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REVIEW ARTICLE

# Metal chelators and neurotoxicity: lead, mercury, and arsenic

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**Abstract** This article reviews the clinical use of the metal chelators sodium 2,3-dimercapto-1-propanesulfonate (DMPS), meso-2,3-dimercaptosuccinic acid (DMSA), and calcium disodium edetate (CaEDTA, calcium EDTA) in overexposure and poisonings with salts of lead (Pb), mercury (Hg), and arsenic (As). DMSA has considerably lower toxicity than the classic heavy metal antagonist BAL (2,3-dimercaptopropanol) and is also less toxic than DMPS. Because of its adverse effects, CaEDTA should be replaced by DMSA as the antidote of choice in treating moderate Pb poisoning. Combination therapy with BAL and CaEDTA was previously recommended in cases of severe acute Pb poisoning with encephalopathy. We suggest that BAL in such cases acted as a shuttling Pb transporter from the intra- to the extracellular space. The present paper discusses if a combination of the extracellularly distributed DMSA with the ionophore, Monensin may provide a less toxic combination for Pb mobilization by increasing both the efflux of intracellularly deposited Pb and the urinary Pb excretion. Anyhow, oral therapy with DMSA should be continued with several intermittent courses. DMPS and DMSA are also promising antidotes in Hg poisoning, whereas DMPS seems to be a more efficient agent against As poisoning. However, new insight indicates that a combination of low-dosed BAL plus DMPS could be a preferred antidotal therapy to obtain mobilization of the intracerebral deposits into the circulation for subsequent rapid urinary excretion.

**Keywords** Metal chelators · DMPS · DMSA · EDTA · Metals

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## Introduction

Chelation is derived from the Greek word chēlē (claw of a lobster). Chelators bind in varying degrees to closely related substances, e.g., metals. The mechanism is the formation of chelator–metal complexes (chelates) that are excreted in urine (Bjørklund 2015). In 1920, Sir Gilbert T. Morgan and Harry D. K. Drew suggested the term chelate for the "caliper-like groups which function as two associating units and fasten to the central atom so as to produce heterocyclic rings" (Morgan and Drew 1920). The use of chelating agents in medicine started about one century ago to alleviate the toxicity of arsenic (As) compounds used for syphilis treatment (Dennie and McBride 1924). In the period 1920–1940, several similar attempts were made to reduce the toxicity of arsenical drugs, which were also used in the treatment of trypanosomiasis (Rosenthal and Voegtlin 1930). In 1941, citrate was tried as an antidote towards acute lead (Pb) intoxication (Kety and Letonoff 1941). Since citrate is metabolically unstable, the success of this experiment was limited. However, it was the beginning of the use of chelation treatment in metal toxicology.

A good chelating agent should reach to the body's metal storage sites and form less toxic metal complexes than the free metal ions. Furthermore, a good chelator should be resistant to biotransformation, be easily soluble in water, and have a high affinity for the toxic metals at the pH of the

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body fluids (Aaseth 1983; Flora and Pachauri 2010). Unfortunately, even today, most available chelators have limited ability to remove metals from the brain tissue, since they do not cross the blood–brain barrier (BBB) (Aposhian 1983; Aposhian et al. 2003).

In cases of metal toxicity, a chelating antidote may be administered intravenously or orally. Depending on the chemical affinity for the toxic metal in question compounds like 2,3-dimercaptopropane-1-sulfonic acid (DMPS, Dimaval, Unithiol), meso-2,3-dimercaptosuccinic acid (DMSA, Succimer), or ethylenediaminetetraacetic acid (EDTA) is given continually for several days or as intermittent courses. The therapeutic response to chelating procedures is related to the way of administration, organ distribution, and, in some cases, previous or combined antioxidant treatment, e.g., with vitamin E, acetylcysteine, or lipoate (Ballatori et al. 1998; Pande and Flora 2002; Kalender et al. 2013).

## Neurotoxicity of lead, mercury, and arsenic

### *Lead*

Lead has high vapor temperature point, and low melting point and its industrial uses are, therefore, widespread (e.g., Pb is used in batteries, pigments, etc.). Industrial applications of inorganic Pb may cause significant environmental pollution. In some countries, Pb intoxication in childhood is still a problem. Lead-containing paint in old houses is a big problem. This is the most important type of Pb exposure in childhood and has been estimated to involve 1 million children in the United States (Gould 2009).

Epidemiological research has revealed that blood lead (BPb) levels lower than 250 µg/L involve a risk for reduced cognitive function in children (Needleman et al. 1990), and the US level of concern is now set to 150 µg Pb/L blood. Classical signs of severe Pb toxicity are ataxia, coma, and convulsions, whereas less severe symptoms of overexposure include anxiety, fatigue, depressed mood, and cognitive problems (Maizlish et al. 1995).

