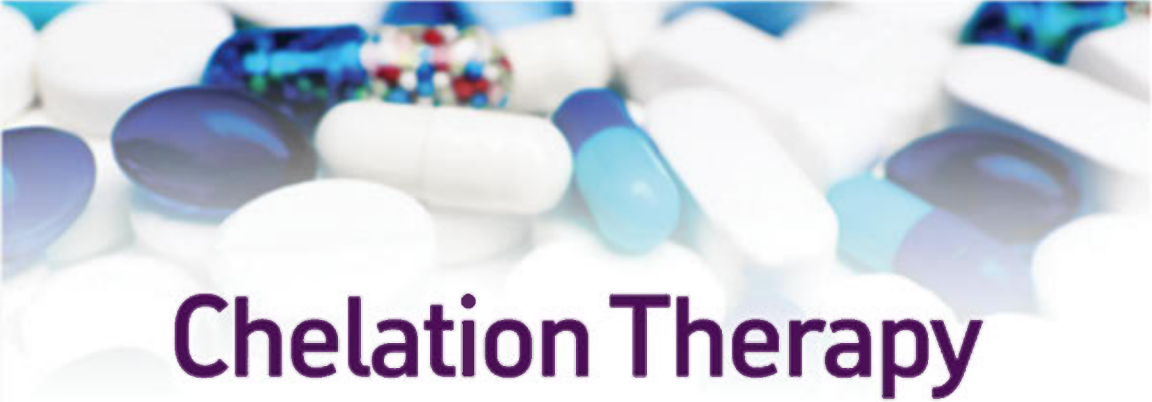

Chelation Therapy

in the Treatment of Metal Intoxication

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Chapter 2

Chelating Agents as Therapeutic Compounds—Basic Principles

Guido Crisponi, Valeria Marina Nurchi

Chapter Outline

2.1 CHEMICAL AND BIOLOGICAL PRINCIPLES FOR IN VIVO CHELATION

Chelation therapy has the intent of scavenging toxic metal ions from the organism, or of attenuating their toxicity by converting them in less toxic compounds, or of transferring them from the site where they exert their toxic action to a compartment where this cannot be executed.

The essential properties of a chelating agent, based on chemical and biomedical considerations, have been better defined through the years. These requisites that are briefly outlined in chapter: General Chemistry of Metal Toxicity and Basis for Metal Complexation will be schematically recapitulated and then discussed in major details here, pointing out the interconnections between them:

1. high stability of the formed complexes, not less than that with endogenous ligands; high stability at physiological pH and at acidic pH of urine;
2. selectivity toward the target metal ion; the chelating agent must not perturb the essential metal status;

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of significant impairment (Ory-Magne et al., 2009; Vidal, Delisle, Rascol, & Ghetti, 2003).

Manganese transporter deficiency due to recessive mutation in *SLC30A10* gene is a rare cause of genetic hypermanganesemia leading to manganese accumulation in many organs, particularly in brain and liver. It manifests as hepatic dysfunction, polycythemia, and neurological symptoms such as dystonia with a characteristic high-stepping (cock-walk) gait, spastic paraparesis, Parkinsonism and motor neuropathy (Quadri et al., 2012; Tuschl et al., 2012).

The recessively inherited metabolic disorder, Wilson's disease (formerly known as hepatolenticular degeneration), caused by mutation in copper transporter *ATP7B* is manifested by symptoms of copper toxicosis. This disease is characterized by a failure to excrete copper into bile, resulting in copper accumulation first in the liver, then in the brain, cornea, kidneys, and other organs (Walshe, 1984). It may be complicated by acute hepatic necrosis leading to the release of copper into the circulation, causing damage to muscle fibers, erythrocyte membranes, and renal parenchyma leading to hemolytic anemia, rhabdomyolysis, and renal failure (Meyer & Zalusky, 1977; Propst et al., 1995). Chronic copper accumulation results in widespread neurological disturbances including tremor, dysarthria, Parkinsonism, dystonia and psychiatric disturbances, and pigmented rings at the corneal rims of the eye referred to as Kayser-Fleischer rings (Dusek, Litwin, & Czlonkowska, 2015).

3.5 TOXICOLOGICAL ANALYSES

The diagnosis of metal poisoning can be confirmed in the acute stage and often in the chronic stage by finding an increased concentration of the suspected metal in the appropriate sample. In general blood is the most useful sample in case of acute or continuous intoxication while urine or hair are more appropriate for detection of chronic stage of poisoning, that is, from weeks to months. Whole blood examination is preferred over serum since metals tend to accumulate in erythrocytes (Blisard, Standefer, & Davis, 1989; Ho et al., 2011). The monitoring of the effect of chelation therapy makes use of metal determinations in blood and/or urine. However, the techniques involved in trace metal analyses in body fluids and tissues present certain difficulties, and such analyses should only be performed in laboratories that are equipped for this purpose and that participate in external quality control. Environmental sampling may need to be performed on air, water, or food. Pills or drug residues in bottles may require analysis after an acute poisoning incident, as may blood, urine, feces or tissue samples from the patient. In particular, examination of blood and urine samples for metal concentration can be considered a routine procedure in the diagnostics.

Also the diagnosis and follow-up of hereditary metal overload diseases require analyses of blood, urine, and sometimes other tissues. The diagnosis

of Wilson's disease depends on analyses of nonceruloplasmin bound serum copper, 24 h urine copper excretion and copper concentration in liver biopsy specimen (Table 3.2). Penicillamine challenge test, that is, increase of urine copper excretion after a dose of D-penicillamine, may be helpful in case of borderline results, but its validity is not universally accepted (Muller et al., 2007). Treatment to produce a negative copper balance is effective with the chelating agents D-penicillamine or triethylenetetramine (trientine) that both increase urinary copper excretion substantially (Aaseth, Skaug, Cao, & Andersen, 2015). Monitoring of 24 h urine copper excretion has to be performed on regular basis to guide chelation treatment dosage and check for patients' compliance (Dusek et al., 2015).

The increased iron deposition characterizing transfusional siderosis and hemochromatosis is accompanied by increased serum iron values with increased saturation of serum transferrin (>30%), and serum ferritin values above reference range. In aceruloplasminemia, the laboratory findings in serum include decreased iron and increased ferritin (Miyajima, 2015) while serum ferritin is decreased in hereditary ferritinopathy (Keogh, Morris, & Chinnery, 2013). Long-term chelation treatment with deferiprone or deferasirox may be beneficial in aceruloplasminemia but its efficacy is variable, particularly with respect to neurological symptoms (Badat, Kaya, & Telfer, 2015; Lindner et al., 2015; Pan, Tang, Chen, Song, & Shang, 2011; Tai et al., 2014).

In the SLC30A10 manganese transporter deficiency syndrome serum manganese levels are typically several times increased (Tuschl et al., 2012). Chelation treatment with intravenous disodium calcium edetate ($CaNa_2$-EDTA) improves clinical symptoms and leads to significantly increased 24 h urinary manganese levels and reduced serum manganese levels (Stamelou et al., 2012). Chelation with $CaNa_2$-EDTA may be helpful also in manganism caused by environmental exposure provided it is started very early (Herrero Hernandez et al., 2006).

