

Chelation Therapy for Toxic Metals

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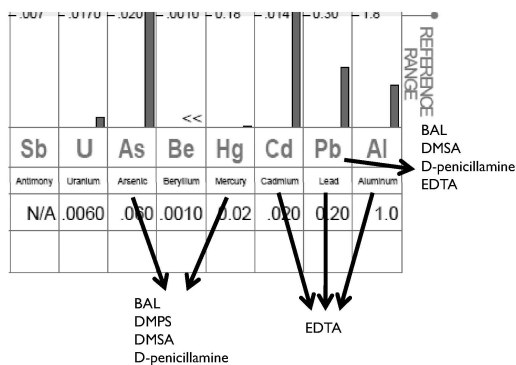
가정의학과

김영상

The following table summarizes chelating agents, the heavy metals they are used to treat, their route of administration, and their brand name.

Chelating Agent	Toxin	Route	Drug
Dimercaprol (BAL)	Arsenic Lead Mercury (inorganic)	i.m.	Dimercaprol Injection B.P. BAL in Oil
Dimercaptosuccinic acid (DMSA, Succimer)	Arsenic Lead Mercury	p.o.	Chemet
Dimercaptopropane-sulfonate (DMPS)	Arsenic Mercury	p.o. i.v.	Bulk form (for compounding by pharmacists)
D-penicillamine	Arsenic Mercury Lead	p.o.	Metalcapase Penicillamine Cuprimine Depen
Ethylenediaminetetra-acetic acid (EDTA) (Edetate disodium)	Iron Lead Cadmium Aluminum	IV	Chealamide Versenate

Toxic Elements from TMA result



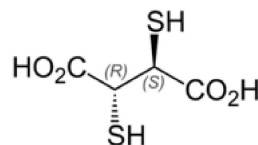
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- ▶ DMSA
- ▶ D-penicillamine
- ▶ Mercury and DMPS
- ▶ EDTA



DMSA

- ▶ Meso-2,3-Dimercaptosuccinic acid
- ▶ Synonym: Succimer; Chemet



- ▶ Transient mild elevations of serum transaminases have been observed in <10% of patients
 - ▶ Check **LFT** prior to starting Tx
- ▶ Drug interactions: None
- ▶ Pregnancy: category C
- ▶ Nursing mothers: If Tx is necessary, mothers should be discouraged from nursing
- ▶ Pediatric use: Safety in patients <1yr has not been established

- ▶ Ensure adequate hydration, normal kidney function, assessment of CBC, and bowel movements are regular
- ▶ Serum and provoked heavy metal test prior to starting regimen
 - ▶ Check serum metals and/or PRBC minerals and/or unprovoked urine (first morning void or random spot urine)
- ▶ Challenging test: check 6-hr urine toxic metals post-DMSA 2,000 mg, or by body weight dosing of 10 mg/kg or 30 mg/kg on an empty stomach.
- ▶ Max dose: 2,250 mg

- ▶ Many different dosing regimens
 - ▶ 5-10 mg/kg every 12h for 2 weeks on, then 2 weeks off
 - ▶ 10 mg/kg every 8h for 3 days, then 11 days off
 - ▶ 100 mg every night Mon-Fri, skip weekend
 - ▶ 500 mg tid
 - ▶ 30 mg/kg divided into 3 doses/day for 5 days on, then 9 days off
 - ▶ 10 mg/kg divided into 2-3 doses/day for 3 days, then 11 days off (extremely sensitive patients do better with a lower dose and with more days off)
 - ▶ Suppository
- ▶ Provide mineral replacement during Tx

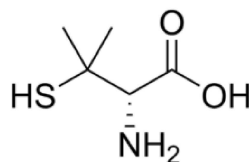


- ▶ Recheck CBC and kidney fx and urine toxic metals periodically
 - ▶ If the patient is on a 30 mg/kg Tx protocol with 5 days on and 9 days off → recheck CBC and kidney fx at 5th round and urine toxic metals at 10th round
- ▶ Assess patient's symptoms during course of Tx
 - ▶ Symptom survey, metabolic screening questionnaire



D-penicillamine

- ▶ Indications
 - ▶ Wilson disease (removal of excess copper)
 - ▶ Reduce cystine excretion in cystinuria
 - ▶ Severe, active rheumatoid arthritis unresponsive to conventional therapy



