Molecular Mechanisms of *in Vivo* Metal Chelation: Implications for Clinical Treatment of Metal Intoxications

Ole Andersen[1] and Jan Aaseth[2]

[1]Department of Life Sciences and Chemistry, Roskilde University, Roskilde, Denmark; [2]Department of Medicine, Kongsvinger Hospital, Kongsvinger, Norway

Successful *in vivo* chelation treatment of metal intoxication requires that a significant fraction of the administered chelator in fact chelate the toxic metal. This depends on metal, chelator, and organism-related factors (e.g., ionic diameter, ring size and deformability, hardness/softness of electron donors and acceptors, route of administration, bioavailability, metabolism, organ and intra/extracellular compartmentalization, and excretion). *In vivo* chelation is not necessarily an equilibrium reaction, determined by the standard stability constant, because rate effects and ligand exchange reactions considerably influence complex formation. Hydrophilic chelators most effectively promote renal metal excretion, but they complex intracellular metal deposits inefficiently. Lipophilic chelators can decrease intracellular stores but may redistribute toxic metals to, for example, the brain. In chronic metal-induced disease, where life-long chelation may be necessary, possible toxicity or side effects of the administered chelator may be limiting. The metal selectivity of chelators is important because of the risk of depletion of the patient's stores of essential metals. Dimercaptosuccinic acid and dimercaptopropionic sulfonate have gained more general acceptance among clinicians, undoubtedly improving the management of many human metal intoxications, including lead, arsenic, and mercury compounds. Still, development of new safer chelators suited for long-term oral administration for chelation of metal deposits (mainly iron), is an important research challenge for the future. *Key words:* BAL, British antilewisite, clinical chelation, dimercaptopropionic sulfonate, dimercaptosuccinic acid, DMPS, DMSA, metal intoxication. *Environ Health Perspect* 110(suppl 5):887–890 (2002).
http://ehpnet1.niehs.nih.gov/docs/2002/suppl-5/887-890anderson/abstract.html

Various human metal intoxications have been treated efficiently by administration of a chelating agent. However, complexation reactions in the human body are influenced by a multitude of factors, including competing metals and ligands, dynamics of circulation, compartmentalization, and metabolism of the chelating agent. Accordingly, *in vivo* chelation reactions may differ extensively from what would be expected from our chemical knowledge about the metal and the chelating agent. Chelating agents can affect metal toxicity by mobilizing the toxic metal into (mainly) urine. However, an important effect of chelation is reduction of metal toxicity. A chelating agent forming a stable complex with a toxic metal may shield biological targets from the metal ion, thereby reducing the local toxicity (*1,2*), even at times after administration when mobilization has not yet occurred, or it may expose the metal to the biological environment and thereby increase the toxicity of the metal. For example, desferrioxamine (DFOA) completely covers the surface of Fe^{3+} during complex formation, thereby preventing iron-catalyzed free radical reactions (*3,4*); however, ethylenediamine-tetraacetic acid (EDTA) is not able to shield the surface of the Fe^{3+} ion but forms an open complex ("basket complex"), thereby increasing the catalytic capacity of Fe^{3+} for generating oxidative stress by about one order of magnitude (*5*).

The oral use of chelating agents is generally considered to require that further exposure to the metal cease in order to avoid chelator-mediated increased intestinal metal absorption. However, orally administered chelating agents forming hydrophilic metal complexes may efficiently reduce intestinal metal uptake and local toxicity at early times after oral intoxication. This was shown for the diethylenetriamine pentaacetic acid (DTPA) complex of Cd^{2+} (*6*). Also orally administered dimercaptosuccinic acid (DMSA) reduced the intestinal uptake and toxicity of oral Cd^{2+} (*2*). Chelation of Ni^{2+} with EDTA and Hg^{2+} with DMSA or dimercaptopropionic sulfonate (DMPS) (*7*) reduced intestinal uptake. Accordingly, oral administration of chelating agents may in some cases offer both reduction of local toxicity and prevention of intestinal metal uptake (*1,2,8*).

