9

The Clinical Use of Lanthanoids

The lanthanoid series consists of 14 elements (cerium to lutetium) and they are also called *f-block metals*, as the valence shell of lanthanoids contains 4f orbitals. Lanthanoids are named after the element lanthanum (La), which itself is a d-block metal. Nevertheless, because of its very similar chemical behaviour, lanthanum is often also classified as a lanthanoid. The term *rare earth metals* describes the lanthanoid series together with lanthanum (La), scandium (Sc) and yttrium (Y).

*The **lanthanoid series** is often given the symbol Ln and referred to the elements La–Lu.*

The trivalent cation is the most stable oxidation state, as the lanthanoids tend to lose three electrons ($6s^2$ and $5d^1$) because of their electronic configuration. The resulting trivalent cations contain a xenon (Xe) core with regard to their electronic configuration with the addition of varying numbers of 4f electrons. The 4f electrons can be found closer to the nucleus, whilst the $5s^2$ and $5p^6$, which are full sub-shells, shield them. Trivalent lanthanoids are often referred to as *triple positive charged noble gases* (Table 9.1).

9.1 Biology and toxicology of lanthanoids

Mostly, lanthanoids are used in the production of batteries, lasers and other technological devices. Some lanthanoids salts, such as the salts of lanthanum, cerium and gadolinium (highlighted in Figure 9.1), are increasingly used in a clinical setting, for example, as a phosphate binder in the treatment of renal osteodystrophy or as MRI (magnetic resonance imaging) contrast agents (CAs).

Lanthanoids (Ln) show a biological behaviour very similar to that of Ca^{2+}, as they have similar ionic radii. Lanthanoids are mostly trivalent and therefore possess a higher charge than Ca^{2+}. Lanthanoids display a high binding affinity to calcium-binding sites in biological molecules and to water molecules. The coordination number for lanthanoids varies from 6 to 12. Mostly, eight or nine water molecules are coordinated to the lanthanoid ion. This is a significantly lower coordination number compared to that of calcium, which is 6.

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Table 9.1 *Lanthanoid series*

Element name	Symbol	Ground-state electronic configuration
Lanthanum	La	$[Xe]6s^2 5d^1$
Cerium	Ce	$[Xe]4f^1 6s^2 5d^1$
Praseodymium	Pr	$[Xe]4f^3 6s^2$
Neodymium	Nd	$[Xe]4f^4 6s^2$
Promethium	Pm	$[Xe]4f^5 6s^2$
Samarium	Sm	$[Xe]4f^6 6s^2$
Europium	Eu	$[Xe]4f^7 6s^2$
Gadolinium	Gd	$[Xe]4f^1 6s^2 5d^1$
Terbium	Tb	$[Xe]4f^9 6s^2$
Dysprosium	Dy	$[Xe]4f^{10} 6s^2$
Holmium	Ho	$[Xe]4f^{11} 6s^2$
Erbium	Er	$[Xe]4f^{12} 6s^2$
Thulium	Tm	$[Xe]4f^{13} 6s^2$
Ytterbium	Yb	$[Xe]4f^{14} 6s^2$
Lutetium	Lu	$[Xe]4f^{14} 6s^2 5d^1$

