11
Chelation Therapy

Chelation therapy is considered as one treatment option for heavy-metal poisoning. It is also used as a potential therapy for Wilson disease, which is caused by a build-up of copper ions in the body (see Chapter 7). The basic principle behind chelation therapy is to capture the metal ions and remove them from the body.

11.1 What is heavy-metal poisoning?

Heavy-metal poisoning is defined as the accumulation of toxic metal in the body, mainly in the soft tissue. There is an on-going debate on how to define heavy metals. Mostly, it is defined as an element that has more than five times the density of water. With regard to danger to human health, all metals that cause harm to the body should be included, such as lead, mercury, arsenic, thallium and cadmium. Some heavy metals, such as zinc, copper, chromium, iron and manganese, are required by the body in small amounts but are toxic in larger quantities (see Chapter 7) (Figure 11.1).

Heavy metals can be taken up by ingestion (food or drink), through air (inhalation) or also by absorption through the skin. Heavy metals are then mostly stored in the soft tissue. Places of exposure can often be traced back to the work place (industrial work, pharmaceutical industry or agriculture). Contaminated sand and soil on playgrounds are known to have been responsible for heavy-metal poisoning in children. Within the human body, toxic heavy metals typically compete with essential metals, such as magnesium, zinc, iron, calcium and others for their receptors. This can lead to irreversible organ damage.

Depending on the type and quantity of heavy metal absorbed, the patient will display varying symptoms. These may include vomiting, nausea, diarrhoea, sweating, headache and a metallic taste in the mouth. In severe cases, heavy-metal poisoning can lead to impairment of cognitive, motor and language skills in the patients. The famous expression ‘mad as a hatter’ originated in seventeenth-century France, where hat makers used a toxic mercury salt (mercuric nitrate) to soak animal hides (Figure 11.2).

Heavy-metal poisoning is diagnosed using blood and urine tests, or by hair, tissue and X-ray analysis. Upper concentration limits in blood depend on the individual metal. Whilst very high concentration levels lead to serious health concerns, it has been shown that, especially in children, even lower levels can lead to chronic health problems. Additionally, the length of exposure can be crucial for developing serious health problems. Exposure to a heavy metal of a long period can be highly toxic even at low levels. Diagnosing the concentration

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H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 11.1 *Periodic table showing examples of metals that are harmful to the human body (black), and metals that are essential in small amounts and toxic in larger quantities (light grey)*

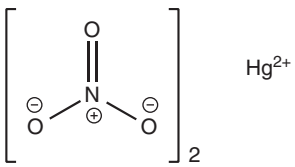

Figure 11.2 *Chemical structure of mercuric nitrate*

of heavy metal, which rapidly clears from the blood, can be fairly difficult. Arsenic clears rapidly from the blood stream, and it might be possible to detect arsenic poisoning in the urine up to ~48–72 h. Acute arsenic poisoning especially after ingestion of arsenic may be visualised by using X-ray diagnosis, as arsenic is opaque to X-rays. Furthermore, arsenic can be detected in hair and nail for a month following the exposure.

The main treatment option for heavy-metal poisoning is the so-called chelation therapy. Chelation therapy is based on the principle that the toxic heavy metal is bound to a chelating agent, which reduces its toxicity and removes it from the human body.

11.2 What is chelation?

Chelation is the binding of molecules to a metal ion and is one of the most important concepts within the area of transition-metal complexes. The molecules or ligands in question are organic compounds and can form more than one bond to the metal ion. These ligands are classified as polydentate ligands, which means that this single ligand has more than one atom that can bind to the central atom in a coordination complex. The ligands are called *chelators* or *chelating ligands* (Figure 11.3).

> ***Chelation*** *is defined as the formation of two or more coordinate bonds between a polydentate ligand and a single atom.*

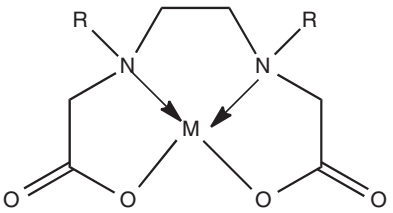

Figure 11.3 *Chemical structure of an example for a chelation complex*

In terms of the nomenclature, the denticity of a ligand is denoted by the Greek letter κ (kappa). If the denticity equals 1, it is a monodentate ligand and only one bond from the ligand to the metal is formed. For bidentate ligands, the denticity equals 2, which means that two coordination bonds are formed from the ligand to the metal. One of the most known examples is EDTA (ethylenediaminetetraacetic acid), which is a hexadentate ligand. EDTA can coordinate to a metal ion via six atoms and therefore is denoted as κ^6-EDTA. It is important not to confuse denticity with hapticity (see Chapter 8), which only refers to bonds that are contiguous (Figure 11.4).