In some cases, the interpretation of toxicological analyses in blood or urine is difficult. Thus, arsenic in urine may be increased also after consumption of nontoxic compounds in seafood. In arsenic, manganese, or thallium poisonings, for example, the diagnosis can be confirmed by taking hair and nail clippings for analysis at a stage when blood and urine concentrations are not reliable or helpful. Evidence of methylmercury absorption can also be obtained from analysis of hair samples even when blood levels have fallen into the reference range. In the diagnosis of lead poisoning, difficulty may arise when exposure had ceased some time ago and much of the lead has been translocated from blood to bone. In such cases, blood lead levels may have returned to the reference interval when diagnosis is attempted. In vivo determination of lead in bone, preferably in finger bone, by X-ray fluorescence, has been used for biological monitoring of deposited lead (Skerfving, Gerhardsson, Schutz, & Stromberg, 1998). A $CaNa_2$-EDTA provocation test has also been used to estimate body burden of lead. A standard $CaNa_2$-EDTA dose will increase the

urinary excretion of stored lead. However, reference values are not defined for this test, and the justification of using the EDTA-test has been questioned (Aaseth et al., 2015; Andersen, 1999).

A case report illustrates the importance of an early and correct diagnosis of lead poisoning (Amundsen, Naess, Hammerstrom, Brudevolt, & Bjerve, 2002). A 54-year-old woman was admitted to hospital with anemia and unspecific gastrointestinal symptoms. Peripheral blood smears and bone marrow aspirate showed basophilic stippling of erythrocytes suggestive of lead poisoning, which was confirmed by high concentrations (>3 μmol/L) of lead in blood. The lead source was the glazing of a ceramic wine jug. Chelating therapy with dimercaptosuccinic acid (DMSA) was started. Monitoring of lead in blood and urine verified the clinical efficacy of DMSA. The initially low hemoglobin became normalized. And the patient returned to work after several months. In contrast, an attempt to treat an arsenic poisoned patient with the same agent, DMSA, was not very successful, as judged from clinical follow-up and repetitive urine analyses (Stenehjem et al., 2007). Trials in Bangladesh have verified that DMSA was practically without effect in arsenic overexposure, whereas dimercaptopropane sulfonate (DMPS) effectively increased urinary arsenic excretion (Guha Mazumder et al., 2001). It is apparent, also from these cases, that routine monitoring of the effect of chelating agents makes use of determinations of metal concentrations in blood and/or urine, in addition to the careful clinical follow-up.

3.6 BIOCHEMICAL MEASUREMENTS

For most metal poisonings, biochemical investigation is required in addition to the determinations of metal concentrations in body fluids. In general, biochemical tests of renal and hepatic function are always required, to assess possible impairments of these organs. Renal tubular dysfunction characterizing overexposure with cadmium, mercury, lead or platinum salts, may be disclosed by determinations of urine β_2-microglobulin, microalbuminuria and/or glycosuria. Poisonings with lead, copper and other metals may give rise to raised levels of liver enzymes in blood (Table 3.1). Combined poisonings with a metal salt and paracetamol may accentuate impairments of hepatic or renal functions. Complete blood count with peripheral smear should be also performed routinely. Anemia with erythrocytes containing basophilic stippling may point toward lead intoxication. As indicated in Table 3.1, mercury poisoning may be accompanied by increased levels of epinephrine in urine (Torres, Rai, & Hardiek, 2000).

In iatrogenic or hereditary siderosis and in Wilson's disease the monitoring of liver function tests and liver enzymes are of particular importance in the evaluation of the disease, and also in the evaluation of the therapy. Low ceruloplasmin is an important marker of Wilson's disease and aceruloplasminemia. In hereditary hemochromatosis, repeated phlebotomy has been effective

more efficiently than i.p. administration. Pharmacokinetic analysis indicated that oral administration gave longer availability of MiAMMSA indicating that MiADMSA was more effective after oral than after i.p. administration.

4.4.2 Clinical Studies

Lentz et al. (1981) described a man who ingested 2 g As_2O_3 in a suicide attempt. After admission, gastric lavage and administration of charcoal was initiated. His condition deteriorated rapidly and chelation therapy with DMSA was started, about 21 h after the ingestion of As_2O_3. 4 × 300 mg of DMSA were administered orally per day for 3 days. The cumulative elimination of As during the 3 days of chelation was 27.03 mg, and the urinary As (u-As) level decreased extensively after cessation of DMSA chelation. The patient had clinical signs of polyneuropathy, but survived.

A 21-year-old man was admitted to hospital in shock after oral intake 2 g of arsenic trioxide. Intensive treatment including hemodialysis and i.m. BAL chelation was unable to prevent death within 37 h. Clinical data indicated multisystem toxicities of arsenic (Levin-Scherz, Patrick, Weber, & Garabedian, 1987).

In Argentina, addition of sodium arsenite to meat by vandals resulted in a mass poisoning, where 718 individuals were affected. Urine samples were obtained from 307 individuals. Increasing symptomatology reflected urine arsenic levels with increasing diarrhea, vomiting, and systemic symptoms at urine arsenic > 0.75 g/L. Since supplies of BAL were very low, patients with u-As up to 0.75 g/L were not chelated, 49 patients with u-As 0.76-5 mg/L received 2 mg/kg BAL i.m. for 10 days, 12 patients with u-As > 5 mg/L received 3 × 2 mg BAL for 2 days, 2 × 2 mg for 2 days and 2 mg the following 6 days. No patients, chelated and nonchelated, reported arsenic toxicity related symptoms at 1 month and 2 years after the poisoning (Roses et al., 1991).

A 28-year old man died after ingesting 75 g of arsenic trioxide. He presented with profuse vomiting and watery diarrhea. X-ray showed radioopacities in the stomach. His bowel was purged with extensive amounts of saline and charcoal was administered. DMSA capsules were administered orally but were vomited, so i.m. BAL was administered. The patient died 16 h after the ingestion (Jolliffe, Budd, & Gwilt, 1991).

A 30-year-old male ingested about 10 g of sodium arsenate. This suicide attempt resulted in anuria, cardiovascular collapse, and hepatic damage. After hospital admission, the patient was immediately given gastric lavage and oral activated charcoal, and supportive measures and hemodialysis were instituted. On the next day, he was chelated with 250 mg BAL i.m. and hemodialysis was repeated. BAL chelation did not increase the hemodialytic As excretion. After 15 days the patient was discharged. (Mathieu et al., 1992).

A 39-year-old 28 weeks pregnant woman and a 30-year-old man were both poisoned by eating arsenic trioxide containing chocolate. They both developed multiple organ failure around 8–10 days after poisoning with life-threatening

a third BAL chelation course. All three children continued to receive NAPA chelation therapy until the results of repeated urine mercury concentration determinations were normal.