Thermodynamic Considerations

In simple cases of formation of metal complexes with polydentate ligands, $M + L_i \rightarrow ML_i$, where M represents the solvated electron pair–accepting metal ion and L_i represents a chelator with i electron-pair–donating ligands (Lewis bases and acids), the overall stability constants is

$$\beta_i = \frac{[ML_i]}{[M][L_i]}. \qquad [1]$$

The stability of this complex depends on $\Delta G = \Delta H - T\Delta S = RT \ln\beta_i$. For a complex with i ligands not associated in one molecule, the change in enthalpy related to bonding often contributes considerably to the free energy because the unfavorable entropy change associated with ordering i independent ligands around one ion counteracts the entropy effect of desolvation of the groups. Accordingly, multidentate ligands form more stable complexes than unidentate ligands because of the fully available entropy contribution from desolvation, and the stability in general increases with the number of rings formed. If one assumes that the enthalpy change due to complex formation does not depend on whether the donor groups are independent or joined in a multidentate ligand (which is not always true, however), the chelate effect should be entirely due to the entropy change. The entropy contribution is indeed often the primary determinant of increased stability of metal complexes with multidentate ligands, but when mutual repulsive forces between charged groups are overcome by introducing them into one molecule, a considerable enthalpy effect may result. This may be illustrated by the thermodynamics of iminodiacetic acid (IDA) and EDTA complex formation with Cd^{2+} (Table 1, Figure 1). Even though the two complexes have the same number of groups (six) available for chelation, the number of rings is increased by one in the EDTA complex, increasing the entropy contribution to stability. Further, assembling the four negatively charged carboxyl groups in EDTA increases the enthalpy contribution. It can easily be calculated that the two contributions are of similar size.

The size of the chelate effect can be visualized from the change in log β for complexes with multidentate ligands with increasing numbers of identical donor groups. Thus, the stability of the Cd complexes with the polyaminopolycarboxylic acids increases in the following series: IDA with three donor groups and log β = 5.71; nitrilotriacetic acid with four donor groups and log β = 9.78; EDTA with six donor groups and log β = 16.36; and

This article is part of the monograph *Molecular Mechanisms of Metal Toxicity and Carcinogenicity.*

Address correspondence to O. Andersen, Dept. of Life Sciences and Chemistry, Roskilde University, Postbox 260, 4000 Roskilde, Denmark. Telephone: 45-4674-2417. Fax: 45-4674-3011. E-mail: Andersen@ruc.dk

Received 18 February 2002; accepted 30 May 2002.

DTPA with eight donor groups and log β = 19.00 (*9*). Similar effects are seen with the series of homologous polyamines, where log β for the Cd complexes increases from 5.45 to 16.10 when the number of donors increases from two to five (*9*). Steric conditions (e.g. ion size and ring size) considerably influence the stability, mainly through changes in Δ*H*.

Hardness/Softness of Metal Ions and Ligands

Determining factors for complex stability are the hardness/softness (HS) characteristics of electron donors and acceptors, discussed in the classical work by Schwarzenbach (*10*) and Ahrland et al. (*11*) and further elaborated into the hard and soft acids and bases (HSAB) concept by Pearson (*12*). The HS characteristics of donor and acceptor atoms in complexation reactions determine not only stability of the formed complex but also the chelator's degree of metal selectivity in relation to competing essential metals present in biological fluids. Further, the HS character determines the selectivity of the toxic metal for the chelator in relation to the competing biological ligands, often available at high concentrations compared with that of the chelating agent. Softness character is related to the ability of the empty frontier orbital of metal ions to accept electrons and to the deformability of the outermost occupied electron orbital of donor groups—that is, the propensity of metals and donors for forming covalent bonds. The ionic index, Z^2/r, where Z and r are the ion's charge and radius, respectively, is positively related to degree of ionic bonding in an ion's complexes. Conversely, the softness of an ion increases with the size of sum of the ionization energies divided by the ionic index (*13*), rI/Z^2. Nieboer and Richardson (*14*) described softness by the covalent index, $X_m^2 r$, where X_m is the electronegativity. The rationale is that X_m is related to the ion's empty frontier orbital energy and thereby to the ion's ability to accept electrons and form covalent bonds. In brief, metal ions and donor groups prefer to form complexes with partners having similar HS character; however, the stability of complexes increases with the softness of both metal and donor. Thus, for a series of cadmium complexes with simple tridentate ligands, made by substituting the imino H in IDA with different functional groups, log β increases from 5.71 (R = H) or 6.75 (R = CH_3) to 9.78 (R = COO^-), 10.53 (R = NH_2), or even 16.72 (R = SH) (*9*):

$$RN(COO^-) + Cd^{2+} \rightarrow Cd^{2+}RN(COO^-). \quad [2]$$

For another series of complexes, log β varies between 12.43 (R = CH_3) and 22.33 (R = SH) (*9*):

$$2RN(COO^-)_2 + Cd^{2+} \rightarrow Cd^{2+}[RN(COO^-)_2]_2. \quad [3]$$

Table 1. Thermodynamics of complex formation of Cd with IDA and EDTA.

