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FUNDAMENTALS OF CHELATION THERAPY, ITS SIGNIFICANCE IN MODERN MEDICINE, MECHANISM OF ACTION AND LIMITATIONS

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Abstract. Chelation therapy is a pharmacological strategy in which organic ligands are administered to bind excess or toxic metal ions, convert them into stable, water-soluble complexes and accelerate their removal from the body. This article reviews the physicochemical basis of chelation, the principal agents used in clinical practice, their role in modern medicine, the mechanisms by which they act, and the limitations that restrict their use. Chelators remain the cornerstone of treatment for heavy metal poisoning, transfusional iron overload, Wilson disease and internal radionuclide contamination. Their effectiveness, however, depends on selectivity, route of administration, timing and the metal burden in target tissues. Lack of selectivity, depletion of essential elements, organ toxicity and the absence of convincing evidence for many off-label indications are the main drawbacks. Rational use requires accurate diagnosis, laboratory monitoring and evidence-based indications.
Keywords: chelation therapy; chelating agents; heavy metals; iron overload; Wilson disease; oxidative stress.

Introduction

Metal ions take part in nearly every area of human biochemistry. Iron, copper, zinc, manganese and magnesium serve as enzyme cofactors, oxygen carriers and structural elements of proteins, yet the margin between sufficiency and harm is narrow for many of them. Non-essential metals such as lead, mercury, cadmium and arsenic have no physiological function and exert toxic effects even at low concentrations [1, 2]. Human exposure arises from mining, smelting, industrial emissions, agrochemicals, contaminated water and food, and traffic-related pollution. Regional studies in Uzbekistan, for example, have reported heavy metal levels in soils of the Surkhandarya and Namangan regions and of Karakalpakstan that exceed permissible norms, which points to the potential for these elements to enter the food chain and underlines the need for clinical preparedness for metal-related disease [3].

At the molecular level, toxic metals bind to sulfhydryl, carboxyl and phosphate groups of proteins and nucleic acids, displace essential metals from their sites, inhibit enzymes and promote the formation of reactive oxygen species, which leads to oxidative stress, mitochondrial dysfunction and cell death [4]. Because these processes depend on the free or

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loosely bound metal ion, a logical therapeutic approach is to capture the metal with a ligand that holds it more tightly than biological targets do. This idea underlies chelation therapy. The word chelate derives from the Greek term for a claw and entered chemistry in 1920; medical use developed rapidly during and after the Second World War, when dimercaprol was created as an antidote to arsenical war gases and edetate compounds were introduced for lead poisoning [1, 2]. The aim of this article is to summarise the fundamentals of chelation therapy, its significance in modern medicine, its mechanism of action and its main drawbacks

A chelator is a molecule that contains two or more donor atoms, usually oxygen, nitrogen or sulfur, which coordinate a single metal ion and form one or more closed rings. The number of donor atoms attached to the metal is called denticity. Bidentate, tridentate and hexadentate ligands, the last represented by EDTA and deferoxamine, surround the ion more completely than monodentate ligands, and five- and six-membered rings are the most stable. Compared with a set of separate monodentate ligands, a multidentate ligand forms a markedly more stable complex, because binding of the first donor atom brings the others into close proximity and because the release of several water molecules increases entropy. This phenomenon is known as the chelate effect [5].

Complex stability is expressed by the stability constant, but in a living system the relevant quantity is the effective affinity under physiological conditions, which depends on pH, on the concentration of competing ligands and on the presence of abundant metals such as calcium, magnesium and zinc [5, 6]. Selectivity follows the concept of hard and soft acids and bases. Hard ions such as Fe3+ prefer hard oxygen donors, for example the hydroxamate groups of deferoxamine, whereas soft ions such as Hg2+, Cd2+ and Pb2+ bind preferentially to sulfur donors, which explains the clinical value of dithiol compounds such as dimercaprol, succimer and unithiol [6]. An ideal therapeutic chelator should have high affinity and selectivity for the toxic metal, form a stable, non-toxic and readily excreted complex, reach the compartments in which the metal is stored, be effective by an acceptable route of administration, and show low toxicity and low affinity for essential metals [1, 6]. No existing agent meets all of these requirements, which is why treatment must be individualised.

Several groups of chelators are used in medicine today. They differ in donor groups, metal preference, solubility, route of administration and safety profile. The most important agents are summarised in Table 1. In severe lead encephalopathy dimercaprol is combined with CaNa2EDTA, and in severe cardiac siderosis deferoxamine may be combined with deferiprone, which illustrates how agents with complementary distribution can be used together [7, 10].