An oral provocation dose of DMSA or DMPS has been used as a diagnostic tool to estimate Hg vapor exposure and body stores of Hg. Roels, Boeckx, Ceulemans, and Lauwerys (1991) studied three groups of workers, one group presently exposed to high Hg vapor levels, another group with reduced Hg exposure and a group removed from Hg exposure. One oral dose of 2 g DMSA increased the average 24 h urinary Hg excretion to around 20 µg Hg in workers removed from exposure and to 600 µg in workers presently exposed to high Hg vapor levels. The excretion was 4 µg in an unexposed control group. The ratios between the average 24 h u-Hg excretions after and before DMSA administration varied between 2.5 and 4, with the highest ratios in those workers who had the highest and most recent Hg vapor exposure. This study indicates that DMSA-induced urinary Hg excretion could be an indicator of renal Hg deposits in individuals without recent Hg exposure. The results suggest that DMSA mobilizes Hg in more shallow depots and that the extent of mobilization could indicate the intensity of recent exposure.

Bluhm et al. (1992) described a group of 53 workers exposed to Hg vapor during repair work in a chloralkali factory. Flame cutting of mercury pipes resulted in spreading of boiling Hg over the workers and high Hg vapor levels. Several workers became ill. Elevated urinary Hg levels several days after the exposure indicated Hg poisoning. Totally 26 workers were hospitalized 19 days or later after the incidence. A 2 week DMSA or NAPA chelation treatment was started at 26 days after the exposure. A group of 12 patients with elevated u-Hg levels 73 days after the exposure received a 4 days chelation treatment with DMSA or NAPA. DMSA chelation increased the u-Hg excretion 3.5–5-fold while the excretion was increased only 2–2.5-fold by chelation with NAPA.

Atta, Faintuch, do Nascimento, R, and Ados (1992) described a gold prospector who presented with headache, fever, and tachypnea. Chelation with BAL and DPA and intensive supportive care were instituted. The patient died from acute respiratory distress.

Aposhian et al. (1992) used the DMPS mobilization test to study Hg exposure and systemic Hg load in populations without occupational Hg exposure. In a group of volunteers a statistically significant correlation was observed between the "amalgam score" (number and size of dental amalgam fillings) and the DMPS-provoked urinary excretion of Hg.

In similar studies Zander, Ewers, Frier, and Brockhaus (1992) and Herrmann and Schweinsberg (1993) found 6–7-fold and 9-fold increases in the average urinary Hg excretion in DMPS mobilization tests. In both studies the urinary Hg excretion was larger in individuals with amalgam fillings than in those without amalgam fillings, both before and after DMPS provocation. Herrmann and Schweinsberg (1993) observed a significant correlation between the "amalgam filling index" and Hg excretion.

Houeto, Sandouk, Baud, and Levillain (1994) described two jewelers who inhaled Hg vapors during melting a Hg containing block of gold. They were admitted to hospital on the next day, short of breath with fatigue, nausea, and pain at various sites and normal renal function. They received chelation treatment first with i.m. BAL for 5 days, then with oral DMSA chelation for another 5 days. Urine and blood Hg levels rapidly fell from high initial values. The urinary Hg elimination increased after change from BAL to DMSA treatment. Blood Hg remained at the same levels.

Singer, Mofenson, Carracio, and Ilasi (1994) described a patient who ingested a stool fixative containing 675 mg $HgCl_2$. The patient was given extensive hydration and rapidly chelated with BAL. The patient did not show systemic signs of mercury poisoning.

Toet, van Dijk, Savelkoul, and Meulenbelt (1994) described a 38-year-old man who in a suicide attempt drank 100 mL of a $HgCl_2$ solution of unknown concentration. He presented with consistent vomiting and bloody diarrhea. He was treated with gastric lavage and activated charcoal and received i.m. BAL chelation. He rapidly deteriorated and developed renal failure. After about 10 h hemodialysis together with plasma expander due to hypovolumic chock and i.v. DMPS chelation was initiated. Despite very high blood Hg levels (>2 mg/L), his kidney function recovered after 10 days. DMPS chelation was reduced from 1.5 to 0.75 g/day and continued for 4 weeks, followed by oral DMSA chelation, 0.9 g/day for another 3 weeks. The patient recovered completely.

Sallsten, Barregard, and Schutz (1994) administered a single oral dose of 0.3 g DMPS to groups of industrial workers and dentists exposed to mercury vapor, a control group with amalgam fillings, and a control group without amalgam fillings. DMPS significantly increased the urinary mercury output in all groups. The increased Hg excretion was larger than in the study by Roels et al. (1991), 3–12 X increase compared to 2.5–4 X increase despite a much lower cherlator dose (0.3 g DMPS vs 2 g DMSA). The Hg excretions during 6 and 24 h after DMPS administration correlated strongly, accordingly a long period of urine collection period is not necessary.

Gonzales-Ramirez et al. (1995) used the DMPS mobilization test to investigate Hg exposure in dentists and dental technicians. The urinary Hg excretion after DMPS provocation was extensively higher than in non-Hg-exposed controls, highest in dentists. The post-DMPS and pre-DMPS Hg excretions correlated strongly. The amount of mercury mobilized by DMPS and scores in neurobehavioral tests showed a significant inverse relationship. This indicates a potential value of the test in diagnosis of adverse Hg exposure.

Koriakov and Gol'dfarb (1995) described symptoms and treatment of 56 patients suffering from Hg poisoning due to use of Hg_2Cl_2-containing creams. The patients had gastrointestinal, hepatic, renal, or dermal disorders. The highest blood Hg level recorded was 800 µg/L. The patients were chelated with DMPS, the most serious poisoning cases were treated with hemoperfusion.

proteinuria occurred after 1–9 months. Minimal change disease should be included as a pathological entity caused by mercury exposure or intoxication.

Mamdani and Vettese (2013) described a 40-year-old man presenting with dry cough, headache, and dyspnea for 3 days. He had labile mood, intention tremor, and tender subcutaneous nodules on the left forearm. Chest radiograph showed numerous small, high-density opacities distributed in both lungs. His urine Hg level was 1249 μg/L and his serum Hg was higher than 160 μg/L. The patient reported mercury exposure from his recently deceased father's old gun box; liquid mercury can be used to clean gun barrels and chambers from lead. A radiograph of the left wrist and forearm showed opacities corresponding to the subcutaneous nodules observed and following the course of veins indicating both subcutaneous and intravenous self-injection of mercury. The patient was chelated with DMPS. On day 5, his state of labile mood had decreased and his tremor had resolved. The urine Hg level had decreased to 692 μg/L. The patient was transferred to an inpatient psychiatric unit.

Beasley et al. (2014) described a suicidal case of mercuric chloride ingestion in a 19-year-old female. She presented with abdominal discomfort and nausea, diarrhea and vomiting of blood-stained fluid after ingestion of 2–4 g of mercuric chloride powder. Radiograph indicated opaque material in the gastric antrum. At 3 h postingestion the blood mercury level was 3.58 mg/L. The patient was transferred to intensive care unit and BAL chelation was initiated. Clinical signs included mild hemodynamic instability, fever, acidosis, leukocytosis, and hypokalemia. The symptoms improved after 2 days and completely resolved within a week.

