

## SELECTED PROBLEMS RELATED TO ENVIRONMENTAL HEAVY METALS EXPOSURE AND CHELATION THERAPY

### WYBRANE PROBLEMY ZWIĄZANE ZE ŚRODOWISKOWYM NARAŻENIEM NA METALE CIĘŻKIE A TERAPIA CHELATUJĄCA

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#### Abstract

**Background:** Exposure to heavy metals leads to functional and metabolic disturbances and many of them are included in pathogenesis of common diseases (arterial hypertension, atherosclerosis, neurodegenerative processes). In this context new therapeutic and prophylactic strategies are necessary. Patients diagnosed with chronic heavy metals intoxication usually require chelation to increase mobilisation of metals from tissues and elimination of them via urine. Acute poisoning with toxic metal may be difficult to diagnosis, especially in case of accidental intoxication or suicidal intention. Patients also require chelation after causative factor is identified. **Objectives:** To describe some problems connected with toxicity of metals poisoning and to review pharmacologic therapies that could have a role in poisoning with metals. **Methods:** A review of the literature was carried out and expert opinion expressed. **Results/conclusion:** Chelation is a common therapy in case of poisoning with toxic metals but it is satisfied only partially. A combined therapy with structurally different chelators or long-term acting chelators could become viable alternatives in the future. A combined therapy with an antioxidant plus chelator may be a good choice in patients chronically poisoned with metals. Exposure to lead should be taken into account during estimation of global cardiovascular risk.

**Key words:** heavy metals, common diseases, chelation, antioxidants

#### Streszczenie

**Wstęp:** Istotnym aspektem przewlekłej ekspozycji na działanie metali ciężkich jest ich udział w patogenezie chorób o znaczeniu społecznym (nadciśnienia tętniczego, miażdżycy, chorób neuro-degeneracyjnych). W tym kontekście niezbędne są nowe strategie profilaktyczne i terapeutyczne. Osoby z rozpoznaniem przewlekłego zatrucia metalami ciężkimi zazwyczaj wymagają stosowania chelatorów w celu zwiększenia mobilizacji metali z tkanek i eliminacji ich z moczem. Ostre zatrucie metalami toksycznymi może być trudne do zdiagnozowania, szczególnie powstałe przypadkowo lub w celach samobójczych. Po zidentyfikowaniu czynnika sprawczego, pacjenci także wymagają chelatowania. **Cel:** przedstawienie wybranych problemów związanych z toksycznością metali ciężkich i przegląd terapii farmakologicznych stosowanych u osób z objawami zatrucia. **Metody:** przegląd piśmiennictwa i opinii ekspertów. **Wyniki/wnioski:** Chelatowanie jest powszechnym sposobem terapii osób z rozpoznaniem zatruciem metalami ciężkimi, ale jest to sposób skuteczny tylko częściowo. Obiecującym sposobem leczenia jest terapia złożona z zastosowaniem chelatorów o różnej budowie lub działających długoterminowo. U pacjentów z objawami przewlekłego zatrucia metalami ciężkimi korzystne jest stosowanie terapii złożonej chelatorem i antyoksydantem. Ekspozycja na działanie ołowiu powinna być czynnikiem uwzględnianym w szacowaniu całkowitego ryzyka sercowo-naczyniowego.

**Słowa kluczowe:** metale ciężkie, choroby społeczne, chelatowanie, antyoksydanty

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## Introduction

The most abundant heavy metals in human environment: lead, cadmium, arsenic, mercury, are redundant to normal function of the human organism. They can exert toxic effects in organs even in the smallest concentration. The lowest safety limit of these metallic content in body fluids or tissues is unknown and settlement acceptable values of intake is only tentative.

Heavy metals are used in many industries, including metals smelting and processing, the manufacturing of batteries, pigments, solder, plastics, cable sheathing, ammunition and ceramics, and battery recycling [1]. Most cases of lead poisoning in adults result from occupational exposure, whereas in children from environmental pollution [2]. The main sources of heavy metals are: dust, soil, water, air, the workplace, food, trinkets, paints, ethnic folk remedies, and cosmetics. Heavy metals are used in the manufacture of Ayurvedic medicinal products, and non standardized manufacturing may result in high levels remaining in the final product [3, 4]. It has been reported, that children toys distributed in Europe are coated with lead containing paint [5]. These sources are potential cause of acute or chronic metal poisoning, including those with lethal consequences. Therefore, in the most developed countries there are effective politics limiting heavy metals emission. Reductions in the use of lead in food processing, the removal of lead additives from gasoline and the reduction of lead in paint have resulted in marked declines in lead exposure in the North American population. Data from the United States show that the mean blood lead level in the US population decreased from 14.6 to 1.5 microg/dL between 1976 and 2001/02 [6].

