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Review

Kill or cure: Misuse of chelation therapy for human diseases

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ABSTRACT

Chelation therapy is a consolidated medical procedure used primarily to reduce the toxic effects of metal ions on human tissues. Its application spans a broad spectrum of disorders, ranging from acute metal intoxication to genetic metal-overload. The use of chelating agents is compromised by a number of serious side effects, mainly attributable to perturbed equilibrium of essential metal ion homeostasis and dislocation of complexed metal ions to dangerous body sites. For this reason, chelation therapy has been limited to specific critical and otherwise untreatable conditions and needs to be monitored within an appropriate clinical context. The aim of this review is to discuss how this "false chelation therapy" developed and in which diseases it is currently applied.

1. Introduction

Chelation therapy (CT) is a consolidated medical procedure used primarily to reduce the toxic effects of metal ions in humans. Current treatment approaches have different mechanisms of action depending upon what occurs after complexing of the targeted metal ions: the complexed metal can be removed from the organism or it can be dislocated to tissues where it does not exert any toxic action or, alternatively, to where its toxic effects can be attenuated through the formation of complexes. Chelating agents embrace a broad spectrum of applications, ranging from acute intoxication and chronic toxicity deriving from occupational, environmental and even iatrogenic causes to the metal toxicity observed in certain genetic diseases. However, their use is constellated by a number of potentially serious side effects, mainly attributable to an imbalance in essential metal ion homeostasis. This disequilibrium depends upon a variety of interrelated factors that are extremely hard to control. Nevertheless, when used in a

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AMA, American Medical Association; CAD, coronary artery disease; CT, chelation therapy; DFO, desferal; DMPS, 2,3-dimercapto-1-propanesulfonic acid; DMSA, meso-2,3-dimercaptosuccinic acid; EDTA, ethylene diaminetetraacetic acid; FDA, Food and Drug Administration; MI, myocardial infarction; NIH, National Institute of Health; TACT, Trial to Assess Chelation Therapy.

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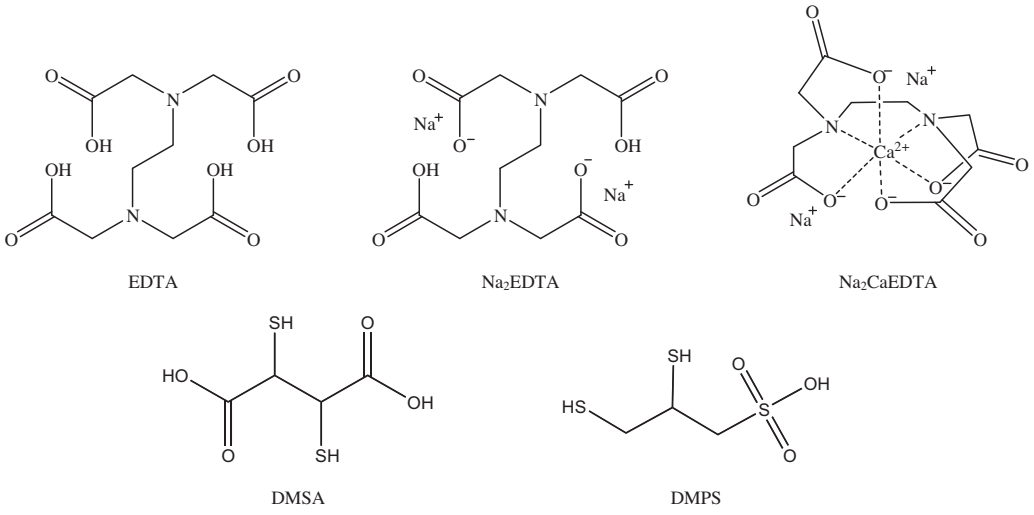

Scheme 1. Structure of EDTA and of its two most used salts, and of DMSA and DMPS.

controlled clinical setting, CT has proven to be an invaluable tool in solving a wide range of clinical problems [1–11]. Desferal (DFO) for the treatment of blood transfused β-thalassemia patients represents the most unequivocal success. Indeed, this drug, has led to dramatic improvements in the quality of life and overall life expectancy of thalassemia patients. According to Bernhardt [12] "β-thalassemia patients now in their 50s who have undergone DFO chelation therapy since childhood are living proof of the value of this drug. Those afflicted with this disease prior to the emergence of DFO, or who have been unable to cope with the demands or cost of DFO therapy, have typically died in their teens".