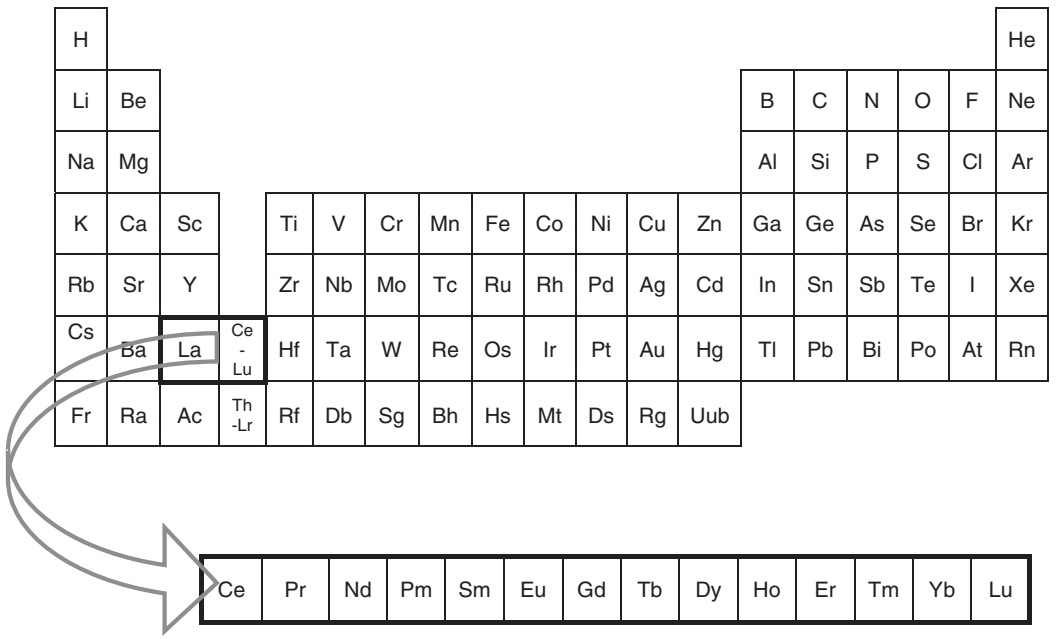

Figure 9.1 *Periodic table of elements; lanthanoids clinically used are highlighted*

Within the human body, lanthanoid ions are known to block the receptor-operated calcium channels. Lanthanoids cannot cross the cell membrane, but they still block the Na^{+}/Ca^{2+} synaptic plasma membrane exchange and therefore inhibit muscle contraction (e.g. in skeletal muscle or cardiac muscle). Lanthanoids can also displace calcium in proteins and enzymes, which can either lead to inhibition or activation of their catalytic activity. In general, lanthanoids mimic the biological behaviour of calcium ions and as a result lanthanoids can be used to study the mode of action of calcium ions in a variety of biological applications.

It is very interesting to look at the toxicity of lanthanoids. In general, lanthanoids are not regarded as toxic, as they cannot cross the cell membrane and therefore are not absorbed if administered orally. Lanthanoids are toxic if they are administered intravenously, as they can then interact with a variety of biological targets. A sudden decrease in blood pressure and sudden cardiovascular complications are signs of acute toxicity. Chronic toxicity manifests itself in liver damage and oedema. After intravenous administration, lanthanoids are often quickly distributed to the liver and the bones [1].

9.2 The clinical use of lanthanum carbonate

The chemical element lanthanum has the symbol La and atomic number 57. It is a silvery white metal and represents the start of the lanthanoid series (Ln).

Lanthanum has two oxidation states, +II and +III, and the latter is the more stable one. The electronic configuration of the resulting La^{3+} ion is $[Xe]4f^{0}$. Lanthanum burns in the presence of air and forms lanthanum(III) oxide:

$$4La + 3O_2 \rightarrow 2La_2O_3$$

Lanthanum reacts with water with the formation of lanthanum hydroxide owing to the electropositive nature of the metal. It also reacts with halogens and forms the respective lanthanum halide salt.

Lanthanum carbonate $La_2(CO_3)_3$ see Figure 9.2 is the only lanthanum salt approved for clinical use. It is used in the managementof hyperphosphataemia, which is defined as high levels of phosphate in the serum blood (Figure 9.3).