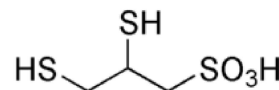
- ▶ Contraindications
 - ▶ Hypersensitivity to drug/class/compound
 - ▶ Pregnancy
 - ▶ Cytotoxic and antimalarial drug use
 - ▶ Aplastic anemia and agranulocytosis Hx
- ▶ Caution
 - ▶ Renal impairment
 - ▶ Myelosuppression
 - ▶ Iron deficiency
 - ▶ Neurologic disease
 - ▶ Elderly patients

- ▶ Protocol for challenge test
 - ▶ Take 500 mg d-penicillamine or N-acetyl-d-penicillamine with each meal and before bed for just 3 days
 - ▶ This is a total of 2 g each day for 3 days for a typical 70 kg adult. This is based on 30 mg/kg. if weight is under 45 kg or over 135 kg, calculation of dose is recommended.
 - ▶ Starting on the morning of the second day, collect in a heavy metal-free container all urine output for the next day (a full 24h cycle)
 - ▶ It is important to collect all the urine
 - ▶ If a urine sample is missed, the collection is incomplete. Start over with a new provocation one week later.
 - ▶ The total volume is an important part of the information to be sent to the analytic lab.
 - ▶ It is desirable, although necessary, to keep the urine refrigerated during the collection period.

- ▶ Protocol for Tx
 - ▶ Use d-penicillamine twice a week (Mon, Thu) for 30-60 days at 7.5 mg/kg taken qd (500 mg qd for most adults)
 - ▶ Supplement Ca, Mg, and Zn particularly on the non-penicillamine days to replace these minerals (which d-penicillamine will chelate along with the other divalent minerals along with toxic or heavy metals)

DMPS

- ▶ 2,3-Dimercapto-1-propanesulfonic acid
- ▶ The synthesis of DMPS was first reported in 1956 by Petrunkin from Kiev, Ukraine.
- ▶ 1978 marketed as Dimaval in Germany PO 10 mg/kg
 - ▶ 40% absorbed in healthy adults
- ▶ IV 3 mg/kg max 250 mg
 - ▶ Shorter half-life only 1.5h
 - ▶ 1-6h urine collection
- ▶ SE: HA, fatigue, nausea, rash





Treatment

▶ DMPS

- ▶ Repeat every 1-2 weeks
- ▶ Repeat challenge testing after every 5-10 infusions
- ▶ Goal or target level?

▶ DMSA

- ▶ Various regimens
- ▶ No evidence

Pre-treatment

- ▶ Not evidence-based but makes good sense
- ▶ Ensure proper GI fx and transit time
 - ▶ Probiotics
 - ▶ Fiber
 - ▶ L-glutamine, enzymes, S. boulardii etc if leaky gut
- ▶ Ensure adequate detoxification
 - ▶ Alkaline urine
 - ▶ Mixed nuts (healthy fats & Se)
 - ▶ Vitamin C & ALA

Other therapies for Hg removal

- ▶ Sweating / Sauna
- ▶ ALA
- ▶ Chlorella
- ▶ Melatonin
- ▶ HMD
- ▶ Zolite
- ▶ Hg Cocktail for us

Hg detox cock-tail

▶ Example 1

- ▶ Vitamin C 2,000 mg
 - ▶ ALA 600 mg
 - ▶ Glutathione 800 mg
- qd~tid with 250-500 cc water
(그 외, SH 기를 가진 약물
비타민C, 셀레늄)



국내 유통 글루타치온
(일반)

동아제약
타치온 50mg

조아제약
에바치온 50mg



SH를 포함하는 약물

리포산
(지축타시드 600mg)

시스테인
(리나지올 500mg)
(류테란 200mg)

▶ Example 2

- ▶ Example 1 +
- ▶ Captomer 250
- ▶ Detox enema
- ▶ Mineral replacement

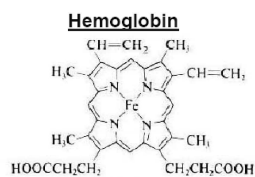
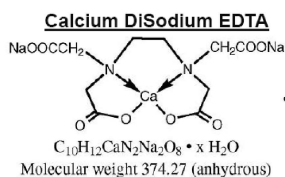


EDTA

(EthyleneDiamineTetraacetic Acid)

Octahedral structure:

- The EDTA molecule binds to a mineral or metal cation by donating up to 6 electron groups.
- By binding at these positions, a cation is surrounded by the EDTA molecule to form an **8 sided (octahedral) structure**.



