



Bionostics, Inc.

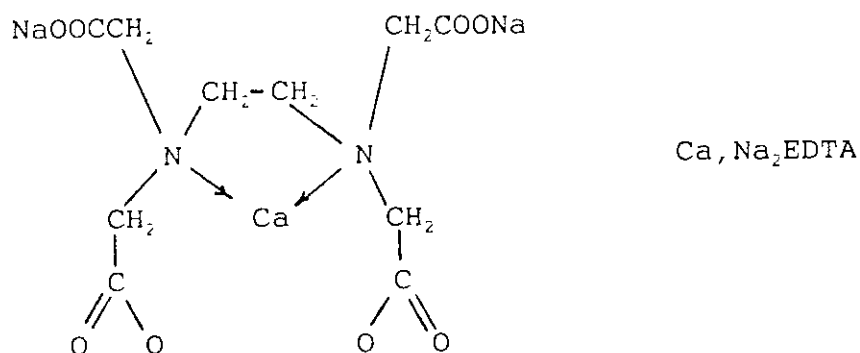
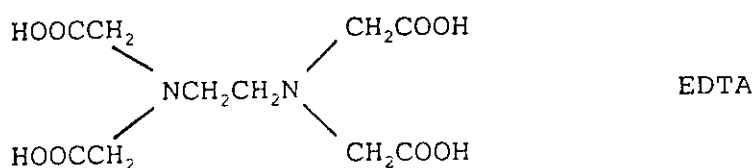
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**MECHANISMS OF DETOXICATION
AND PROCEDURES FOR DEXTOXIFICATION**

Jon B. Pangborn, Ph. D.

EDTA

EDTA is an acronym for ethylene, diamine, tetraacetic acid which is stabilized in salt forms using sodium as disodium ethylene, diamine tetraacetate and an atom of an element which can be displaced by a toxic atom (ion) in the blood stream. Usually, this to-be-displaced element in EDTA is calcium or magnesium. Below are the structures of EDTA and Ca,Na₂-EDTA, called "Edetate Calcium Disodium". See Merck Index entries 3480, 3481, 3482.



EDTA is a synthetic amino acid. It is not accepted by the active transport process of cells and, therefore, is primarily extracellular in activity and function [1]. Also, it must be administered intramuscularly or intravenously.

When administered properly, EDTA is an effective chelating agent for many metal ions, trivalent, divalent, and some quadravalent ones. EDTA acts primarily in the blood plasma (and in kidney glomeruli). EDTA can influence toxics inside a cell only by enhancing the concentration gradient, enhancing diffusion, and freeing up active transport processes that may be inhibited by extracellular toxics.

EDTA DETOXIFICATION USES

Two EDTAs are in therapeutic use.

I. Ca,Na₂EDTA is "Versenate" or "edetate calcium disodium injection" by 3M Pharmaceuticals (Riker). See 1994 Physician's Desk Reference page 1275; or Facts and Comparisons page 707 (February 1988 update).

II. Mg,Na₂EDTA is the version authorized by the American Board of Chelation Therapy (ABCT) and described by ACAM protocol. For information on Board Certification issues for Chelation Therapy,

contact Jack Hank, ABCT, 70 West Huron Street, Chicago, IL, 312/266-7246 or 800/356-2228.

To obtain the ACAM Protocol booklet, contact -
The American College of Advancement in Medicine (ACAM)
23121 Verdugo Drive, Suite 204
Laguna Hills, CA 92653
Phone 714-583-7666

Per the FDA and Medicare, and as described in Drug Facts and Comparisons, Ca, Na₂EDTA is appropriate for lead toxicity or encephalopathy. Na₂EDTA (which becomes MgNa₂EDTA per ABCT/ACAM procedure) is approved for hypercalcemia and digitalis toxicity.

According to established chelation chemistry (in vitro), EDTA chelates the following, in order of affinity calculated from the equilibrium constant [2]. Because Ca,Na₂EDTA or Mg,Na₂EDTA is used instead of EDTA, the order given below may change slightly from theoretical equilibrium calculations.

Vanadium ⁺³
Iron ⁺³
Mercury ⁺² (but it is very poor for Hg⁺¹, HgCH₃)
Titanium ⁺³
Copper ⁺²
Nickel ⁺²
Lead ⁺²
Titanium ⁺⁴
Cadmium ⁺²
Zinc ⁺²
Cobalt ⁺²
Aluminum ⁺³
Iron ⁺²
Manganese ⁺²
Vanadium ⁺²

Tin also is significantly chelated by EDTA; documented stability constants for Sn⁺² and Sn⁺⁴ were not found.

