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EFFECT OF ORAL DITHIOL COMPOUND TREATMENT IN ACUTE ARSENIC
TRIOXIDE POISONING IN MICE

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ABSTRACT

The efficacy of BAL (2,3-dimercaptopropanol), DMPS (2,3-dimercaptopropanesulfonate) and DMSA (2,3-dimercaptosuccinic acid) in reducing the ⁷⁶As burden was investigated in ⁷⁶As-arsenite poisoned mice (n = 6/group). 30 min after a s.c. injection of 85 μmol/kg ⁷⁶As-arsenite (LD5), 0.7 mmol/kg BAL (in peanut oil or in saline), DMPS, DMSA (both in saline) or saline (controls) were given by gastric tube. The ⁷⁶As content of heart, lung, liver, kidney, spleen, small intestine, large intestine, brain, testes, muscle and skin was measured by a gamma counter 0.5, 2, 4, 6 and 8 h after the arsenic injection. DMPS was the most effective compound in decreasing organ arsenic content, followed by DMSA > BAL in saline > BAL in oil > saline. In the small and large intestine, DMPS markedly increased the arsenic content, indicating a shift from renal to fecal elimination and thereby a lower arsenic load for the kidney. Brain arsenic content was significantly increased by BAL, both in saline and in oil, but decreased by DMPS and DMSA. Comparison of the ⁷⁶As-arsenic elimination out of the brain following BAL treatment and the ¹⁴C-BAL content in brain of mice treated with ¹⁴C-BAL (in saline and oil) indicates that BAL is eliminated faster out of the brain than arsenic. The results suggest that BAL mediates increased arsenic penetration across the "blood-brain-barrier" followed by a ligand exchange of arsenic to intracellular molecules while BAL leaves the brain cells.

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Introduction:

In the forties, DL-2,3-dimercaptopropanol (British-Anti-Lewisite, BAL; Peters et al. 1945) was found to be an effective antidote in poisonings by trivalent arsenicals. The acute toxicity of BAL itself is relatively high and the usual method of administration is inconvenient. This drug is usually dissolved in oil and has to be injected deep intramuscularly (i.m.) followed often by local damage. The dithiols DL-2,3-dimercaptopropanesulfonate (DMPS; Petrunkin 1956) and meso-2,3-dimercaptosuccinic acid (DMSA; Liang et al. 1957) are much better soluble in water and can be administered intravenously (i.v.) or orally. Why BAL should not be given orally has not been discussed and there are only few data on the antidotal efficacy of BAL dissolved in saline. In only one paper so far (Kreppel et al. 1989), oral treatment with BAL dissolved in oil or in saline has shown to be effective in reducing lethality in experimental arsenic poisoning. Hence, the effectiveness of BAL in a hydrophilic and a lipophilic solvent, given via gastric tube, was compared to the effectiveness of DMPS and DMSA in reducing the arsenic content in the body of mice poisoned with arsenite. Furthermore, the effect of arsenic on the dithiol content of the organs was determined using ¹⁴C-labeled BAL and DMSA.

Materials and Methods:

Male NMRI mice, 25 - 30 g, (ITF Tuttlingen, FRG) received standard diet (Alma H 1003, Botzenhardt KG, Kempten, FRG) and tap water ad libitum. 6 animals were randomly allotted to each group.

Following chemicals were used:

Arsenite: 99,99 %, Sigma, St.Louis, MO; 85 µmol/10 ml saline
BAL: DL-2,3-dimercaptopropanol, pure, Serva, Heidelberg, FRG; 0.7 mmol/10 ml saline or peanut oil
DMPS: DL-2,3-dimercaptopropanesulfonate sodium salt x H₂O, 95 %, Heyl & Co, Berlin, FRG; 0.7 mmol/10 ml saline
DMSA: meso-2,3-dimercaptosuccinic acid, 98 %, EGA-Chemie, Steinheim/Albuch, FRG; 0,7 mmol/10 ml saline, pH 6.5
76-arsenite: carrier free, 2.2 mCi, > 99 %, Institut für Radiochemie, TU München, Garching, FRG
14C-BAL: Carbonyl-14C, 2.04 mCi, > 99 %, Du Pont De Nemours, Dreieich, FRG
14C-DMSA: Carbonyl-14C, 2.00 mCi, > 99 %, Du Pont De Nemours, Dreieich, FRG

Arsenic elimination was measured as follows:

0 min: 85 μ mol/kg 73-arsenite s.c.
30 min: 0.7 mmol/kg BAL, DMPS or DMSA via gastric tube (p.o.). BAL was dissolved in peanut oil (oleum arachidis) or in saline. DMPS and DMSA were dissolved in saline.
At 30 min, 2 h, 4 h, 6 h and 8 h:
73-arsenic content was measured in several organs (heart, lung, liver, kidneys, spleen, small intestine (incl. content), large intestine (incl. content), brain, testes, muscle and skin) with a gamma counter.