What is EDTA Chelation Therapy?

- EDTA chelation therapy is an **Intravenous** treatment used for:
 - FDA approved uses:
 - Removing heavy metals (lead) - CaEDTA
 - Treating hypercalcemia - NaEDTA
 - Controlling ventricular arrhythmias secondary to digitalis toxicity - NaEDTA
 - Non-FDA approved uses:
 - As an anti-oxidant by controlling lipid peroxidation
 - Reducing platelet stickiness in the management of atherosclerosis

EDTA Binding of Metal Ions

At pH 7.4, H₂O

**Fe³⁺ > Hg²⁺ > Cu²⁺ > Al³⁺ > Ni²⁺ >
 Pb²⁺ > Co²⁺ > Zn²⁺ > Fe²⁺ > Cd²⁺ >
 Mn²⁺ > Mg²⁺ > Ca²⁺**

EDTA is effective in chelating toxic metals with a specific gravity above 5.0, i.e. the heavy metals Hg, Pb, and Cd.

Commercial preparations of EDTA

IMPORTANT

- DiSodium EDTA (NaEDTA) – approved by the FDA for use in:
 - Hypercalcemia
 - Ventricular Arrhythmias associated with Digitalis Toxicity
- Calcium DiSodium EDTA (CaEDTA) – approved by the FDA for use in:
 - Removal of lead and other heavy metals
 - It is excreted primarily by the kidney with about 50% excreted in one hour and over 95% excreted within 24 hours.
 - Almost none of the compound is metabolized
 - Only about 5% is absorbed from oral administration

Commercial preparations of EDTA

WARNING

NaEDTA must only be given by the intravenous (IV) route. If it is administered intramuscularly (IM), the patient will experience severe pain associated with tissue sloughing at the injection site.

NaEDTA must only be given by slow IV infusion at 1gm / hour (16mg/min) or less.

Before initiating chelation therapy always:

- Perform an H&P on your patient.
- Check
 - **Liver function tests**
 - **BUN / Cr, UA and Creatinine clearance**
 - CBC with Dif, electrolytes, EKG
 - Whole blood lead and provoked urine lead levels
 - condition specific work-up.
- Inform patient of risks and benefits of NaEDTA:
 - Pain / bleeding at infusion site
 - Hypoglycemia
 - Renal toxicity
 - Zinc deficiency

IV Na EDTA Chelation Protocol – 50mg/kg/day at 1gm/hour

250cc – 500cc	Sterile Water
2.0cc	Vitamin B6 (100mg/cc)
1.0cc	B complex 100
20cc	Sodium Bicarbonate 1mEq/ml
5cc	Procaine
1.0cc	Vitamin B5 (250mg/cc)
10.0cc	Vitamin C (500mg/cc)
5.0cc	Magnesium Sulphate
1.0cc	Potassium Chloride 2Meq/cc)
10 - 20cc	DiSodium EDTA (150mg/cc) adjust per Cackcroft Gault Formula
2.5cc	Heparin (5000U/cc)

IV Ca EDTA Chelation Protocol

100cc	Normal Saline
1.0cc	Vitamin B6 (100mg/cc)
0.25cc	Vitamin B1 (100mg/cc)
0.25cc	B complex 100
1.0cc	Vitamin B12 (1000mcg/cc)
2.0cc	Vitamin B5 (250mg/cc)
3.0cc	Vitamin C (500mg/cc)
2.0cc	Magnesium Chloride (200mg/cc)
1.0cc	Potassium Chloride (2Meq/cc)
5 – 10cc	Calcium DiSodium EDTA (300mg/cc) adjust per Cackcroft Gault Formula
0.1cc	Heparin (5000U/cc)



Summary



- By understanding how EDTA chelation works you can safely and effectively administer treatment
 - Remember – first do no harm and be prepared
 - Replace minerals in between treatments
 - Zinc and Iron if needed
 - Be prepared for side effects
 - Low blood sugar, vein irritation, change in kidney function
 - Decrease pain during administration