Kobidze, Urushadze, Afandiyev, Nemsadze, and Loladze (2014) described a case of intentional self-injection of metallic mercury. A 22-year-old male with a medical history of suicidal poisoning with ethylene glycol presented with fatigue, pain and tremor in limbs, and skin rash 4 months after i.v. injection into his antecubital vein of metallic mercury from several thermometers. CT scan of the thorax and the abdomen showed numerous small, high density opacities in liver, both lungs, and right kidney. He had no clinical pulmonary malfunction or hepatic or renal biochemical abnormalities despite minor symptoms of tremor, erethism, knee joints arthralgia and lower extremities weakness. He was chelated with 20 mg/kg per day i.m. DMPS. After a month of chelation, blood mercury levels had decreased from 134 to 105 μg/L. The case demonstrated only mild acute toxicity after i.v. administration of an unknown amount of metallic mercury. The patient was recommended long-term DMPS treatments with repeated measurements of blood Hg levels.

Cicek-Senturk et al. (2014) described a 52-year-old woman admitted to hospital with high fever, a rash over the entire body, sore throat, nausea, itching, and muscle pain. Autoimmune diseases, infectious pathologies, and malignancy were excluded by diagnostic evaluation. Several organs of the patient were involved and fever persisted for 4 weeks. Repeated questioning about potential

workers were given DMSA in an increasing dosage from the first to the sixth day. A marked fall in blood lead concentration was accompanied by a significant increase in urinary lead and copper excretion but without effect on urinary calcium, iron, magnesium, or zinc excretion (Friedheim, Graziano, Popovac, Dragovic, & Kaul, 1978). Succimer-treated lead exposed children with low blood lead levels below 450 µg/L, aged 12–33 months, had a clear reduction of blood lead after one week of therapy (42%). In this study, DMSA produced a mean difference from placebo of 45 µg Pb/L during 6 months of follow-up and 27 µg Pb/L during 12 months. However, DMSA did not improve scores on test of cognition, behavior or neuropsychological function (Rogan et al., 2001). Apparently, chelation therapy is not indicated for children with blood Pb levels below 450 µg/L (2.2 µmol/L).

Although DMSA is effective for the treatment of lead intoxication, adverse effects have been reported. They include gastrointestinal discomfort, skin reaction, mild neutropenia, and elevated liver enzymes. A strong musculocutaneous reaction in one case of chronic lead poisoning (Grandjean, Jacobsen, & Jørgensen, 1991) and hemolytic anemia was reported in a worker with occupational lead exposure (Gerr, Frumkin, & Hodgins, 1994).

The efficacy of DMSA in binding and mobilizing mercury has been shown in a number of animal studies reviewed by Aposhian (1983) and Aaseth et al. (1995). The mobilization and removal of methylmercury by extracorporeal complexing hemodialysis with DMSA has given promising results in experiments on dogs (Kostyniak, 1982). In a study of children aged 12−33 months, DMSA treatment gave a modest reduction in organic mercury concentration after one week, and slowed or prevented the accumulation of organic mercury after multiple courses in 5 months (Cao et al., 2011). No effect was seen on the blood cadmium levels in the same group (Cao et al., 2013).

Both DMSA and DMPS have a therapeutic potential in cases of acute intoxication by arsenic and inorganic mercuric salts (Kosnett, 2013), although DMPS appears to be the most efficient agent in these latter poisonings. And the antidote needs to be administered early after the poisoning, preferably within minutes to hours. Contrary to BAL these agents do not redistribute arsenic or mercury to the brain.

Low-level mercury exposure in children might result from the addition of the antiseptic agent thiomersal in vaccines. Thiomersal is metabolized to ethylmercury in the human body. It has been claimed that this mercurial even in minute doses might lead to the serious medical condition of autism (Bernard, Enayati, Redwood, Roger, & Binstock, 2001). This hypothesis led to the proposal of mercury chelation with DMPS or DMSA as therapy for autism (Kidd, 2002). However, no peer-reviewed papers have reported mercury excess in blood, urine, or hair of subjects suffering from autism (Aschner & Walker, 2002; Wecker, Miller, Cochran, Dugger, & Johnson, 1985). Critical reviews have concluded that the scientific support for mercury chelation in autism is lacking (Davis et al., 2013; Crisponi et al., 2015).

Thus, several drugs with chelating properties are in routine use in cardiovascular and cerebrovascular diseases today. But the present authors consider disodium EDTA chelation therapy to be hazardous and contraindicated. Its use is ethically unjustified in modern cardiology.

7.7.2 Alzheimer's Disease

Preventive measures against Alzheimer's disease include a healthy lifestyle with adequate physical and mental activity and healthy food habits, which is also recommended in patients at risk of atherosclerotic diseases. However, here it is of particular interest that high levels of copper and iron are present in the insoluble beta-amyloid plaques in post-mortem brains from patients suffering from Alzheimer's disease (Castellani, Moreira, Perry, & Zhu, 2012; Ahuja, Dev, Tanwar, Selwal, & Tyagi, 2015). Thus, a pathological distribution of these essential trace elements appears to play a role in the misfolding and aggregation of amyloid precursor protein (APP) and presumably in the dementia progression (Guo et al., 2013). The toxicity of excessive amounts of iron is exemplified by the fact that increased amounts of iron will inhibit furin activity, which is important for the activation of secretases. Thus, lowered levels of furin may enhance the amyloidogenic pathway (Ward, Dexter, & Crichton, 2015). In addition, iron may modulate APP processing through the presence of a putative iron responsive element in APP-mRNA (Rogers et al., 2002). Early studies (Crapper McLachlan et al., 1991) showed that there was a significant reduction in the rate of decline of daily living skills in the 48 AD patients who received desferrioxamine (125 mg i.m. twice daily5 days/week for 24 months) when compared to AD patients receiving placebo. Despite such positive results, there have been no other clinical studies reported where any of the iron chelators have been investigated for their clinical efficacy in this disease.

Currently only one family of metal binding agents, PBT2 (5,7-dichloro-2-(dimethylamino)-methyl)-8-hydroxyquinoline) is in clinical trials for the treatment of Alzheimer's diseases. It mainly binds excesses copper and zinc and presumably iron in the brain, thereby diminishing the amount of amyloid plaque formation and relocating these metal ions to depleted cellular and neuronal compartments (Lannfelt et al., 2008).

7.8 MODIFICATION OF TOXIC EFFECTS OF METALS

Under this heading are included examples of therapeutic measures in metal poisoning that are directed toward a modification of the tissue response to the poison or to an alteration in the biochemical or metabolic state of the subject.

7.8.1 Modification of Inflammatory Response in Tissues

Chronic beryllium disease is characterized by an inflammatory response that is granulomatous in nature and that seems to result from a hypersensitive reaction

Chelation Therapy

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Chelation Therapy in the Treatment of Metal Intoxication presents a practical guide to the use of chelation therapy from its basic chemistry to available chelating antidotes and the application of chelating agents. Several metals have long been known to be toxic to humans, and continue to be difficult to treat. These challenges pose particular problems in industrial settings, for example, lead smelting is known to be associated with hemopoietic alterations and paralyses, and the inhalation of mercury vapor in mercury mining is extremely detrimental to the central nervous system.