Chelator	Complex	log *K*	ΔH	ΔS
IDA	CdL_2	1,019	–55	29
EDTA	Cd*L*	1,646	–91	44

Data from Martell and Smith (*9*).

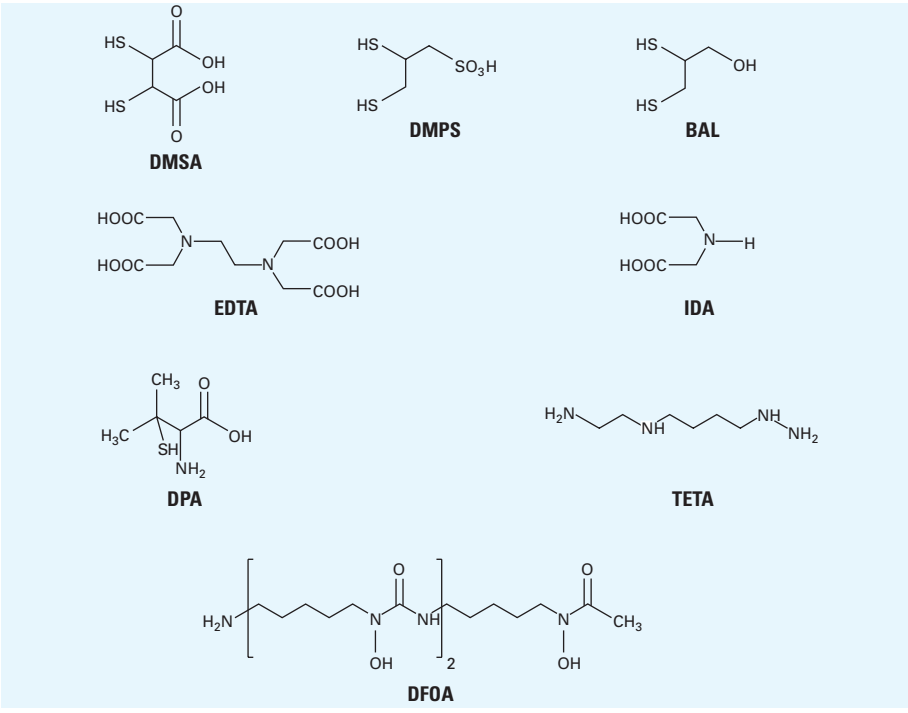

Figure 1. Chelating agents considered in this review. DPA, D-penicillamine; TETA, triethylenetetramine.

Competition, Rate Effects during Ligand Exchange, and Toxicokinetics

The concentrations of "free" toxic metals are often very low in biological systems because of the availability of numerous small biological ligands forming mixed aquo-bioligand complexes with metals. Therefore, complexation reactions *in vivo* between toxic metals and "therapeutic" chelating agents most often occur as a series of ligand and/or metal exchange reactions. Even if the equilibrium constant is highly favorable, complex formation *in vivo* may be limited because of rate effects, competition by other ligands/metals, and systemic transport kinetics of the chelator. Under physiological conditions, numerous small mono- and bidentate ligands as well as functional groups in proteins participate in chelation reactions and compete for chelating agents. Ca^{2+}, present at a concentration of about 1 mM, is the most important metal species competing for clinical chelating agents. Anticipating that equilibrium is achieved, and that the *ML* complex is quantitatively excreted in urine, the efficiency, *E*, of a chelating agent for mobilizing a toxic metal can be described as

$$E = \frac{[ML]}{[M]} \quad [4]$$

because the potential for mobilizing the metal depends on the degree of formation of the *ML* complex. In the simple situation of one major biological competing metal, Ca^{2+}, and a total chelator concentration L_t, the conditions for a large *E* can be visualized from the standard stability constants:

$$E = \frac{[ML]}{[M]} = \beta_{ML} \times [L]. \quad [5]$$

By introducing the stability constants for the metal and calcium complexes into this expression and defining the concentration of L_t as the sum of all forms of the chelator in plasma, Schubert (*15*) derived

$$E = \frac{\beta_{ML}}{\beta_{CaL}} \times \frac{[L_t]}{[Ca^{2+}]}. \quad [6]$$

The mechanisms and kinetics of ligand exchange reactions have been extensively reviewed by Margerum et al. (*16*). They supply data for a range of divalent ions, that the rates of both solvent exchange and ligand exchange are related to the HS character of electron donors and acceptors. The rate of

complex formation depends on whether the chelator can easily get a grip on the metal ion by displacing a solvent molecule or a monodentate ligand to obtain the initial coordination site. The nature of this ligand exchange reaction determines whether the formed mixed complex is more or less stable than the disrupted complex. If a more stable complex is formed, further ligand exchange reactions are thermodynamically facilitated, sometimes even when subsequent ring opening is involved. The next step is formation of the first ring by coordinating a second donor group of the multidentate ligand to the metal ion, whereby the chelate effect decreases the rate of dissociation of the complex. Such processes may occur at a reasonable speed. If the initial complexation reaction involves breaking a preexisting chelate ring formed with a biological multidentate ligand, the process is often much slower. Besides the number of donor groups available for electron pair donation, that is, the maximum number of rings formed contributing to the chelate effect (the HS character of these donors), steric conditions for simultaneous access of ligands to coordination positions on the metal ion determine formation rate and overall stability. Also, lipophilicity, metabolic stability, and rate of (most often urinary) clearance are important.

Because of the complexity of biological systems, effects of antidotal chelators are often better described quantitatively from results of animal experiments or clinical treatments than by theoretical calculations of, for example, *E*. Increased mobilization of the toxic metal in experimental animals or humans, most often evaluated from urinary output, and decreased mortality or toxicity among exposed animals are major end points. The mobilizing effectiveness (ME) is expressed either as the factorial increase MEF in urinary and fecal excretion between treated and un- or pretreated animals or humans, or as the fractional retention MEQ of the metal in organs of treated animals relative to controls (*17*). The therapeutic effectiveness (TE) may be expressed for acute metal intoxication by the factorial change TEF in LD_{50} (the dose killing 50% of exposed animals) due to the chelation treatment (*17*). Similarly, two chelators may be compared from results of animal experiments by their relative potency, which is the ratio between equally effective doses, or by their relative efficiency (RE) the ratio of effects at equimolar doses (*17*). Because the efficiency of different chelators toward acute metal toxicity may vary extensively in some combinations allowing 100% survival even after doses considerably higher than LD_{99} (*1*,*2*), the RE method has limited applicability.

New Paradigms in Clinical Chelation Treatment: The Exit of BAL

EDTA, D-penicillamine, and British antilewisite [2,3-dimercaptopropanol (BAL)] came into clinical use after World War II to treat lead and mercury intoxication, and copper intoxication in Wilson disease (*18*), which is today treated with triethylenetetramine (*19,20*). In 1962, DFOA was shown to increase urinary iron excretion in patients with thalassemia (*21*). Today, DFOA is also used to treat aluminum intoxication and iron storage toxicity in sickle cell anemia patients. During the 1950s DMSA and DMPS came into use in China (*22–24*) and the Soviet Union (*25,26*). Since the 1970s these drugs have been available as experimental drugs in the Western countries. DMSA and DMPS are efficient antidotes for intoxications with several divalent metals besides lead and mercury as well as some organometal or metalloid compounds (*8*,*27*). Both chelators are available as tablets for oral administration, which are stable for long periods at room temperature, and DMPS also as a dry preparation for parenteral administration after hydration. In China, DMSA has been administered parenterally to hundreds of patients (*22*). BAL is unstable, susceptible to oxidation, and difficult to store as a ready-for-use preparation. It has a low therapeutic efficacy in most cases, and because of high toxicity, BAL is suited only for brief treatment of acute intoxications. It can be administered only by intramuscular injection, normally in peanut oil. Administration of local anesthesia beforehand is necessary because the injection is very painful. Presently available experience indicates that DMSA or DMPS can substitute for BAL in most clinical situations, resulting in safer and more efficacious treatment.