### *Mercury*

Mercury (Hg) exposure may come from different sources, either as inorganic or organic Hg. Among inorganic mercurials, elemental Hg ($Hg^0$) is the most important in human toxicology. Mercury vapor is rapidly absorbed upon inhalation. Elemental Hg is extracted from cinnabar ores and refined by heating. Dental amalgams that still are used in many countries contain elemental Hg. Elemental Hg volatilizes at room temperature. After Hg is taken up in the lungs, it crosses the blood–brain barrier (BBB) rapidly. Intracellularly, it is oxidized to ionic $Hg^{2+}$, which is retained by the brain cells for years (Berlin et al. 2015), explaining the symptoms of chronic toxicity with depression of mood, anxiety, insomnia, tremor, and cognitive problems. Exposure of organic Hg in humans is caused by the consumption of methylmercury (MeHg; $CH_3Hg^+$) polluted fish or from the use of vaccines containing the preservative thimerosal. Organic Hg from vaccines is rapidly metabolized to ethylmercury ($C_2H_5Hg^+$). Ethylmercury and MeHg also pass across the BBB and lead to deposition in brain cells. Although defects in sensory functions are usual presenting symptoms of organic Hg poisoning, cognitive dysfunctions are also reported (Berlin et al. 2015).

### *Arsenic*

Arsenic exposure may result from contaminated groundwater or other sources. Among symptoms reported in residents exposed to As-contaminated drinking water are peripheral neuropathy and cognitive and memory impairment (Kilburn 1997).

Here, it should be recalled that clinical and epidemiological studies have shown correlations between aberrant exposure for Pb, Hg, and As, and several neurodegenerative diseases, including autism spectrum disorder (ASD), Alzheimer's disease, Gulf War Illness, amyotrophic lateral sclerosis, and multiple sclerosis (Chen et al. 2016), actualizing a discussion on presumably efficient metal antidotes for mobilization of brain deposits.

## EDTA

As the first clinically introduced chelator, EDTA was synthesized in 1935 (Hargreaves and Cohen 2011). It is a polyaminopolycarboxylic acid which is a colorless and water-soluble compound (Fig. 1). After World War II, numerous navy personnel who had repainted the hulls of ships got Pb poisoning (Guinee 1972). The patients got EDTA treatment. In 1950, CaEDTA chelation therapy in Pb poisoning was approved by the US Food and Drug Administration (FDA) (Flora and Pachauri 2010). The approved antidote is the calcium salt of disodium edetate (CaEDTA, calcium EDTA), whereas disodium edetate ($Na_2$EDTA, disodium EDTA) may cause hypocalcemia and is not a recommended therapy in Pb poisoning (Gerhardsson and Aaseth 2016).

With four oxygen atoms and two N atoms for metal ion coordination (Fig. 1), EDTA binds extracellular Pb strongly, eliminating the metal rapidly in the urine. Raised urinary excretion of cadmium (Cd) and Hg might also result from CaEDTA treatment (Sears 2013). However, CaEDTA has not been proven successful in the treatment of Cd and Hg poisonings.

CaEDTA is not metabolized and is mostly distributed in extracellular fluid. However, it may to a minor extent redistribute Pb to the brain after acute Pb poisoning (Kazantzis

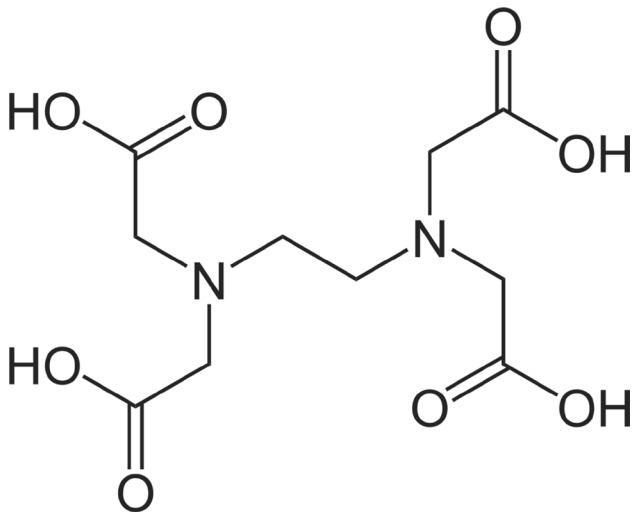


**Fig. 1** Ethylenediaminetetraacetic acid (EDTA) is a polyaminopolycarboxylic acid and a colorless, water-soluble synthetic compound with chemical formula $C_{10}H_{16}N_2O_8$

2007). Overall, CaEDTA leads to a more pronounced reduction of essential minerals such as magnesium, manganese, and chromium than DMPS or DMSA (Sears 2013).

