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Comparison of Chelating Agents DMPS, DMSA and EDTA for the Diagnosis and Treatment of Chronic Metal Exposure

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Authors' contributions

This work was carried out in collaboration between both authors. Author EBB designed the study, performed the statistical analysis, wrote the protocol, wrote and edited the manuscript with the help of author YMB. Both authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Several chelating agents are presently used among environmental physicians to diagnose and treat a chronic metal overexposure. We evaluated and compared the binding capacity of the most common chelating agents DMPS (2, 3-dimercapto-1-propanesulfonic acid), DMSA (dimercaptosuccinic acid), also called Succimer) and EDTA (ethylene diamine tetraacetic acid) for the potentially toxic metals Antimony (Sb), Arsenic (As), Cadmium (Cd), Lead (Pb) and Mercury (Hg). Secondly, we evaluated how the nutrient elements Calcium (Ca), Copper (Cu) and Zinc (Zn) are affected by the chelating agents tested.
Study Design: Through ICP-MS (Inductively Coupled Plasma Mass Spectroscopy) analysis of urine from environmentally burdened patients, we determined which chelating agent in oral or injectable form has the best potential to be used as a provocation test for the diagnosis of multiple metal over exposure, and which chelating agent is best used for the detoxification treatment of a single metal exposure.
Place and Duration of Study: Micro Trace Minerals and Friedle Laboratories, Hersbruck/Regensburg, Germany, between January 2011 and February 2013.
Methodology: Data utilized is based on urine samples from chronically exposed

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patients, male and female adults, received from chelation therapists. Acutely intoxicated patients were not included.
Results: The intravenous application of DMPS is most suitable for the diagnosis and treatment of a single or multiple metal exposure, involving the metals Sb, As and Hg. Both EDTAs (NaCaEDTA and NaEDTA), administered intravenously, are the agents of choice for Cd, while Pb can be chelated using DMSA, DMPS, or the EDTAs. Both EDTAs have a strong Zn binding ability, but only NaEDTA is suitable for binding appreciable amounts of Ca. DMPS best binds Cu.
Conclusion: The intravenous application of DMPS is most useful for the diagnosis of multiple metal overexposure. It is also the treatment of choice for Sb, As and Hg and has the strongest Cu binding ability of the chelators tested.

Keywords: DMPS; DMSA; EDTA, arsenic; cadmium; copper; lead; mercury.

1. INTRODUCTION

Due to the threat of chemical warfare during World War I, the role of chelating agents, also referred to as antidotes has been well documented [1]. Protection methods and decontamination techniques were investigated and developed by governmental agencies to potentially protect people from the devastating effects of chemical agents. British Anti Lewisite (BAL) was developed as a specific chelating agent for arsenicals, leading to the less toxic chelating agents DMPS and DMSA [2]. International poison centers list the use and indication of these and other antidotes for cases of acute intoxications and provide emergency guidelines for physicians confronted with acute cases of metal poisoning.

With the increase in environmental pollution, chronic diseases caused by low-grade metal exposures are on the rise [3]. Typically, patients afflicted with environmental diseases suffer from diffuse symptoms and the diagnosis and treatment of these sub-acute multiple exposures largely depends on proper laboratory evaluation, which in turn aids in the selection of the appropriate chelating agent for treatment.

Tests utilized to diagnose a chronic metal intoxication involve blood and urine testing [4]. However, for most patients afflicted with chronic exposures blood and urine test results are generally inconspicuous, often providing inconclusive information for treatment. Blood and urine tests reflect immediate exposure through food, drink, air or other means [5]. With long term exposures, the daily metal intake is generally too low to significantly raise blood or urine metal concentration above existing reference ranges as set by the various environmental agencies such as the Environmental Protection Agency (EPA) and the German Umweltbundesamt (UBA). Low grade toxic exposures can be the cause of health issues, but conventional diagnoses make it difficult to prove the point.

To determine the degree of a long term, low grade exposure, environmental physicians developed provocation tests [6]. Such a provocation test involves the use of a metal-binding chelating agent to provoke a response. Because chelating agents have a strong ability to bind metals, the oral or intravenous application of such a chemical agent forces metal binding not only of the easily accessible metals in blood but also of metals stored in body tissue.

The most commonly used chelating agents are the traditional antidotes DMSA, DMPS and EDTA. They are administered in the oral form (DMSA+DMPS), as an injectable (DMPS) or

infused intravenously (EDTA). After metals are bound, the metal-chelating complex is excreted through the renal pathway. Consequently, the urine metal concentration following chelation treatment exceeds the metal concentration of unprovoked (random) urine. Depending on a patient's metal burden, the post chelation urine sample may show a significantly elevated metal concentration.