ADMINISTRATION OF EDTA

Measure creatinine clearance to determine that renal function is within normal limits so that the detoxifying agent with its toxic burden can clear the kidneys. Therapy with EDTA is contraindicated in renal insufficiency unless a dialysis procedure is used to clear toxics from the blood. (This is a hospital procedure involving specialists in urology, toxicology and dialysis.)

Contraindications for EDTA include: renal impairment or insufficiency, pregnancy or lactation, and active liver disease. Extreme care should be used if the patient is on anticoagulant therapy or has a history of congestive heart failure. Depletion of necessary and essential elements will occur with repeated EDTA treatments, and periodic monitoring and daily supplementation are required. Essential elements susceptible to depletion include: zinc, calcium, magnesium, iron, manganese, copper, chromium, and possibly vanadium [3,4].

The protocol for use of $\text{Ca,Na}_2\text{EDTA}$ is published in -
(a) Drug Facts and Comparisons, Facts and Comparisons Inc., St. Louis, MO (1-800-223-0554), page 707 (dated Feb. 1988).

(b) Physician's Desk Reference ("PDR"), Medical Economics Data Production Co, Montvale, NJ, 1994 p 1275.

(c) See also Harrison's Principles of Internal Medicine [1], page 855 for brief discussions of EDTA, BAL, D-Penicillamine and Deferoxamine.

Protocols for use of and information about $\text{Mg, Na}_2\text{EDTA}$ should be obtained from the ABCT and ACAM sources listed on the previous page.

In general, DMSA, DMPS and D-Penicillamine should not be used concurrently with EDTA because of elemental affinity interferences (discussed previously, page 109, 110). Per Facts and Comparisons (ibid) page 713i (dated June 1991): "Chelation Therapy (e.g. EDTA): co-administration of succimer [DMSA] with other chelation therapy is not recommended." There are literature references, including Harrison's Principles, op.cit., p. 853, where double therapies are mentioned. However, these reported therapies seem to be for single element toxicities, e.g. "BAL" (dimercaprol) + EDTA for lead. But, are we certain that only lead is present at excessive levels? Sequential therapies appear safer based on chemistry principles. With lead, for example, a course of IV EDTA treatments followed by a course of oral D-penicillamine treatments avoids elemental affinity interferences and should remove lead even from bone tissue [5].

Twenty four hours before starting EDTA treatment, mineral supplements should be discontinued because many of the elements in such supplements will simply load up the EDTA. The excreted toxic element yield will be less if the EDTA is loaded with Zn, Fe, Ca, etc. (Plenty of these elements will be excreted anyway.)

Arginine may be given in the 24-hour period before IV or IM EDTA to enhance Ni detoxication. Glycine may be given just before IV or IM EDTA to enhance Al and Hg detoxification. Reduced glutathione may be given just before IV or IM EDTA to enhance Cd, Pb, Hg and Ni detoxification.

MONITORING EDTA DETOXIFICATION THERAPY

The biological half life of EDTA in the body ranges from 1.5 to 3 hours. (Bloodstream half life is short and may be only 45 minutes.) Monitoring EDTA chelation therapy is by periodic urine element analyses on 8 to 12 hour collections. A 9-hour urine collection typically catches more than 90% of the chelated elements. A 24-hour collection can be used but is not necessary and may actually dilute the toxic concentrations obtained in the first 9 hours.

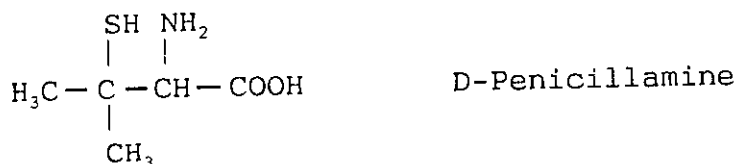
Before starting EDTA therapy, it is advisable to do a whole blood or blood cell elemental analysis to determine baseline levels of essential elements. Blood element analysis should be repeated periodically (at least after each 10 EDTA treatments) to monitor levels of key essential elements: Ca, Mg, Zn, etc.