Chelation therapy has been approved for systemic iron overload, lead poisoning and other metal toxicities. Several chelating agents have been approved for use in humans with each one having specific affinity for a given metal ion or set of metal ions. Despite the limited approved indications for the use of chelators, advertisements for the treatment of numerous other conditions can easily be found on the web. Although the advertised treatments have no scientific basis, they are proposed to the public in such an appealing way that it may be difficult to effectively counteract the phenomenon.

Many of these expensive, lengthy "treatments" are administered directly into the bloodstream in an office setting. Others are advertised for use at home. Purported uses include:

1. treating arteriopathies (in particular atherosclerosis) by removing calcium from arterial plaques;
2. treating intermittent claudication (painful leg cramps sometimes due to atherosclerosis);
3. curing or improving symptoms of autism;
4. preventing or curing neurodegenerative diseases and multiple sclerosis.

In all these cases, improvement up to full recovery is largely advertised on the basis of anecdotal patient reports. Unapproved use of chelation therapy has resulted in harm and even death. This is an unacceptable risk in the absence of a proven benefit. Several unapproved "chelators" are marketed for home use. The U.S. Food and Drug Administration (FDA) recently warned several companies that they are breaking the law by marketing such "therapies", reminding them that all approved chelating drugs require a prescription.

Based on the National Health Statistics Report published in 2007, the use of chelation has increased by 68% since 2002, passing from 66,000 to 111,000 adults using CT [13], most of whom with no clinical or laboratory indications for this kind of therapy. Overall, there appears to be a prevalence for the inappropriate use of chelation therapy in cardiovascular disease [14].

In our opinion, scientists with years of experience in these topics have both the duty and responsibility to warn the members of the scientific community of these facts and to provide them with precise and detailed information on the possible toxic effects of CT. The purpose of this review is to describe how "false chelation therapy" historically developed, and in which disorders CT is presumed to be effective, including coronary and peripheral arteriopathies and autism.

2. Coronary and peripheral arteriopathies

The first report of chelation therapy dates back to the early 1950s and describes the use of ethylenediaminetetraacetic acid (EDTA) (see Scheme 1) in patients affected by lead toxicity [15]. These preliminary findings prompted further investigation into the possible applications of EDTA. The apparent success of EDTA in reducing calcium deposits [16] led Clarke et al. [17] to use this chelator in patients affected by angina, and other authors to use it in various forms of atherosclerosis [18–20]. Subsequently, CT evolved to constitute infusions of disodium EDTA (a molecule that binds divalent and trivalent cations, including calcium, magnesium, lead, cadmium, zinc, iron, aluminum and copper and facilitates their excretion via the kidneys) and vitamins [20,21].[1]

Throughout the decades, despite the clear lack of scientific evidence in support of CT for vascular diseases and the mounting opposition of Health and Medical Associations, chelation practitioners have increasingly used EDTA for the treatment of coronary and peripheral arteriopathies on the sole basis of favorable anecdotal case reports. They claim that EDTA chelation therapy is helpful against atherosclerosis, cardiac disease and peripheral vascular diseases, such as intermittent claudication. This has resulted in an extensive and inappropriate use of CT, aggravated by the fact that many patients have been led to consider this treatment approach a valid substitute for other well-recognized medical treatments. The

[1] This typical *Chelation therapy* includes a series of intravenous infusions of a solution containing 0.5 L sterile water, besides Na_2EDTA (3 g), $MgCl_2$ (2 g), KCl (2 mEquiv.) procaine HCl (0.100 g), ascorbate (7 g), $NaHCO_3$ (0.840 g), pantothenic acid (0.250 g), heparin (2500 units), thiamine (0.100 g) [22].