Table 1. Principal chelating agents, clinical targets and main limitations [1, 6–10].

Agent	Main clinical targets	Principal limitations
Dimercaprol (BAL)	Arsenic, inorganic mercury, gold; severe lead poisoning (with CaNa2EDTA)	Painful intramuscular injection, hypertension, tachycardia; unsuitable for cadmium and iron
CaNa2EDTA	Lead	Parenteral use, nephrotoxicity, zinc depletion; fatal hypocalcaemia if the disodium salt is used
Succimer (DMSA)	Lead, arsenic, mercury	Gastrointestinal upset, rash, transient rise of transaminases, zinc loss

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Unithiol (DMPS)	Mercury, arsenic	Hypersensitivity reactions, limited availability in some countries
D-Penicillamine, trientine	Copper in Wilson disease	Hypersensitivity, nephropathy and autoimmune reactions (penicillamine); copper deficiency if overtreated
Deferoxamine	Acute iron poisoning, transfusional iron overload	Prolonged parenteral infusion, poor adherence, ocular and auditory toxicity
Deferiprone, deferasirox	Transfusional iron overload	Agranulocytosis (deferiprone); renal, hepatic and gastrointestinal toxicity (deferasirox)
Ca-DTPA, Zn-DTPA	Plutonium, americium, curium	Depletion of zinc and other trace metals (Ca-DTPA); mainly extracellular action

Chelation is the treatment of choice for acute and chronic poisoning by lead, arsenic and inorganic mercury when exposure is confirmed and clinical or laboratory criteria are met [8, 9]. In children with markedly elevated blood lead concentrations, oral succimer has largely replaced parenteral regimens, while CaNa2EDTA retains a place in lead encephalopathy, usually after dimercaprol [10]. In arsenic and mercury poisoning, early treatment with dithiol chelators lowers body burden and relieves symptoms, although the evidence comes mainly from case series and animal data and the benefit declines as the delay before treatment grows [9].

Perhaps the greatest contribution of chelation to modern medicine is the management of transfusional iron overload in thalassaemia major, sickle cell disease and myelodysplastic syndromes. Humans have no physiological pathway for iron excretion, so every transfused unit of red cells adds iron that deposits in the liver, heart and endocrine glands, where redox-active iron catalyses the formation of hydroxyl radicals through the Fenton reaction. The introduction of deferoxamine and later of the oral agents deferiprone and deferasirox has considerably improved survival and reduced cardiac and endocrine complications in these patients [7]. In Wilson disease, a genetic defect of biliary copper excretion leads to copper accumulation in the liver and brain; lifelong therapy with D-penicillamine or trientine promotes urinary copper excretion, and zinc salts are used to reduce intestinal copper absorption. Diethylenetriaminepentaacetic acid (DTPA) salts are used for decorporation of plutonium, americium and curium after internal contamination [1].

Chelation is also being explored beyond classical toxicology. Because iron and copper catalyse oxidative damage, chelators and chelator–antioxidant combinations are investigated in neurodegenerative, cardiovascular and oncological disease, and experimental work shows that combining a chelator with an antioxidant can improve the outcome of metal detoxification [11]. Natural products are a further direction: in a study from Uzbekistan, methanolic garlic extract reduced cadmium-induced changes in the reproductive organs and liver of female rats, and the authors proposed garlic as a possible adjunct to chelation therapy for cadmium toxicity [12]. Such findings are preliminary, come from animal models and require clinical confirmation. The best-known test of chelation outside toxicology, the Trial to Assess Chelation Therapy (TACT), found that a multicomponent EDTA-based infusion regimen produced a modest reduction in cardiovascular events in patients with a previous myocardial infarction, with the

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benefit most evident among participants with diabetes. A high rate of treatment discontinuation and the lack of a clear mechanism mean that the trial generated a hypothesis rather than a recommendation for routine practice [13]

The action of a chelator can be described as a sequence of events. First, the agent reaches the compartment that contains the metal: plasma, extracellular fluid or, in the case of lipophilic agents such as deferiprone, the intracellular space. Second, it competes for the metal with endogenous ligands such as albumin, transferrin, metallothionein, glutathione and the active sites of enzymes, and the metal is transferred to the chelator when the resulting complex is favoured both thermodynamically and kinetically. Third, a water-soluble complex is formed in which the reactive coordination sites of the metal are shielded, so that it can no longer inhibit enzymes or catalyse radical reactions. Finally, the complex is eliminated, mainly by glomerular filtration and tubular secretion in urine and, for some agents, partly through bile and faeces [1, 2, 6].