The chronic poisoning with heavy metals has been still an important global toxicological problem. Beyond toxicity of metals in organs and tissues (neuro-, hepato-, nephro-, cardio-, vaso-, myelo-, genotoxic and carcinogenic effect), which has been profoundly elucidated, a new problem appeared, that is participation of heavy metals in pathogenesis of common diseases, such as atherosclerosis, diabetes mellitus or neurodegenerative processes.

In this article some problems related to heavy metal toxicity and the up-to-date treatment of patients with metal intoxication is discussed with a special interest in new aspects and novel strategies of this treatment.

## Some problems related to toxicity of heavy metals

The human sensitivity to toxic effect of heavy metals differ depending on the age, sex, general

health status, quantitative and qualitative alimental deficiency, diet, smoking, life style, place of inhabitation and socio-economical status, hygienic habituation, summarized occupational and environmental exposition to xenobiotics. The important differentiating factor is genetic predisposition to metal toxicity resulting from existence of genetic polymorphism of protein participating in modified by metal metabolic pathways. This area is nearly unknown, however genetic conditioned susceptibility to metal action is important not only in context of typical toxicological consequences. There exists a lot of convincing evidence indicating causative connection between exposition to some metals and occurrence of common diseases. The most results concern the impact of lead in small doses on the cardiovascular system. From the 60. years the former century the numerous experimental, clinical and epidemiological studies were performed indicating the significant effect of this metal on the all regulatory levels of cardiac and vascular reactivity including contribution of renal function [7-14]. Recently it was shown, that selected genes can modify the toxic effect of lead and simultaneously may participate in development of arterial hypertension. ALAD(1) homozygotes might be more susceptible for lead-induced disturbances in heme biosynthesis [15, 16] or spermatogenesis [17] than ALAD(2) and more susceptible for genotoxic effect of lead than ALAD(1-2) carriers [18]. Concurrently ALAD polymorphisms indirectly, influencing renal function, can facilitate lead-induced hypertension. In Korean workers exposed to large doses of lead, association between ALAD polymorphism and renal parameters as well as modification by ALAD in associations between blood lead and/or DMSA-chelatable lead and three renal outcomes (BUN, serum creatinine and creatinine clearance) was observed. Also the eNOS variant allele were found to be connected with degree of lead induced renal insufficiency [19]. On the other hand, as well lead, as some genes, i.e. gen for vitamin D receptor (VDR) may independently influence blood pressure and hypertension risk. The common VDR genotype (BB and Bb vs. bb), blood lead, tibia lead, and DMSA-chelatable lead were all positive predictors of systolic blood pressure [20].

At present it is known, that chronically acting lead causes arterial hypertension and atherogenic changes in lipid metabolism [8, 21, 22]. Lead disturbs endothelial function, enhances inflammatory reaction and influences essential metals homeostasis [23, 24].

Induced by lead arterial hypertension is associated with chronic exposition to this metal in small doses, related to blood lead levels from 10 microg/dL to 40 microg/dL. The hypertension

can be associated also with blood lead level lower than 10 microg/dL, i.e. when exposure was in the past and now it is representative by increased level of lead in bone. It is systolic-diastolic hypertension, responsive weaker to beta adrenoreceptors blockers [25] and with modified reaction to hypotensive action of calcium antagonists and angiotensin converting enzyme inhibitors [26].

Independently on the lipid changes lead influences lipid peroxidation. In vessel walls lead in small doses induces adaptive-defense response, stimulating antioxidant enzyme activity whereas in greater doses inhibits this activity [27]. These different changes are associated with different function: lead in small doses increases reactivity of postsynaptic alpha-adrenoreceptors to catecholamines and simultaneously enhances vasodilatory effect of endogenous nitric oxide [28]. Thus vasoconstrictor effect of lead is accompanied by compensatory endothelial response. Lead in greater doses causes changes conducive persistent vasoconstriction: decreased nitric oxide pool or bioavailability, and increase synthesis or release both endothelin and vasoconstrictor prostaglandins [11, 29]. Additionally changes in essential metals homeostasis induced by lead facilitate as well vasoconstriction as oxidative stress [10]. Changes in passive and active vascular tone, endothelial mediators release, smooth muscle cells proliferation together with monocytes and lymphocytes activation, can promote induction atherosclerotic lesions. Lead influencing the metabolism of glycosaminoglycans can be responsible for atherosclerosis complications [30]. Chronic exposition to lead should be recognised as cardiovascular risk factor with the all therapeutic and prophylactic consequences. Also cadmium has been indicated in the etiology of arterial hypertension. There is less convincing evidence related to connection between chronic exposure to tin and cardiovascular diseases, aluminium and Alzheimer disease, mercury and autism, however these relationship are more probable.

