

DMSA AND DMPS- WATER SOLUBLE ANTIDOTES *FOR* HEAVY METAL POISONING

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Introduction

This article reviews the pharmacological properties and the uses of two important antidotes for heavy metal poisoning. Meso-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-l-propanesulfonic acid, Na salt (DMPS) are relatively new antidotes-new, that is, to the western world. Although DMSA was introduced originally by Friedheim et al (1) to increase uptake of antimony during schistosomiasis therapy, Liang et al (77) at Shanghai in 1957 were the first to report its effectiveness as an antidote for heavy metal poisoning. The synthesis and some of the metal binding properties of DMPS were reported in 1956 by Petrunkin from Kiev (3). Shortly thereafter, DMPS became an official drug in the Soviet Union, where it is known as Unithiol (4).

Between 1956 and 1975, DMSA and DMPS were studied extensively, at both the basic science and clinical levels, in the People's Republic of China, the Soviet Union, and Japan. Some of these investigations have been cited and can be found in an earlier review (5). In the USA and Western Europe, however, these two compounds received very little attention until recently. A paper by Friedheim & Corvi (6) in 1975, dealing with DMSA for the treatment of mercury poisoning, and the recent production and availability of DMPS from Heyl & Co., Berlin, stimulated investigators to "rediscover" and study these two metal-binding agents. DMSA and DMPS are water soluble chemical analogs of dimercaprol (British Anti-Lewisite, BAL).. In contrast to BAL, they have less toxicity, greater water solubility, and limited lipid solubility, and are effective when given orally.

Procedures for synthesizing DMPS (3, 10), DMSA (11), 3sS-DMSA (12, 13), and [2,3-¹⁴C]-DMSA (14) have been reported. DMSA and DMPS have been labeled with ⁹⁹Tc for use in renal scanning (15, 16). DMPS is manufactured by Heyl & Co., Berlin, who distribute it as DIMA V AL\$. DMSA is available from a variety of biochemical specialty firms in the USA. In the Soviet literature, it is called Succimer.

There have been a number of reports dealing with the stability constants of metal complexes of DMSA or DMPS (17,18). It has been claimed that the greater the stability constant for a given metal ion complex, the greater the mobilization of that ion when the metal-binding agent is given (19). In the case of mercury complexes, however, there does not appear to be any relationship between survival rates of animals and stability constants (20). DMPS forms complexes with heavy metals that scarcely differ in their stability from metal-BAL complexes except for Cd. The Cd-BAL complex is more stable than the Cd-DMPS complex (21). The stability's of DMSA complexes, based on their stability constants (22), were found to be in the following order: Cd²⁺, Pb²⁺, Fe³⁺, Hg²⁺, Zn²⁺, Ni²⁺. The Cd complex was the most stable; the Ni complex the least stable. The term chelate has been avoided in this review because by definition a chelate is a ring structure. Since the structure of many of the complexes of DMSA or DMPS has not been rigorously proven, the term metal complex instead of metal chelate is used.

DMSA AND DMPS AS ANTIDOTES FOR HEAVY METAL POISONING

Arsenic

It is rather surprising that since the late 1940s, BAL has remained the drug of choice in the USA for the treatment of As poisoning (23). It has many disadvantages, e.g. high toxicity, low therapeutic index, unpleasant side effects, limited water solubility, instability in solution, and the need to administer by im injection. Side effects, including nausea, vomiting, and headache, have been experienced by 50% of the patients receiving BAL. By 1958, however, publications were beginning to appear in the Soviet literature indicating the superiority of DMPS as an antidote for As poisoning (9). By 1965 the effectiveness of DMSA for this purpose was reported in the Chinese and Soviet literature (25, 26)

The ⁷⁶As content of 12 organs was sharply reduced when DMPS, 30 mg/kg, sc, was given to rabbits (27a). At 24 h after DMPS treatment, ⁷⁶As elimination in the urine was greater in rate and amount. In rats and rabbits (27b), DMPS prevented the lethal effects of many As compounds, e.g., arsenous oxide, sodium arsenite, calcium arsenite, Paris green, neodiar-senol, sodium arsenate, and osarsol, if given within 1 h after the As com-

found. Structures have been proposed for the soluble As-DMPS complexes formed by DMPS and different arsenic compounds. Classical thioarsenite ring structures connected in certain cases by additional linear DMPS molecules and having, in some cases, a DMPS : As ratio of 3 : 2 have been suggested.