There is some evidence that EDTA treatment can protect rat kidneys from ischemic damage possibly through the stimulation of NO production (Flora and Pachauri 2010). The antidote has since the 1950s been used in the treatment of vascular disease (Clarke et al. 1956; Flora and Pachauri 2010), especially by physicians who practice complementary medicine. The original theory was that EDTA could operate by scavenging calcium from fatty plaques and thereby provoke their breakdown (Clarke et al. 1955). The TACT (Trial to Assess Chelation Therapy) was a randomized, double-blind, placebo-controlled clinical study to evaluate the health effects of EDTA chelation therapy (Lamas et al. 2012). The study was supported by the US National Institutes of Health and was carried out in 1708 nonsmokers who were 50 years or older. The patients in this study had an acute myocardial infarction at least 6 weeks before the trial started and were otherwise medically stable. While 839 of the patients were randomized to the intravenous chelation arm, 869 patients were randomized to placebo. The protocol specified 40 intravenous infusions of at least 3 h each. For the active chelation arm, the chelation solution was composed to match the standard solution used by practitioners of this therapy. Thus, this solution contained not only disodium EDTA (3 g), but also ascorbic acid (7 g), magnesium chloride (2 g), procaine hydrochloride (100 mg), potassium chloride (2 mmol/L), sodium bicarbonate (840 mg), unfractionated heparin (2500 U), thiamine (100 mg), pyridoxine (100 mg), pantothenic acid (250 mg), and sterile water to make up 500 mL of solution. The placebo solution consisted of 500 mL of physiological saline with the addition of glucose (1.2%) (Lamas et al. 2012). The primary endpoints in the study included myocardial infarction, all-cause mortality, hospitalization for angina, stroke, and coronary revascularization (Lamas et al. 2012). As much as 30% of the enrolled patients discontinued this treatment with series of infusions, due to various reasons. During the 4-year period of follow-up, the difference in the primary endpoint, 26.5% in the EDTA group vs. 30.0% in the placebo group, just reached statistical significance ($p = 0.035$). In a pre-specified subgroup analysis, the 31% of the study population with diabetes showed greater benefit for the primary endpoint compared with nondiabetic patients (Escolar et al. 2014). However, the glucose content in infusions to placebos in the diabetic group might have contributed to the apparently positive results of EDTA in the study, since most of the benefit of chelation was seen in diabetic patients. The content of vitamins, minerals, and unfractionated heparin in the chelation arm might also have contributed to their positive observations (Nissen 2013). It should be underlined here that the conventional medical therapy with orally administered drugs, that also possess chelating properties, e.g., captopril and other ACE inhibitors, in comparable clinical conditions, appear to have at least comparable efficacy in reducing myocardial reinfarction, coronary revascularization, and stroke (Pfeffer et al. 1992; Kazantzis 2007; Gerhardsson and Aaseth 2016). Furthermore, serious side effects such as renal function impairment and pronounced hypocalcemia have been reported during EDTA treatment. Surprisingly, these side effects did not occur in the TACT study (Sears 2013), which might be attributed to the extensive panel of supplementations, i.a. with magnesium, manganese, copper, and chromium, given to the enrolled patients. In addition, it might be speculated if a possible minor cardioprotective effect of EDTA might be related to the resolution of oxidative stress (Kuklinski et al. 1994; Ernst 2000), a mechanism suggested for other cardioprotective principles (Alehagen et al. 2015).

However, severe chronic and acute Pb intoxication remain the indications for EDTA chelation (Lee et al. 1995; Besunder et al. 1997; Sánchez-Fructuoso et al. 2002). And the present discussion on the TACT study is included to underline that chelation therapy should only be used in diseases directly related to metal toxicity (Kosnett 2010).

If not properly administered, EDTA treatment can have serious side effects, as already discussed. CaEDTA side effects observed during treatment of Pb poisoning include a febrile reaction with headache, myalgia, nausea, and vomiting (Kazantzis 2007). Ernst reported nine fatal outcomes of EDTA chelation. Even if the causality was not clear in all cases, some were associated with myocardial infarction or cardiac arrhythmias (Ernst 2009). Three deaths associated with EDTA chelation treatment were reported by the Centers