Clinical experience has demonstrated that acute and chronic human intoxications with a range of metals can be treated efficiently by administration of chelating agents. *Chelation Therapy in the Treatment of Metal Intoxication* describes the chemical and biological principles of chelation in the treatment of these toxic metal compounds, including new chelators such as meso-2,3-dimercaptosuccinic acid (DMSA) and D,L-2,3-dimercapto-1-propanesulfonic acid (DMPS). This book is useful to toxicologists, pharmacologists, medical chemists, and clinicians who are interested in chelation as a swift and effective treatment for metal intoxication.

Key Features

- Presents current findings on the potential for chelation as a therapy for metal intoxication
- Offers practical guidelines for selecting the most appropriate chelating agent
- Includes coverage on radionuclide exposure and metal storage diseases
- Describes the chemical and biological principles of chelation in the treatment of toxic metal compounds

Related Titles

- Flora, *Handbook of Arsenic Toxicology*, January 2015, 9780124186880
- Nordberg, Fowler & Nordberg, *Handbook on the Toxicology of Metals, 4th Edition*, October 2014, 9780444594532
- Haschek, Rousseaux & Wallig, *Haschek and Rousseaux's Handbook of Toxicologic Pathology, 3rd Edition*, June 2013, 9780124157590

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Mercure ;
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KEYWORDS
Mercury;
Metal;
Poisoning;
Chelating agent

Mercure, plomb, arsenic, aluminium, cadmium, cobalt, chrome... L'inquiétude sur la présence dans notre environnement d'éléments approximativement désignés sous l'intitulé de « métaux lourds » est de plus en plus répandue, relayée et amplifiée par les médias et par internet. Cette peur est exploitée, y compris parfois dans la communauté médicale, chez un nombre croissant de patients en errance thérapeutique et sert de prétexte à de pseudo-diagnostics d'intoxication puis à divers et coûteux traitements non validés voire dangereux. Sans attendre la fin des polémiques sur les effets sanitaires de telle ou telle exposition chronique, des données suffisantes existent pour évaluer dès maintenant les outils diagnostiques utilisés, notamment les métalluries provoquées. À l'image de leurs homologues américains [1] et dans l'intérêt des malades abusés qui les interrogent fréquemment, la Société de toxicologie clinique et la Société française de toxicologie analytique ont souhaité réagir et faire une mise au point scientifique sur l'usage et le mésusage des chélateurs.

Les seules indications de l'administration de chélateurs sont les intoxications par certains métaux ou métalloïdes, en particulier les intoxications par le plomb, le mercure et l'arsenic.

Le diagnostic de l'intoxication par un métal nécessite toujours l'association :

- de signes cliniques et/ou paracliniques traduisant les effets toxiques connus du métal ;
- et de valeurs élevées d'indicateurs biologiques validés de l'exposition ou de la dose interne du métal.

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L'exposition chronique à certains métaux ou métalloïdes est associée à un risque élevé de certains cancers (par exemple, l'exposition à l'arsenic est associée à une augmentation des risques de carcinomes cutanés, de cancer broncho-pulmonaire, de cancer des voies urinaires et de plusieurs types de tumeurs hépatiques), mais les tumeurs surviennent longtemps après le début de l'exposition et souvent, longtemps après qu'elle a cessé ; l'administration de chélateurs n'en est pas un traitement et il n'y a pas, à ce jour, de preuve qu'elle les prévienne. Contrairement à ce qu'affirment certaines publications parascientifiques (et avec elles, certains praticiens), il n'y a pas de preuve suffisante d'une association causale entre une contamination par un élément métallique et certaines affections, telles que l'autisme, la sclérose en plaques, la maladie de Parkinson, le syndrome de fatigue chronique, la goutte, les maladies cardiovasculaires, la dégénérescence maculaire ou la myofascite à macrophages. Chez ces malades comme chez n'importe quel individu, l'administration de chélateurs ne peut se justifier que si le diagnostic d'intoxication est établi par la constatation d'effets toxiques caractéristiques de la substance et d'une élévation de la concentration d'un ou plusieurs indicateurs biologiques de l'exposition et/ou de la dose interne.

Les indicateurs biologiques d'exposition ou de la dose interne utilisés pour le diagnostic de l'intoxication par un élément métallique sont des paramètres scientifiquement validés. Des indicateurs de référence sont identifiés pour la surveillance des expositions et le diagnostic des intoxications par les principaux métaux et métalloïdes[1]. Des bases de données nationales et internationales permettent d'identifier ces indicateurs et les valeurs de référence utilisables pour chacun d'entre eux (par exemple, en France, la base Biotox, publiée par l'Institut national de recherche et de sécurité [INRS]).

Les indicateurs biologiques d'exposition ou de dose interne qui ne sont pas validés ne peuvent être utilisés pour le diagnostic d'une contamination par un métal. Leur emploi dans ce but par un praticien ne peut traduire que l'ignorance de ce dernier [2]. Les exemples les plus fréquents de tests non validés improprement employés pour démontrer une contamination par un élément métallique sont la mesure de concentrations salivaires (éventuellement, après mastication), le dosage simultané d'un grand nombre d'éléments dans divers milieux et les tests de provocation. Ces derniers consistent à mesurer la quantité ou la concentration d'un élément dans les urines après l'administration d'un chélateur. Il existe des tests de provocation validés pour un nombre limité de métaux et qui sont applicables dans des conditions précisément déterminées : nommément, pour le cuivre (dans le cadre de la maladie de Wilson), pour le fer (dans le cadre de l'hémochromatose) et pour le plomb (pour décider du traitement de l'intoxication saturnine, à certains niveaux de plombémie). La majorité des éléments métalliques sont présents et mesurables chez la plupart des individus et l'administration d'un chélateur en augmente l'excrétion urinaire chez tous : la comparaison des concentrations mesurées dans ces circonstances aux valeurs de référence en population générale est évidemment erronée. Plusieurs sociétés savantes nord-américaines ont publié des mises au point destinées aux praticiens et au public sur l'emploi abusif de ces tests prétendument diagnostiques [3—5].

Pour que les résultats des analyses soient interprétables, les dosages de métaux doivent être réalisés dans le respect de règles strictes visant les conditions du prélèvement, de son transport et de sa conservation, ainsi que la qualité de l'analyse par le laboratoire. Celui-ci doit se conformer aux bonnes pratiques de laboratoire et avoir mis en place des procédures de contrôle de qualité internes et externes [6]. Le prescripteur doit s'assurer du respect de l'ensemble de ces procédures de contrôle de qualité. Une dizaine de laboratoires français des secteurs public et privé répartis sur le territoire national sont en capacité d'effectuer des dosages de qualité de tous les éléments métalliques d'intérêt. Le choix d'un laboratoire doit toujours être motivé et le recours à un laboratoire situé en dehors du territoire national doit être fondé sur des arguments techniques et/ou économiques précis.