In a search for better antidotes of arsenic, a series of mercaptoalkanesulfonates were synthesized (28). In addition to DMPS and iso-DMPS, two other compounds were found to be active as As antidotes. They were 2,3-dimercaptopropoxyethanesulfonate, Na salt and 3(1,3-dimercaptoisopropylmercapto)-propanesulfonate, Na salt. When given to rats 15 min after AS₂O₃, iso-DMPS gave greater protection than DMPS. Similar results were found in rabbits. The mercapto groups of iso-DMPS are on the first and third carbon atom. Iso-DMPS, however, is less stable during preservation, slightly more toxic, and more difficult to prepare than DMPS.

DMSA is effective as an arsenic antidote in humans (29), mice (30, 31), and rats (26, 32). It is effective po, ip, sc, and im. Although DMSA increases arsenic excretion in rats (26, 32), the rat is so different from other mammals in its metabolic handling of arsenic that the National Research Council has recommended that rats not be used for arsenic studies (33).

The D and L isomers of DMPS have been studied individually and found to be equally active in preventing and reversing the inhibition by sodium arsenite of the activity of mouse kidney pyruvate dehydrogenase enzyme complex, *in vitro*, and the lethal effects of sodium arsenite in mice (C. A. Hsu and H. v. Aposhian, to be submitted). Neither is there any significant difference between such *in vitro* and *in vivo* activities of the meso- and *DL* forms of DMSA (C. A. Hsu and H. V. Aposhian, to be submitted).

Tadlock & Aposhian (30) have reported that as little as 0.07 mmol of DMPS or DMSA per kg given ip immediately after sodium arsenite protects mice against the lethal effects of sodium arsenite. The dimercapto compounds were also active orally. Dimercapto therapy could be delayed for at least 90 minutes after the administration of arsenite.

In one of the few papers comparing DMPS and DMSA quantitatively in experimental therapy of arsenic intoxication, it was shown that either compound, when given ip, increased the LD₅₀ of sodium arsenite in mice by about 4-fold (31). In addition, the ED₅₀ of DMPS or DMSA ip in mice receiving a LD₁₀₀ dose of sodium arsenite sc was 0.06 mmol/kg. The therapeutic index of DMSA was almost 3 times greater than that of DMPS because the LD₅₀ of DMSA is about 3 times greater than that of DMPS (31). A quantitative comparison has demonstrated that DMPS is 28 times more effective than BAL for arsenic therapy in mice (34).

DMSA was found to be useful in the treatment of a 46-year-old man who ingested 2000 mg of arsenic in a suicide attempt (29). Treatment with 300

mg DMSA every 6 h po for 3 days caused an increase in the urinary excretion of arsenic with eventual recovery. DMPS has also been effective in human arsenic poisoning (N. P. Weger, personal communication). Not only are DMPS and DMSA analogous in chemical structure to BAL, but they are also analogous in their biological activity when used po, im, or sc to prevent the lethal systemic action of lewisite in rabbits (8). The treatment of arsine (AsH₃) poisoning is quite different from that of other arsenic compounds. Arsine is a gas and a potent hemolytic agent. The recommended treatment for AsH₃ intoxication in the Soviet Union is mercaptid, which is 1,2-propanedithiol-3-(p-tolylthioel). Mercaptid is a clear oily liquid that is readily soluble in organic solvents but insoluble in water. It is readily oxidized, of low toxicity and is given usually im as a 40% solution. It has been suggested that its lipotropic properties promote its penetration into the red cells, where it is needed for arsine oxidation and therapy (35). A mechanism for its action has been proposed (35), involving oxidation to a disulfide after injection. The disulfide then oxidizes arsine. The oxidation products are converted to water-soluble cyclic thioarsenites and excreted. A series of thiol compounds have been tested in rats as antidotes for arsenic trioxide and arsine (36). Those active as antidotes for arsenic trioxide were not antidotes for arsine and vice versa. DMPS and BAL are contraindicated in acute arsine poisoning since they do not inactivate arsine and can create conditions for increasing arsine toxicity (35). The successful treatment with DMPS and mercaptid of an acute case of arsine poisoning in a human has been described (37) recently. It is clear from the Soviet literature that there is not complete agreement as to the use of DMPS for the treatment of arsine poisoning (35, 37).

