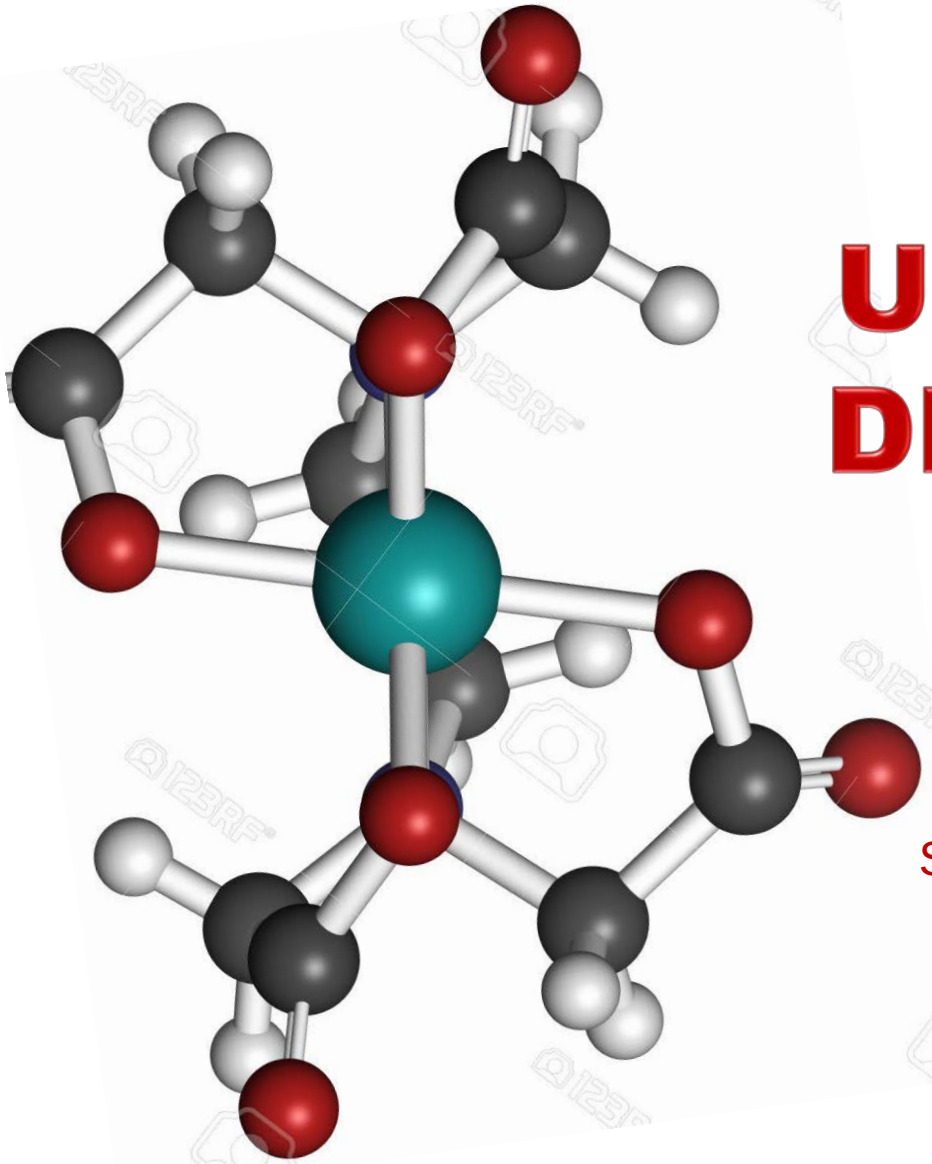
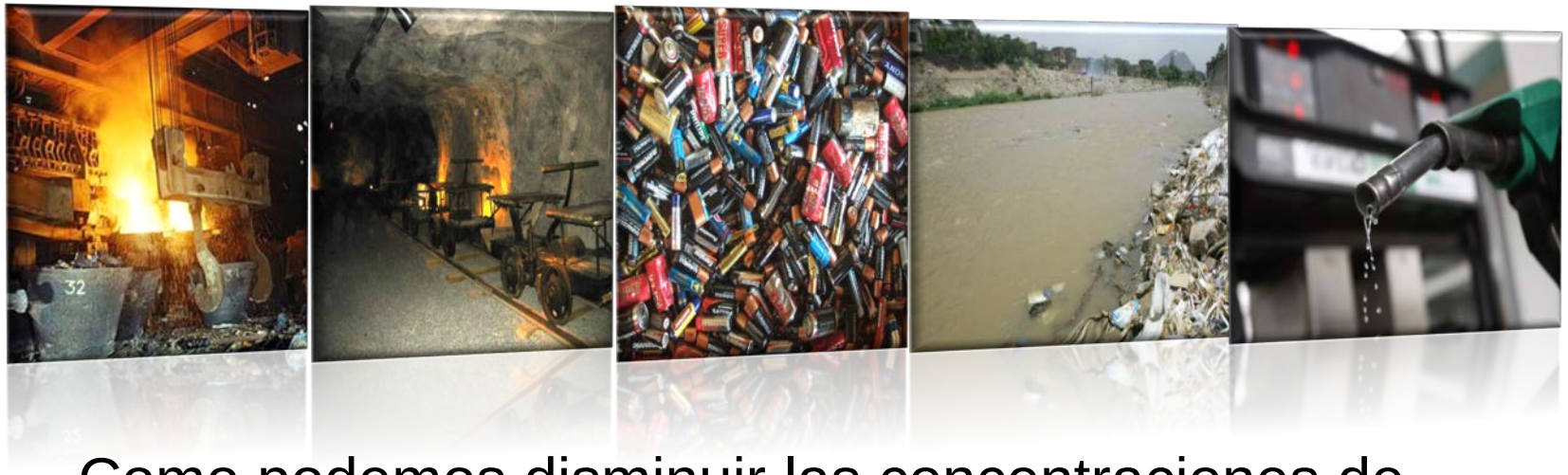