for Disease Control and Prevention (CDC). Hypocalcemia was present in all of these cases. In addition, there seems to have been an inappropriate management in the therapeutic setting in situations with serious side effects, such as lack of adequate clinical monitoring and substitution of minerals and essential metals when needed (Brown et al. 2006). EDTA causes greater losses of essential minerals [zinc (Zn), iron (Fe), Ca and Mg] than DMSA and DMPS (Sears 2013). Other reported side effects of EDTA chelation include glucosuria, hypotension, lacrimation, nasal congestion, and mucocutaneous lesions (Kazantzis 2007). In animals and humans, it has been observed that CaEDTA chelation may redistribute Pb from bone to the brain. Therefore, in severe Pb poisonings, it has been recommended to combine CaEDTA (usual dose: 30–50 mg/kg per day), with orally administered DMSA (Crinnion 2011). In severe cases with encephalopathy, treatment with i.v. infusion of CaEDTA can be combined with parenterally administered DMSA or BAL (Chisolm 1968) during the initial 2 or 3 days (Aaseth et al. 2016) before the treatment regimen is continued with oral DMSA monotherapy (usual dose: 10 mg/kg per day). DMSA is often administered in successive intermittent 5-day courses in such cases (Grandjean et al. 1991; Aaseth et al. 2016). Whereas BPb is lowered during the therapeutic course, a rebound effect is usually observed in the drug-free intervals, explained from a redistribution of Pb from bone and presumably also from the brain (Andersen 1999). In the treatment of cases with moderate or severe Pb poisoning without encephalopathy, i.v., CaEDTA treatment should be replaced by p.o. DMSA monotherapy because of the adverse effects of CaEDTA (Aposhian et al. 1995).

## DMSA

During World War II, BAL (British Anti-Lewisite, 2,3-dimercapto-1-propanol) had been developed by the research group of Rudolph Peters for use in the treatment of As poisoning caused by the toxic gas Lewisite (Peters et al. 1945). BAL treatment was later shown effective in human As and Hg poisonings. Therefore, BAL became the primary metal-binding antidote in the Western world for several decades (Eagle et al. 1946; Stocken 1947; Hruby and Donner 1987; Aposhian et al. 1995; Andersen 1999). It was later replaced by DMSA and DMPS (Hruby and Donner 1987; Aposhian et al. 1995; Andersen 1999), which are water-soluble dithiols and derivatives of BAL (Fig. 2).

The chemical synthesis of DMSA was described in 1949 (Owen and Sultanbawa 1949). It was originally used by Friedman et al. (1954) to increase the antimony (Sb) uptake during treatment of the parasite infection schistosomiasis (Friedman et al. 1954). Liang and co-workers (1957) were the first who demonstrated that DMSA was an efficient metal chelator (Liang et al. 1957). From the mid-1950s, DMSA was studied and used in the treatment of metal poisoning in the Soviet Union (Petrunkin 1956) and China (Liang et al. 1957; Wang et al. 1965; Ding and Liang 1991). In the United States and Europe, researchers recognized and began to use DMPS as well as DMSA in the 1980s (Aaseth and Friedheim 1978; Planas-Bohne 1981; Alexander et al. 1982; Aposhian 1983; Graziano 1986).

DMSA can be given orally, rectally (as suppositories), or intravenously. Whole blood and plasma half-lives and the half-life of elimination of DMSA via urine are less than 4 h in adult humans (Maiorino et al. 1990; Dart et al. 1994). The half-life may be longer in people with Hg or Pb toxicity (Sears 2013). DMSA is hydrophilic and easily absorbed in the gastrointestinal tract. The absorption rate of orally given tablets is around 20% and is dependent on a healthy status of the gut. After the oral administration, 95% of the absorbed DMSA is bound to plasma proteins (albumin) probably with to sulfhydryl groups (Miller 1998). Only a very little amount of DMSA is available as a free drug (Sears 2013). Most of an oral DMSA dose is excreted via urine, another part via the feces. In the body, it is mostly metabolized to various disulfides with cysteine (Aposhian 1983; Moulton et al. 1995; Bradberry and Vale 2009). DMSA is not present in

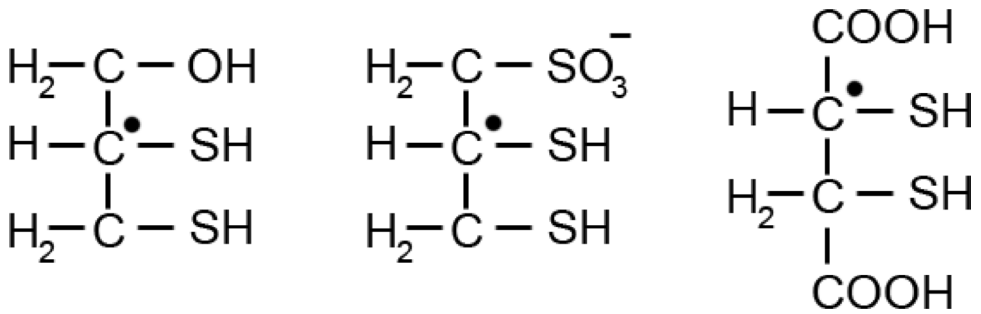


**Fig. 2** Chemical structures of BAL (British Anti-Lewisite, 2,3-dimercapto-1-propanol) with chemical formula $C_3H_8OS_2$ (left), and its water-soluble derivatives, 2,3-dimercapto-1-propanesulfonic acid (DMPS) with chemical formula $C_3H_8O_3S_3$ (in the middle), and dimercaptosuccinic acid (DMSA), with chemical formula $HO_2CCH(SH)CH(SH)CO_2H$ (right). The three molecules have an asymmetric carbon atom that is marked in the figure. Usually, the meso forms are used clinically