## Pharmacologic therapies in poisoning with metals

Chelation therapy has historically been used to reduce the body burden of heavy metals in patients with severe symptoms and highly elevated circulating levels of heavy metals. However, a small number of controlled clinical trials have evaluated the benefits of this therapy in heavy metal poisoning but in some cases chelation has effect comparable to placebo [31].

Chelating agents are organic compounds capable of linking together metal ions to form complex

ring-like structures called chelates. The chelate is subsequently excreted in the urine. Effectiveness of chelation depends on whether the chelating agent is able to reach the intracellular site where the heavy metal is firmly bound [32]. This intracellular availability is conditioned by many factors, e.g. ionic diameter intra/extracellular compartmentalization, and excretion. Hydrophilic chelators are most effective in excretion metals in urine, but they weaker-complex intracellular metal deposits, whereas lipophilic chelators can redistribute toxic metals to lipid-rich organ, for example, the brain.

In developed countries workers occupationally exposed to metals at high concentrations (i.e. copper founders) are subject to oblige to biological monitoring. Chelation practised in this monitoring decrease body burden with toxic metals. This system protect against metal toxicity but data about protection against induced by metal other consequences are missing. In the nearest future it is worth to begin studies on the effect of chelation on arterial blood pressure in workers exposed to lead.

The chelation is performed using calcium disodium ethylenediamine tetra acetic acid (CaNa<sub>2</sub>EDTA) and preceded calcium. Contraindications to chelation is hypocalcemia or kidneys insufficiency. D-penicillamine and British anti-lewisite (BAL) have been also used as antidotes for acute and chronic poisoning. 2, 3-dimercaprol (BAL) has long been the mainstay of chelation therapy for lead or arsenic poisoning. A thiol chelating agent, meso 2,3-dimercaptosuccinic acid (DMSA), an analogue of BAL, has been tried successfully in animals as well as in a few cases of human lead and arsenic intoxication. DMSA could be a safe and effective method of treatment, but one of the major disadvantages of chelation with DMSA has been its inability to remove lead from the intracellular sites because of its lipophobic nature. There are reports of beneficial activity of prophylactic administration of calcium especially in young women exposed occupationally to lead. Simultaneously, there were no evident profits from the intake of vitamins C and/or E [32].

A vast majority of problems deal with chelation therapy in acutely heavy metals poisoning. Iron is an essential element for normal cell metabolism but in excess quantities is highly cytotoxic and even lethal. It affects almost every organ being systemic intracellular poison. Iron absorption is normally carefully regulated to avoid accumulation as there is no physiological mechanism to eliminate iron excess from the body. The main causes of acute iron poisoning in adults include suicide attempts and iron overdose during pregnancy. However, patients with anemia treated with iron in high doses by various

routes simultaneously, in some condition (i.e. hypoproteinemia) can reveal symptoms of acute iron poisoning. The toxicity can be result of a cumulative effect of iron on cells. We have reported iron poisoning resulting from combined oral and parenteral iron administration [33]. We could not base our diagnosis on desferrioxamine test, because of our patient was admitted into clinic three days after iron ingestion. We decided to give desferrioxamine therapeutically to our patient on 3rd day after exposure. The chelator was given by intramuscular route because this drug given intravenously can evoke hypotension as a side effect. In the state of hypoperfusion desferrioxamine could not reach therapeutic level in circulation and appeared to be not effective. On the other hand the first 24 hours urine collection following desferrioxamine administration was 9700 ml (as a phase of polyuria in renal failure), so interpretation of the test was not possible. Suspecting iron intoxication we decided to continue chelation therapy, as our patient revealed fatal prognostic indicators: coagulopathy, shock and acute liver failure. In our case the next argument confirming diagnosis was sudden improvement and total recovery as mentioned in the literature by other authors.

In chronic overloading with ferrum, where life-long chelation may be necessary, new safer chelators for oral administration are wanted.

## Methods for therapy

Despite many years of research, an effective treatment of patient poisoned with heavy metals is difficult to realize. In this aspect new trends in chelation therapy including combined treatment, are promising. This includes the use of structurally different chelators or a combination of an adjuvant and a chelator to provide better clinical and biochemical recovery in addition to lead mobilization.

Kalia et al. compared the therapeutic efficacy of captopril and DMSA either individually or in combination against arsenite induced oxidative stress and mobilization of metal in rats [32]. Treatment with DMSA was effective in increasing ALAD activity while, captopril was ineffective when given alone. Captopril when co-administered with DMSA also provided no additional beneficial effect on blood ALAD activity but significant brought altered platelet counts back to the normal value. In contrast, administration of captopril alone provided significant beneficial effects on hepatic oxidative stress, and in combination with DMSA provided a more pronounced recovery in the thiobarbituric acid reactive substances (TBARS) level compared to the individual effect of DMSA or captopril. Interestingly, combined administration of captopril

with DMSA had a remarkable effect in depleting total arsenic concentration from blood and soft tissues. These results lead to the conclusion that captopril administration during chelation treatment had some beneficial effects particularly on the protection of inhibited blood ALAD activity, and depletion of arsenic level. It seems that a co-administration of an antioxidant is more beneficial than monotherapy with the chelating agents, in order to achieve optimal effects of chelation in arsenite toxicity [32].