The term *chelate effect* is used to describe the preferred binding of a chelating ligand to a metal ion in comparison to the corresponding amount of monodentate (nonchelating) ligand under the same reaction conditions. The most widely known example is the reaction of a transition metal (e.g. Cu^{2+}) with 1 equiv of the bidentate ligand ethylenediamine (en) or with 2 equiv of the monodentate ligand amine (NH_3) (Figure 11.5).

The reaction of the bidentate ligand ethylenediamine results in the formation of a chelate complex in which the ligand forms two bonds to the metal centre and a five-membered ring is formed (see Figure 11.6). The same reaction takes places with 2 equiv of the monodentate ligand amine. Nevertheless, under the same reaction conditions, the concentration of the five-membered coordination complex (product A) will be significantly higher than product B. This is called the *chelate effect*.

The chelate effect increases with the number of chelate rings formed. This explains why EDTA is a very good chelating agent, as it can form up to six coordinating bonds to the metal centre. In general, the chelate

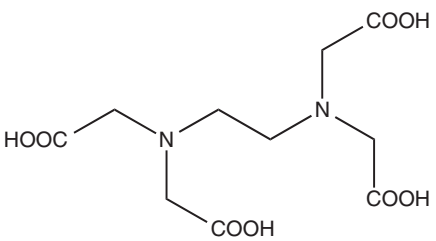

Figure 11.4 *Chemical structure of EDTA*

$$Cu^{2+} + 3en \rightarrow Cu(en)_3{}^{2+}(A)$$

$$Cu^{2+} + 6NH_3 \rightarrow Cu(NH_3)_6{}^{2+}(B)$$

Figure 11.5 *Complexation of Cu^{2+} with ethylenediamine (en) or amine*

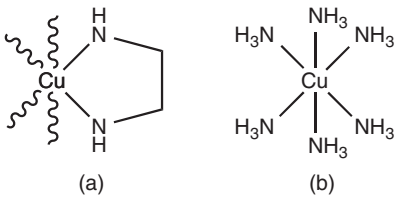

Figure 11.6 *Coordination of Cu^{2+} with ethylenediamine (a) and NH_3 (b)*

effect can be explained by using a thermodynamic approach, which considers the equilibrium constants for the reaction. Nevertheless, this will not be further discussed here, as it is beyond the scope of this book.

11.3 Chelation therapy

As previously mentioned, chelation therapy is one treatment option for most heavy-metal poisoning. A chelating agent (antidote), which is specific to the metal involved, is administered to the patient orally, intramuscularly or intravenously. Dimercaprol (BAL, British anti-Lewisite), calcium disodium edetate and penicillamine are the three most common chelating agents used in the treatment of heavy-metal poisoning. The unlicensed drug Succimer (DMSA, *meso*-2,3-dimercaptosuccinic acid) may be valuable in the treatment of most forms of heavy-metal poisoning including lead, arsenic and mercury. These and other chelating agents such as unithiol (DMPS, 2,3-dimercapto-1-propanesulfonic acid) and α-lipoic acid (ALA) are also used in alternative medicine, which has led to much criticism and discussion. So far, no medical study has proven the effectiveness of chelation therapy for any clinical application other than heavy-metal poisoning.

The mode of action is based on the ability of the chelating agent to bind to the metal in the body's tissues and form a chelate. This complex is then released from the tissue and travels in the bloodstream. Finally, the complex is filtered by the kidneys and excreted in the urine. Unfortunately, this process requires admission to the hospital because it may be painful and it is important to stabilise the vital functions of the patient. The patient additionally may require treatment for complications associated with heavy-metal poisoning, including anaemia and kidney failure or shock reactions.

Chelation therapy is an especially effective treatment option for poisoning with lead, mercury and arsenic. It is very difficult to treat cadmium poisoning, and so far no really effective therapy has been found.

11.3.1 Calcium disodium edetate

Calcium disodium edetate, also referred to as *calcium sodium EDTA*, stands for the chemical compound 2,2′,2″,2‴-(ethane-1,2-diyldinitrilo)tetraacetic acid, which is a synthetic amino acid. Edetate refers to the calcium disodium salt of the chelating agent with the formula $(HO_2CCH_2)_2NCH_2CH_2N(CH_2CO_2H)_2$. In the United States, it is found under the name calcium disodium versenate. Edetate is mainly used to complex di and trivalent metal ions. Edetate can bind to metals via the four carboxylate and two amine groups, and it forms specially strong complexes with Co(III), Cu(II), Mn(II) and Fe(III) (Figure 11.7).

