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Chelation of Lead with DMPS and BAL in Rats Injected with Lead

Teresa A. Twarog and M. George Cherian

Department of Pathology, Health Sciences Centre, University of Western Ontario, London, Ontario, Canada N6A 5C1

The current treatment of lead poisoning is limited to a few chelating agents such as EDTA, BAL, and D-penicillamine (CHISOLM 1968). Their medical use is somewhat restricted because of toxic side-effects. Thus, the search for better chelating agents for treatment of metal poisoning is essential. Although a water-soluble derivative of BAL, the sodium salt of dimercaptopropanesulfonate (DMPS) was suggested to be effective in the therapy of lead poisoning (ANATOVSKAYA 1962), little work has been done on this compound. Unlike BAL, this compound can be administered orally for effective chelation of metals. The therapeutic effects of DMPS have been reported (GABARD 1976; CLARKSON et al. 1981) for various forms of mercury intoxication. However, it is not effective in chronic cadmium poisoning (CHERIAN et al. 1982).

In this study, we have compared the efficacy of DMPS and BAL in the tissue mobilization of lead from lead-poisoned rats. Both these compounds are structurally similar with vicinal thiol groups, but are metabolized differently.

MATERIALS AND METHODS

Twenty-five male Sprague-Dawley rats weighing 150-200 g were divided into 5 groups of 5 rats each and were given access to standard laboratory chow and deionized water ad lib. Groups 2-5 were given daily i.p. injections of 2 mg lead/kg as lead acetate dissolved in deionized water for a period of 7 days. Group 1, the control group, received no treatment. On day 7, the animals were placed in separate stainless steel metabolic cages for urine collection. Group 2, the lead control group, received no further treatment. Chelation treatment for Groups 3-5 began 48 h subsequent to the final lead injection. These groups were treated i.p. daily for 3 days as follows: Group 3 with DMPS (50 umol/kg), Group 4 with BAL (50 umol/kg), and Group 5 with a combination of 50 umol/kg each of BAL and DMPS (Sigma Chemicals, St. Louis, MO). Twenty-four-h urine samples were collected from each rat two days before and during chelation treatment. Aminolevulinic acid (ALA) was estimated by the method of WADA et al. (1969). All the rats were sacrificed at the end of the 3-day treatment period by aortal exsanguination under light pentobarbital anesthesia. Tissue samples were

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weighed, and approximately 0.2 g were digested in 1 mL of concentrated nitric acid. Urine, blood, and tissue hydrolysates were diluted with deionized water, and lead was analyzed by flameless atomic absorption spectrophotometry in a graphite furnace (SCHEUHAMMER & CHERIAN 1982). The results were analyzed by a Student's t-test as described by SOKAL & ROHLF (1969).

RESULTS AND DISCUSSION

The urinary excretion of lead in lead-injected rats decreased gradually when the lead treatment was discontinued (Figure 1) in Group 2. As expected, the urinary lead excretion increased in all other groups immediately after treatment with DMPS (Group 3), or BAL (Group 4), or combination (Group 5).

The efficacy of DMPS was confined mainly to the first day of treatment, and the excretion of lead diminished on subsequent days of treatment. Injections with BAL caused urinary lead to increase slowly with each sequential dose. Group 4 rats excreted more lead in their urine, over the total chelation period, than did Group 3 rats; Group 5 rats, receiving combined therapy, excreted more lead than either DMPS or BAL given alone.

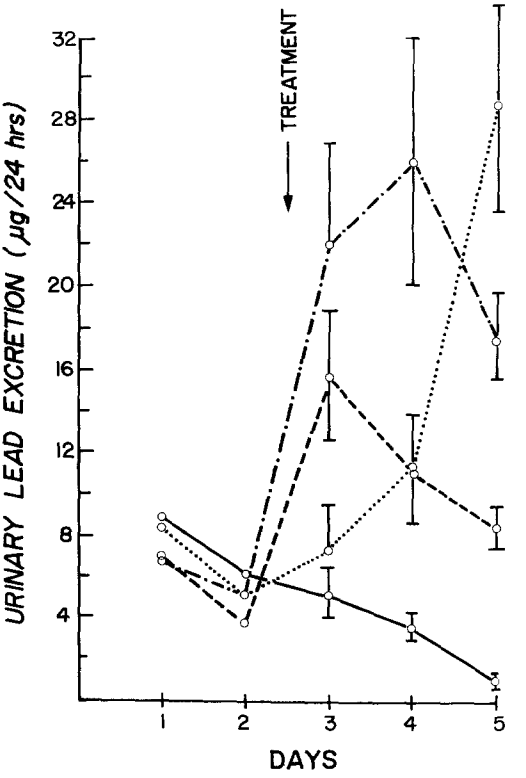

Fig. 1. Urinary lead excretion in lead-poisoned rats following treatment with lead alone, Group 2 (——); DMPS, Group 3 (– –); BAL, Group 4 (•••); and combined therapy, Group 5 (–•–).

Estimations of urinary ALA, a biologic indicator of lead poisoning, are shown in Figure 2. All three forms of treatment showed a reduction in ALA excretion. Thus, the chelators appeared to reactivate the inhibited ALA dehydratase, indicating the effectiveness of these agents in the management of lead poisoning. However, this effect was less prominent in the DMPS treated group as compared to other treatments, on the first day of chelation.