The therapeutic effect therefore has three components: an increase in metal excretion, which reduces total body burden; interruption of continuing toxicity by sequestration of the free ion; and mobilisation of the metal from tissue stores, which is slow and explains the need for repeated courses. Highly polar chelators such as CaNa2EDTA and DTPA remain largely extracellular, which makes them effective against metal in blood and on bone surfaces but much less effective against intracellular and brain deposits. Lipophilic agents, including dimercaprol and deferiprone, enter cells and the nervous system more readily, which is an advantage for intracellular iron but also carries a risk of redistribution of a toxic metal into sensitive tissues [1, 6]. Chelators also act indirectly: by removing redox-active iron and copper they interrupt Fenton-type reactions and lipid peroxidation, and by relieving inhibition of thiol-dependent enzymes such as δ-aminolevulinic acid dehydratase, which is blocked by lead, they allow partial normalisation of haem synthesis [4, 11]

The first limitation is incomplete selectivity. Most chelators bind several metals, and CaNa2EDTA, succimer, unithiol, DTPA and penicillamine increase the urinary excretion of zinc, copper and other essential elements. Prolonged courses can therefore cause deficiency that impairs enzyme function and immunity, so mineral status needs monitoring and in some regimens supplementation [1, 2]. Disodium EDTA, which, unlike the calcium salt, binds plasma calcium, has caused fatal hypocalcaemia and must never be substituted for CaNa2EDTA [2].

The second limitation is toxicity of the agents themselves. Examples are nephrotoxicity of EDTA, painful injections and hypertension with dimercaprol, hypersensitivity and autoimmune syndromes with penicillamine, neutropenia and agranulocytosis with deferiprone, and renal, hepatic and gastrointestinal toxicity with deferasirox. Deferoxamine requires prolonged parenteral infusion, which reduces adherence, and may damage vision and hearing [1, 7]. Dimercaprol is contraindicated in cadmium poisoning because its complex with cadmium increases renal injury [1].

The third limitation concerns efficacy. Chelators remove metal that is accessible, whereas metal fixed in bone, brain or intracellular compartments is mobilised only slowly. In children with moderate blood lead concentrations, succimer lowered blood lead but did not improve neuropsychological outcomes, which shows that reducing a laboratory value is not the same as reversing established damage [10, 14]. Treatment is most useful when started early, guided by a confirmed exposure and appropriate testing, and it does not replace removal of the source of exposure. Outside accepted indications, chelation has been promoted for conditions such as

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autism, atherosclerosis and chronic fatigue without convincing evidence, and deaths from misuse have been reported. Urine collected after a provoking dose of a chelator gives misleadingly high metal values and should not be used for diagnosis [2].

Safe chelation depends on a sequence of clinical decisions. The first is confirmation of exposure and of its clinical significance, which relies on appropriate biological samples such as whole blood for lead, 24-hour urine for arsenic and mercury, and serum ferritin, liver iron concentration and cardiac magnetic resonance for iron overload, rather than on empirical treatment. The second is the choice of agent and route according to the metal, the severity of poisoning and the age and renal function of the patient. The third is monitoring during treatment, which includes renal and hepatic function, blood counts, urinary and serum levels of essential elements and, where relevant, the metal concentration itself, so that the course can be stopped when the burden has fallen or toxicity appears [1, 6, 9].

Research is now directed towards agents with greater selectivity, better oral bioavailability and the ability to cross the blood–brain barrier, as well as towards macromolecular and nanoparticle-based chelators that stay in the circulation longer and may be less likely to remove essential metals [2, 7]. Another promising line is combination therapy, in which two chelators with different tissue distribution or a chelator and an antioxidant are used together to remove metal from several compartments while limiting oxidative injury [7, 11]. Environmental data from Uzbekistan and other regions that show soil contamination by lead, cadmium and zinc suggest that prevention, biomonitoring and early recognition of exposure will remain at least as important as treatment [3]

Chelation therapy rests on sound coordination chemistry: a ligand with high affinity for a particular metal converts it into a stable, excretable complex and prevents it from damaging biological targets. This principle has produced effective treatments for heavy metal poisoning, iron overload, Wilson disease and radionuclide contamination, and it remains an active field of research that includes antioxidant combinations and natural adjuncts. At the same time, lack of selectivity, loss of essential elements, toxicity, route of administration and limited access to intracellular and cerebral metal pools restrict its use, and evidence for many proposed indications is weak. Chelators should therefore be prescribed only for established indications, under laboratory control and together with elimination of the source of exposure, while the development of more selective, less toxic and orally active agents remains an important direction for future work.

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