Utilización de DMSA y DMPS

Núria Corominas
S. Farmacia Hospital Clínic Barcelona

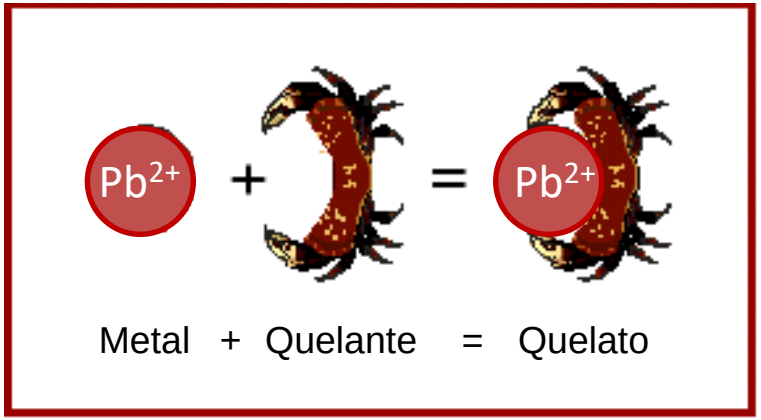
II Jornada d'antídots
15 de juny 2017



Como podemos disminuir las concentraciones de metales tóxicos en nuestro organismo?

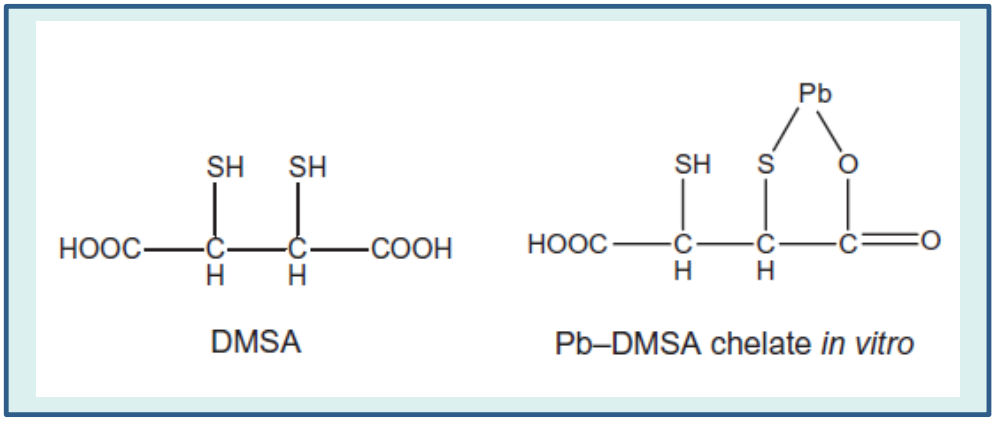
- Con agentes quelantes como el DMSA y el DMPS

Quelar = *Khele* (garra, pinza)