Edetate is indicated for the treatment of lead poisoning, which was especially a big problem for navy personnel after World War II. Staff repainting the navy ships with lead-based paint were exposed to the heavy metal and suffered from symptoms of lead poisoning. Around this time, edetate was introduced as a medicinal chelating agent. The side effects include nausea, diarrhoea and abdominal pain. It can lead to

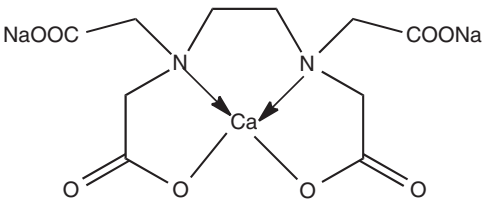

Figure 11.7 *Chemical structure of edetate*

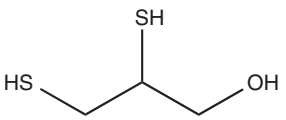

Figure 11.8 *Chemical structure of dimercaprol*

renal damage if given as over dosage [1]. Nevertheless, these side effects are less serious/invasive than those of most other chelating agents being used. Edetate is typically administered by intravenous infusion for up to 5 days [1].

Other clinical applications include the application of chromium-EDTA, which can be used to evaluate kidney function. It is administered intravenously and its filtration into the urine is monitored. Chromium-EDTA exits the human body only via glomerular filtration as it is not secreted or metabolised in any other way. EDTA and its salts can act as an anticoagulant for blood samples and is therefore often found as additives in blood sampling bottles.

11.3.2 Dimercaprol (BAL)

Dimercaprol (BAL) is a chelating agent used as an antidote for arsenic, antimony, bismuth, gold and mercury poisoning [1]. It has the chemical name 2,3-dimercapto-1-propanol and is a clear, colourless or slightly yellow liquid (Figure 11.8).

British scientists at the University of Oxford also developed BAL during World War II as an antidote to Lewisite. Lewisite is an arsenic-based chemical warfare agent used in form of a blister gas. Further research showed that it can be used as an antidote against a variety of toxic metals. Additionally, it was used in the treatment of Wilson disease, which is a chronic disease in which the body retains excess amounts of copper (see Chapter 7).

Heavy-metal poisoning often results from the coordination of the metal to sulfhydryl groups of enzymes, which means that these enzymes are blocked for their activity. BAL also contains sulfhydryl groups and basically competes with the enzymes for the coordination of the metal. The chelated complex is then excreted in the urine. Whilst BAL removes a range of heavy metals, it also seems to increase the concentration of some metals in the human body and therefore limits its use. It is not indicated as an antidote for cadmium (increased levels are found in the kidneys after treatment), selenium or iron poisoning [1].

Unfortunately, BAL itself is very toxic and has only a narrow therapeutic window. Its multiple side effects include, amongst others, hypertension, malaise, tachycardia, nausea, diarrhoea, burning sensation and muscle pain. The administration is by intramuscular injection and is fairly painful. Because of its instability in water, it is formulated with peanut oil as solvent.

11.3.3 Dimercaptosuccinic acid (DMSA)

DMSA is a modification of BAL containing two thiol groups, which are responsible for the unpleasant smell, and two carboxylic acid groups. DMSA is also known under the name Succimer. It chemical name is *meso*-2,3-dimercaptosuccinic acid and the chemical formula is $HO_2CCH(SH)CH(SH)CO_2H$. There are two diastereomeric forms, meso and the chiral DL forms, with the meso isomer being used as chelating agent (Figure 11.9).

DMSA was developed in the 1960s and replaced BAL and edetate in some countries for the treatment of lead, arsenic and mercury poisoning. Furthermore, the dimethylester modification of DMSA has been successfully used for the treatment of heavy-metal poisoning.

11.3.4 2,3-Dimercapto-1-propanesulfonic acid (DMPS)

DMPS is also a thiol-containing chelating agent. It also contains sulfhydryl groups and an additional sulfate group. Researchers in the former Soviet Union found that DMPS is a useful chelating agent and has some effect as an antidote to mercury (Figure 11.10).

11.3.5 Lipoic acid (ALA)

Lipoic acid, also known as α-*lipoic acid* (*alpha-lipoic acid*) or *thioctic acid*, has the formula $C_8H_{14}S_2O_2$ and systematic name 5-(1,2-dithiolan-3-yl)pentanoic acid. It contains a disulfide group, which can be transformed in the body to a dithiol group (Figure 11.11).