significant amounts in red blood cells (RBC), and its distribution is limited to the extracellular space (Maiorino et al. 1990). DMSA enhances urinary excretion of thiophilic metals (Pb, Hg, As, Ag, and Cd), and it has been reported to remove a significant fraction of Pb and MeHg from animal brains (Aaseth et al. 1995). Renal clearance for DMSA is greater in healthy adults than in children (Dart et al. 1994). In a case series of 17 Pb-poisoned adults that got oral DMSA chelation therapy, it increased the average excretion of Pb 12 times and rapidly reversed neurological and gastrointestinal symptoms (Bradberry et al. 2009a).

DMSA is considered to be the optimal antidote for moderate-to-severe Pb intoxication.

The present guidelines (Treatment guidelines for lead exposure in children 1995) involve that environmental Pb removal from the environment is the action of choice at BPb levels in the range up to 450 µg/L (2.2 µmol/L), whereas chelation treatment is recommended at BPb levels above 450 µg/L (2.2 µmol/L), preferably with DMSA (Succimer). DMSA was registered in USA in 1991 to be used as an oral chelator in the treatment of children with BPb > 450 µg/L (FDA 1991). Based on human case and cohort studies, as well as animal experiments, DMSA is recommended as a chelator used in moderate-to-severe Pb poisonings. The combined parenteral treatment with CaEDTA and BAL is more toxic and was not better than DMSA alone. In parenteral intoxicated rats oral DMSA lowered the Pb levels in liver, kidney, brain, and blood more effective than injected EDTA (Flora et al. 1995). Rats with prolonged exposure to Pb in drinking water that repeatedly got doses of DMSA had a substantial reduction in Pb levels in blood, liver, kidney, and brain. However, the Pb levels in bone were not significantly affected. However, when intermittent DMSA treatment courses are administered, Pb levels in blood will increase weeks or months after the periods with DMSA treatment. This phenomenon is known as the rebound effect and is ascribed to a secondary redistribution of Pb from bone to soft tissues (Cory-Slechta 1988).

There have been published many small cohort and case studies of humans with Pb intoxication, who have received chelation treatment: Five lead smelter workers with Pb poisoning were treated with oral DMSA for about 1 week (Friedheim et al. 1978). This treatment reduced the BPb level by about 50%. Nine Pb-poisoned workers were chelated with oral DMSA for at least 5 days. The BPb levels were reduced by around 50% (range 35–81%), and urinary Pb excretion was substantially increased. There were clinical indices after 3-week chelation treatment of these patients that the Pb poisoning had improved or stabilized (Fournier et al. 1988). Gustavsson and Gerhardsson (2005) reported a patient with severe Pb poisoning symptoms after accidental ingestion a Pb bullet in a game meal. Years after the incident, the bullet was removed, and the patient was treated for 1 year with DMSA. This treatment alleviated signs and symptoms (Gustavsson and Gerhardsson 2005).

Rogan et al. (2001) included 780 children in the age 12–33 months who had BPb levels in the exposed range but below 2.2 µmol/L (450 µg/L) into a randomized placebo-controlled double-blind trial of up to three courses of treatment with DMSA or placebo (Rogan et al. 2001). During the first 6 months, the BPb levels in the DMSA group were reduced with 0.22 µmol/L compared to the concentrations in the placebo group. However, DMSA did not improve scores on tests of cognition or neuropsychological function. The investigators concluded that DMSA reduced BPb in the studied range (low-level exposure), but with no benefit in the cognitive and behavioral endpoints (Dietrich et al. 2004). Graziano et al. (1992) treated children with BPb levels above 2.2 µmol/L and found that DMSA decreased BPb and corrected biochemical indices of Pb toxicity (Graziano et al. 1992). The study of Liebelt et al. (1994) confirmed the efficacy and safety of DMSA in cases overexposed to Pb (Liebelt et al. 1994).