EDTA REFERENCES

1. Braunwald E. et al., Harrison's Principles of Internal Medicine, McGraw Hill Book Co, NY, 11th ed (1987), p. 855.
2. Chaberek S. and A.Martell, Organic Sequestering Agents, op. cit. pp 572,73.
3. Pangborn J., Bionostics, Inc., as observed from DDL urine element reports.
4. Riordan J.D., E. Cheraskin and M. Dirks, "Mineral Excretion Associated with EDTA Chelation Therapy". J. Advancement in Med. 3 no. 2, Human Services Press, NY, Summer 1990, pp 111-24.
5. Braunwald E. et al., Harrison's Principles of Internal Medicine, op.cit. p. 853.
6. Protocol Booklet, the American College of Advancement in Medicine (ACAM), 23121 Verdugo Drive, #204, Laguna Hills, CA 92653, 714-583-7666.

D-PENICILLAMINE

D-Penicillamine is "Cuprimine" (Merck) or "Depen" (Wallace). Other commercial names that have been used are: Depamine, Cuprenil, "DMC", and Mercaptyl. D-penicillamine is a monosulphydryl compound, 3-mercapto-D-valine, or dimethylcysteine.

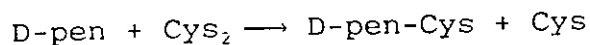


Penicillamine is a degradation product of penicillin antibiotics, and preparation of the compound can be by hydrolysis of penicillins.

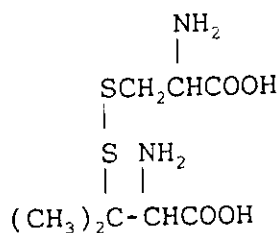
Penicillamine (D-pen) is indicated for a number of therapeutic applications and is well described in Drug Facts and Comparisons [1] and the Physician's Desk Reference [2]. Uses of penicillamine as stated in Drug Facts and Comparisons (June 1991 insert, page 714) are: rheumatoid arthritis, Wilson's Disease (removes excess copper), metal poisoning (iron, mercury, lead, arsenic), and cystinuria.

In rheumatoid arthritis, administration of D-pen lowers IgM rheumatoid factor by dissociation of macroglobulins. It is hypothesized that D-pen inhibits some T-cell functions thereby reducing autoimmune activity; this is unproved (author's opinion). This use of D-Pen is approved and described in the PDR.

In acute cystinuria (also an approved use), D-pen can be used to form a disulfide and reduce the amount of cystine (Cys₂) -



D-pen-Cys disulfide is -



is the least-soluble amino acid in urine, and it precipitates form crystals and stones in acute cystinuria. The D-pen disulfide is more soluble than Cys₂; therefore, D-pen is therapeutic in this condition.

D-PENICILLAMINE DETOXIFICATION USES

In Wilson's disease, D-pen forms a complex with copper, two molecules of D-pen to each Cu^{++} ion, and the soluble complex removes copper via urine and probably bile. This use of D-pen is FDA approved and is described in the PDR.

Drug Facts and Comparisons [1] credits D-pen with forming soluble complexes with: iron, mercury, lead and arsenic, thereby being therapeutic in "poisoning" by these metals. However, this application of D-pen is not approved (licensed) by the FDA [3], and this application is not in the 1994 PDR.

From studies of urine element profiles at DDI, this author concludes that D-pen has good affinity for and good urinary detoxification yields for the following (in order of perceived affinity) -

copper	arsenic
silver	manganese
nickel	cobalt
cadmium	tin
mercury	iron
zinc	molybdenum
lead	

N-acetyl-D-penicillamine is credited with being an excellent detoxifier of inorganic mercury [3], but this version of D-pen is not in the US Formulary, is not FDA approved and is not commercially available in the US.

ADMINISTRATION OF D-PENICILLAMINE

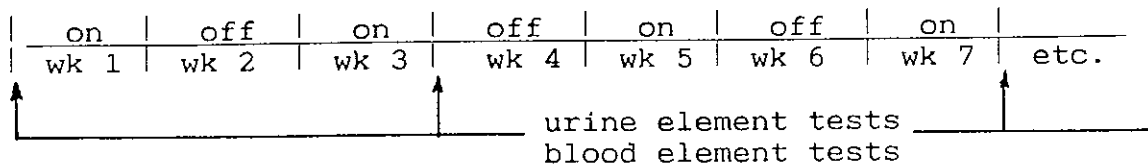
D-pen is offered in 250 mg capsules (Cuprimine, Merck) and tablets (Depen, Wallace). Although the usual adult dosage in cystinuria is 2000 mg/day, toxic individuals can react adversely to this dosage. One capsule qid (1000 mg/day total) is the maximum oral dose that is generally tolerated (per physician communications to Bionostics). The 250 mg, qid dosage is scaled down for children. For details, please refer to Drug Facts and Comparisons [1] or the PDR [2].