A provocation test should always be preceded by a random urine test (also referred to as unprovoked urine), even though test results of unprovoked urine are generally within the expected reference range. It is the comparison of the metal concentration in unprovoked versus the provoked urine that provides valuable information about the body burden. A high metal concentration of a provocation test reflects excessive tissue storage.

Thus, a provocation test (also referred to as a challenge or mobilisation test) is a means to detect long term metal overexposure; it allows the physician to assess a patient's total body burden. A provocation test also shows which of the toxic metals found in excess is of main concern. With this information, the physician can select the appropriate chelating agent and gauge an appropriate treatment schedule. To this date, the use of chelating agents is accepted in clinical toxicology for the treatment of acute poisonings. The use of chelation in environmental medicine, a medical branch outside toxicology, is not considered main stream medicine for the diagnosis and treatment of sub-acute, chronic exposures. Around the globe, chelation therapy is widely practiced, especially in Germany. Environmental physicians use chelating agents for the diagnosis and treatment of chronic metal overexposures and the demand for the services of environmental physicians is increasing. The diagnosis of metal-related chronic intoxication and the following chelation treatment is used for a wide variety of metal-related ailments such as allergies, arthritis, skin diseases, neurological disorders and more.

For decades, Poison Centers around the world have provided guidelines to physicians for the treatment of acute exposure [7]. Medical associations, particularly in Germany, the Netherlands and elsewhere, have used this knowledge to modify treatment approaches to suit chronic metal exposures [8]. The following chelating agents are presently the chelators of choice for German physicians where the pharmacological situation permits the use of these agents for the treatment of acute or chronic intoxications. Other countries may be less lenient. The chelating agents listed may not be available in every country.

- NaCaEDTA or NaEDTA are listed as antidotes for metal intoxication including lead and cadmium among others. NaEDTA (sodium edetate) is also listed as a chelator for calcium in the treatment of hypercalcemia [9].
- DMSA has been FDA-approved as an antidote for lead poisoning in children in 1991, but has also been used for the treatment of mercury intoxication. Poison centers list DMSA as an antidote for arsenic and mercury, or as a general antidote for heavy metal exposure [10].
- DMPS has been registered under the name of Dimaval in Germany. It is listed as an antidote for arsenic, lead, organic and inorganic mercury and a number of unspecified heavy metal compounds.

While chelating agents are officially used for the diagnosis and treatment of an acute metal intoxication, the use of chelating agents for the diagnosis and treatment of a chronic metal burden is not yet fully accepted in conventional medicine.

Today's people are exposed to a variety of metals, and it was our aim to confirm and add to existing information. We therefore have evaluated the metal binding of the above named chelating agents, applied orally or intravenously. We compared the metal-binding capacity of the common chelators for the metals Sb, As, Cd, Hg and Pb. Fig.1 demonstrates that metals such as lead are readily bound by all chelating agents tested, whereas mercury is not.

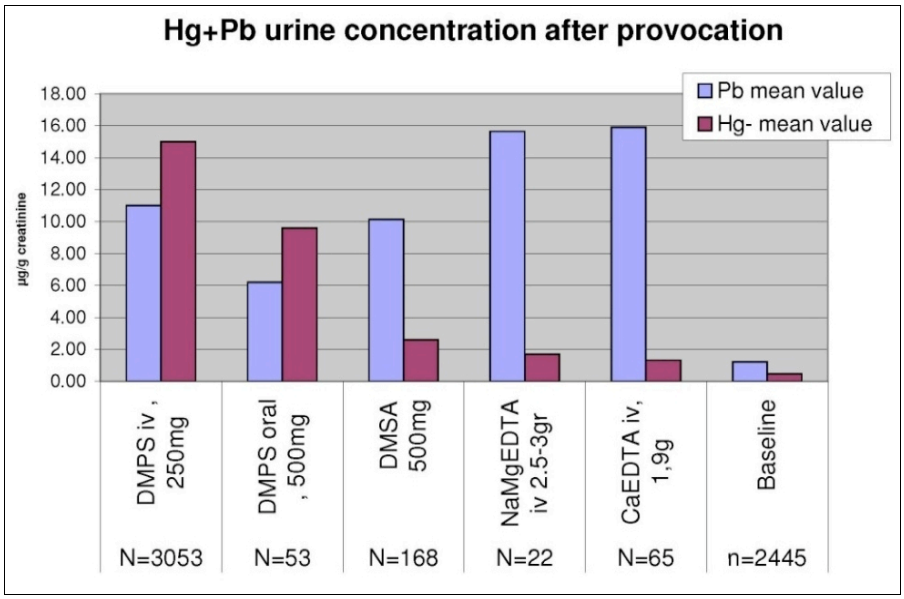

Fig. 1. Mean urine lead and mercury concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

We confirmed that the chelating agents tested are metal selective, showing varying binding capacities with essential elements such as calcium, copper and zinc. This information should be useful for the prevention of nutrient deficiencies for patients undergoing long term chelation therapy.