These studies suggest that oral DMSA is the most efficient and safe chelation treatment regimen presently available in Pb moderately poisoned cases. Animal and human data indicate that DMSA should be considered the preferred antidote to mobilize Pb from soft tissues (Cao et al. 2015), but bone Pb deposits appear to be more resistant. However, a rebound of BPb levels after chelation courses is observed in any chelation treatment of chronic Pb intoxication. This rebound, apparently due to the mobilization of bone Pb, may call for repeated chelation courses, and a resulting displaced brain-to-blood equilibrium is presumed to extract Pb from the brain. At present, the knowledge about the effects of chelation on Pb-induced neurotoxicity is primarily based on the evaluations of single cases and small groups. However, there are no doubts that chelation in severe poisonings can reduce the neurotoxicity of Pb (Arnold and Morgan 2015).

DMSA has been considered to be the optimal antidote for organic Hg poisoning (Andersen 1999). Thus, DMSA was an effective antidote in animal experiments of acute systemic $CH_3HgCl$ intoxication (Aaseth and Friedheim 1978). DMSA administered orally during an 8-day period after the injection of $CH_3Hg^+$ reduced significantly the Hg level in the brain, an effect that may be secondary to the reduced blood levels rather than true penetration of the antidote across the BBB. Later, DMSA and DMPS were found to ameliorate MeHg-induced developmental toxicity in experimental animals (Domingo 1995). Cao et al. (2011) used blood samples from a randomized clinical study of 767 children who had received DMSA treatment (Cao et al. 2011). The researchers found that mean organic Hg concentration in the DMSA group, compared to placebo, fell with 17% after three courses of treatment ($p$ value 0.048). The modest reduction of blood mercury

(BHg) might be related an organ-to-blood redistribution and thus prevention of the accumulation over time.

In several studies, DMSA, as well as DMPS, effectively increased Hg elimination in animals exposed to inorganic mercuric salts (Aaseth et al. 1982, 1995). Both these dithiols reduced mortality in $HgCl_2$-poisoned animals (Nielsen and Andersen 1991). Roels et al. (1991) found significantly increased Hg excretion in urine of a group of workers exposed to elemental Hg vapor after intake of 2 g DMSA (Roels et al. 1991). They estimated that the excreted Hg mainly reflected Hg depots in the kidneys. Animal experiments have also indicated a good correlation between Hg in urine and reduction of renal depots after DMSA treatment (Buchet and Lauwerys 1989). Apparently, DMSA does not effectively chelate inorganic Hg in the brain (Buchet and Lauwerys 1989; Aposhian et al. 2003; George et al. 2004). Combined data indicate that DMSA, as well as DMPS, are effective chelators in experimental acute organic and to some extent also inorganic Hg intoxication.

The literature shows that DMSA is of benefit in copper (Cu) poisoned laboratory animals (Jones et al. 1981; Aposhian et al. 1989; Pethran et al. 1990), but experimentally DMPS is reported to be more efficient (Jones et al. 1981; Aposhian et al. 1989). Both DMPS and DMSA have in vitro been found to reduce Cu-induced hemolysis of human RBC (Aaseth et al. 1984; Yang et al. 1987). Further research is needed to assess the role of these antidotal agents in the treatment of Cu poisoning or Wilson's disease (Walshe 1984, 1985).

DMSA is effective in the treatment of antimony poisoning (Ding and Liang 1991; Tsopelas 2013). In animal studies, DMSA has been shown to reduce the lethality more than dimercaprol (Ding and Liang 1991). The research found that DMPS and DMSA in mice are the most efficient antidotes in the treatment of antimony potassium tartrate poisoning, and DMSA is the most effective of the two (Basinger and Jones 1981). DMPS has been used with apparent success in pediatric cases of antimony potassium tartrate poisoning (Iffland and Bösche 1987; Jekat and Kemper 1990).

The information on the effect of DMSA on silver (Ag) toxicity is sparse, but the antidote is found to reduce the mortality of Ag chloride and Ag nitrate in mice (Pethran et al. 1990; Ding and Liang 1991). The literature about tin (Sn) and metal chelators, in general, is limited. In a few published studies with mice and rats, DMSA appears to be an antidote against dialkyl tin compounds and dibutyltin dichloride (Hennighausen et al. 1988; Merkord et al. 2000). DMSA was found to be less effective than DMPS against dibutyltin dichloride (Merkord et al. 2000). However, in contrast to DMPS, DMSA provided protection against hemolysis of human erythrocytes incubated with tributyltin (Gray et al. 1986, 1987). No effect of either DMPS or DMSA on palladium (Pd) toxicity is documented in the literature (Mráz et al. 1985; Ruprecht 2008), but the data are limited.

DMSA is the least toxic agent among the dithiol agents (Graziano 1986; Aaseth et al. 2016). It also has the advantage that no significant amounts of essential metal are lost (Fe, Ca, and Mg), although minor changes in the Cu metabolism have been observed (Aposhian et al. 1989). However, DMSA does not significantly cross the cell membrane.