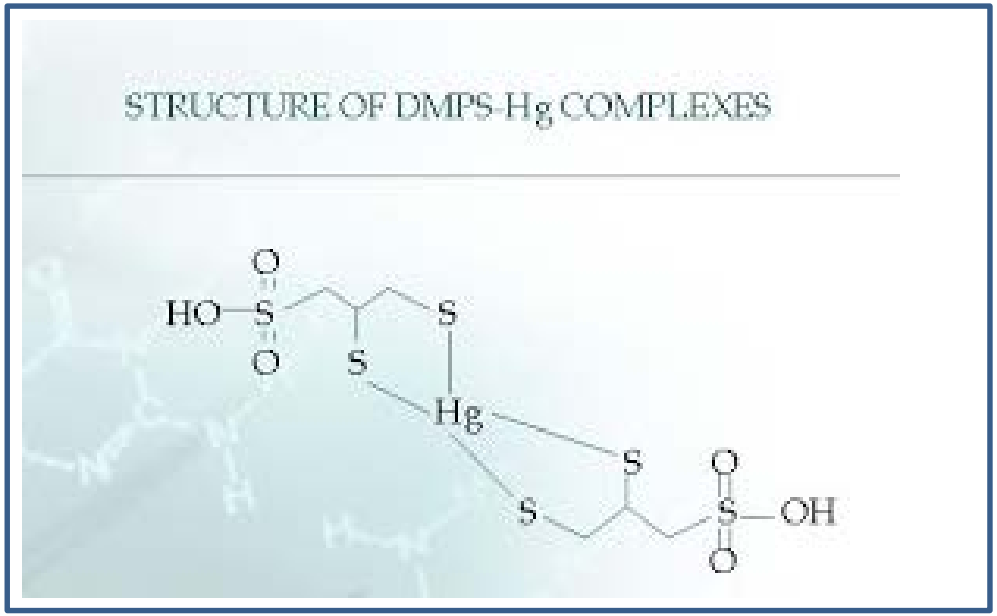


Estructuras químicas

DMSA



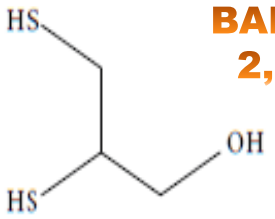
DMPS



Fuentes de exposición a metales

- WHO: aproxidamente 4,9 millones de muertes por año (8,3% del total de la mortalidad mundial) es atribuida a la exposición ambiental y al manejo inapropiado de sustancias químicas, entre las que se encuentran los metales

Prüs-Ustün A, et al. Environ Health 2011;10:9



BAL (British Anti-Lewisite)
2,3 dimercaptopropanol

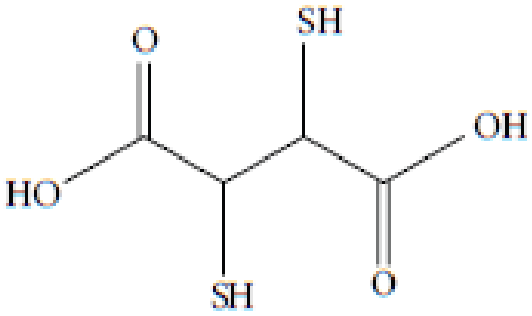
As, Hg, Pb

DMSA

ácido meso-Dimercaptosuccínico

Succímero

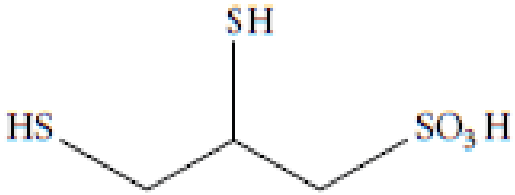
(SUCCICAPTAL®)



↓

Pb Hg

As, Cd, Ag
Cu, Sn



↑

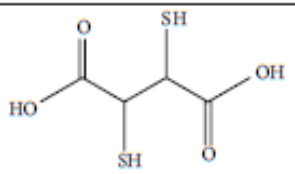
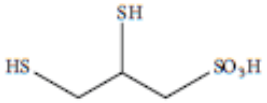
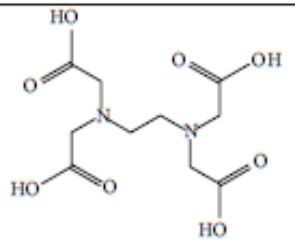
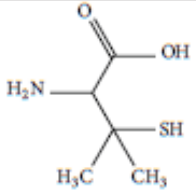
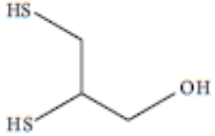
DMPS

ácido 2,3-Dimercapto-1-propanosulfónico

Unitiol

(DIMAVAL®)

Table 1: Overview of chelation drugs.