$$2La + 6H_2O \rightarrow 2La(OH)_3 + 3H_2$$

$$2La + 3Cl_2 \rightarrow 2LaCl_3$$

Figure 9.2

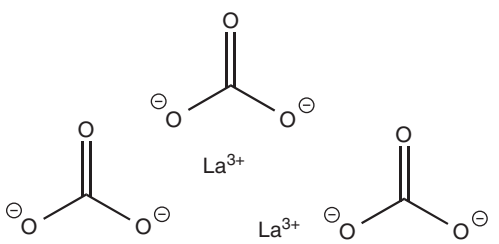

Figure 9.3 *Chemical structure of lanthanum carbonate*

Patients with end-stage renal failure (ESRF) often present high levels of phosphate in the serum as a result of the failure of the kidneys. The serum phosphate level of a healthy human is in the range 0.8–1.5 mmol/l [2], whereas this level is significantly increased in patients with kidney failure. High phosphate levels are linked to a decrease of calcium serum levels and the release of the so-called parathyroid hormone (PTH). This can manifest itself in renal osteodystrophy, which can have severe pathological consequences such as bone malfunction (see Section 3.4.4). Also, increased levels of PTH are observed, which can lead to secondary calcification of muscles and vascular tissue. Nearly half of the deaths of dialysis patients with ESRF are due to cardiac events.

The average phosphate intake ranges from 1000 to 1500 mg/day. In a healthy human, phosphate is absorbed in the gastrointestinal (GI) tract and excreted via the kidneys. In patients with ESRF, phosphate excretion via the kidneys is reduced and therefore accumulates in the serum. A common treatment option includes the binding of phosphate already in the GI tract before it can enter the blood stream. The ideal phosphate binder should bind phosphate with high affinity, should not be absorbed in the GI tract and should be excreted via the faeces. Aluminium salts were used until the early 1980s as phosphate binders. Aluminium phosphate is readily formed but not absorbed. Unfortunately, the aluminium salt (aluminium hydroxide) itself is absorbed in the GI tract and has been found to be toxic. Specific toxicity to the central nervous system (CNS) was observed.

As an alternative treatment option, calcium salts were and still are used as phosphate binders. Calcium salts, such as calcium acetate and calcium carbonate, are very successful treatment options especially in patients undergoing dialysis. The main issue is that calcium ions can be absorbed and this can lead to hypercalcaemia, which is defined as high levels of serum calcium ions. This can further increase the risk of tissue calcification and cardiac events.

Further research has led to a variety of drugs, with sevelamer hydrochloride being one of the most successful ones. Sevelamer is a hydrogel containing cross-linked polyallylamine chains. The negatively charged phosphate can be bound to the positively charged amine groups of the hydrogel in the intestines and removed via the faeces.

Furthermore, lanthanum carbonate has been successfully studied as a phosphate binding agent. Lanthanum carbonate fulfils the criteria for a good phosphate binder as stipulated above: nontoxic, rapid binding of phosphate, not absorbed in the GI tract and easily excreted. A comparative study of a variety of lanthanum salts showed that $La_2CO_3 \cdot 4H_2O$ has the best phosphate binding properties at a variety of pHs. This means that phosphate can be bound in the stomach (very low pH) and the complex remains intact whilst travelling through the GI tract where the pH is higher. Pharmacological studies have shown that lanthanum carbonate is poorly absorbed when administered orally and that more than 90% is excreted via the faeces. No specific toxicity has been observed either. Lanthanum carbonate hydrate is marketed under the name Fosrenol and has received approval in Europe and the United States for its clinical use in patients with chronic renal failure [1].

Lanthanum carbonate hydrate is usually given with an initial dose of 0.75–2.25 g of elemental lanthanum in divided doses with meal. The dose needs to be reviewed every 2–3 weeks until a maintenance dose (1.5–3 g) is achieved. Patients should be advised to chew the tablets before swallowing. Most common side effects include disturbances of the GI tract, resulting in diarrhoea and constipation [3].

9.3 The clinical application of cerium salts

The element cerium has the chemical symbol Ce and atomic number 58. It is a silvery and soft metal, which easily is oxidised in air. Cerium has three oxidation states, +II, +III and +IV, the last being the more stable one. The electronic configuration of the resulting Ce^{4+} ion is $[Xe]4f^0$. Ce^{+2} is the rarest oxidation state and the resulting electronic configuration is $[Xe]4f^2$.