Side Effects and Toxicity of BAL, DMSA, and DMPS

A considerable fraction of individuals treated with BAL experience unpleasant side effects, including nausea, vomiting, sweating, high fever, hypertension, and tachycardia. BAL administration increased the brain deposition of arsenite (*28*) and organic mercury compounds (*29*) and increased the toxicity of cadmium (*30*) and lead (*31*) in animal experiments. DMPS does not redistribute arsenic, lead, or inorganic mercury to the brain (*28*,*32*), and DMSA chelation decreases the brain deposition of lead (*33*) and methylmercury (*34*). BAL is significantly more toxic than DMPS, which is slightly more toxic than DMSA. Representative LD_{50} values selected from the large number of published toxicity studies are are given in Table 2.

In the only reported case of a DMSA overdose, a 3-year-old girl ingested approximately 2.4 g DMSA or 185 mg/kg body weight without clinical signs of intoxication (*40*). During the last two decades, many patients have been treated with DMSA in the United States and with DMPS in Europe, with a very low frequency of toxic side effects necessitating discontinued treatment. Adverse reactions during treatment with DMSA or DMPS include gastrointestinal discomfort, skin reactions, mild neutropenia, and elevated liver enzymes. For both compounds, symptoms may subside, allowing continued therapy. DMPS seems to be better tolerated than is DMSA with respect to gastrointestinal symptoms but may cause hypotension, especially after rapid intravenous infusion. Some patients, especially those with allergic asthma symptoms, may develop hypersensitivity to DMPS (*41*,*42*).

For DMSA two serious reactions to therapy have been reported: DMSA chelation of a man with chronic lead intoxication was discontinued because of a strong mucucutaneous reaction to the drug (*43*). A 45-year-old African-American man developed hemolytic anemia during DMSA chelation for occupational lead intoxication. After cessation of treatment, the hematological values normalized. The patient was glucose 6-phosphate dehydrogenase deficient, a genetic trait known to contraindicate BAL chelation because of risk of hemolysis (*44*). For DMPS, severe toxicity has not been reported in peer-reviewed literature except for a case of Stevens-Johnson syndrome in a lead-intoxicated patient after eight daily oral doses of 200 mg/m^2 DMPS (*45*). DMSA is registered in the United States as a drug for treatment of lead intoxication. DMPS is registered in Germany for treatment of mercury intoxication; however, it is not approved in the United States, so unless special permission is given by the U.S. Food and Drug Administration, it is not lawful for physicians to use it in the United States, nor is it lawful for pharmacies to compound it. Still, DMPS is being illegally used by members of the alternative health industry to treat people allegedly suffering from mercury intoxication, most often claimed to be due to amalgam

Table 2. Representative LD_{50} values for clinically relevant dimercapto chelating compounds.

Compound	Species	Administration route	LD_{50}	Reference
BAL	Mouse	Intraperitoneally	90–180 mg/kg	(*35,36*)
DMSA	Mouse	Orallly	4.34 g/kg	(*37*)
DMSA	Mouse	Intraperitoneally	2.48 g/kg	(*38*)
DMPS	Mouse, rat	Intraperitoneally	1.1–1.4 g/kg	(*28,39*)

fillings. Similar uses occur in European countries. Anecdotal information suggests that a very low fraction of individuals develops severe reactions after parenteral administration of DMPS.

Conclusions and Directions of Future Studies

During the last 15 years DMSA and DMPS have gained more general acceptance among clinicians, undoubtedly improving the management of many human metal intoxications. Still, knowledge is needed in several basic research areas of *in vivo* chelation of metals, for example,

- molecular mechanisms of action of clinically important chelators
- intracellular and extracellular chelation in relation to mobilization of aged metal deposits and the possible redistribution of toxic metal to sensitive organs such as the brain
- effects of chelators on metal biokinetics during continued exposure to the metal, especially possible enhancement or reduction of intestinal metal uptake
- combined chelation treatment with lipophilic and hydrophilic chelators, which presently has a minimal clinical role
- minimization of the mobilization of essential trace elements during long-term chelation
- fetotoxic and teratogenic effects of chelators
- development of orally administrable chelators
- development of less toxic chelators for chronic treatment of genetic metal storage diseases

Especially the two last points, continued development of orally administrable chelating agents for efficient, nontoxic mobilization on a home-patient basis over extended time periods (even life-long chelation) of aged deposits of toxic metal (e.g., Al, Cd, Fe, Hg, and Cu) will probably be a main future research issue. Also, extensive animal experiments comparing the efficacies of classical chelators (especially BAL) with those of DMSA and DMPS in acute intoxications using relevant exposure routes (i.e., oral administration of relevant species of the metals, as well as inhalation of Hg vapor) is a prerequisite for phasing out the old chelators in uses where more effective alternatives are now available.