There were also some attempts to use antioxidants as it has been long known to reduce the free radical-mediated oxidative stress while thiol chelators have been used to treat arsenic toxicity. The therapeutic efficacy of melatonin or N-acetylcysteine (NAC) was studied individually and in combination with DMSA in reducing lead concentration in blood and other soft tissues. Administration of melatonin and NAC individually, provided significant protection to lead induced disturbed antioxidant defense that may significantly compromise normal cellular function [34]. Administration of melatonin and NAC (a thiol containing antioxidant), also provided a significant protection to TBARS levels, reduced glutathione (GSH) and oxidized glutathione (GSSG) contents in tissues, suggesting their ability to act as a free radical scavenger and in protecting cells against toxic insult.

Interestingly, combined treatment of DMSA and NAC provided more pronounced efficacy in restoring altered biochemical variables and in reducing body lead burden than monotherapy with DMSA. The results thus, suggest the involvement of ROS in lead toxicity and a pronounced beneficial role of NAC in therapeutic implications of lead poisoning when co-administered with a thiol chelator (DMSA) supporting the hypothesis that cellular redox status may be significantly reversed by utilizing a thiol containing antioxidant compound. It can be concluded that, combined therapy with an antioxidant moiety and a thiol-chelating agent may be a better choice for treating plumbism [34].

It was suggested that concomitant administration of an antioxidant could play a significant and important role in abating a number of toxic effects of lead when administered along with the thiol chelators. Flora et al. also investigated affect of taurine, an amino acid and a known antioxidant, either alone or in combination with DMSA in the treatment of subchronic lead intoxication in male rats [35]. DMSA was able to increase the activity of ALAD, while both taurine and DMSA were able to significantly increase GSH level towards normal. Animals treated with taurine significantly reduced the alterations in some of the biochemical parame-

ters indicative of oxidative stress. TBARS levels reduced significantly in liver, kidney and red blood cells, while GSH level increased. Activity of superoxide dismutase (SOD) also showed an increase in blood and brain in animals treated with taurine. The data also provided a promising role of taurine during chelation of lead by potentiating the depletion of blood, liver and brain lead compared to DMSA alone.

Chelation is a beneficial therapy in case of chronic intoxication with heavy metals. This therapy is of smaller significance in case of acute poisoning, which is a result of a complex clinical situation. Acute metal intoxication usually proceeds with multiorgan distress syndrome, determining contraindication to treatment with chelators. Symptoms of kidney or liver dysfunction limit credibility of indicators monitoring chelator's effectiveness. As a rule, patients need the intensive care and symptomatic treatment. However, at the moment allowing to include chelators, chelation therapy can determine a prognosis. In workers occupationally exposed to heavy metals chelation can serve as a prognostic procedure, useful in occupational risk estimation. It also enables to undertake appropriate actions. Temporary or lasting discontinuation of exposure to lead at work before, before clinical symptoms appear, results in significant decrease of the occupationally lead poisoning.

However, due to metal accumulation in tissues, chelation is not a fully effective therapy and needs repeating doses of drugs, usually administered in parenteral way. A therapy combined with an antioxidant plus chelator does not seem to be the best choice for all of the patients poisoned with metals. This therapy can be beneficial, only if an antioxidant is simultaneously a chelator, as it is in case of N-acetylcysteine. Additive impact of both chelators is then expected. The effect of therapy with an antioxidant is significantly dependent on the patient's oxidative status at the beginning of the treatment. This effect, according to antioxidant potential, can be beneficial as well as aggravating. It concerns especially these metals, which do not undergo Fenton's reaction: cadmium, lead, mercury. Additionally, the use of antioxidants without chelators, i.e. in prevention of cardiovascular diseases, did showed only equivocal benefits resulting from antioxidant supplementation. On the contrary, some of them showed increased number of cardiovascular end points and the incidence of neoplasms. New long-term chelators consisting of structurally different components (including N-acetylcysteine) are needed.

Summarizing, chronic exposition to heavy metals is significant factor in pathogenesis of arterial

hypertension or atherosclerosis. In many countries the exposure to lead (also to cadmium, mercury and gold) is taken into account as hypertensinogenic factor. Also in Poland exposure to lead should be taken into account during estimation of global cardiovascular risk.

Chelation is a common therapy in case of poisoning with toxic metals but it is only partially satisfactory because of metal accumulation in tissues. A combined therapy with long term, structurally different chelators could become viable alternatives in the future.

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