Chemical name (common names, abbreviations)	Structure	Activation metabolism	Coordination (binding) groups	Elements chelated
2,3-bis(sulfanyl)butanedioic acid (Dimercaptosuccinic acid; Succimer; Dimercaptosuccinic acid; *DMSA*; Suximer; Tin Salt; Succicaptal; Chemet) **DMSA**		Excretion via urine >90% as DMSA—cysteine disulfide conjugates.	Oxygen and sulfhydryl	Lead Arsenic Mercury Cadmium Silver Tin Copper
Sodium 2,3-bis(sulfanyl)propane-1-sulfonate (Sodium Dimercaptopropanesulfonate; *DMPS*; Unithiol; Dimaval; Unitiol; (+)-DMPS; (−)-DMPS) **DMPS**		84% of IV dose excreted through urine	Oxygen and sulfhydryl	Mercury Arsenic Lead Cadmium Tin Silver Copper Selenium Zinc Magnesium
2-[2-[bis(carboxymethyl)amino]ethyl-(carboxymethyl)amino]acetic acid (Ethylenediaminetetraacetic acid; Edetic acid; *EDTA*; Edathamil; Endrate; Versene acid; Sequestrol; Titriplex; Havidote; Cheelox; Versene; Calcium Disodium Versenate (edetate calcium disodium injection, USP) **EDTA**		Not metabolized. Excreted unchanged, generally coordinated with a different divalent cation	Oxygen	Lead Cadmium Zinc (Mercury thought to be too strongly bound in tissues to be mobilized, but this is not clinical experience)
(2S)-2-amino-3-methyl-3-sulfanylbutanoic acid (3-Sulfanyl-D-valine; *Penicillamine*; D-Penicillamine; Cuprimine; Depen; Penicillamine; Mercaptyl; Artamine; Cuprenil; Perdolat; Trolovol **D-PENICILAMINA**		Rarely excreted unchanged; excreted mainly as disulfides	Oxygen, hydroxyl, sulfhydryl, and amine	Copper (Wilson's disease) Arsenic Zinc Mercury Lead
2,3-bis(sulfanyl)propan-1-ol (Dimercaprol; British Anti-Lewisite; *BAL*; 2,3-Dimercaptopropanol; Sulfactin; Dicaptol; Dimersol; Antoxol; Panobal; Dithioglycerine; Dithioglycerol) **BAL**		Excreted unchanged in urine	Sulfhydryl and hydroxyl	Arsenic Gold Mercury Lead (BAL in combination with $CaNa_2EDTA$)

Information from US National Library of Medicine PubChem: http://pubchem.ncbi.nlm.nih.gov/search/search.cgi.

Sears ME. Scientific World Journal; 2013;2013:219840

Quelación eficaz

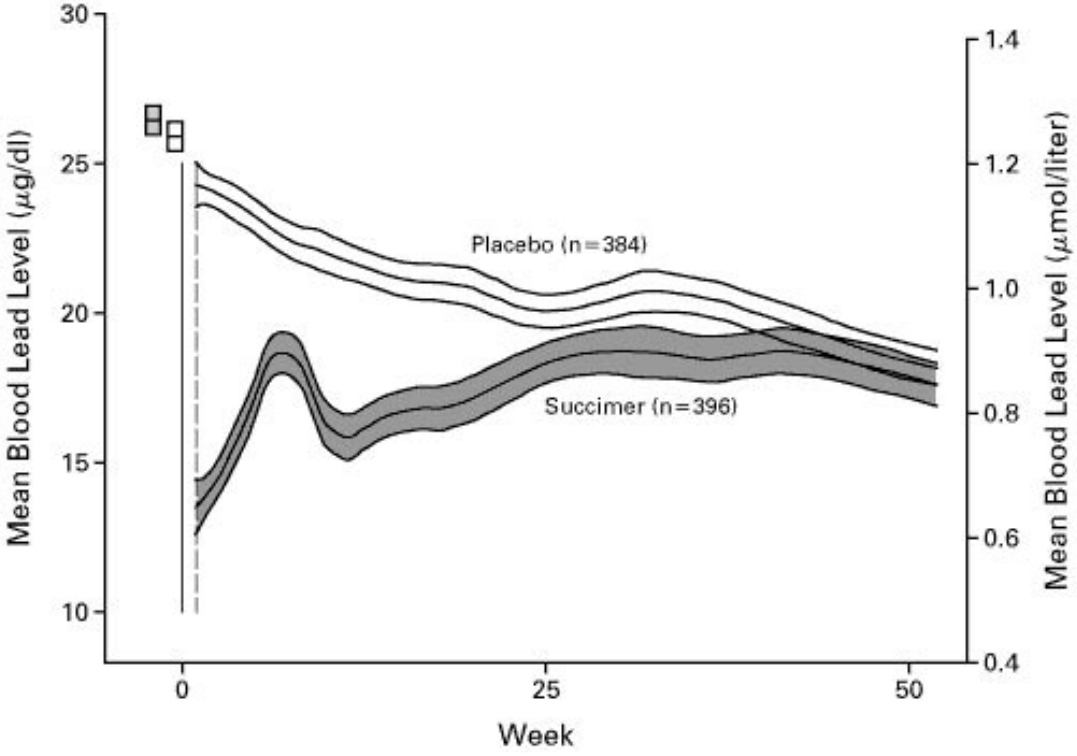
- Capacidad de unión del quelante al metal tóxico
- Quelantes endógenos