Le dépassement de la valeur de référence en population générale d'un indicateur biologique d'exposition (ou de la dose interne) n'implique pas automatiquement l'indication d'un traitement chélateur. Les chélateurs efficaces ne sont pas dépourvus d'effets indésirables et leur emploi doit s'appuyer sur une évaluation des risques pour la santé, prenant en compte les relations dose—effet de la substance toxique et la tolérance du médicament. Les indications des traitements chélateurs sont, en pratique, bien codifiées dans tous les traités de toxicologie médicale.

L'usage abusif de chélateurs, en l'absence d'indication validée, est une pratique rapidement croissante en Europe et en Amérique du Nord. Qu'elle traduise une dérive commerciale exploitant l'anxiété et la fragilité de certains patients ou seulement l'ignorance de l'état actuel des connaissances par les prescripteurs, c'est une conduite inacceptable. Elle est assez souvent aggravée par le fait que les mêmes praticiens proposent de fournir à leurs patients (et à des prix prohibitifs) :

- des médicaments qui ne sont pas commercialisés en France, en prétextant d'une plus grande efficacité (en France, c'est le cas du dimercaptopropane sulfonate [DMPS], dont le pouvoir chélateur n'est pas, dans la plupart des indications potentielles, supérieur à celui d'autres médicaments présents sur le marché et qui peut être responsable d'accidents thérapeutiques sévères ; c'est la raison pour laquelle, il n'est, en principe, pas disponible dans notre pays) ;
- des médicaments « naturels » sans effets thérapeutiques démontrés : ail, bentonite, chlorelle et autres algues, coriandre (cilantro), chlorophylle, cystéine, spiruline, vitamine C...

Aux États-Unis, après des essais inefficaces d'information des prescripteurs au cours des années 2000, certains

[1] Par exemple : pour le plomb, la plombémie; pour le mercure inorganique, la concentration sérique ou urinaire du métal; pour le mercure organique, la concentration du mercure dans le sang total ou dans les cheveux; pour l'arsenic inorganique, la somme des concentrations urinaires d'arsenic inorganique, d'acide monométhylarsonique et d'acide diméthylarsinique ou d'arsenic dans les cheveux.

organismes professionnels recommandent de pénaliser les prescriptions abusives [7].

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O30

Dosages urinaires post-chélation des métaux lourds et pseudoscience : il faut agir !

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Contexte

Les termes « métaux lourds » et « détoxication » exercent une fascination dépassant de loin la toxicologie médicale. Les centres antipoison (CAP) ont toujours été sollicités sur divers traitements ou diagnostics « alternatifs », mais un type d'appels émerge récemment, concernant des analyses hors consensus réalisées à l'étranger mais prescrites et justifiant la prise en charge par des praticiens français d'« intoxications aux métaux lourds ». Nous rapportons 3 cas récents pour interpeller autorités sanitaires, médicales, et scientifiques.

Description des cas

En 4 mois (novembre 2014 à février 2015), le CAP de Marseille a été interrogé par trois patients (hommes de 54 et 56 ans, femme de 55 ans) pour avis sur les résultats inquiétants de dosages métalliques urinaires post-chélation (respectivement par DMSA oral, DMPS iv et ZnDTA + DMPS iv). Réalisées en Allemagne par le laboratoire M, ces recherches ont été prescrites par des généralistes naturopathes consultés depuis 4 à 18 mois, après des années d'errance thérapeutique dans la prise en charge d'un état chronique aspécifique (asthénie,

douleurs et tensions musculaires, insomnie, anxiété, etc.) et de plus en plus handicapant. L'« analyse minérale » comporte le dosage en µg/g de créatinine de 33 éléments, sans indication de méthode, comparé à des valeurs « de base » (gouvernementales) et « d'orientation » (issues de l'expérience du laboratoire) et 2 pages de commentaires mal traduits. Des notions de « littérature », « accréditation » (ISO 17025) ou « contrôle qualité » sont mises en avant. Comme le matériel de prélèvement, les chélateurs ont été obtenus via Internet, et pour certains injectés au cabinet. Si 2 patients se sont montrés ouverts à la remise en cause de ces résultats et ont accepté de voir un interniste (jamais consulté jusqu'ici), la 3e, persuadée du « génie » de son thérapeute, a refusé toute critique et autre avis médical.

Discussion

La similitude des profils de ces patients comme celui de leurs médecins est frappante. Elle souligne l'existence d'une population de malades mal pris en charge autant que le ciblage mercantile dont ils sont l'objet. En France, pays marqué par des scandales sanitaires décrédibilisant toute parole officielle, un des prétextes à ces « dosages » est la controverse sur le mercure des amalgames dentaires et ses effets différés chez l'adulte. Aux États Unis, c'est la peur pour l'enfant qui est exploitée, avec la mise en avant d'un lien entre métaux lourds et troubles autistiques, pour justifier d'un recours massif à la chélation [1]. Face à ce phénomène, dès 2010 les autorités sanitaires et sociétés savantes américaines se sont clairement positionnées [1], [2] et ont alerté professionnels et grand public sur des pratiques officiellement qualifiées de frauduleuses. À ce jour, malgré les enjeux scientifiques, éthiques et légaux, rien en France ne vient contrer les pseudo-scientifiques relayés sur Internet et dans les médias, où un documentaire récent montrait un interniste hospitalier baser à son tour sa consultation sur les résultats du laboratoire M. Le 25/02/2015, le site institutionnel de son centre hospitalier régional se targuait même d'être « reconnu par le Conseil international de toxicologie clinique de métaux lourds », organe pro-chélation auto-proclamé accréditeur.

Conclusion

Le besoin d'approfondir les connaissances, notamment sur les expositions chroniques, et surtout d'améliorer l'écoute et la prise en charge de certains patients, ne doivent pas être niés. Mais d'abord dans l'intérêt des malades, et aussi au nom de leurs disciplines dévoyées, les toxicologues, analystes et cliniciens, doivent réagir et dénoncer des pratiques que certains qualifieraient d'abus de faiblesse et d'escroquerie en bande organisée.

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POSITION STATEMENT

American College of Medical Toxicology Position Statement on Post-Chelator Challenge Urinary Metal Testing

American College of Medical Toxicology

Published online: 31 March 2010

Keywords Urinary metal testing · Post-chelation testing

Heavy metals, such as lead and mercury, are ubiquitous in the environment [1–3]. Exposure in human populations is constantly occurring, and detectable levels of lead and mercury are commonly found in blood and urine of individuals who have no clinical signs or symptoms of toxicity and may be considered background or reference values [1–5]. Although urine testing for various metals in an appropriate clinical context, using proper and validated methods, is common and accepted medical practice, the use of post-challenge (a.k.a., post-provocation) urine metal testing, wherein specimens are typically collected within 48 h of chelation agent administration, is fraught with many misunderstandings, pitfalls, and risks. The American College of Medical Toxicology issues this position statement in disapproval of the use of post-challenge urinary metal testing in clinical practice and the use of such test results as an indication for further administration of chelating agents.