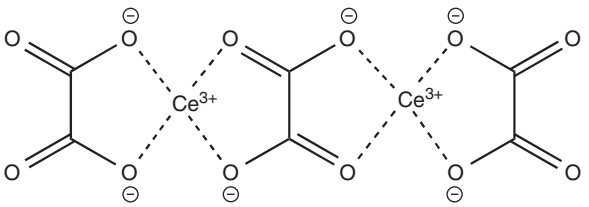

Figure 9.4 *Chemical structure of cerium(III) oxalate*

The clinical use of cerium dates back to the mid-nineteenth century, when cerium(III) oxalate was used as an antiemetic. The exact mode of action is unknown, but it is believed to be a local effect limited to the GI tract. This is based on the fact that lanthanoids are not easily absorbed after oral administration, as previously discussed, and that cerium oxalate has a low aqueous solubility. Nevertheless, the clinical use of cerium salts as antiemetic was eventually replaced by antihistamines (Figure 9.4) [1].

At the end of the nineteenth century, several Ce^{3+} salts were under investigation for their antibacterial activity in burn wounds. Especially, cerium nitrate [$Ce(NO_3)_3$] showed broad activity against a variety of pathogens and was subsequently used in combination with silver sulfadiazine. Initial studies were very successful and an estimated reduction of 50% of the mortality rate was suggested. It was believed that this result was due to the synergistic antimicrobial effect of both reagents [1].

Recent studies have shown that cerium nitrate has no significant effect on pathogens from burn wounds. Furthermore, research has shown that the suppression of the immune system in patients with serious burn wounds is a main factor for mortality. It has also been shown in animal models that cerium nitrate is a modulator of the burn-associated immune response. Nowadays, this is believed to be the main role of cerium(III) nitrate when used as part of a combination treatment of burn victims. Currently, the cerium salt is used in combination with silver sulfadiazine in individual cases for the treatment of life-threatening burn wounds. Reports suggest that wound healing improves, mortality rates drop and graft rejection rates are also significantly lower [1].

9.4 The use of gadolinium salts as MRI contrast agents

The chemical element gadolinium has the chemical symbol Gd and atomic number 64. It is a silvery white metal, which is malleable and ductile. The dominant oxidation state of gadolinium salts is +III, with the resulting electronic configuration $[Xe]4f^7$.

Gadolinium is a relatively stable metal upon exposure to dry air. Nevertheless, it tends to oxidise once it is exposed to moisture, as it slowly reacts with water. Gadolinium is used in microwave applications and in the manufacturing of compact discs and computer memory. Gadolinium is often used in alloys. With as little as 1% gadolinium, the properties and workability of iron and chromium improve.

Solutions containing gadolinium salts are used as CAs for MRI as a clinical application. Using this method, it is possible to detect and observe pathological and physiological alteration to living tissue. MRI used in medicine uses the so-called relaxation properties of excited hydrogen nuclei found in water and lipids in the human tissue. Relaxation refers to an effect known in physics and chemistry, where there is a delay between the application of an external stress to the system and its response. Within a strong magnetic environment, which is produced in an MRI scanner, excited hydrogen nuclei show different behaviours depending on their environment.

MRI can be carried out without any CAs, but the use of a suitable CA can enhance the imaging properties. The basic idea is that the water relaxation rates are altered in the presence of a CA, which leads to additional

and/or enhanced information displayed in the images. In contrast to their role in the X-ray imaging, the CAs themselves are not displayed in the images. Nowadays, around a third of MRI scans are undertaken using CAs, and organ perfusions, kidney clearance and changes in the blood–brain barrier can be detected (Figure 9.5).