Quelante ideal

- Alta afinidad por el metal tóxico
- Baja toxicidad
- Farmacocinética apropiada
- Formación del quelato con rápida eliminación

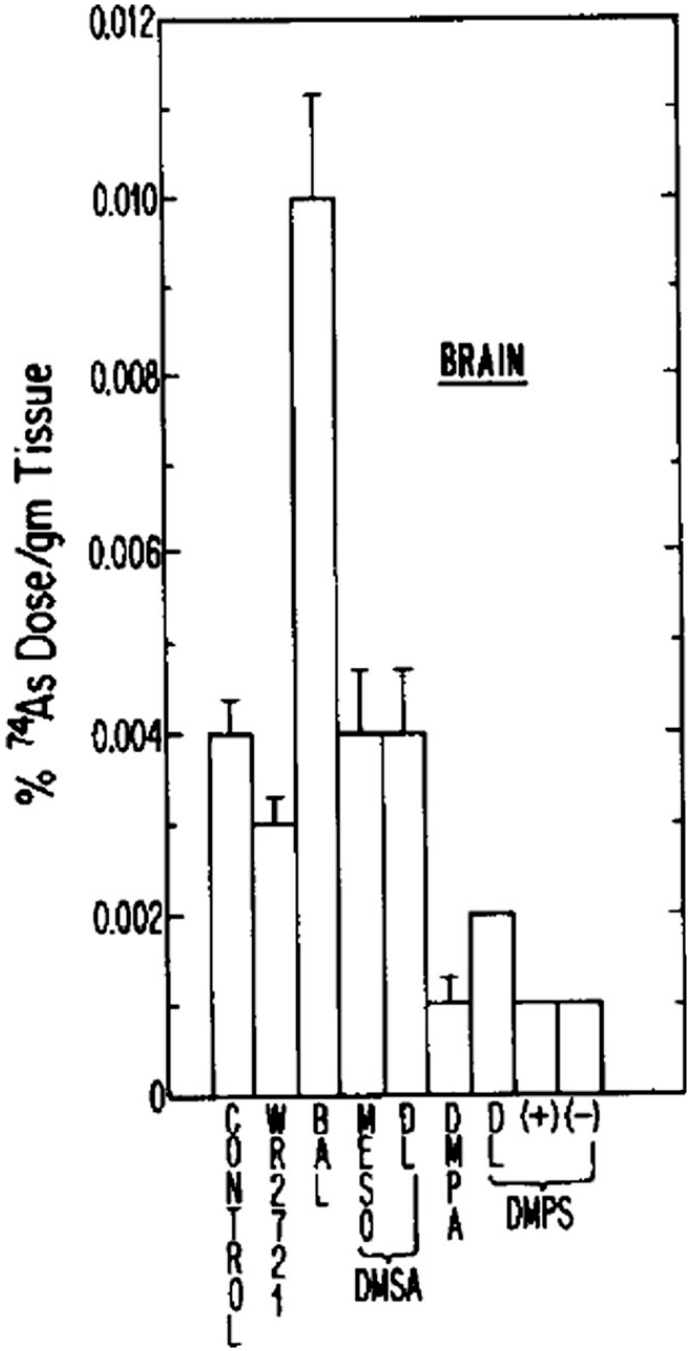
QUELACION

REDISTRIBUCIÓN



“REBOUND”

Treatment of lead-exposed children (TLC) Trial Group. Pediatr res 2000;48:593--599



QUELACION

REDISTRIBUCIÓN

"REBOUND"

Kosnett MJ. J Med Toxicol 2013;9:347-354

DMSA

Presentación: Caps 200 mg

Dosificación:

- 10 mg (350 mg/m^2)/kg/8h, durante 5 días, seguir con 10 mg (350 mg/m^2)/kg/12h durante 2 semanas
- 10 mg (350 mg/m^2)/kg/8h, durante 5 días, varios días sin tratamiento y seguir con un segundo ciclo de 5 días