In current evidence-based medical practice, urinary testing is commonly used in the biomonitoring of exposure to certain metals such as arsenic and inorganic mercury and the severity of their associated toxicity. It is accepted practice to conduct such testing, e.g., in exposed individuals with clinical evidence of peripheral neuropathy, as long as validated collection and analytical methods are employed prior to, or after, a sufficiently long time interval (e.g., 3–5 days) following administration of a chelating agent, i.e., applied to non-challenge urine specimens, and the results are compared to appropriate reference values [5, 6]. In some non-evidence-based medical practices, however, assessment of metal poisoning is frequently based on non-validated post-challenge urine metal testing, which invites inappropriate comparison to normal urine reference ranges [4–7].

Chelating agents such as dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonic acid (DMPS), dimercaprol, and edetate calcium disodium ($CaNa_2$–EDTA) bind metallic and metalloid elements and have been shown to increase their elimination from the body. Chelating agents have been found to mobilize metals in healthy individuals who have a body burden considered normal for a standard reference population, as well as in those who are determined to have a high body burden of the same metallic species [4, 8–11]. More specifically, urine specimens collected in relatively close temporal proximity to administration of chelating agents, i.e., post-challenge specimens, are expected to have increased concentrations of metallic elements. This includes elements, such as zinc, that are essential to normal physiologic functions and maintenance of good health.

Normal reference values for non-challenge urine metal test results vary among and within different populations. Ranges for these values have been established in nationally certified laboratories that meet proficiency standards for urinary metal testing [5]. However, scientifically acceptable normal reference values for post-challenge urine metal testing have not been established [10]. In addition, scientific investigation to date has failed to establish a valid correlation between prior metal exposure and post-challenge test values [10]. Despite the lack of scientific support to do so, it is also a common practice of some laboratories and care providers to provide or apply non-challenge normal reference values as

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a comparative means of interpreting results of post-challenge urine metal testing [5]. Currently, available scientific data do not provide adequate support for the use of post-challenge urine metal testing as an accurate or reliable means of identifying individuals who would derive therapeutic benefit from chelation.

Unfortunately, the practice of post-challenge urine metal testing and its application to assessment of metal poisoning often leads to unwarranted and prolonged oral and/or intravenous administration of chelating agents, in response to the results of serial post-challenge testing that remain elevated above non-challenge reference values. Chelation therapy based on such laboratory values, in addition to being of no benefit to patient outcome, may actually prove harmful [5, 12]; catastrophic outcomes such as acute fatal hypocalcemia have been reported following the improper use of a chelating agent, edetate disodium (Na_2–EDTA) [13]. In addition, the safer formulation of this agent, $CaNa_2$–EDTA, has been demonstrated to increase urinary excretion of essential minerals such as iron, copper, and zinc [8, 14]. There is published experimental evidence that deleterious effects may occur when chelation is applied in the absence of prior lead exposure [15]. Other chelating agents such as DMSA and DMPS may also increase the elimination of certain essential elements, as well as promote target organ redistribution of metallic elements of concern such as mercury [16–18].

It is, therefore, the position of the American College of Medical Toxicology that post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning.

Disclosure This statement has been developed by members of the ACMT with principal contribution in writing by Nathan Charlton, M.D. and Kevin L. Wallace, M.D., F.A.C.M.T., reviewed and approved by the ACMT Practice Committee and Board of Directors, and opened to comment by all members of the College. Disclosure statements for participating members of the ACMT Practice Committee and ACMT Board of Directors are available.

June 2009

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LA VEILLE DES ACTEURS DE LA SANTÉ

« L'hôpital public abandonne plusieurs centaines de patients qui frappaient à ses portes » (Communiqué)

14/07/2015 Émis par : NAM

LES 'CHÉLATIONS' PERMETTENT DE REPÉRER ET DE SOIGNER LES INTOXICATIONS AUX MÉTAUX LOURDS. DEPUIS QUE LE CHR D'ORLÉANS PROPOSAIT CES THÉRAPIES, DE TRÉS NOMBREUX MALADES ÉTAIENT DANS L'ATTENTE D'UNE PRISE EN CHARGE. MAIS AU LIEU DE LEUR VENIR EN AIDE, L'HÔPITAL RENONCE BRUTALEMENT À LES SOIGNER…

Le 1er février dernier, dans le documentaire Alerte au Mercure [1], le Dr Marie-Christine Boutrais expliquait comment elle diagnostique et soigne, au Centre Hospitalier Régional (CHR) d'Orléans, des intoxications chroniques aux métaux lourds grâce à des 'chélations' : on injecte chez le patient des 'chélateurs', c'est-à-dire des molécules qui se lient fortement aux métaux (mercure, plomb, cadmium, arsenic, etc.) stockés dans les organes, afin de les 'neutraliser' et de permettre aux malades de les éliminer par les selles et les urines.

Ces chélateurs disposent en France d'une autorisation de mise sur le marché (AMM) hospitalière, mais ils ne sont habituellement utilisés qu'en cas d'intoxication aiguë. La particularité de la démarche du Dr Boutrais est de proposer, lorsqu'un patient souffre de symptômes généraux dont les examens classiques n'ont pu identifier la cause, un 'test de mobilisation' qui permet de vérifier l'imprégnation métallique ; si ce test s'avère positif, l'intoxication chronique est traitée avec les chélateurs.

« En réalité, explique le Délégué Général de Non Au Mercure (NAM) Geoffrey Begon, d'autres médecins en France pratiquent ce type de soins. Mais par crainte de l'Ordre des médecins, ils ont dû se réfugier dans une semi clandestinité. Résultat : non seulement ces soins sont à la charge du patient – ce qui éloigne les plus pauvres de toute espérance de prise en charge – mais leur sécurité ne peut pas être assurée de façon optimale. »

A l'hôpital d'Orléans, les frais sont supportés par la collectivité et la thérapie bénéficie d'un encadrement hospitalier, extrêmement rassurant. Aussi, depuis février, les demandes explosent : plusieurs centaines de patients sont dans l'attente d'une prise en charge !

Mais voici que les centres anti-poisons, qui ont toujours rejeté l'hypothèse des intoxications chroniques, entament une campagne de diffamation. Ainsi, le 4 juin, le Dr Mathieu Glaizal intervient lors de la 5ème journée de Toxicologie et Médecine d'Urgence sur le thème : Dosages urinaires post-chélation des métaux lourds et pseudoscience : il faut agir [2] ! Sur la base de 3 témoignages de patients ayant réalisé des chélations pour mesurer leur imprégnation en mercure [3], le médecin s'inquiète de « l'existence d'une population de malades mal pris en charge », mais surtout du « ciblage mercantile dont ils sont l'objet », qu'il qualifie « d'abus de faiblesse » et « d'escroquerie en bande organisée ».