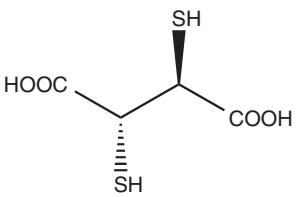

Figure 11.9 *Chemical structure of DMSA*

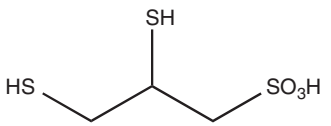

Figure 11.10 *Chemical structure of DMPS*

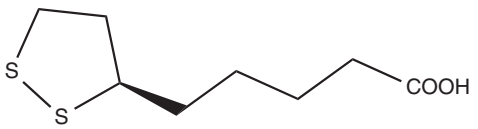

Figure 11.11 *Chemical structure of ALA*

ALA has been on the market since the 1950s as a dietary supplement. It is a natural antioxidant usually made by the body. The advantage of ALA over other antioxidants such as vitamin C and E is that it is soluble both in water and in fat [2]. Researchers in the former Soviet Union found that ALA can chelate mercury once it is transformed into the dithiol-containing compound. ALA can penetrate both the blood–brain barrier and the cell membrane and therefore would be a very interesting chelating agent. Nevertheless, there is much debate about its mode of action, side effects and effectiveness. Other antidotes, such as BAL and DMSA, are more efficient in the removal of heavy metals. ALA has not received FDA approval as a chelating agent, but it is still sold as a food supplement.

11.4 Exercises

11.4.1 Sodium calcium edetate is usually administered by intravenous infusion. A 5 ml ampule contains 200 mg/ml sodium calcium edetate.

(a) What is the number of moles of calcium sodium edetate present in one ampule? Express your answer in moles.

(b) What is the concentration of calcium sodium edetate in one ampule? Express you answer in moles per litre.

11.4.2 Dimercaprol is usually administered by intramuscular injection. A 2 ml ampule typically contains 50 mg/ml dimercaprol.

(a) What is the number of moles of dimercaprol present in one ampule? Express your answer in moles.

(b) What is the concentration of dimercaprol in one ampule? Express you answer in moles per litre.

11.4.3 Draw the structure of all enantiomers of DMSA and discuss which one is used clinically.

11.4.4 Draw the chemical structure of the cobalt(II)–EDTA complex ion.

11.4.5 Draw the chemical structure of Hg^{2+} coordinated by dimercaprol.

11.5 Case studies

11.5.1 Disodium edetate

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of solutions for infusion containing disodium edetate. According to your brief, you are supposed to analyse the active pharmaceutical ingredient (API), following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain amount of the solution is diluted in water and hexamethylenetetramine together with HCl is added. The resulting solution is titrated against a solution of lead nitrate using xylenol orange triturate as indicator [3].

(a) Research the type of titration described. Describe the chemical structure and mode of action of the indicator.
(b) Formulate the relevant chemical equations.
Typically, disodium edetate is dispensed as 5 ml ampules containing 200 mg/ml of the API. For the analysis, an amount of solution containing theoretically 0.3 g disodium edetate $\times 2H_2O$ is dissolved in water. Hexamethylenetetramine (2 g) and dilute HCl are added to this solution, which is then titrated against 0.1 M lead nitrate solution in the presence of xylenol orange triturate as the indicator [3].
(c) How many milligrams of the API are there in one ampule?
(d) For each titration, the following volume of lead nitrate has been used:

9.0 ml	8.8 ml	8.6 ml

Calculate the real amount of disodium edetate $\times 2H_2O$ present in your sample. Express your answer in grams and moles.
(e) Critically discuss your result in context with the stated value for the API.
(f) Research the typically accepted error margins.

11.5.2 Dimercaprol

Dimercaprol injections can be used as for the treatment of heavy-metal poisoning. Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of solutions for injections containing dimercaprol. The chelating agent is typically dispensed in 2 ml ampules containing 50 mg/ml of dimercaprol. According to your brief, you are supposed to analyse the API, following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain amount of injection is dissolved in methanol. Diluted HCl and an iodine solution are added and the resulting solution is titrated against sodium thiosulfate [3].

(a) Research the type of titration described and how the endpoint is detected.
(b) Formulate the relevant chemical equations.
According to its label, a 2 ml ampule of dimercaprol contains 50 mg/ml. An amount of solution theoretically containing 0.10 g dimercaprol is dissolved in methanol. Dilute hydrochloric acid (20 ml, 0.1 M) is added together with 50.0 ml of a 0.05 M iodine solution. After 10 min, the solution is titrated against a 0.1 M sodium thiosulfate solution [3].
(c) How many milligram of the API are there in one ampule?

(d) For each titration, the following volume of sodium thiosulfate has been used:

16.95 ml	17.10 ml	17.00 ml

Calculate the real amount of dimercaprol present in your sample. Express your answer in grams and moles.

(e) Critically discuss your result in context with the stated value for the API.

(f) Research the typically accepted error margins.

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