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Review

Chelation therapy in intoxications with mercury, lead and copper

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ABSTRACT

In the present review we provide an update of the appropriate use of chelating agents in the treatment of intoxications with compounds of mercury, lead and copper. The relatively new chelators meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-propanesulphonate (DMPS) can effectively mobilize deposits of mercury as well as of lead into the urine. These drugs can be administered orally and have relatively low toxicity compared to the classical antidote dimercaptopropanol (BAL). D-Penicillamine has been widely used in copper overload, although 2,3-dimercaptosuccinic acid or tetrathiomolybdate may be more suitable alternatives today. In copper-toxicity, a free radical scavenger might be recommended as adjuvant to the chelator therapy.

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Introduction

Acute and chronic intoxications with mercury, lead and copper compounds can be treated efficiently in many cases by using chelation therapy. Recent development in the therapy of intoxications with these compounds justifies the present update. The efficiency of the relatively new chelating agents meso-2,3-dimercaptosuccinic acid (Succimer or DMSA) and D,L-2,3-dimercapto-1-propanesulfonic acid (Dimaval or DMPS) in lead and mercury poisoning has turned out to be superior to that of classical chelator 2,3-dimercaptopropanol (British Anti Lewisite, BAL).

In the long-term treatment of metal storage diseases, the chelation therapy is of crucial importance. Previous treatment for Wilson's disease used D-penicillamine (dimethyl cysteine) or triethylene tetramine (trientine or Trien) to enhance copper excretion [1,2] but today DMSA [3] and tetrathiomolybdate [4] are alternative drugs of low toxicity. The aim of this overview is to give an update of the clinical use of these chelating agents in poisoning or overload with mercury, lead or copper compounds.

Mercury

Mercury is extracted from cinnabar ores (HgS) by heating the ores in a current of air and collecting the vapor formed. The reaction for this extraction can be shown as:

$$HgS + O_2 \rightarrow Hg + SO_2$$

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China has been the top producer of elemental mercury in the world with almost two-thirds global share of mercury ores [5]. Because of the high toxicity of elemental mercury vapor, both the mining of cinnabar and the refining for mercury are hazardous that result in serious occupational health problems with numerous historic stories of mercury poisoning. Also, the wide use of inorganic mercury salts (Hg^{++}) in the chemical industry, organic mercury compounds in seed dressing, and elemental mercury in industrial processes, scientific instruments and dentistry have resulted in environmental pollution and health effects. The management of intoxication by mercury compounds is complicated by the differences in the toxicokinetics of inorganic salts (Hg^{++}), elemental mercury vapor (Hg^0) and various types of organomercurials (e.g. CH_3Hg^+).

Inorganic mercury salts are poorly absorbed, only about 10% in the intestinal tract [6], and deposit mainly in the kidney, a target organ for Hg^+ and Hg^{++} [7]. In contrast, the net retention of elemental mercury vapor (Hg^0) is significantly higher, about 80%. At very high acute dosage, mercury vapor induces respiratory symptoms. After absorption in the lungs most of the Hg^0 in the blood is oxidized to Hg^{++} then excreted into urine. However, due to its lipophilicity, a fraction of Hg^0 penetrates into the brain and other organs with subsequent oxidation to Hg^{++}. As the Hg^{++} ion does not pass cell membranes easily, this mechanism leads to trapping of Hg in the central nervous system, the critical target of Hg^0. Organic mercury compounds, e.g. methyl mercury (CH_3Hg^+), are highly lipophilic and thus absorbed completely after oral exposure and deposited in the brain or pass the placenta barrier. Accordingly, neurotoxicity and fetotoxicity are critical effects of these compounds.

Mercury poisonings were previously treated with the chelators BAL and D-penicillamine. However, BAL is now considered to be contraindicated in such poisonings, because it increases the brain deposition of inorganic as well as organic mercury [8,9]. DMSA was an efficient antidote in acute systemic $HgCl_2$ or CH_3HgCl intoxication in experimental animals [10,11], whereas the effect of penicillamine was small or negligible. In the latter studies oral administration of DMSA during 8 days after injection of CH_3Hg^+ reduced the brain Hg level significantly, an effect that may be secondary to the reduced blood levels rather than true penetration of the chelates across the blood–brain barrier. Later, DMSA and DMPS were found to ameliorate methyl mercury-induced developmental toxicity in experimental animals [12]. In several studies in mice or rats injected with inorganic mercuric salts, DMSA or DMPS effectively increased Hg elimination [13–15]. Both agents reduced mortality induced by lethal doses of $HgCl_2$ [16]. The combined animal data indicate that DMSA and DMPS are efficient antidotes in experimental acute inorganic and organic mercury intoxication. Although the isoamyl ester of DMSA may be a more efficient mobilizer of body stores of Hg than DMSA and DMPS, human use of this latter derivative must await extensive safety testing.

