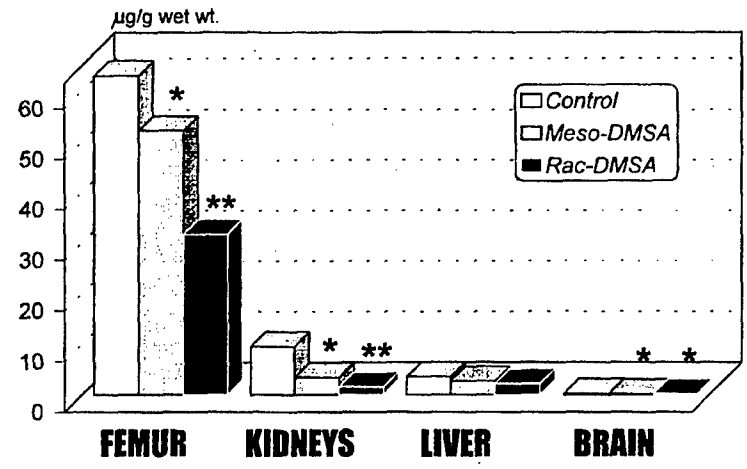

Figure 1. Lead concentration in femur and organs of 8-week-old female rats after treatment with *meso-* or *rac*-DMSA (3). Animals were loaded intraperitoneally with 5 mg/kg body weight of lead (as acetate) for five consecutive days. Treatment with *meso-* or *rac*-DMSA was administered for four days at the dose of 0.5 mmol/kg each day. Significant difference to the control is indicated by one asterisk; two asterisks denote difference between treated groups.

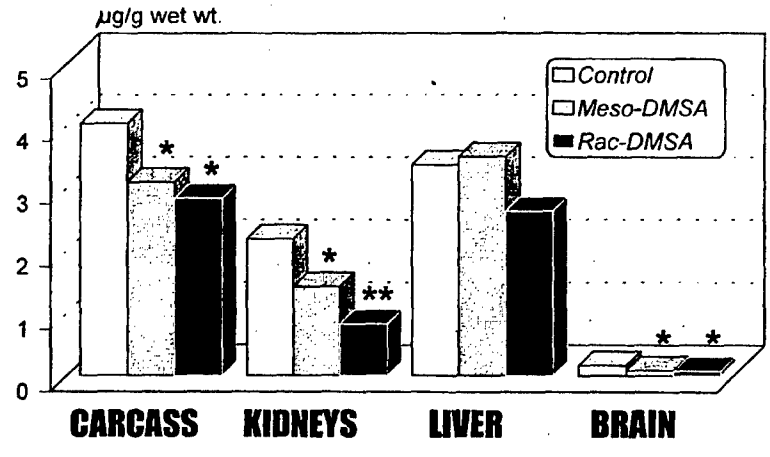

Figure 2. Lead concentration in carcass and organs of suckling 7-day-old rats after treatment with *meso-* or *rac*-DMSA (4). Animals were loaded with a single intraperitoneal dose of 0.5 mmol/kg of lead (as acetate). Chelating agents *meso-* or *rac*-DMSA were given orally twice 24 and 48 h later at a dose of 0.5 mmol/kg. Significant difference to the control is indicated by one asterisk; two asterisks denote difference between treated groups.

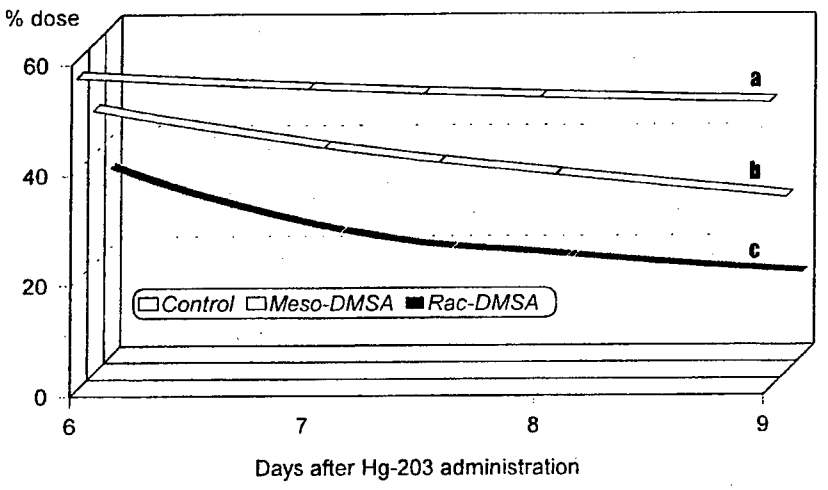

Figure 3. Mercury-203 retention in the whole body of 7-week-old rats after treatment with *meso-* or *rac*-DMSA (5). Animals received 0.5 mg $HgCl_2$/kg body weight labelled with ^{203}Hg by a single intraperitoneal injection. A four-day oral treatment with chelators started 5 days later at a dose of 1 mmol/kg. Significant differences between groups are indicated by different letters.