Est-ce le contrecoup de cette communication ? Quelques jours après, l'association NAM reçoit les premiers signalements selon lesquels l'hôpital d'Orléans mettrait fin aux chélations. Une rumeur bientôt confirmée par la direction de l'hôpital.

Marie Grosman, conseillère scientifique de NAM, dénonce une série de décisions contraires à l'intérêt des patients : « Voilà un centre antipoison qui s'insurge contre une « pseudoscience », le dosage de mercure urinaire post-chélation. Que ne fustige-t-il pas le dogme, farouchement défendu depuis des années par les instances dentaires, d'un mercure toxique partout sauf lorsqu'il vient obturer les dents ! Voilà bien le véritable scandale. Et si la population française est en Europe la plus contaminée par ce redoutable toxique, elle le doit aussi à la complicité des centres antipoison, qui depuis des années rejettent a priori l'hypothèse d'une intoxication due à l'absorption de mercure issu des amalgames et refusent de prendre en compte ce type d'analyses, allant jusqu'à conseiller aux malades une prise en charge psychiatrique.

« Et voilà un hôpital qui devant cette grossière accusation de

pseudoscience se hâte de tout arrêter, décevant les espoirs considérables qu'il avait nourris. Une attitude scientifique aurait été, au contraire, de faire progresser les connaissances, en vérifiant la reproductibilité des tests de mobilisation réalisés avec le DMSA ; de mettre en place une étude en double aveugle permettant d'évaluer l'efficacité de ces thérapies. Hélas, c'est le choix de l'ignorance qui l'a emporté, laissant de très nombreux malades dans le désarroi. »

On peut difficilement faire abstraction du contexte : dernièrement, l'Agence du médicament (ANSM) réaffirmait qu'il serait impossible de s'intoxiquer avec le mercure des amalgames. Voilà plus de 15 ans que NAM avance le contraire : avec la fermeture de ce service, il devient effectivement impossible de trancher.

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Nouvelles de MTM **N° 12 - mars 2016**

L'actualité du laboratoire

En bref

Nous savons combien le temps est précieux et du peu dont nous disposons pour lire de longs articles. C'est pourquoi nous avons résumé les informations importantes. Contactez-nous pour en savoir plus.

Gammes de référence et d'orientation

Nous avons actualisé les gammes existantes et ajouté de nouvelles valeurs d'orientation pour les traitements associés tels que le ZnDPTA et le DMPS.

Ceci permettra une évaluation et une comparaison des résultats d'analyse plus précises.

Plus n'est pas forcément mieux

Nous avons émis, statistiquement, l'hypothèse qu'une augmentation de la substance chélatrice élevait, dans la même proportion, les valeurs d'excrétion urinaire. D'après nos données, nous pouvons conclure que ce n'est pas le cas. Nous avons vérifié les données suivantes, fournies par Heyl (Berlin), fabricant du Dimaval :

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DMPS (voie orale) - Excrétion urinaire de cuivre

DMPS (voie orale) en mg/kg	Excrétion de cuivre en %
25	171
50	197
100	235

Le fabricant du Dimaval établit la biodisponibilité du DMPS par voie orale à environ 50 %. C'est en accord avec notre comparaison de données urinaires du DPMS selon qu'il est pris par voie intraveineuse ou voie orale. L'évaluation statistique des données d'excrétion urinaire obtenue après la prise en intraveineuse d'1 ampoule de DMPS (250mg de substance active) versus 5 ampoules de DMPS (1250mg de substance active), administrées l'une après l'autre lors de la même séance, a eu peu d'effet. De fait, la médiane suggère que la prise de plusieurs ampoules de DMPS n'a pas d'avantage. À l'exception du cuivre, du sélénium, du zinc et du niveau de créatinine urinaire, la concentration médiane en éléments toxiques dans l'urine est restée la même, ou a légèrement diminué.

- **DMSA (voie orale) - Biodisponibilité et excrétion de métaux proportionnelle à la dose**

La biodisponibilité de la substance chélatrice est affectée par le mode d'administration et le PH du milieu dans lequel elle circule. Les mentions internationales situent la biodisponibilité du DMSA entre 20 et 50 %. Nous supposons que la fonction gastro-intestinale est un facteur important dans la détermination de la biodisponibilité du chélateur par voie orale, sa liaison aux métaux et l'excrétion urinaire. Les chélateurs oraux trouvent, puis se lient aux métaux situés dans l'appareil digestif ; la liaison aux métaux des matières fécales affecte donc l'excrétion urinaire de ceux-ci. Le 'nettoyage' de l'appareil digestif devrait peut-être avoir lieu avant une analyse d'urine par provocation ou simulation. L'attention portée au PH semble être justifiée.

Nous avons comparé la concentration en métaux dans l'urine d'une dose de 500mg (voie orale) avec celle d'une dose de 1000mg et avons trouvé une légère différence dans l'excrétion de ceux-ci. Voir le tableau ci-dessous :

DMSA (voie orale)	N = nombre d'analyses	Plomb	Mercure	Cuivre	Fer	Zinc
500mg	169	12.0	3.7	57.8	15.8	700
1000mg	219	13.8	3.9	75.2	15.6	700

Valeur moyenne de créatinine en mcg/g

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Association de traitements

Il n'y a pas d'avantage à combiner des agents chélateurs de fonction similaire (i.e. dithiol vicinal tels que le DMSA ou le DMPS), particulièrement s'ils sont pris de la même manière (voie orale). Lorsque l'EDTA par voie intraveineuse est associé au DMSA par voie orale, les appareils digestif et vasculaire sont détoxifiés en même temps ; cependant les statistiques impliquant l'analyse urinaire de métaux ne fournissent pas la preuve que des traitements associés augmentent l'excrétion rénale de ceux-ci, plus que ne le ferait une administration unique d'EDTA par voie intraveineuse. L'analyse de métaux contenus dans les selles peut fournir des réponses concernant la détoxification fécale.

Ateliers médicaux et conférences

Conférences internationales & ateliers 2016

Séminaires non-médicaux

09/04/2016 **Actualité sur la chélation, diagnostics et traitements**
Nuremberg, Allemagne (Allemand)

Détails et mises à jour :

http://www.microtrace.fr/fr/seminaire

Études et analyses

L'EDTA et le TACT (Essai en vue d'évaluer le traitement par chélation), second essai

Le *National Center for Complementary and Integrative Health* (NCCIH), qui fait partie des Instituts américains de la santé (*National Institutes of Health* ou *NIH*) a attribué $800 000 au *Mount Sinai Medical Center of Florida* et au *Duke Clinical Research Institute* pour lancer la planification annuelle du TACT 2 (second essai en vue d'évaluer le traitement par chélation).

Nous suggérons que l'effet de l'EDTA dans la détoxification des métaux soit inclus dans l'étude. La chélation par l'EDTA supprime les métaux toxiques du système vasculaire, en réduisant ainsi l'inflammation tout en augmentant le flux sanguin ; ceci peut être documenté.

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N'hésitez pas à nous contacter si vous avez des questions.

Nous vous souhaitons un agréable moment.

Bien à vous,

E. Blaurock-Busch et toute son équipe.

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