Measure creatinine clearance to determine that renal function is within normal limits so that the detoxifying agent with its toxic burden can clear the kidneys. Therapy with D-penicillamine is contraindicated in renal insufficiency unless a dialysis procedure is used to clear toxics from the blood. (This is a hospital procedure involving specialists in urology, toxicology and dialysis.)

For diagnostic tests, a 48-hour trial period is adequate with one 250 mg capsule/tablet qid, six hours apart on each of the two consecutive days. The diagnostic urine collection is done on the second day; skip the first urination of day 2, collect urine for 24 hours including the first urination of day 3.

0 24 hrs 48hrs
 dose pre-collection period • dose and collection period

Suggested therapy for detoxification is one week on D-pen and one week off, alternating, with urine element analyses after weeks 3, 7 and 10 (if the therapy is continued this long). Often the levels of toxic elements are down to expected ranges after 7 weeks (4 weeks of D-pen administration).



This alternating schedule allows sensitive individuals to recover from symptoms due to mobilization of the toxic and from physiological effects such as pyridoxal 5-phosphate depletion (see contraindications and concerns, below).

Discontinue vitamin and mineral supplements 24 hours prior to day 1 of the 48 hour trial diagnostic period and 24 hours prior to and during the weeks of D-pen use in detoxification therapy. Do not give GSH or Cys or Cys₂ during D-pen administration. To enhance nickel removal, arginine may be given concurrently with D-pen. Also, glycine can be given to enhance Hg removal. If glycine complexes (excess) aluminum, there is no (theoretical) interference with D-pen. (But, see arginine and glycine sections for their contraindications.)

During the "off weeks", supplement with nutrients, especially copper (unless copper is the targeted toxic), vitamin B₆, and glutathione. Cysteine (and glutathione) can be depleted by penicillamine.

Contraindications and concerns with D-penicillamine include but may not be limited to the following.

1. Renal insufficiency
2. Pregnancy or lactation
3. Vitamin B₆ deficiency or pyridoxal 5-phosphate coenzyme dysfunction. D-penicillamine forms a thiazolidine derivative with pyridoxal phosphate and depletes this coenzyme.
4. Cysteine/cystine deficiencies (determined by plasma and urine amino acid analysis). Penicillamine therapy can further deplete these amino acids and can (further) reduce the supply of glutathione. This can cause liver damage if other xenobiotic toxics are present.

5. Penicillin sensitivity or allergy. Cross reaction with D-penicillamine is theoretically possible but rarely observed with synthetic D-penicillamine.

6. Copper depletion can occur as can depletion of manganese, iron, molybdenum and possibly chromium. Supplementation of these (and other) essential elements is usually necessary during "off" weeks.

MONITORING D-PENICILLAMINE DETOXIFICATION THERAPY

Monitoring is done by urine and whole blood or blood cell element analyses per the schedule suggested above. The urine shows what and how much is being removed. The blood shows the repletion that is needed for essential elements. 40 to 70% of oral D-penicillamine is absorbed from the GI tract. About 50% of this is excreted in the feces; 50% in the urine (42% within 24 hours). A 24-hour urine collection is the most satisfactory for representative results. The clock starts when the first D-pen tablet or capsule is taken.

An initial whole blood element analysis is advisable before therapy begins to establish baseline levels of essential elements. This analysis should be repeated periodically, probably when urine elements also are measured (after 3 and 7 weeks), or more often if depletion of essential elements is suspected.

D-PENICILLAMINE REFERENCES

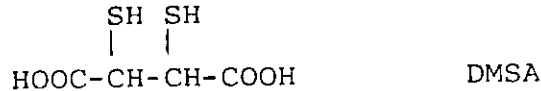
1. Drug Facts and Comparisons. Facts and Comparisons, St. Louis, MO, pgs 714-717, June 1991.

2. Physicians' Desk Reference (PDR), Medical Economics Data Production Company, Montvale NJ, 1994, pages 1424-27 (Cuprimine, Merck) and pages 2468-2471 (Depen, Wallace).