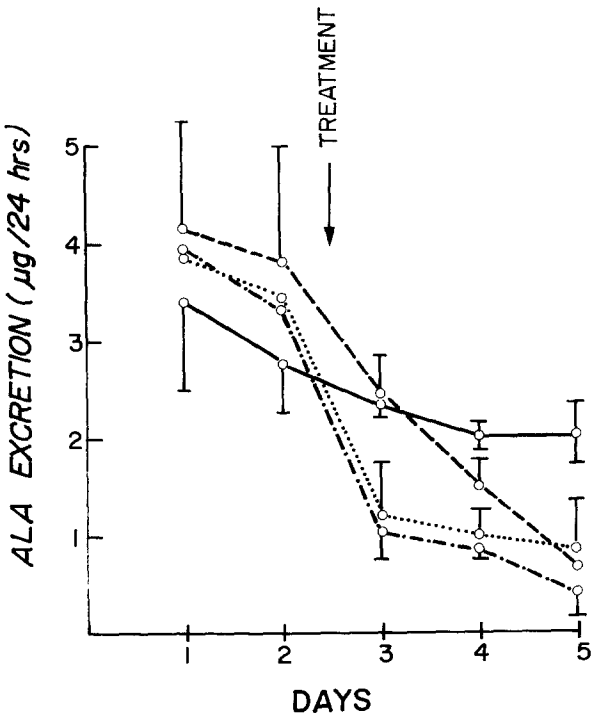

Fig. 2. ALA excretion in lead-poisoned rats following treatment with lead alone; Group 2 (——); DMPS, Group 3 (– –); BAL, Group 4 (•••); and combined therapy, Group 5 (–•–).

Table 1 compares the concentration of lead in blood and bone after chelation therapy. The blood lead levels of Group 3 animals were not significantly different from the lead control group. However, Group 4 and Group 5 rats had blood lead levels significantly lower than the non-treated animals. Bone lead levels of DMPS treated animals did not differ statistically from the lead control. BAL was effective in removing bone lead and the combination therapy was equally effective as BAL given alone.

Lead content of soft tissues is shown in Table 2. Neither of the chelators given alone or in combination had an effect in decreasing hepatic or brain lead levels. Renal lead, however, was significantly decreased by both DMPS and BAL, given singly or together.

Table 1. Blood and Bone Content of Lead in Control and Lead Exposed Rats with Various Modes of Treatment (Mean ± S.E.M.)

Group	Blood (ug/dL)	Bone ug/g
Control	1.10 ± 0.24	0.25 ± 0.41
Lead Control	42.78 ± 4.84	123.57 ± 11.75
Lead + DMPS	43.40 ± 11.63	73.42 ± 23.98
Lead + BAL	*15.18 ± 1.45	*51.23 ± 9.82
Lead + BAL + DMPS	*22.84 ± 1.49	*49.66 ± 17.00

* Differs from lead control group ($p < 0.05$)

Table 2. Soft Tissue Lead in Control and Lead Exposed Rats with Various Modes of Treatment (Mean ± S.E.M.)

Group	Liver (ug/g)	Kidney (ug/g)	Brain (ug/g)
Control	0.05 ± 0.26	0.10 ± 0.41	0.15 ± .03
Lead Control	2.05 ± 0.19	12.22 ± 2.52	1.00 ± .56
Lead + DMPS	2.72 ± 0.85	*3.34 ± 1.10	1.39 ± .96
Lead + BAL	2.57 ± 1.13	*3.99 ± 2.04	0.83 ± .03
Lead + BAL + DMPS	2.78 ± 1.91	*2.93 ± 0.88	1.27 ± .17

* Differs from lead control group ($p < 0.05$)

The distribution of DMPS in rats, following DMPS treatment has been studied by GABARD (1978). This study showed that the highest concentrations of DMPS were found in the kidneys and lowest in the brain.

Most of the lead in the kidney following lead exposure is shown to be bound to nuclear inclusion bodies in proximal tubules (ANGEVINE et al. 1962). The high renal clearance of DMPS leads to a considerable concentration of this compound in the plasma ultrafiltrate which passes through the proximal tubule (GABARD 1978). Thus, the DMPS is able to remove the lead specifically from the kidney. The low levels of DMPS in brain tissue during chelation are reflected by the poor mobilization of lead from the brain.

HOFMANN & SEGEWITZ (1975) studied the effects of DMPS on lead-poisoned rats, and by using the same dose of DMPS as the present study, found that DMPS could reduce bone lead levels significantly over a period of several weeks. Since DMPS is a water-soluble compound, it must act extracellularly, and thus, depletion of bone stores of lead may be caused by a redistribution of lead in the body during the long treatment period in this study.

BAL is a lipophilic compound and thus able to penetrate cellular membranes and remove lead from red blood cells (HAMMOND &

ARONSON 1960). Rapid removal of lead from red blood cells might facilitate more rapid mobilization of lead from soft tissues (CHISOLM 1968). This does not appear to be the case in this study as soft tissue lead levels are approximately equal in both DMPS and BAL treated animals.

In the present study, equimolar amounts of BAL had a greater effect in total removal of lead from the body than DMPS (urine, blood, bone), but it may not necessarily be the drug of choice due to its side-effects and route of administration. Since the renal effects of lead poisoning are the most detrimental, DMPS, which acts specifically to remove lead from the kidney and is less toxic than BAL, may be a preferred chelating agent. Finally, there does not appear to be any distinct advantage of using a combination treatment of BAL and DMPS in lead poisoning.

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