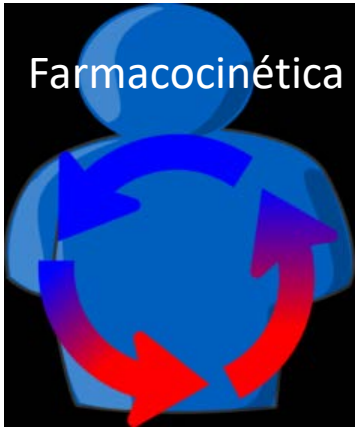
Período libre de tratamiento entre ciclos

DMPS

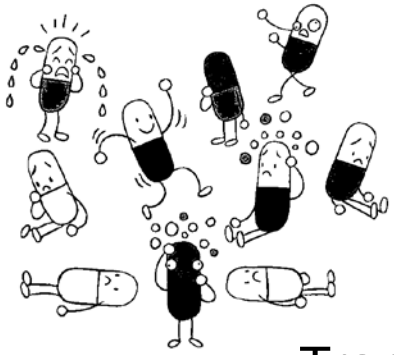
Presentación: Caps 100 mg

Intoxicación aguda: 12 a 24 caps a lo largo de 24h

Intoxicación crónica: 300 mg – 400 mg en 24 h divididas en 2 o 3 tomas



	DMSA	DMPS
➢ ABSORCION	20 % de la dosis	40 % de la dosis
➢ DISTRIBUCION	Extracelular Unión a albúmina >95%	Extracelular Unión a albúmina >80%
➢ METABOLISMO	Disulfuro de cisteína	Disulfuros cíclicos
➢ EXCRECION	Renal como disulfuro de cisteína (90%) e inalterado (10%). Heces: fármaco no absorbido	Renal (46%-59%), biliar

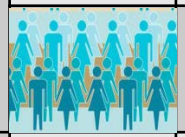


EFECTOS ADVERSOS

Transitorios y reversibles al suspender el tratamiento

- Moderado aumento de transaminasas
- Reacciones cutáneas: exantema, prurito
- Neutropenia leve
- Molestias gástricas (náuseas, vómitos)
- Tratamientos prolongados, disminución de Zn y de Cu

EVIDENCIA CIENTIFICA

	Pb	Hg	As	Cu	Sb	Bi	^{210}Po	Be	Cd	Co
DMSA										
										
										
DMPS										
										
										

 Estudios animales

 Estudios Observacionales o controlados con pocos pacientes/Casos clínicos

 Casos clínicos

 Estudios aleatorizados y controlado

N Engl J Med. 2001 May 10;344(19):1421-6.

The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead.

Rogan WJ[1], Dietrich KN, Ware JH, Dockery DW, Salganik M, Radcliffe J, Jones RL, Ragan NB, Chisolm JJ Jr, Rhoads GG; Treatment of Lead-Exposed Children Trial Group.

Author information

Abstract

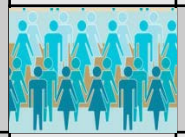
BACKGROUND: Thousands of children, especially poor children living in deteriorated urban housing, are exposed to enough lead to produce cognitive impairment. It is not known whether treatment to reduce blood lead levels prevents or reduces such impairment.

METHODS: We enrolled 780 children with blood lead levels of 20 to 44 microg per deciliter (1.0 to 2.1 micromol per liter) in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer, a lead chelator that is administered orally. The children lived in deteriorating inner-city housing and were 12 to 33 months of age at enrollment; 77 percent were black, and 5 percent were Hispanic. Follow-up included tests of cognitive, motor, behavioral, and neuropsychological function over a period of 36 months.

RESULTS: During the first six months of the trial, the mean blood lead level in the children given succimer was 4.5 microg per deciliter (0.2 micromol per liter) lower than the mean level in the children given placebo (95 percent confidence interval, 3.7 to 5.3 microg per deciliter [0.2 to 0.3 micromol per liter]). At 36 months of follow-up, the mean IQ score of children given succimer was 1 point lower than that of children given placebo, and the behavior of children given succimer was slightly worse as rated by a parent. However, the children given succimer scored slightly better on the Developmental Neuropsychological Assessment, a battery of tests designed to measure neuropsychological deficits thought to interfere with learning. All these differences were small, and none were statistically significant.

CONCLUSIONS: Treatment with succimer lowered blood lead levels but did not improve scores on tests of cognition, behavior, or neuropsychological function in children with blood lead levels below 45 microg per deciliter. Since succimer is as effective as any lead chelator currently available, chelation therapy is not indicated for children with these blood lead levels.