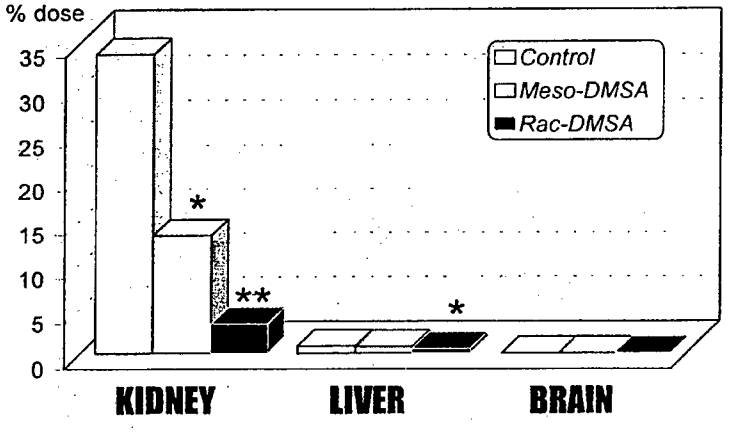

Figure 4. Mercury-203 retention in organs of 7-week-old rats after treatment with *meso-* or *rac*-DMSA (5). Animals received 0.5 mg $HgCl_2$/kg body weight labelled with ^{203}Hg by a single intraperitoneal injection. A four-day oral treatment with chelators started 5 days later at a dose of 1 mmol/kg. Significant difference to the control is indicated by one asterisk; two asterisks denote difference between treated groups.

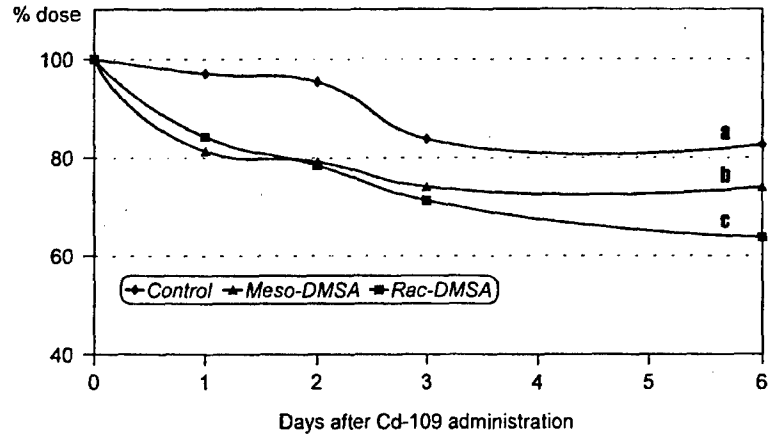

Figure 5. Cadmium-203 retention in the whole body of 4-week-old rats after treatment with *meso*- or *rac*-DMSA (6). Animals received 0.03 mg of $CdCl_2$ x H_2O labelled with ^{203}Cd in a single intraperitoneal injection. Two oral treatments with chelators started immediately and 24 hours later at a dose of 1 mmol/kg. Significant differences between groups are indicated by different letters.

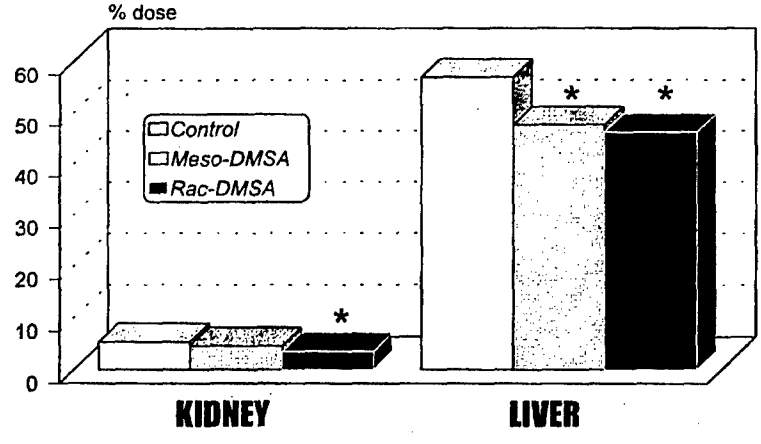

Figure 6. Cadmium-203 retention in organs of 4-week-old rats after treatment with *meso*- or *rac*-DMSA (6). Animals received 0.03 mg of $CdCl_2$ x H_2O labelled with ^{203}Cd in a single intraperitoneal injection. Two oral treatments with chelators started immediately and 24 hours later at a dose of 1 mmol/kg. Significant difference to the control is indicated by asterisk.