Antidote elimination was measured as follows:

0 min: 85 μ mol/kg arsenite s.c.
30 min: 0.7 mmol/kg ¹⁴C-BAL or ¹⁴C-DMSA i.p. or via gastric tube (p.o.). BAL was dissolved in peanut oil (oleum arachidis) or in saline. DMPS and DMSA were dissolved in saline.
At 2 h, 4 h, 6 h and 8 h:
¹⁴C-dithiol content was measured in several organs (heart, lung, liver, kidneys, spleen, brain, testes, muscle and skin) with a liquid scintillation counter. Samples were pretreated with hydrogenperoxide (30 %, Merck-Schuchard, Hohenbrunn, FRG) and tetraethylammoniumhydroxide (20%, Merck-Schuchard, Hohenbrunn, FRG). As a scintillation cocktail Omniszintisol (Merck, Darmstadt, FRG) was used.

Statistical comparisons ($p < 0.05$) between treatment groups and controls were performed using the non-parametric Wilcoxon-Mann-Whitney test and Kruskal-Wallis test.

Results:

The effect of dithiol treatment on arsenic content in various organs, and the elimination of the antidotes is shown in figure 1 to 3.

BAL solution in saline and in oil significantly decreased the ⁷⁶As content in the liver. However, the effect of equimolar amounts of DMPS and of DMSA was markedly higher and occurred faster compared to BAL.

Pretreatment with arsenic only slightly affected the ¹⁴C-dithiol liver content. Compared to ¹⁴C-BAL contents, much less ¹⁴C-DMSA was found in the livers, indicating a higher elimination rate of DMSA.

DMSA rapidly decreased brain 76-arsenic content while BAL (both in saline and in oil) significantly increased brain 76-arsenic content. Pretreatment with arsenic only slightly affected the 14C-dithiol brain content. Compared to 14C-BAL contents, much lower amounts of 14C-DMSA were found indicating a higher elimination rate of DMSA.

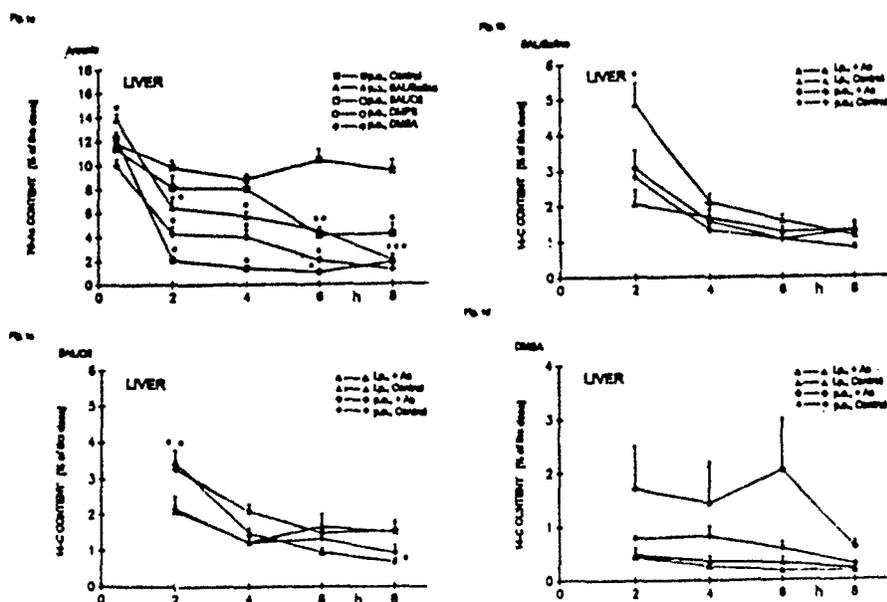


FIGURE 1 a - d
76-ARSENIC CONTENT AND 14C-DITHIOL CONTENT IN THE LIVER

Mice received 85 $\mu\text{mol/kg}$ arsenite, s.c., and 30 min later 0.7 mmol/kg BAL (in saline or in oil) or DMSA, s.c. or p.o. Arsenic (Fig. 1. a) BAL (Fig. 1 b, c) and DMSA (Fig. 1. d) were radiolabeled.