References and Notes

1. Andersen O. Oral cadmium exposure in mice: toxicokinetics and efficiency of chelating agents. CRC Crit Rev Toxicol 20:83–112 (1989).
2. Andersen O. Choice of chelating antidotes for acute cadmium intoxication. Toxicol Environ Chem 23:105–120 (1989).
3. Halliwell B. Protection against tissue damage *in vivo* by desferrioxamine: what is its mechanism of action? Free Rad Biol Med 7:645–651 (1989).
4. Tilbrook GS, Hider RC. Iron chelators for clinical use. Metal Ions Biol Syst 35:691–730 (1998).
5. Singh S, Khodr H, Tayler MI, Hider RC. Therapeutic iron chelators and their potential side-effects. Biochem Soc Symp 61:127–137 (1995).
6. Andersen O, Nielsen JB, Svendsen P. Oral cadmium chloride intoxication in mice: effects of chelation. Toxicology 52:65–79 (1988).
7. Nielsen JB, Andersen O. Effect of four thiol containing chelators on disposition of orally administered mercuric chloride. Hum Exp Toxicol 10:423–430 (1991).
8. Andersen O. Principles and recent developments in chelation treatment of metal intoxication. Chem Rev 99:2683–2710 (1999).
9. Martell AE, Smith RE, eds. Critical Stability Constants, Vols 1–4. New York:Plenum Press, 1974–1977.
10. Schwarzenbach G. Organic complex forming compounds. Experientia (suppl 5):162–192 (1956).
11. Ahrland S, Chatt J, Davies NR. The relative affinities of ligand atoms for acceptor molecules and ions. Quant Rev Chem Soc 12:265–276 (1958).
12. Pearson RG, ed. Hard and Soft Acids and Bases. Stroudsburg, PA:Dowden, Hutchinson and Ross, 1973.
13. Williams RJP, Hale JD. The classification of acceptors and donors in inorganic reactions. Struct Bond 1:249–281 (1966).
14. Nieboer E, Richardson DHS. The replacement of the nondescript term "heavy metals" by a biologically and chemically significant classification of metal ions. Environ Pollut 1:3–26 (1980).
15. Schubert JS. Einige medizinische und biologische anwendungen von chelatkomplexen. Chimia 11:113–114 (1957).
16. Margerum DW, Cayley GR, Weatherburn DC, Pagenkopf GK. Kinetics and mechanisms of complex formation and ligand exchange. In: Coordination Chemistry, Vol 2 (Martell AE, ed). ACS Monograph 174. Washington, D.C.:Americal Chemical Society, 1978;1–220.
17. Catsch A, Harmuth-Hoehne AE. Pharmacology and therapeutic applications of agents used in heavy metal poisoning. Pharmacol Ther A1:1–118 (1976).
18. Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. Am J Med 21:487 (1956).
19. Walshe JM. Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. Q J Med 42:441–452 (1973).
20. Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine). Lancet 1:643–647 (1982).
21. Smith RS. Iron excretion in thalassemia major after administration of chelating agents. Br J Med 2:1577–1582 (1962).
22. Ding G-S, Liang Y-Y. Antidotal effects of dimercaptosuccinic acid. J Appl Toxicol 11:7–14 (1991).
23. Liang YI, Shi J, Chen L, Ding G. Studies on antibilharzial drugs VI. The antidotal effects of sodium dimercaptosuccinate and BAL-glucoside against tartar emetic. Acta Physiol Sinica 21:230–234 (1957).
24. Wang CS, Ting KS, Wu CC. Chelating therapy with Na-DMS in occupational lead and mercury intoxications. Chin Med J 84:437–439 (1965).
25. Petrunkin VE. Synthesis and properties of dimercapto derivatives of alkylsulfonic acids. I: Synthesis of sodium 2,3-dimercaptopropylsulfonate (unithiol) and sodium 2-mercaptoethyl sulfonate. Ukr Khim Zh 22:603–607 (1956).