3. Braunwald E., et al., Harrison's Principles of Internal Medicine, op. cit., page 855.

DMSA

DMSA is "Succimer" or "Chemet" (McNeil). Chemically, it is meso-2,3-dimercaptosuccinic acid. It is a di-sulfhydryl compound.



DMSA was approved by the FDA in February 1991 for use in lead poisoning in children. Lead poisoning is defined as a whole blood lead level equal to or exceeding 45 µg/dL (450 ppb, 0.45 ppm) [1,2]. To this author, this criterion also appears to precede the CDC lowering of the threshold of concern for blood lead. Referring back to page 84 in the section on LEAD, it is obvious that this definition of lead poisoning is too high. As of 1991, the US CDC threshold of concern for lead in children is 10 µg/dL [3]. Symptomatology to lead in children has been variously reported at levels above 5 µg/dL.

DMSA is said to form "chelates" [1,2] of heavy metals. From basic principles of chemistry, it appears that DMSA should form sulfur-metal bonds at the sulfhydryl groups, thus conjugating or possibly complexing with metal ions. Besides lead, DMSA is credited with the ability to remove mercury and arsenic. [2].

DMSA DETOXIFICATION USES

Based on observations of urine element analyses performed at Doctor's Data Laboratory, DMSA is observed (by this author) to have affinity for the following elements.

lead	molybdenum
cadmium	copper
mercury	zinc
silver	manganese
nickel	iron
arsenic	tin

ADMINISTRATION OF DMSA

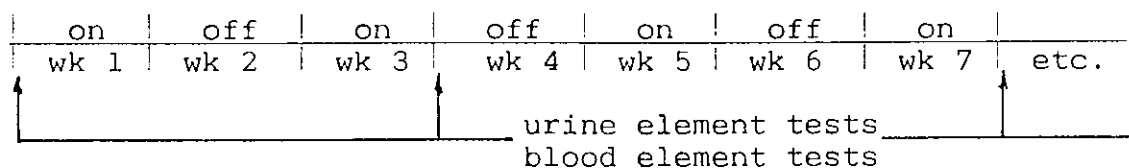
DMSA is offered in capsule form, 100 mg per capsule. In this form (McNeil), the DMSA is actually coated on tiny beads, and the beads contain other (inactive?) ingredients: providone (polyvinyl pyrrolidone, a dispersing agent), sodium starch glycolate, corn-starch, and sucrose. Also in the capsules are gelatin (the capsule material), iron oxide, and titanium dioxide as whitener. (Inclusion of these metals in the capsule is unfortunate.)

Measure creatinine clearance to determine that renal function is within normal limits so that the detoxifying agent with its toxic burden can clear the kidneys. Therapy with DMSA is contraindicated in renal insufficiency unless a dialysis procedure is used to clear toxics from the blood. (This is a hospital procedure involving specialists in urology, toxicology and dialysis.)

For a two day diagnostic trial with 24-hour urine collection during the second day, the approximate provocation dose of DMSA is 10 mg/Kg body weight given tid or every eight hours. This also is the "starting dosage" per Facts and Comparisons [2]. A table for pediatric doses of DMSA is presented in Facts and Comparisons (page 713j).

0 24 hrs 48hrs
 dose pre-collection period • dose and collection period

Suggested therapy for detoxification is one week on DMSA and one week off, alternating, with urine element analyses after weeks 3, 7 and 10 (if the therapy is continued this long). Often the levels of toxic elements are down to expected ranges after 7 weeks (4 weeks of DMSA administration). Continuous use of DMSA for more than 3 weeks has not been established as safe.



This alternating schedule allows sensitive individuals to recover from symptoms due to the mobilization of toxics, and from possible side effects of DMSA.

Discontinue vitamin and mineral supplements 24 hours prior to day 1 of the 48 hour trial diagnostic period and 24 hours prior to and during the weeks of DMSA use in detoxification therapy. Do not give GSH or Cys or Cys₂ during DMSA administration. To enhance nickel removal, arginine may be given concurrently with DMSA. Also, glycine can be given to enhance Hg removal. If glycine complexes (excess) aluminum, there is no (theoretical) interference with DMSA. (But, see arginine and glycine sections for their contraindications).

During the "off weeks", supplement with nutrients, especially essential trace elements such as copper, zinc and manganese. Glutathione may be beneficial during "off weeks" because of the cysteine-depleting effects of DMSA.