Lead

Of all the poisonings by various heavy metals, none seems as insidious as the exposure of children to low levels of Pb found in urban environments of the USA (38). It is recognized that blood Pb concentrations of as little as 20-25 $\mu\text{g}/100\text{ ml}$ cause irreversible CNS damage in young children (7). The sources of urban Pb remain controversial (38). If ever there appears to be a need for the use of a prophylactic against a heavy metal, the protection of urban children against Pb seems one. The first report (40) of the use of DMSA to treat occupational poisoning by metals was from Peking and Shanghai in 1965. DMSA was found to be as effective as CaNa₂ EDTA in the treatment of occupational Pb poisoning and as effective as DMPS in the treatment of occupational Hg poisoning, judged by increases in the urinary excretion of the offending metal.

The successful treatment with DMPS of 60 men with chronic Pb poisoning was reported in 1962 from the Soviet Union (41). They were given 250

mg/day for 20 days. The signs and symptoms of chronic Pb poisoning subsided in the treatment group. When Pb acetate was given intraarterially to rabbits and followed 4 h later with DMSA, the urinary excretion of Pb was 10 times greater than that of the control group (22). In addition, DMSA treatment of rabbits with chronic Pb acetate poisoning resulted in a 7-fold increase in Pb excretion; CaEDTA increased Pb excretion 10-fold in another group.

DMSA given sc or po to rabbits previously challenged with Pb acetate not only increased the excretion of circulating Pb but also removed Pb from tissue and bone (42). Also, the disturbances in porphyrin metabolism usually seen with Pb intoxication were prevented (42).

DMSA, D-penicillamine (D-pen), and EDTA have been compared for their influence on tissue Pb concentrations of mice pretreated with Pb acetate (43). DMSA was the most effective in decreasing tissue Pb. In the brain, a critical organ in Pb intoxication, DMSA reduced the Pb content while D-pen was without effect. Further studies using 30 mg DMSA/kg each day for five days showed that DMSA also increased Pb excretion in rats poisoned with Pb acetate (44). In response to DMSA, about two thirds of the Pb excreted by rats appeared in the urine and about one third in the feces. Using HAL, however, the ratio of Pb excretion was reversed and fecal excretion was greater. DMSA did not influence the absorption of Pb from the GI tract.

DMSA was given for six days to five lead-poisoned smelter workers (45). The results of the treatment confirmed the earlier studies by the Chinese in 1965 (40) with DMSA and occupational Pb poisoning. Treatment (45) consisted of approximately 8-13 mg DMSA/kg/day on the first day with increases to 28-42 mg/kg/day on the last day. DMSA, given orally, increased Pb excretion and reduced the Pb concentration of the blood from 97 to 43 mcg/dl. No side effects or renal toxicity were detected. It was concluded (45) that DMSA seemed "to be safe and effective for the treatment of Pb poisoning." The use of DMSA and DMPS for prophylaxis against experimental Pb poisoning has been studied and found effective (42, 46a). A recent report (46b) indicates that thiamin (vitamin B1) may have a beneficial effect in the prophylaxis and treatment of Pb poisoning in that it prevented the accumulation of Pb in the tissues of calves given toxic amounts of Pb acetate. Combined therapy using thiamin and/or DMSA and DMPS should be investigated.

Mercury

The problem of treating intoxication by methylmercury (MeHg) is of more recent concern than that of mercuric chloride. DMSA, DMPS, and N-acetyl-DL-penicillamine (NAPen) have been shown in a number of studies

to have some beneficial properties in removing MeHg from the mammalian body. The mercury content of the kidney, liver, and brain of mice or guinea pigs exposed to MeHgBr was decreased by posttreatment with DMSA (6). These experiments were extended (47) to show that smaller amount of DMSA could be used, greater delay before treatment was possible, and DMSA was effective po. In addition, DMSA was shown to be four times more effective than D-pen for increasing the urinary excretion of mercury. Rats poisoned with MeHg preferred to drink water containing DMSA (2.5 mg/ml) rather than water without it (48).

The activities of DMSA, DMPS, and NApén in mobilizing MeHg in the mouse have been compared by Aaseth & Friedheim (49). The mercapto compounds were incorporated in a diet that was fed to mice from 4 to 12 days after MeHg injection. By the 12th day, DMSA therapy decreased the whole body content of Hg to 19% of that found in the untreated controls. NApén and DMPS were less effective as shown by values that were only 47% and 72%, respectively, of the controls. Of paramount importance is the influence of these metal-binding compounds on the mercury content of the brain, the target organ of MeHg. DMSA accelerated Hg elimination from the brain, but DMPS had no effect. Hg in the blood, kidneys, and liver decreased the most in the DMSA group and least in the DMPS group. The cumulative urinary excretion of Hg was greatest in the DMSA-treated mice and least in the DMPS group.