26. Petrunkin VE. The synthesis of thiolic compounds as antidotes of arsenic and heavy metals. Trudy Nauch Konf Kiev 7–18 (1959).
27. Aposhian HV, Maiorino RM, Gonzales-Ramirez D, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Dart RC, Aposhian MM. Mobilization of heavy metals by newer, therapeutically useful chelating agents. Toxicology 97:23–38 (1995).
28. Hoover TD, Aposhian HV. BAL increases the arsenic-74 content of rabbit brain. Toxicol Appl Pharmacol 70:160–162 (1983).
29. Berlin M, Ullberg S. Increasing uptake of mercury in mouse brain caused by 2,3-dimercaptopropanol (BAL). Nature 197:84–85 (1963).
30. Dalhamn T, Friberg L. Dimercaprol (2,3-dimercaptopropanol) in chronic cadmium poisoning. Acta Pharmacol Toxicol 11:68–71 (1955).
31. Germuch FG, Eagle H. The efficacy of BAL (2,3-dimercaptopropanol) in the treatment of experimental lead poisoning in rabbits. J Pharmacol Exp Ther 92:397–410 (1948).
32. Aposhian MM, Maiorino RM, Xu Z, Aposhian HV. Sodium 2,3-dimercapto-1-propanesulfonate (DMPS) treatment does not redistribute lead or mercury to the brain of rat. Toxicology 109:49–55 (1996).
33. Cory-Slechta DA. Mobilization of lead over the course of DMSA chelation therapy and long term efficiacy. J Pharmacol Exp Ther 246:84–91 (1988).
34. Aaseth J, Friedheim EA. Treatment of methyl mercury poisoning in mice with 2,3-dimercaptosuccinic acid and other complexing thiols. Acta Pharmacol Toxicol 42:248–252 (1978).
35. Zvirblis P, Ellin RI. Acute systemic toxicity of pure dimercaprol and trimercaptopropane. Toxicol Appl Pharmacol 36: 297–299 (1976).
36. Stine ER, Hsu C-A, Hoover TD, Aposhian HV, Carter DE. *N*-(2,3-Dimercaptopropyl)phthalamidic acid: protection, *in vivo* and *in vitro*, against arsenic intoxication. Toxicol Appl Pharmacol 75:329–336 (1984.
37. Stohler HR, Frey JR. Chemotherapy of experimental *Schistosomiasis mansoni*—influence of dimercaptosuccinic acid on toxicity and antischistosomal activity of sodium antimony dimercaptosuccinate and other antimony compounds in mice. Ann Trop Med Parasitol 58:431–438 (1964).
38. Aposhian HV, Carter DE, Hoover TD, Hsu C-A, Mariano RM, Stine E. DMSA, DMPS and DMPA as arsenic antidotes. Fundam Appl Toxicol 4:S58-S70 (1984).
39. Aposhian HV, Tadlock CH, Moon TE. Protection of mice against lethal effects of sodium arsenite—a quantitative comparison of a number of chelating agents. Toxicol Appl Pharmacol 61:385–92 (1981).
40. Sigg T, Burda A, Leikin JB, Gossman W, Umanos J. A report of pediatric succimer overdose. Vet Hum Toxicol 40:90–91 (1998).
41. McNeill Consumer Products Co. Chemet product information. Fort Washington, PA:McNeill Consumer Products Co., 1994.
42. Heyl GmbH. Fachinformation: Dimaval (DMPS). Berlin: HEYL Chemish-pharmazeutische Fabrik GmbH & Co., 1990.
43. Grandjean P, Jacobsen IA, Jørgensen PJ. Chronic lead poisoning treated with dimercaptosuccinic acid. Pharmacol Toxicol 68:266–269 (1991).
44. Gerr F, Frumkin H, Hodgins P. Hemolytic anemia following succimer administration in a glucose-6-phosphate dehydrogenase deficient patient. Clin Toxicol 32:569–575 (1994).
45. Chisolm JJ. BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. Clin Toxicol 30:493–504 (1992).