Contraindications and concerns with DMSA include but may not be limited to the following.

1. Renal insufficiency
2. Pregnancy or lactation
3. Cysteine/cystine deficiencies (determined by plasma and urine amino acid analysis). DMSA therapy can further deplete these amino acids and can (further) reduce the supply of glutathione. This can cause liver damage if other xenobiotic toxics are present.
4. DMSA-provoked sensitivity or allergy. Because DMSA can form disulfides with the body's natural antioxidant, anti-inflammatory and detoxication agents, allergic sensitivity or reactivity to otherwise unrelated substances can occur or be enhanced.
5. Despite what the PDR or Facts and Comparisons say about DMSA, copper depletion can occur as can depletion of zinc, manganese, iron, and molybdenum. Supplementation of these (and other) essential elements is usually necessary during "off" weeks. Calcium and magnesium also may be needed.

A tabulation of possible DMSA side effects is provided in Facts and Comparisons page 713i. It is not known if DMSA depletes pyridoxal 5-phosphate (as D-pen does).

MONITORING DMSA DETOXIFICATION THERAPY

Monitoring is done primarily by 24-hour urine and whole blood or blood cell element analyses per the schedule suggested above. The urine shows what and how much is being removed. The blood shows the repletion that is needed. An initial whole blood element analysis is advisable before therapy begins to establish baseline levels of essential elements. This analysis should be repeated periodically, probably when urine elements also are measured after 3 and 7 weeks, or more often if depletion of essential elements is suspected.

About one - half of orally administered DMSA is absorbed from the GI tract. About one half of the absorbed DMSA is excreted via the urine and bile in 24-48 hours.

DMSA REFERENCES

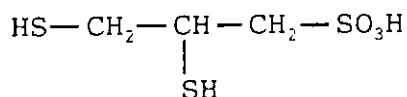
1. Physicians Desk Reference, 1994, op. cit., pp. 1334,35.

Facts and Comparisons, op. cit., p.713g

Lead Poisoning in Young Children CDC, US Dept. Health Services, Atlanta, GA, Oct. 1991.

DMPS

DMPS is 2,3 dimercapto-1-propane sulfonic acid, usually provided as the sodium salt: Na-2,3-dimercaptopropane-1-sulfonate. It is also called "Dimaval" (Heyl). DMPS is in the Merck Index, entry no. 3197 [1].



DMPS is an improved version of Dimercaprol ("BAL") that was developed as an anti-gas warfare agent, specifically against the arsenic-containing gas called "Lewisite" (dichloro-2-chlorovinyl-arsine).

DMPS is not listed in the Physician's Desk Reference or in the pharmacy text Facts and Comparisons. It is produced by Chemisch-Pharmazeutische Fabrik of Berlin under the company trade name "Heyl". It is, however, available from certain pharmacies in the US. Administration is by intramuscular injection, or by slow-push intravenous injection. Literature reports of oral administration also are published [2,3]. Specific directions for administration should be obtained from the Heyl drug package insert or the pharmacy.

DMPS DETOXIFICATION USES

DMPS has affinity for and removes the following elements (as observed in urine element tests at DDI).

mercury, very efficiently	chromium, chromates
lead	cobalt
silver	molybdenum
cadmium	copper
nickel	zinc
arsenic	manganese
antimony	gold
bismuth	

ADMINISTRATION OF DMPS

DMPS is not described in the US Formulary. The following is a direct excerpt from the Heyl "Information and directions for use, Dimaval"

Dosage

The individual dosage schedule depends on the severity of the intoxication and on the other methods of treatment employed.

About 5 mg/kg body weight are administered.

Suggested dosing schedule for severe acute poisoning (adult):

250 mg (1 ampoule) 4-hourly for the first 24 hours. The following 24 hours 250 mg 6-hourly. Depending on the patients conditions (according to the measured metal concentrations in blood, urine, dialysate) the intervals between injections may be prolonged to 8 or 12 hours. Then change to oral administration form.

Mode and duration of administration

In severe cases and as initial dose Dimaval may be administered by slow intravenous injection. Otherwise it is administered by intramuscular or subcutaneous injection.

Dimaval injection solution must not be diluted in infusion solutions.

Notice:

Treatment with Dimaval does not exclude other methods for treatment of acute intoxication such as lavage of stomach, hemodialysis and/or peritoneal dialysis, forced diuresis, administration of parenteral electrolytes and glucose.