The efficacy of DMSA > DMPS > NApén = D-pen for removing methyl mercuric chloride from erythrocytes, in vitro, (50) was confirmed in vivo by Planas-Bohne (51) with rats receiving ^{203}Hg -methylmercury ip. When the animals were sacrificed, the content of ^{203}Hg -MeHg and $^{203}\text{Hg}^{2+}$ in the liver and kidney was measured separately. DMSA was most effective in removing the mercurial from all organs except the kidneys, for which DMPS was better. NApén showed only marginal effectiveness. DMSA removed more of the organic Hg while DMPS removed more of the inorganic Hg. A combination of DMPS and DMSA removed mercury from most organs.

There is disagreement about the relative potencies of DMPS and NApén (49,51). The differences have been attributed to species differences, routes of administration, and doses of metal-binding agents.

The efficacy of some of the treatments of the victims of the 1971-1972 methylmercury poisoning disaster in Iraq has been published at last (52a). The $t_{1/2}$ of MeHg in the blood was used as an indication of the efficacy. The mean $t_{1/2}$ values obtained were as follows: no treatment, 63 days; DMPS, 10 days; thiolated resin, 20 days; D-pen, 26 days; and NApén, 24 days. No adverse effects were seen in any treatment group. A conclusion of the study was that the use of these mercury-mobilizing agents is justified for weeks or months after exposure to MeHg. Such a conclusion is important as it is

not known in what length of time, after MeHg exposure, maximum brain damage occurs.

The most effective agent for removing mercury from the brains of rats given ^{203}Hg -MeHg iv was DMSA, which was better than NApén, which was better than D-pén (52b).

Based on experiments in the dog, the mobilization and removal of MeHg by extracorporeal complexing hemodialysis with DMSA appear very effective and most promising (52c). There is general agreement that BAL should be avoided in treating organic mercury poisoning because in mice the complexes it forms appear to accelerate the distribution of mercury from blood into tissues (53), in particular the brain.

When MeHg was given to pregnant rats, and 1 day later DMSA treatment (40 mg/kg/day) was started, there was a 70% decrease in the mercury content of the brains of progeny pups compared to controls whose dams did not receive DMSA (54a). Okonishnikova & Rozenberg have proposed the use of DMSA to prevent occupational poisoning in the workers of mercury industries (54b).

Treatment of inorganic Hg poisoning appears less complicated. Of 15 metal-binding agents given ip to rats, DMPS appeared to be most effective in enhancing urinary excretion and decreasing tissue Hg of rats given ^{203}Hg C12 iv (55). The biliary excretion of $^{203}\text{Hg}^{2+}$ in rats was increased by DMPS (56). The influence of DMPS and DMSA on the distribution and excretion of mercuric chloride in the rat has been compared (57). DMPS was more efficient in removing inorganic Hg from the body. If maximum tolerated dose is used as the criterion, however, DMSA > BAL > DMPS for increasing the urinary excretion of $^{203}\text{HgCl}_2$ according to the Ding group (25). EKGs of guinea pigs and rats demonstrated that DMSA could prevent the cardiotoxicity caused by iv HgC12 (25). A thiolated resin, which is not absorbed, has been given orally to trap the mercury in the bile. By stopping the enterohepatic recirculation of Hg, the resin increased the fecal excretion (59).

As the importance of the biliary route for the excretion of mercury is increasingly recognized (60), the introduction of N-(2,3-dimercaptopropyl) phthalamidic acid (DMP A) for experimental therapy in the mouse by Yonaga's group (61) is significant. DMP A (75 mg/kg, sc) enhanced the rate of bile flow and the excretion of mercury into the bile in mice given HgC12. This has been suggested as the mechanism for the action of DMP A (61). After DMP A treatment, fecal excretion of Hg increased dramatically; tissue and blood concentrations of Hg decreased. DMP A was more potent than equimolar amounts of either BAL or *DL-pén* in Hg mobilization and excretion. Further studies with this new dimercapto compound will be anticipated with great interest.