The trivalent cation Gd^{3+} is useful as a CA for MRI, as it is a paramagnetic compound (see Section 7.1.2 for the definition of paramagnetism) with the electronic configuration $[Xe]4f^7$. Gd^{3+} has seven unpaired electrons in its valence shell, which endows it with the paramagnetic properties. Gd^{3+}-containing CAs affect the image quality of an MRI in two ways: (i) Paramagnetic Gd^{3+} complexes can coordinate water molecules and exchange them for water molecules in their environment, which are coordinated to the metal centre. A typical Gd^{3+} complex is an eight-coordinated metal complex in which the ninth binding site is available for the coordination of water. As previously discussed, the typical coordination number for lanthanoid complexes

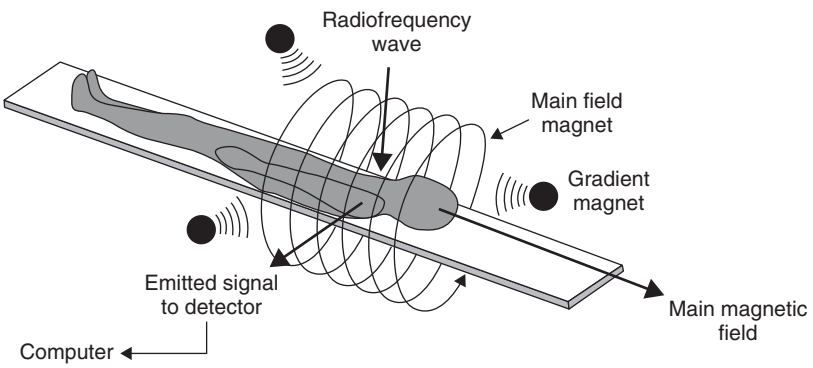

Figure 9.5 *Schematic diagram of a patient in a magnetic resonance imaging (MRI) instrument. The main magnetic field is created by an electromagnet, and the field in many specific planes within the tissue of the patient is modified by gradient electromagnets. After analysis using a computer program, a 3D image of the relaxation lifetimes of water molecules in the tissue of the patient is obtained [4] (Reproduced with permission from [2]. Copyright © 2009, John Wiley & Sons, Ltd.)*

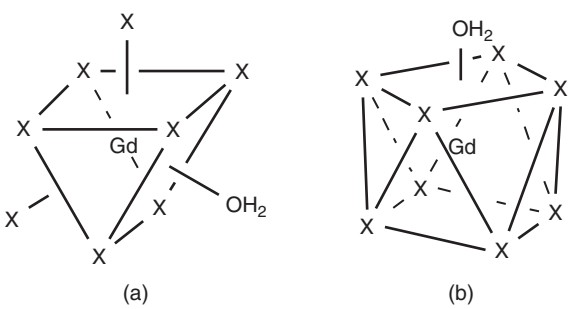

Figure 9.6 *Coordination geometries of Gd^{3+} MRI CAs: (a) tricapped trigonal prism and (b) monocapped square antiprism. Depending on the structure of the octadentate ligand, which contributes eight donor groups to Gd^{3+}, denoted by X, and the location of the water molecule, each geometry can exist in a number of isomeric forms [4] (Reproduced with permission from [2]. Copyright © 2009, John Wiley & Sons, Ltd.)*

is 9. (ii) In addition, the paramagnetic Gd^{3+} creates a small local magnetic field, which influences the water molecules that are not coordinated to the metal centre (Figure 9.6).

Solutions of paramagnetic organic Gd^{3+} compounds are administered intravenously, and they enhance the images obtained by MRI. The trivalent ion itself has no physiological function in the human body and is highly toxic. Therefore, Gd^{3+} is administered as stable chelate in which the lanthanoid is chelated by an