Special notice

Opened ampoules must not be stored. Left over solution is to be discarded.

Do not use the preparation after the date of expiration!

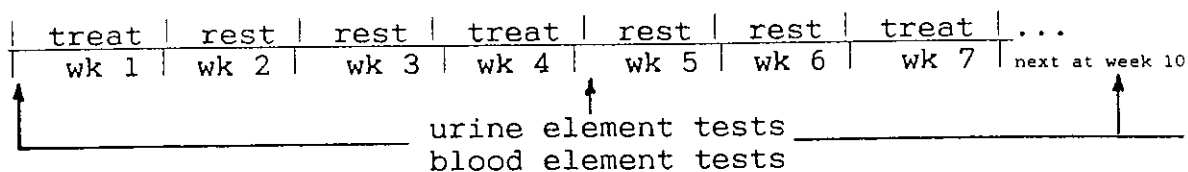
Administration form/package size

5 ampoules (à 5 ml)

Heyl
Chemisch-pharmazeutische Fabrik, D-1000 Berlin 37

Measure creatinine clearance to determine that renal function is within normal limits so that the detoxifying agent with its toxic burden can clear the kidneys. Therapy with DMSA is contraindicated in renal insufficiency.

Per information to Bionostics from doctors experienced in the use of DMPS, the slow-push intravenous administration works best. One ampoule (5 cc containing 250 mg DMPS) is injected directly into a vein over a three-to-five minute period. Only one DMPS administration (injection) is done during the week of treatment. Few patients have sufficient tolerance for this every week; most do better with one or two week rest periods between DMPS administrations.



Discontinue all mineral supplements 24 hours before administration of DMPS. Do not give GSH, Cys, Cys₂ or N-acetylcysteine concurrently with DMPS. There is no need to give any assisting agent with DMPS for mercury removal. Five to ten treatments usually are sufficient for detoxification.

There are possible side effects from DMPS. Per Heyl, and directly excerpting from their information sheet:

"Side effects

"Parenteral administration of DMPS may be accompanied by decrease in blood pressure or tachycardia. Seldom nausea, vertigo, general weakness or paleness may occur (5-10 min. after injection).

"Skin rashes may occur very rarely. The symptoms are reversible after discontinuation of the drug."

These side effects are very similar to those known to possibly occur with administration of BAL, D-Penicillamine, or DMSA.

Other contraindications and concerns with DMPS include but may not be limited to the following.

1. Renal insufficiency
2. Pregnancy or lactation
3. Diabetes
4. Cysteine/cystine deficiencies (determined by plasma and urine amino acid analysis). DMPS therapy can further deplete these amino acids and can (further) reduce the supply of glutathione. This can cause liver damage if other xenobiotic toxics are present.
5. DMPS-provoked sensitivity or allergy. Because DMPS can form disulfides with the body's natural antioxidant, anti-inflammatory and detoxication agents, allergic sensitivity or reactivity to otherwise unrelated substances can occur or be enhanced.
6. Besides mercury, DMPS removes essential trace elements: copper, zinc, manganese, chromium, molybdenum. Repletion of these probably will be necessary.
7. Another caution concerns dental amalgams, and this caution is controversial and not well understood at this writing. Because DMPS is a powerful conjugator for mercury and because it will find its way into saliva, it may remove "loose" or surface mercury from amalgams. This may or may not be harmful. DMPS is an excellent mercury scavenger for use after amalgam removal.

MONITORING DMPS DETOXIFICATION THERAPY

For a matter of hours after injection, a large portion of the DMPS is available to combine with toxic elements. Various literature reports indicate that active detoxication of mercury, chromate and lead occurs for periods of two to nine hours after injection [2,4]. Additional time is needed for the toxic-agent complex to be

completely excreted. A 24-hour urine collection period beginning with the time of injection is appropriate to monitor the removal of the toxic [5]. Besides complexing with (toxic) elements, DMPS also combines with thiols by formation of S-S bonds. Mixed disulfides, such as DMPS-cysteine and DMPS-glutathione, occur and can be found in the urine some hours after injection of DMPS. Once the DMPS is conjugated with cysteine, glutathione, or another organosulfur compound, its ability to detoxify heavy metals is greatly reduced and may be virtually gone. In studies with humans presenting lead and/or mercury toxicity, after 15 hours, most (90%) of the DMPS in urinary excretion was conjugated in disulfide form [5]. Therefore, the urine collection period should start with the time of the infusion and continue for at least 12 hours.