Increasing evidence indicates that DMSA and DMPS can be used safely in the treatment of human poisoning by various mercury compounds, as indicated by several case and cohort reports. A group of 26 workers who had inhaled significant amounts of Hg vapor in a chloralkali factory were hospitalized more than two weeks after the exposure. A 14-day period of chelation treatment with either DMSA or acetylated penicillamine was given. While DMSA increased the urinary Hg excretion almost five-fold, the penicillamine derivative increased the excretion only about two-fold [17]. A 38-years-old male who was initially treated with BAL after intake of a hazardous dose of a $HgCl_2$-solution, developed acute renal failure during this regimen, before intravenous treatment with DMPS was initiated and combined with hemodialysis. Despite continuing high blood Hg levels his kidney function was regained after 10 days. Parenteral DMPS was given during 4 weeks, and then oral DMSA was administered for another 3 weeks. The patient recovered completely [18]. Using blood samples from a randomized clinical trial of DMSA treatment of 767 children (1–3 years of age) with lead exposure, Cao and colleagues [19] measured blood methyl mercury before and 1 week after the treatment beginning (either DMSA or placebo), and they did a repeated determination in a 20% random sample of the children who received 3 courses of the same treatment ($n = 67$). Compared to the place group, the adjusted mean organic mercury concentration in the DMSA group fell 17% after three courses of treatment (p value of a trend = 0.048). A modest reduction of blood mercury in this group might be related to an organ-to-blood redistribution and prevention of the accumulation over time.

Therapeutic effectiveness of DMPS in cases of poisonings with Hg_2Cl_2 has also been reported [20]. Such poisonings have been precipitated by the use of Hg_2Cl_2-containing creams that are still used for dermal cosmetic application [21], resulting in acute or chronic poisoning. DMPS had been given 12 women orally for 5 days who had used a facial cream which contained Hg_2Cl_2 for up to 10 years. After 24 h of the administration, a significant increase of urinary mercury excretion was observed [22]. In occupational exposure situation, a challenge test was conducted in 8 workers who had been exposed to mercuric chloride by production of a calomel skin-bleaching lotion. The researchers found greatly increased urinary mercury and progressively lowered body burden of mercury during and after three courses of DMPS treatment [23].

Due to the low toxicity and high efficacy of DMSA and DMPS, both compounds are chosen as the antidotes in various forms of mercury poisoning [24]. Especially the experimental data, but also the limited human data indicate that DMPS is a highly effective chelation antidote in acute and chronic intoxications with inorganic Hg compounds, including elementary Hg vapor [25], while DMSA works better for detoxification of organic mercury compounds. As yet, DMSA and DMPS are not recommended for the treatment of patients suffering from neurological diseases [26]. It should be emphasized here that a challenge for further research is to mobilize mercury from the brain in cases of elemental Hg^0 vapor exposure [27]. Thus, while the Hg^{++}-DMPS complex is rapidly cleared from the circulation, it might be hypothesized that combined treatment with a lipophilic chelator could bring about a removal of Hg^{++} from the 'critical' cerebral cells. This hypothesis involves that the lipophilic chelator can act as a 'shuttling agent' for DMPS that operates in the extracellular space.

Lead

Lead (Pb) has widespread industrial uses in alloys, pigments, batteries and other applications. Because of its low melting point and high vapor pressure, industrial uses of inorganic lead may cause extensive local environmental pollutions. Childhood lead intoxication is still a serious problem in some countries, particularly in low-standard housing groups. Lead toxicity may also arise after using certain herbal medication [28]. The most important source of childhood lead exposure is lead-containing paint in old houses, which has been estimated to involve more than 1 million children in the United States (US) [29].

Since epidemiological evidence has indicated a risk of cognitive impairment in children at blood lead levels lower than 250 μ/L [27], the US Centers for Disease Control and Prevention (CDC) has revised the definition of childhood threshold of concern downward from 250 μg/L (1.2 μmol/L) to 150 μg/L in blood. However, present guidelines [30] involve that environmental lead removal is the action of choice at blood Pb levels in the range 150–450 μg/L (0.7–2.2 μmol/L), whereas chelation treatment is indicated at blood Pb levels above 450 μg/L (2.2 μmol/L), preferably with DMSA (Succimer). Succimer was registered in USA in 1991 for oral chelation treatment of children with blood Pb > 450 μg/L [31].