2. MATERIALS AND METHODS

2.1 Sample Collection

Micro Trace Mineral's database is the source of data for this statistical evaluation. Over the past 10 years, we methodically supplied physicians with detailed information about chelating agents, asked clinics to submit samples with treatment details, including the amount of chelating agents used, patient history, treatment and urine collection time.

For this study, the urine data utilized is based on samples received during January 2011 until February 2013 from mostly German physicians, practicing chelation therapy. Protocol instructions, including sampling instructions were provided to physicians. The samples included in our study are from chronically exposed patients, 45% male and 55% female adults. Acutely intoxicated patients were not included. To avoid external contamination, samples were collected into metal-free tubes, provided by the laboratory. Samples were shipped to the laboratory via regular post or courier.

2.2 Sample Testing

For urine sample digestion the following method was used:

- 500µL Urine were pipetted in a 15 mL tube
- +50µL of Internal Standard Solution was added (Sc,Y,Ho) à 200ppb
- +500µL nitric acid (HNO3) Supra Quality, 69 %
- +8.95mL Millipore-Water was added after approximately. 2 min for final dilution.

Urine metal analysis was performed using the 7700 Series Inductively Coupled Mass Spectrophotometer (ICP-MS) with Agilent's Octopole Reaction System (ORS), a new and improved type of mass spectrometers, which provide sensitive, robust, interference-free analysis of difficult, high-matrix samples. With five times the sensitivity of its predecessor and increased matrix tolerance, the ORS system replaces both GFAA and ICP-OES instruments in addition to older generation ICP-MS systems [11].

Certified urine standards and in-house standards were used for quality control and for validation processes. To avoid the potentially great margin of error that can result from the patients' fluid intake, or from incorrectly provided sample volume, results are reported in mcg/g creatinine for all elements, except calcium. For this macro-element values are reported in mg/g creatinine. Patient age and sex was used to determine urine creatinine levels [12].

2.3 Statistics

To statistically evaluate metal binding, we separated samples according to the type and amount of chelating agent used. We paid attention to application and urine collection time.

We compared the mean value of the urine metal concentration before and after provocation tests.

Baseline urines represent a morning or spot urine that has not been provoked with any chelating agent. Prior to sampling, patients were informed not to eat fish for 3 days prior to sampling, because fish can contain high amounts of arsenic or mercury. Patients were also instructed not to take supplements or algae products to avoid intake of metals.

For the provocation tests, the following chelating agents were used:

oral DMSA
oral and intravenously applied DMPS
NaCaEDTA vs NaMgEDTA, both applied intravenously.

Mean results of the urine provocation test results were compared to mean baseline urine values.

3. DISCUSSION AND RESULTS

3.1 Specifics about Chelating Agents

3.1.1 DMPS

DMPS belongs to the thiol group, binding metals to sulfhydryl groups. DMPS is registered in Germany since 1997 under the name Dimaval (Heyl, Berlin) and is available as a prescription item in various countries [13]. It is available in capsule form for oral treatment (1 capsule DMPS-Heyl contains 100 mg) and in 5 ml ampules, containing 250 mg for intravenous application. DMPS ampules are also available as Unithiol from Russia.

DMPS is routinely used as an antidote for heavy metal poisoning, and for the treatment for chronic metal overexposure. It is a water soluble analog of BAL that shows no potential risk of redistributing metals to the central nervous system [14]. Most importantly, DMPS causes fewer side effects than BAL. The most common one, following parenteral application of DMPS is a local skin reaction of only temporary nature but even that has been linked to the mercury intoxication rather than the DMPS application [15]. In some cases, reactions were reportedly due to a person's subjective sensitivity, which was also noted after the use of placebos [16]. Oral DMPS is considered one of the safest and most effective chelating agents [17].

For German environmental physicians, intravenously delivered DMPS is the treatment of choice for chronic metal overexposure. DMPS is considered most effective for the binding and elimination of arsenic and mercury. It is most commonly used as a general provocation test for heavy metal screening, especially mercury. Our data shows that DMPS is also useful for lead (Fig. 1) DMPS is able to bind with most toxic metals that are of interest to environmental physicians.

DMPS provocation tests are used by physicians prior to the onset of treatment to diagnose the severity of the metal burden. Depending on the metal exposure, oral or intravenously applied DMPS or any of the other chelating agents (DMSA, EDTAs) may be used for follow-up treatments and the treatment regimen may involve weekly or monthly treatments, given over a period of time. A repeat provocation test is usually recommended after 10 chelation treatments or a 3-month treatment period. The follow-up provocation test is used to evaluate patient response and treatment success.