Initially and after every other DMPS treatment, a 12-to-24 hour urine collection is done, and a whole blood or blood cell element analysis is advisable. The urine shows what and how much is being removed. The blood shows the repletion that is needed for essential elements.

DMPS REFERENCES

1. Merck Index, 11th ed., Merck & Co, Rahway NJ 1989, pp 506,07.
2. Aposhian H.V., et al., "Urinary Mercury after Administration of 2,3-dimercaptopropane-1-sulfonic acid:Correlation with Dental Amalgam Score", FASEB Journal 6 (7), April 1992, pp.2472-76.
3. Molin A., et al., "Mobilized Mercury in Subjects with Varying Exposure to Elemental Mercury Vapor" Int. Arch. Occupational and Environ. Health 63 (3), 1991, pp 187-92.
4. Aposhian H.V., et al., "Human Studies with the Chelating Agents, DMPS and DMSA", J. Toxicology - Clin. Tox. 30 (4), 1992 pp 505-28.
5. Maiorino R.M., et al., "Determination and Metabolism of Dithiol Chelating Agents. XII. Metabolism and Pharmacokinetics of Sodium 2,3-dimercaptopropane-1-Sulfonate in Humans", J. Pharmacol & Exp. Therap. 259 (2), 1991 pp 808-14.

THE REBOUND

All detoxification treatments, whether they are desensitization - nutrient supplementation - sauna for organic xenobiotics, or synthetic complexing or chelating agents for toxic elements can appear to have the patient clear of the toxic per blood or urine tests. Then, 30 to 60 days later, more of the xenobiotic or toxic element shows up and symptoms or manifestations of toxicity can reappear. This is because toxics often are sequestered in tissues that have limited exchange and transport pathways. Lead in bone tissue is an example.

To address this problem, all patients should be retested 30 to 60 days after discontinuation of the detoxification treatment. A urine provocation-type test is best for heavy elements with a 24-hour urine element analysis.

For oral-type detoxifying agents or provocations, the two-day test sequence is recommended.

0 24 hrs 48hrs
dose pre-collection period ● dose and collection period

SUMMARY TABLE: OPTIMAL URINE COLLECTION PERIOD

Agent	Average Biological Half Life, hrs.	Optimal Collection Period, hrs.
EDTA	1.5-3	9-12
D-Penicillamine	24-30	24
DMSA (oral)	24-48	24
DMPS (IV-push)	6-12	12-24

The clock for urine collection starts when the treatment starts.

TEN THINGS TO WATCH OUT FOR IN ELEMENTAL DETOXICATION

1. Don't do anything without laboratory tests especially those for kidney clearance.
2. If using natural agents (glycine, GSH, citric acid), be sure the diet does not contain toxic elements. These agents will increase uptake as well as excretion.
3. If you're going to use two synthetic agents simultaneously, know what you're doing. In general, don't do this.
4. Don't use cysteine or acetylcysteine in known cases of mercury, nickel, or iron toxicity. These toxics will go wherever the cysteine takes them.
5. Don't administer pyridoxine or pyridoxal 5-phosphate simultaneously with D-Penicillamine. For patients needing B₆, give the B₆ 24 to 48 hours after the last D-penicillamine tablet.
6. Don't administer GSH, Cys, or Cys₂ simultaneously with DMSA, D-Penicillamine or DMPS. If you do, you will form mixed disulfides and decrease the yield of excreted toxics. (You may use GSH 24 hours before, or 48 hours afterward; observe GSH contraindications.)
7. Don't give mineral supplements immediately preceding or concurrently with treatments for element detoxification.
8. Need to stop the DMSA, D-pen or DMPS action due to severe reactivity? Usually, you can shut the action down in about 90 minutes by giving oral GSH, reduced L-glutathione, 20 to 25 mg/Kg body weight. This is an emergency brake; observe GSH contraindications.
9. In between treatments, be sure to supplement needed, essential elements.
10. Always insure that the patient drinks plenty of pure water during and after detoxification treatments. Higher than usual urine volumes are expected at these times.

Age, years	Usual Expected 24-hr Urine Volume, ml	Detoxication Treatment Urine Volume, ml
1-4	250-900	500-1500
5-12	450-1600	900-3000
13-99	750-2250	1500-4000

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