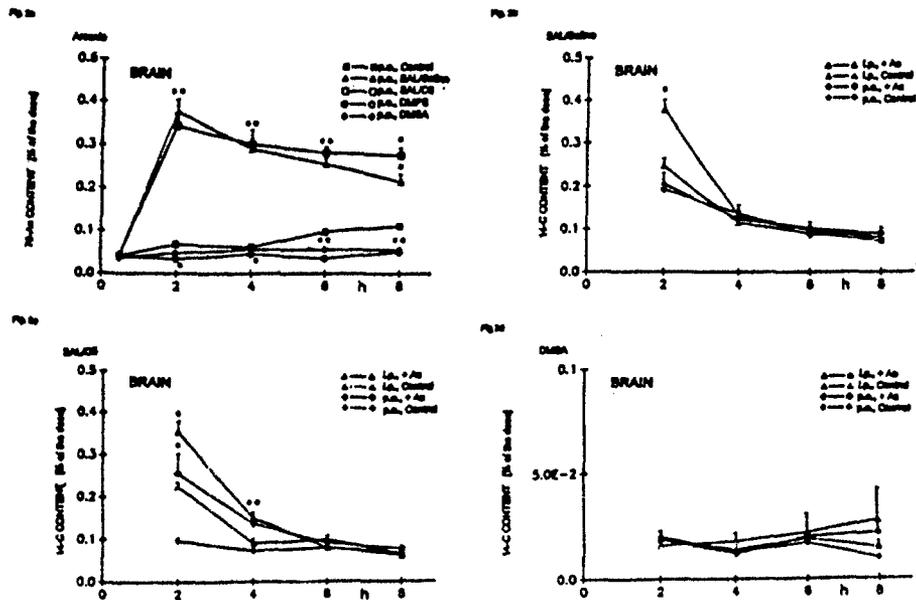


FIGURE 2 a - d
 76-ARSENIC CONTENT AND 14C-DITHIOL CONTENT IN THE BRAIN
 Arsenic (Fig. 2a) and ¹⁴C content (2b-BAL/saline, 2c-BAL/oil, 2d-DMSA) of mice brains treated as described in Fig 1 are shown.

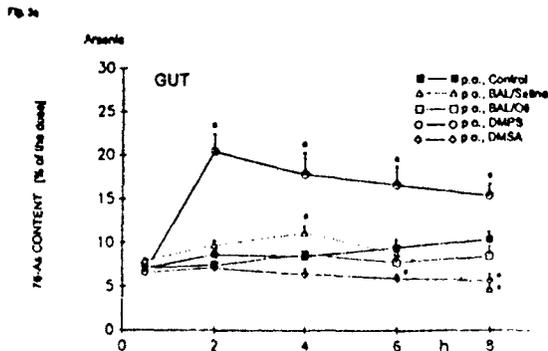
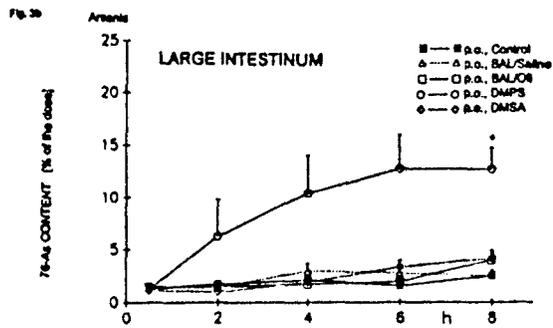
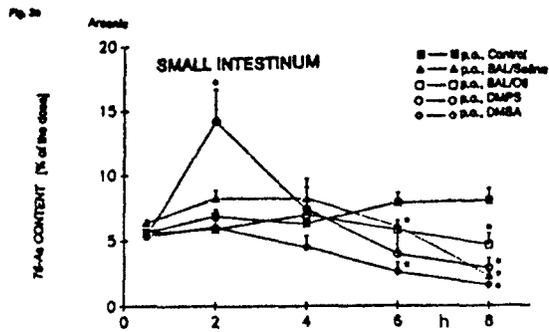


FIGURE 3 a - c
 76-ARSENIC CONTENT IN SMALL AND LARGE INTESTINE

In mice treated as described in Fig 1 DMSA markedly increased the 76-arsenic content in the small intestine (2 h)(Fig 3a) and in the large intestine (2 - 8 h)(Fig 3b). 76-As content in the gut is shown in Fig 3c.

Summary:

1. BAL, both in saline and in oil, was well tolerated given i.p. and via gastric tube.
2. In general, the antidotal effect of BAL was higher if dissolved in saline than in oil.
3. DMPS and DMSA were superior to BAL in decreasing organ arsenic contents.
4. Arsenic only slightly increased dithiol retention in organs.
5. The data indicate a shorter biological half life of DMSA compared to BAL.
6. Comparing the 76-arsenic elimination to the elimination of the ¹⁴C radioactivity from the brain following BAL treatment (in saline and oil) indicates that BAL is eliminated faster than arsenic. The data suggest that BAL mediates increased arsenic penetration across the "blood-brain-barrier" followed by a ligand exchange of arsenic to intracellular molecules, while BAL leaves brain cells again.
7. Following DMPS treatment, increased arsenic amounts were found in the gut indicating a shift from renal to fecal excretion which would result in a lower arsenic load of the kidney.

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