Adverse reactions range from skin reactions, gastrointestinal discomfort, and mild neutropenia to elevated liver enzymes (Aposhian 1983). Rare side effects of DMSA treatment are mucocutaneous eruptions which resolve when the medication is stopped (Ramsey et al. 1996; Grandjean et al. 1997). Miller's meta-analysis (Miller 1998) proved DMSA's efficiency and safety in studies and concluded that it is the first choice antidote to being recommended in Pb and organic Hg poisonings, based on safety, oral dosing, and urinary excretion when compared with other chelating agents. DMSA provocation was also reported to be able to confirm long-term metal exposure when suspected from hair mineral analysis (Blaurock-Busch et al. 2010).

DMSA provocation has been proposed as a diagnostic test for heavy metal intoxication by some authors (Frumkin et al. 2001), while other authors do not recommend provocation tests to assess the body burden of toxic metals at all, because acceptable reference values for post-challenge urine metals have not been established (Aaseth et al. 2015).

## DMPS

In the 1950s, DMPS was invented and first used in the former Soviet Union (Petrunkin 1956; Klimova 1958; Lee et al. 1995; Flora and Pachauri 2010) and was later also used as a drug in China (He et al. 1984) (Fig. 2). HEYL Chem.-pharm. Fabrik GmbH und Co. KG in Berlin introduced in the early 1970s DMPS on the German market for oral administration (Ruprecht 2008). Nowadays, the active substance is available in various countries as a prescription drug in capsule form for oral treatment (1 capsule Dimaval® contains 100 mg DMPS), and in 5-ml ampoules (DMPS-Heyl®), containing 250-mg DMPS for intravenous application. DMPS treatment is in Germany approved for Hg poisoning. In the United States, the antidote is not approved. Therefore, physicians in the US cannot prescribe it without special permission from the Food and Drug Administration. However, American pharmacies are allowed to compound DMPS (Flora and Pachauri 2010). The usual daily dose varies between 3 and 10 mg/kg body weight. For oral DMPS, the absorption rate has been reported to be approximately 40% (Hurlbut et al. 1994), which is higher than the absorption rate of DMSA (Maiorino et al. 1994). Upon parenteral use, DMPS is usually given intravenously even if intramuscular applications do exist. It is quickly converted into a disulfide form. The

half-life of DMPS in the various organs is about 20 min, and the distribution is not dose-dependent (Gabard 1978). In other organs, particularly the brain, relatively small concentrations were found in animal experiments (Aposhian 1983). The main part is excreted via the urine and some via bile with a half-life of 20 h after administration on average (Aaseth et al. 2015). It has been recommended to monitor essential minerals (Cu, Zn, Se, and Mg) and give supplements if required, before and after treatment (Torres-Alanís et al. 2000). It is hydrophilic and exists mostly in the extracellular space, while a fraction may enter the intracellular compartment (Andersen 1999).

Many studies prove its efficiency to chelate metals in the body (Graziano 1986). It increases the urinary excretion of several metals (As, Cd, Pb, Hg, Cu, and Zn). Treatment with DMPS results in some increase in the urinary excretion of Cu and Zn (Rooney 2007; Joshi et al. 2008), which, in some patients, may give deficiency symptoms. Therefore, it is recommended to monitor Cu and Zn levels during such chelator therapy (Kaji 2004). DMSA is less toxic and affects less body's mineral balance than DMPS (Joshi et al. 2008). Therefore, when the two antidotes otherwise are considered equivalent, DMSA should be used (Aschner et al. 2006; Bjørklund 2015).

DMPS has been considered to be the antidote of choice in inorganic Hg poisoning (Andersen 1999; Rafati-Rahimzadeh et al. 2014). For example, a 38-year-old man was first treated with BAL after intake of a hazardous dose of a HgCl2 solution. During this regimen, he developed acute renal failure, before he received intravenous treatment with DMPS in combination with hemodialysis. Despite continuing high BHg levels, his kidney function improved, and parenteral DMPS was given for 4 weeks, after which the patient recovered (Toet et al. 1994). In an occupational setting, eight workers had been exposed to mercuric chloride by the production of a calomel skin-bleaching lotion. Upon treatment with DMPS, p.o., the researchers observed greatly increased urinary Hg and substantially lowered burden of Hg after three courses of DMPS (Gonzalez-Ramirez et al. 1998). Human and experimental data support that DMPS is very effective in the treatment of acute and chronic inorganic Hg poisonings (Böse-O'Reilly et al. 2003), while DMSA appears to be the drug of choice in over exposure to organic Hg compounds. A challenge for further research is to mobilize $Hg^{++}$ from the brain after elemental $Hg^{0}$ vapor exposure. It might be supposed that combination of DMPS with lipophilic chelator could bring about a transfer of $Hg^{++}$ from the brain to blood and thus act as a 'shuttle' for the extracellularly operating DMPS.