EVIDENCIA CIENTIFICA

	Pb	Hg	As	Cu	Sb	Bi	^{210}Po	Be	Cd	Co
DMSA										
										
										
DMPS										
										
										

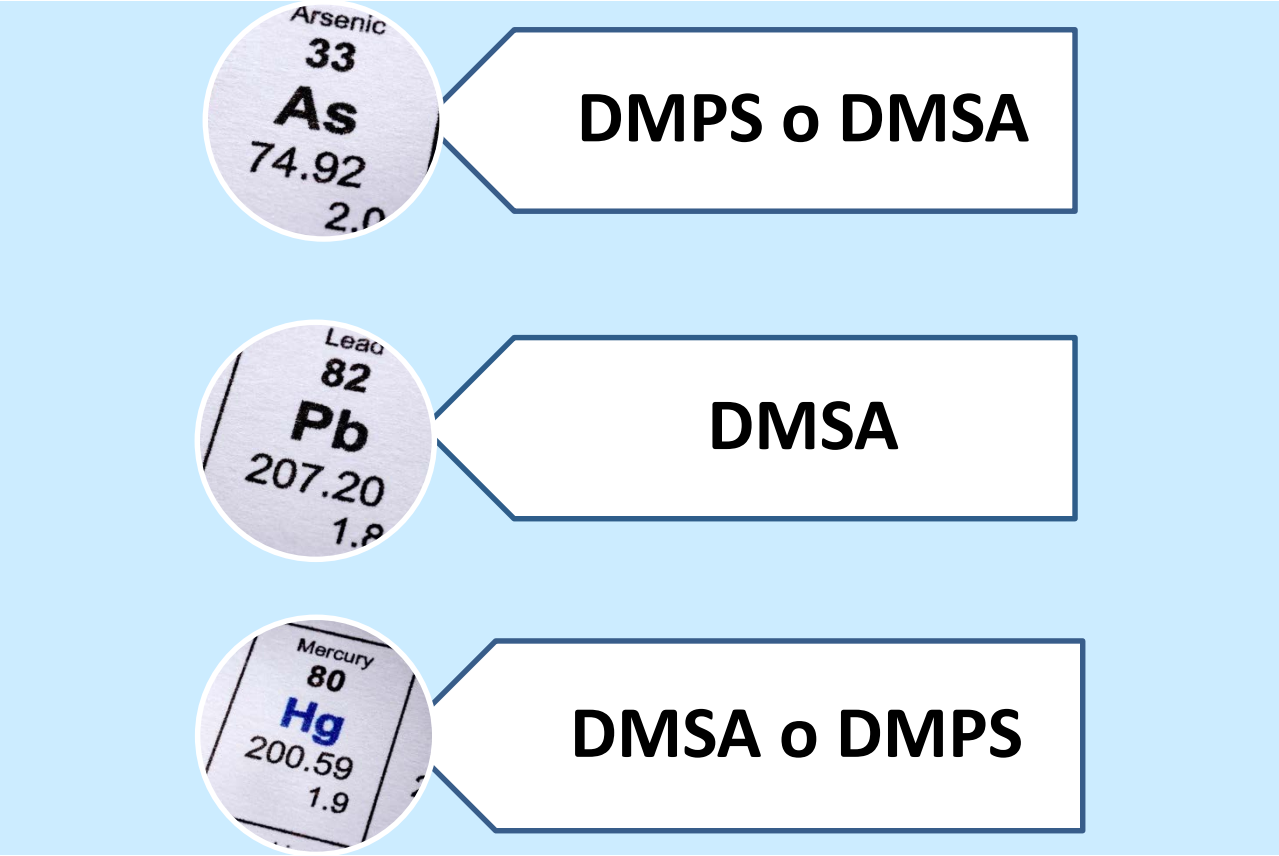
 Estudios animales

 Estudios Observacionales o controlados con pocos pacientes/Casos clínicos

 Casos clínicos

 Estudios aleatorizados y controlado

Toxicidad crónica



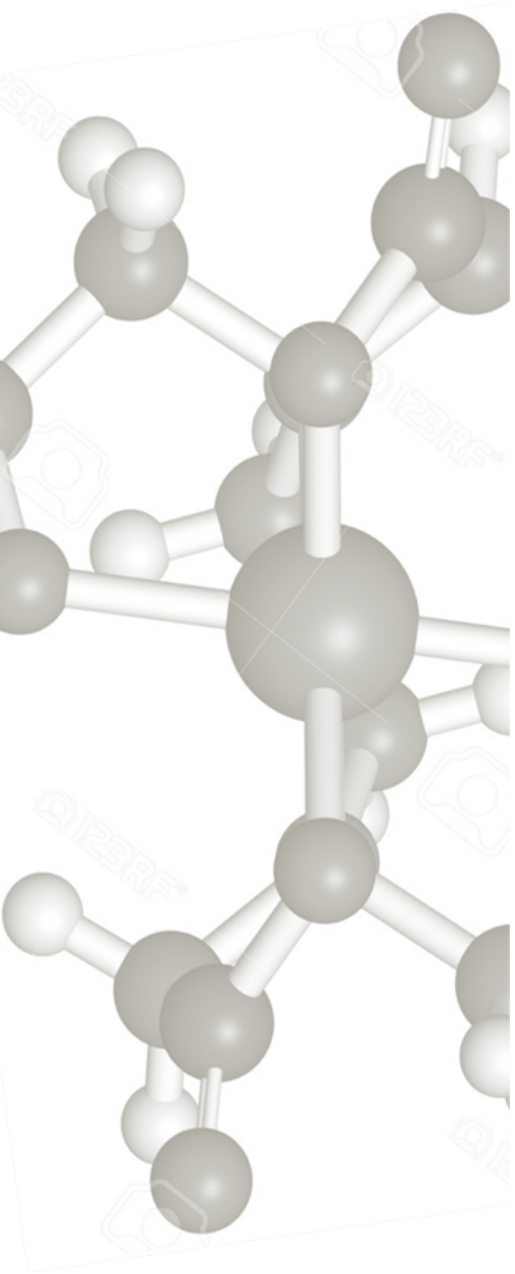
Sears ME. The Scientific World Journal. 2013;9:347-354

Recomendaciones para el tratamiento con quelantes en intoxicación crónica

Table 7
Chelation in chronic metal poisoning. References can be found in [55].

DFO for aluminum compounds, L1 and deferasirox are potential chelators
DMPS for chronic poisonings by arsenic compounds
DFO, L1 or deferasirox for iron overload
DMSA for chronic poisonings by lead compounds