For adults, the DMPS provocation test involves the application of 1 ampule of DMPS, injected intravenously at a slow rate of 1 ml per 2 minutes. The patient must void the bladder before the injection is started and the urine collection is started after the injection has been finished. For most patients, the 2h collection time is not difficult. Most can hold urine for that period of time and because handling of the urine is minimized, contamination is less likely. The DMPS provocation schedule involves the comparison of a urine test results before and after application of either the oral or intravenous application.

Oral DMPS is rarely used for the provocation test due to its reduced bioavailability. For oral DMPS the bioavailability is approximately 40%, which means more than half of the orally provided substance is not absorbed, remaining in the digestive tract until excreted [18].

The half-life of DMPS in the various organs is about 20 minutes and the distribution is not dose-dependant [19]. DMPS is not able to cross the blood brain barrier [20]. After intravenous application, the highest concentration of DMPS reaches plasma and kidneys and is seen in urine within two hours [21]. In other organs, particularly the brain, relatively small concentrations were found [22]. Excretion of DMPS and its metabolites is relatively fast. In humans, the half life in plasma after intravenous application is 30-45 min.

After oral application, the highest concentration of DMPS was seen after 3 h. Within 5-6 h about 80% was excreted in the urine. No accumulation was found after repeated use of DMPS (oral or injectable form) [23]. DMPS effectively binds antimony, arsenic and mercury.

Fig. 2 shows that the intravenous administration of 1 ampule DMPS, containing 250 mg in 5 cc, exceeds the antimony excretion of oral DMPS and the other chelators tested.

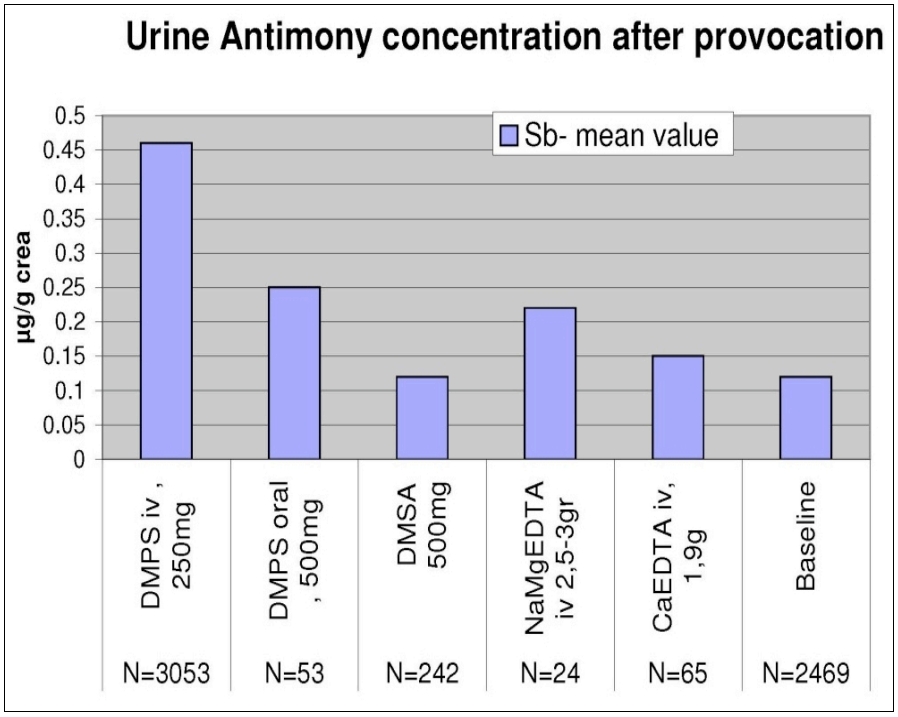

Fig. 2. Mean urine antimony concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

Arsenic overexposure is not a common problem in Germany. However, Fig. 3 shows that the urinary mean value of arsenic obtained after the oral application of DMPS, 500mg, exceeded the mean value obtained from the intravenous application of DMPS, 250mg.

Cadmium is highly toxic and worldwide, industrial exposure is on the rise. Cadmium exerts toxic effects on the kidneys, the skeletal and the respiratory system. Endocrine disruption through environmental exposure is a rising cause of concern, affecting animals and humans. The EDTAs effectively bind cadmium as can be seen from Fig. 4.