DMPS is also efficient in As poisoning (Gersl et al. 1997; Guha Mazumder et al. 2001). It has been reported that modest As intoxication can be adequately treated with DMPS p.o. In a study by Guha Mazumder et al. (2001), therapy with DMPS significantly improved the condition of patients with chronic As intoxication caused by As polluted drinking water (Guha Mazumder et al. 1998). In a similar setting, DMSA was without significant clinical efficacy (Guha Mazumder et al. 1998), an observation which is consistent with other studies (Stenehjem et al. 2007).

There is relatively little information about the effect of DMPS on Ag toxicity, but some studies show that the antidote reduces the toxicity of Ag in dogs and mice (Romanov 1967; Pethran et al. 1990).

DMPS has been demonstrated to be a better chelator than DMSA to remove inorganic Hg from the kidney and to a minor extent from brain (Aposhian 1983; Aaseth et al. 1995). DMPS was shown to reduce the Hg load in rats via the multidrug resistant protein (Mrp2) (Bridges et al. 2008, 2011). Bradberry et al. (2009a, b) describe a patient with considerable neurological symptoms due to Hg poisoning, which after treatment with DMPS were reversed (Bradberry et al. 2009b). A paper from the Philippines describes DMPS treatment in patients with high Hg levels. The patients were from a gold mining community, and most of them improved significantly after a 2-week treatment (Böse-O'Reilly et al. 2003).

For Hg, it has been indicated that DMPS and DMSA form simple complexes rather than true chelates (George et al. 2004). This in vitro study has precipitated the assumption that they are suboptimal as metal antidotes. However, no other antidotes are currently available with the same advantages as these two chelating agents with relatively low toxicity and high water solubility.

Diagnostically, tests utilized to diagnose a chronic metal intoxication involve blood and urine testing (Chang et al. 1996; Nordberg et al. 2007). Both indicator media reflect recent exposure to food, drink, and air. A provocation test consists of two urine samples, one is taken before, and the other is taken after the use of a chelator (Aposhian et al. 1997). Because DMPS is capable of binding with most toxic metals, it is the chelating agent commonly used as a general provocation test for toxic metal screening. For the DMPS provocation test, the urine metal concentration is measured before and after application of either the oral or intravenous application. By comparing test values, the metal burden may be assessed. However, reliable reference intervals for healthy individuals are still lacking.

### Combination of chelators to mobilize lead, mercury, and arsenic

In conjunction with Monensin, a polyether antibiotic, DMSA proved to be even more efficient in mobilization Pb from brain and kidneys than when used alone. The proposed mechanism for this is that Monensin can act as a shuttle for Pb out of cells, in exchange for external sodium

ions. This would induce an efflux of Pb also from cerebral deposits to the extracellularly acting dimercaptosuccinic acid thereby enhancing its effectiveness (Hamidinia et al. 2006). Recent studies have shown that DMSA is safer than CaEDTA as far as extracellular scavenging of lead is concerned, since the Pb–EDTA complex might be redistributed to the brain (Aaseth et al. 2016). MiADMSA (monoisoamyl-2,3-dimercaptosuccinic acid) is an analog of DMSA that is capable of crossing biomembranes. Treatment with MiADMSA in combination with DMSA is currently in the development to be used in the future (Flora and Pachauri 2010; Aaseth et al. 2016).

In rat experiments, it has been found that MiADMSA can reduce tissue levels of glutathione disulfide, chelate intracellular Cd und reduce oxidation reactions (Flora and Pachauri 2010). DMSA monoesters have a lower toxicity and a higher affinity than DMSA diesters against As intoxication. They are, therefore, a better treatment option (Flora and Pachauri 2010). In combination with N-acetylcysteine, MiADMSA significantly reduced the oxidative stress induced by chelation therapy (Kannan and Flora 2006).

Veno-venous haemodiafiltration (CVVHDF) has been proposed for cases of acute Hg poisoning in conjunction with DMPS (Boscolo et al. 2009). Dargan reported a case of a man with severe Hg poisoning (1 g mercuric sulfate) who had presented with acute hematemesis and had rapidly deteriorated in the emergency room. He was saved by the combination of the two methods. He had developed no neurological symptoms and was symptom-free 5 months after his 50 days in the hospital (Dargan et al. 2003). In chronic cases, mobilization of intracerebral deposits of inorganic Hg is difficult. Further studies are fully justified to explore the potential benefits of combination therapy of the water-soluble DMPS with possible shuttling agents such as MiADMSA or BAL.

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