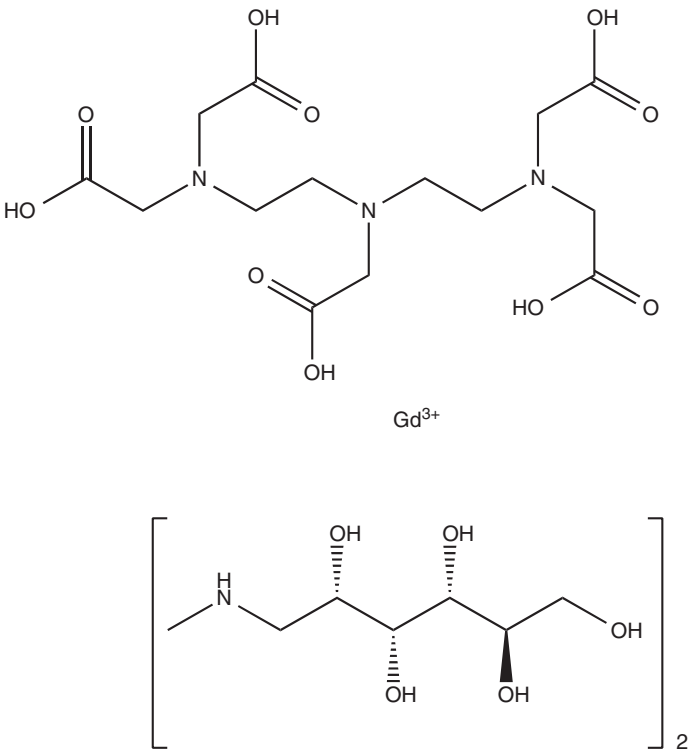

Figure 9.7 *Chemical structure of Magnevist*

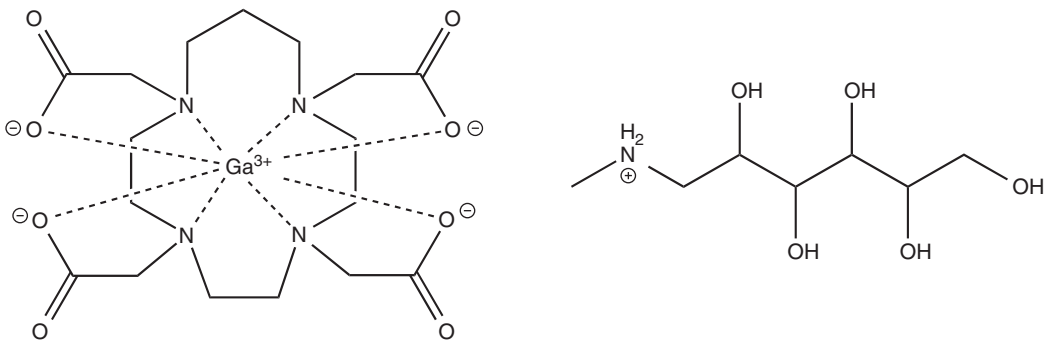

Figure 9.8 *Chemical structure of Dotarem*

organic ligand and as a result exhibits a significantly lower toxicity. The most widespread clinical examples are Magnevist™ and Dotarem™ (see Figures 9.7 and 9.8), both approved by the FDA for their use as CAs in MRI. Gadolinium-containing chelates are around 50 times less toxic than the 'free' Gd^{3+} in salts such as $GdCl_3$. Gadolinium-containing chelates are typically cleared from the blood plasma within a few hours (half-life <2 h) and excreted via the urine [1]. In contrast, free Gd^{3+} ions remain in blood serum for significantly longer; only 2% is excreted after 7 days [1].

9.5 Exercises

9.5.1 Write the electronic configuration for the following:

(a) La
(b) La^{2+}
(c) Eu
(d) Eu^{3+}
(e) Er
(f) Ce^{3+}

9.5.2 Draw the Lewis structures for the following compounds:

(a) Lanthanum nitrate
(b) Lanthanum sulfate
(c) Lanthanum acetate

9.5.3 A typical solution of Dotarem for injection is labelled with gadoteric acid, 0.5 mmol/ml/100 ml. Calculate

(a) the amount of gadoteric acid in gram;
(b) the corresponding amount of DOTA;
(c) the corresponding amount of gadolinium oxide.

9.6 Case study: lanthanum carbonate tablets

Research the properties and clinical use of lanthanum carbonate tablets. Summarise your findings in a drug monograph, which could be published in a Pharmacopoeia. Your drug monograph should contain the following aspects:

1. Chemical structure
2. Action and use
   (a) Preparation
3. Chemical formula
4. Definition
5. Content
6. Characteristics
   (a) Appearance
   (b) Solubility
7. Identification (two different forms of identification)
   (a) Identification A
   (b) Identification B
8. Assay to quantify the API (active pharmaceutical ingredient)
9. Impurities.

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