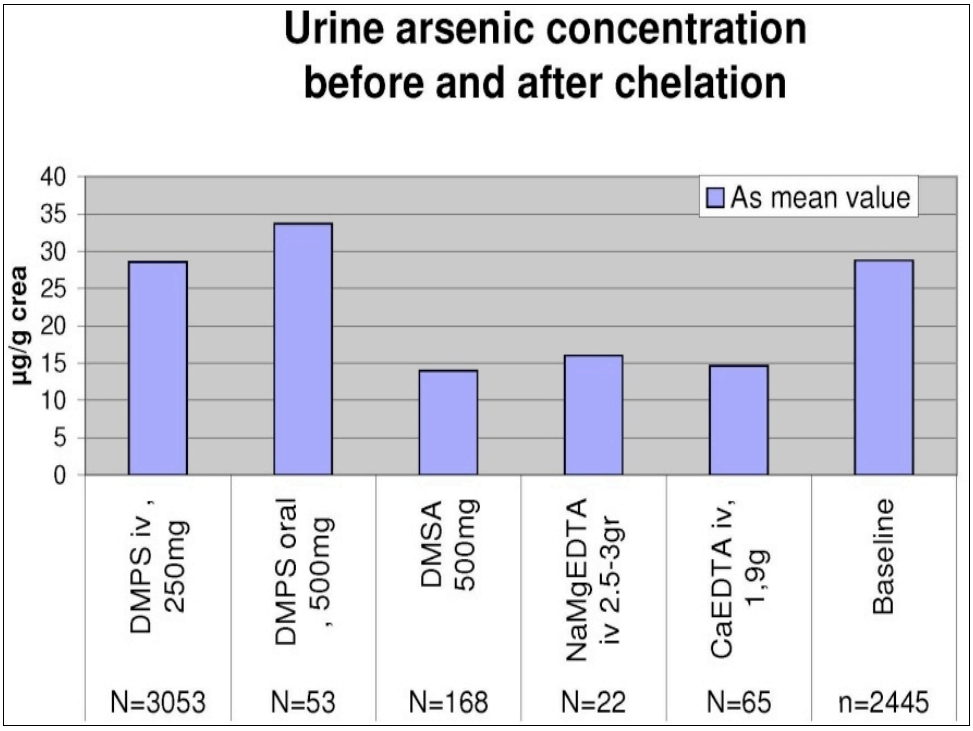

Fig. 3. Mean urine arsenic concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

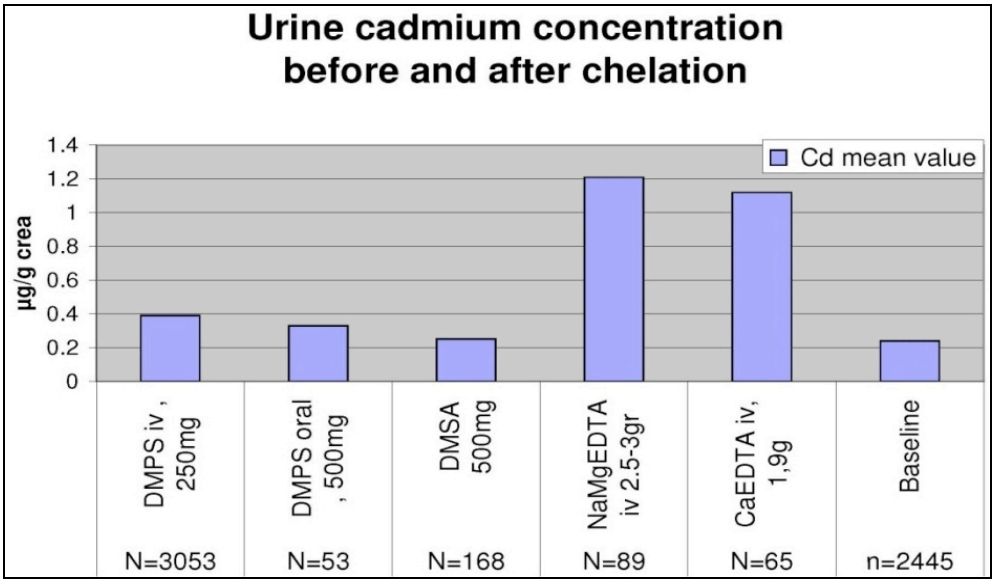

Fig. 4. Mean urine cadmium concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

Copper is a nutritional element, needed for the detoxification pathway, and deficiency symptoms are well documented [24]. Fig. 5 indicates that DMPS is a strong copper chelator, thus care must be taken to prevent nutritional deficiency that may be induced through long term use of DMPS chelation:-