DMPS for chronic mercury poisonings from mercury

Andersen O, et al. J Trace Elem Med Biol. 2016;38:74-80



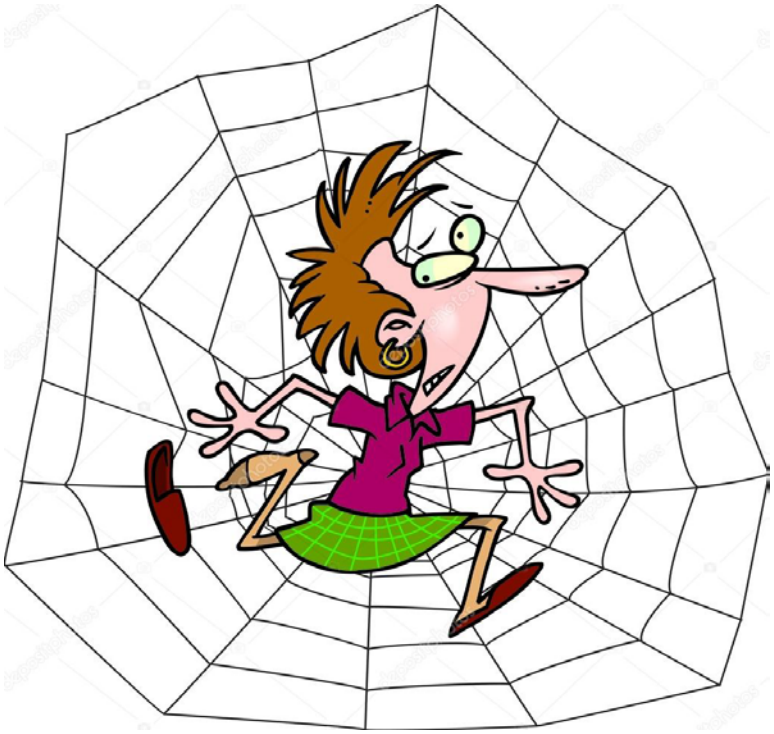
CONCLUSIONES

- La terapia de quelación en la intoxicación por metales se considera generalmente útil y recomendada en muchos casos. Sin embargo, esta recomendación se fundamente en una evidencia científica baja

- DMSA y DMPS han mostrado ser eficaces en casos de intoxicación por plomo y mercurio

- DMSA y DMPS se presentan como opciones más seguras que los quelantes clásicos (BAL, EDTA,...) y con ventajas de conveniencia (vía de administración oral)

- Con datos muy limitados, DMSA y DMPS constituyen opciones a tener en cuenta en la intoxicación por otros metales (As, Sb, Co…), así como en el tratamiento de la enfermedad de Wilson (DMSA).



Muchas gracias