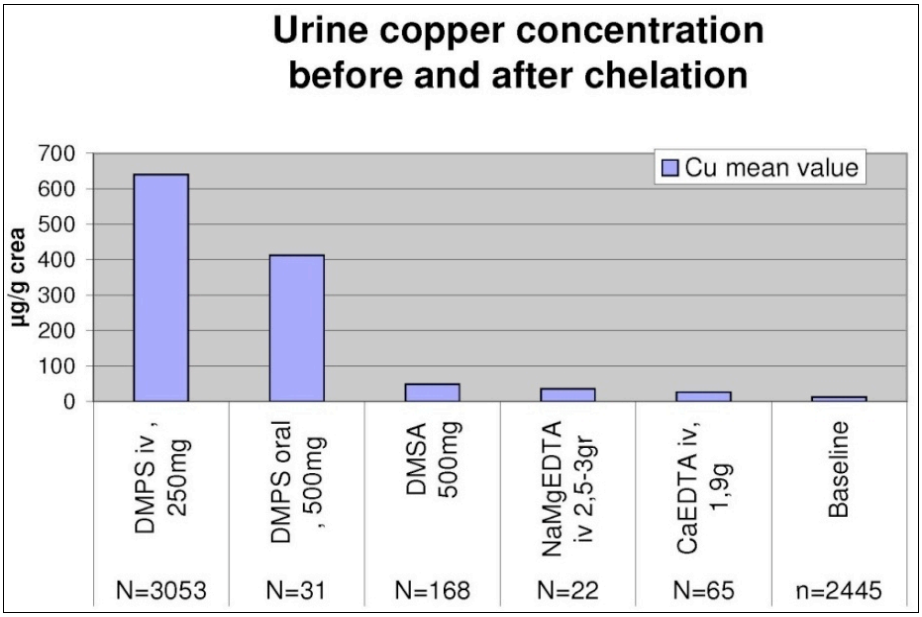

Fig. 5. Mean urine copper concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

At the same time, DMPS may provide treatment options for patients suffering from copper storage disease:-

3.1.2 DMSA, also called succimer

Like DMPS, this chelating agent belongs to the thiol compounds, binding metals with sulfhydryl groups. In the USA, DMSA was registered under the trade name of Chemet. It has been FDA approved for the treatment of lead poisoning in pediatric patients with elevated blood lead levels. The recommended treatment dose is 10-30mg/kg body weight. DMSA has a history of being used for the detoxification of chronic metal overexposure in young children, including the autistic and sensitive adults [25].

Like DMPS, Succimer is a water soluble analog of dimercaprol (BAL), has a wide therapeutic index and few side effects. DMSA has a good binding ability with lead and is more suitable for mercury than any of the EDTAs (Fig.1) [26]. With a history of safe use in children, it has been used as a chelating agent for lead and mercury exposure [27].

In adult human volunteers, the peak metal concentration occurred in 3.0+0.45h after 10 mg/kg dosing orally. DMSA has been found to be primarily albumin-bound in plasma through a disulfide bond with cysteine with very little remaining unbound [28,29]. Like oral DMPS, the bioavailability for oral DMSA is at best 40% [30]. The oral bioavailability in fasted patients is less, approximately 25%. Simultaneous administration of fat increases the oral bioavailability

to approximately 40%. The majority of the elimination occurs within 24 hours and >90% is excreted as DMSA-cysteine disulfide conjugates. Renal clearance is greater in healthy adults than in children [31].

Clinical trials showed that oral DMSA is effective in the treatment of children with autism and heavy metal toxicity (NIH 2008) [32]. Unlike DMPS and EDTA, the urine zinc excretion is only mildly increased following DMSA application but not to a clinically important extent, (Fig. 6) another benefit of oral DMSA chelation.

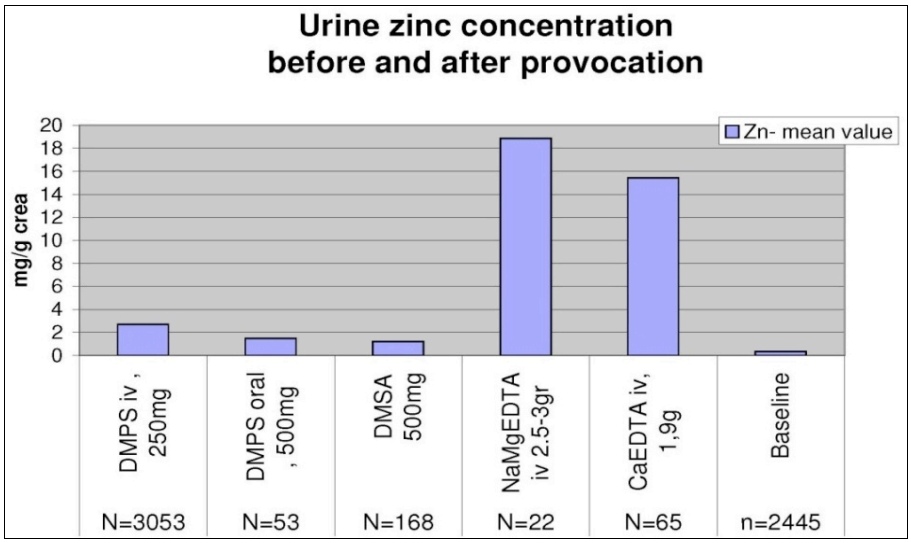

Fig. 6. Mean urine zinc concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

3.2 The EDTAs

These chelating agents belong to the group of Aminopolycarboxylic acids. Poison Centers list two types of EDTA, namely NaCaEDTA (calcium-disodium ethylenediamine tetraacetic acid(http://www.allacronyms.com/cat/7/CANAEDTA/calciumdisodium_ethylenediamine_tetraacetic_acid/1363396) and NaEDTA (ethylenediaminetetraacetic acid, also refered to as Disodiumedetat) as antidotes for lead, chromium, cobalt, vanadium, zinc, cadmium and radioactive metals. The California Poison Control System lists CaEDTA (brandname Versenate) for heavy metal poisoning. NaEDTA is not listed, however, both EDTAs effectively bind Cadmium [33].

Our data indicate that both EDTAs are best used for the detoxification treatment of cadmium and lead (Table 1).

The difference between NaCaEDTA and NaEDTA needs attention. NaEDTA easily binds with calcium and is thus used as an anticoagulant for preserving blood specimens. In medicine, NaEDTA is listed as an antidote for calcium in the treatment of hypercalcemia. Because of this calcium-binding ability, NaEDTA should not be used in children. NaEDTA (or NaMgEDTA) has shown to be beneficial in the treatment of vascular disease as was recently

documented by the TACT study [34]. EDTA chelation is considered safe if used according to protocol [35].

Chelation therapists using NaEDTA, generally complex the agent with magnesium, thus turning NaEDTA into NaMgEDTA, simply because the addition of magnesium supports calcium elimination and prevents phlebitis. Magnesium increases coronary artery dilation [36].

While NaEDTA is capable of binding free calcium, the chelating agent NaCaEDTA is already bound to calcium, hence it does not bind with calcium. Instead, it exchanges calcium for other metals such as lead. Fig.7 indicates that the urinary calcium excretion happens at about the same rate following chelation with NaEDTA as it does with NaCaEDTA. However, there is one significant difference: NaEDTA binds with systemic calcium. NaCaEDTA adds calcium to the blood stream, a fact that warrants careful consideration. DMSA and DMPS do not noticeably bind with calcium.

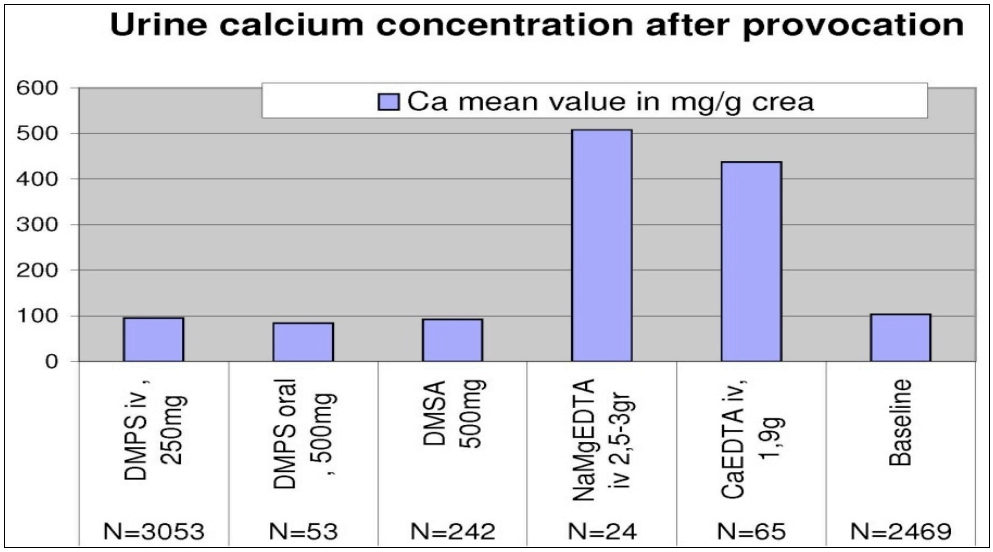

Fig. 7. Mean urine calcium concentration after provocation with the chelating agents DMPS, DMSA and the EDTAs

4. SUMMARY OF RESULTS

Our data indicate that chelating agents can be used for the diagnosis and treatment of acute or chronic metal exposure. DMPS seems most suitable for the diagnosis of multiple metal exposures, its growing use as a provocation test is justified. While DMPS does not show the strong lead and cadmium binding of the EDTAs (Fig. 1,4), the overall chelating effect of DMPS makes this chelating agent more suitable to be used as a provocation test for the diagnosis of a total body burden, providing information about a patient's body burden. Table 1 may serve as a guideline for physicians.

Table 1. Provocation and Treatment Test Guideline for the most effective use of chelating agents DMPS, DMSA and the EDTAs

Element	DMPS oral	DMPS i.v.	NaMgEDTA i.v.	CaEDTA i.v.
Antimony	2nd choice	best		
Arsenic	2nd choice	best		
Cadmium		2nd choice	best	best
Calcium			only choice	
Lead		2nd choice	best	best
Mercury	2nd choice	best		
Copper	2nd choice	best		
Zinc		2nd choice	best	best

The DMPS provocation test can be managed in any medical practice. The patient voids the bladder before the injection is started, and injection time is about 10 minutes (1ml/2min). The urine collection time of 2h is started after the injection has been finished. For most patients, the 2h collection time is not difficult. Most can hold urine for that period of time. Because handling of urine is minimized, contamination is less likely.

Table 1 shows that the DMPS provocation test is suitable for the detection of Sb, As, Cd, Hg and Pb (Table 1) and Fig. 1 one demonstrates that mercury is best chelated by oral and intravenously applied DMPS. While the provocation test is not capable of detecting nutritional deficiencies, it provides information about a patient's zinc and copper excretion. (Fig. 5,6) Similarly, DMPS is suitable for detoxification treatments of single and multiple metal exposures.

The EDTAs are less suitable as provocation tests, mainly because the infusion time of 1g / h and the urine collection time of infusion time plus 45 min is more time consuming and hence less practical. However, for the treatment of multiple exposures involving Cd, Ca and Pb, the intravenous application of NaEDTA (or NaMgEDTA) is best, though lead and cadmium exposures could also be treated with DMPS. DMSA is a weaker chelating agent, suitable for lead intoxicated children and sensitive adults. It has the benefit of not affecting the nutritional status at a significant rate (Fig. 5,6,7).

Chelating agents have a strong affinity for metals, including the nutrient metals. Chelating agents such as DMPS have a strong copper binding ability, EDTA strongly binds zinc. NaMgEDTA has a significant ability to bind calcium, whereas NaCaEDTA does not. If a patient's nutritional status is not evaluated, the prolonged and indiscriminate use of chelating agents could lead to iatrogenic nutritional deficiency disorders. According to our results, chelation treatment should be preceded by a careful nutritional evaluation and if need be, followed by nutritional supplementation. During prolonged chelation treatment schedules, attention must be paid to a patient's nutritional status, prior to and during the chelation program.

5. CONCLUSION

The information provided by our study indicates that a DMPS provocation test is useful in the evaluation of chronic metal exposures. Provocation test results allow the physician to identify the type of metal exposure (single or multiple) and aid in the selection of the most appropriate chelating agent for treatment. Provocation test results also provide important

information that aid the physician in estimating treatment schedules. Through repeated provocation testing, treatment success is documented.

Furthermore, our data could lead to potentially new treatment applications. For instance, DMPS, being a powerful copper chelator, could be useful for the maintenance of Wilson's disease; NaMgEDTAs with its strong calcium binding ability, provides an option for the treatment of disorders involving calcium build up in tissue.

None of the chelating agents discussed can be considered superior to any of the others. Each chelating agent has its place. When selecting a chelator, careful evaluation must be given to the most significant metal exposure, meaning laboratory tests have to serve as a basis for the appropriate treatment choice. Provocation tests, especially the DMPS provocation test, could be routinely used to evaluate a patient's metal burden.

For the treatment of a multiple metal exposure, DMPS is most suitable when an overexposure to Sb, As and Hg is suspected. The intravenous application binds metals more effectively than the oral application.

If only cadmium and / or lead need to be detoxified, both EDTAs (NaCaEDTA or NaEDTA) are the chelating agents of choice, both are equally useful. Both need to be applied intravenously and at a slow rate of maximal 1 g / hr (VanderSchaar 2012).

Oral DMSA is not a strong chelating agent, but has a good lead binding ability. Since it does not effectively bind the essential elements calcium, copper and zinc, it is suitable for children and sensitive adults.

When it comes to treating hypercalcemia, only NaEDTA (or NaMgEDTA) is of use. NaCaEDTA is contraindicated. The chelating agents DMPS and DMSA are of no use.

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COMPETING INTERESTS

The authors declare that no competing interests exist.

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