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Enhanced vasculotoxic metal excretion in post-myocardial infarction patients following a single edetate disodium-based infusion

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ABSTRACT

Toxic metals have been associated with cardiovascular mortality and morbidity. We have hypothesized that enhanced excretion of vasculotoxic metals might explain the positive results of the Trial to Assess Chelation Therapy (TACT). The purpose of this study was to determine whether a single infusion of the edetate disodium-based infusion used in TACT led to enhanced excretion of toxic metals known to be associated with cardiovascular events.

Methods: Twenty six patients (post-MI, age > 50 years, serum creatinine ≤ 2.0 mg/dL) were enrolled in this open-label study. Urinary levels of 20 toxic metals normalized to urinary creatinine concentrations were measured at baseline in overnight urine collections, for 6 h following a placebo infusion of 500 mL normal saline and 1.2% dextrose, and for 6 h following a 3 g edetate disodium-based infusion. Self-reported metal exposure, smoking status, food frequency, occupational history, drinking water source, housing and hobbies were collected at baseline by a metal exposure questionnaire.

Results: The mean age was 65 years (range 51–81 years). All patients were male. 50% had diabetes mellitus and 58% were former smokers. Mean (SD) serum creatinine was 0.95 (0.31) mg/dL. Toxic metals were detected in the baseline urine of > 80% of patients. After placebo infusion there were no significant changes in total urinary metal levels. After edetate infusion, total urinary metal level increased by 71% compared to baseline (1500 vs. 2580 μg/g creatinine; P < 0.0001). The effect of edetate was particularly large for lead (3835% increase) and cadmium (633% increase).

Conclusions: Edetate disodium-based infusions markedly enhanced the urinary excretion of lead and cadmium, toxic metals with established epidemiologic evidence and mechanisms linking them to coronary and vascular events.

1. Introduction

This study was designed to explore one hypothesis proposed to explain the unexpectedly positive results of the Trial to Assess Chelation Therapy (TACT) (Lamas et al., 2013), that reduction in cardiovascular events in response to edetate disodium chelation may be related to enhanced excretion of vasculotoxic metals, particularly lead and cadmium. Environmental pollutants have long been thought to contribute to cardiovascular disease (Cosselman et al., 2015). In particular, there is a wealth of epidemiologic and mechanistic evidence linking lead and cadmium to the progression of atherosclerosis (Lustberg and Silbergeld, 2002; Menke et al., 2006; Navas-Acien et al., 2004; Weisskopf et al., 2009; Menke et al., 2009; Tellez-Plaza et al., 2008, 2012, 2013a; Navas-Acien et al., 2005; Revis et al., 1981; Agarwal et al., 2011a; Messner et al., 2009; Bergström et al., 2015; Aalbers and Houtman, 1985; Voors et al., 1982). For other toxic metals, the link to atherosclerosis is less robust (Nigra et al., 2016). Lead and cadmium are toxic divalent cations with no physiological role that are acquired from the environment via the respiratory or gastrointestinal tracts. After absorption, these metals are deposited in many tissues including bone and calcified tissues for lead, and liver, kidney, and the walls of arteries for cadmium. Neither lead nor cadmium can be readily eliminated, and both metals accumulate in the body with half-lives measured in decades. Ethylene diamine tetraacetic acid and its salts (e.g edetate disodium and edetate calcium disodium) are chelators able to avidly bind many cations with valences +2 to +6, forming stable soluble complexes, which can be

Abbreviations: TACT, Trial to Assess Chelation Therapy; edetate disodium, (disodium ethylenediamine tetra acetic acid, Na_2EDTA); FDA, Food and Drug Administrations; MI, Myocardial Infarction;; IND, Investigational New Drug; ICP- MS, Inductively Coupled Plasma Mass Spectrometry; CI, Confidence Interval; IQR, Interquartile Range; SD, Standard Deviation; MRI, Magnetic Resonance Imaging; NSF, Nephrogenic Systemic Fibrosis

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excreted in the urine. The Food and Drug Administration (FDA) has approved edetate calcium disodium to treat lead toxicity.

Clarke et al., in 1956, first reported a symptomatic benefit of edetate disodium in patients with atherosclerotic heart disease (Clarke et al., 1956). At that time, its beneficial effect was thought to be secondary to removal of calcium from the atherosclerotic plaque. Recently, TACT reported that in patients with a prior myocardial infarction (MI), an edetate disodium based infusion, compared with a placebo infusion, significantly reduced recurrent cardiovascular events (Lamas et al., 2013, 2014; Escolar et al., 2014). The hypothesis that edetate disodium enhanced vasculotoxic metal excretion in post-MI patients, however, has been untested.

In this study, we investigated the pattern of spontaneous (baseline) urinary excretion of twenty toxic metals in patients with a prior MI, and the effect on metal excretion of a single edetate disodium-based or placebo infusion identical to those used in TACT. We also investigated the association of urinary metal levels with lifestyle and food intake.

2. Methods

This was an unblinded cross sectional study evaluating the urinary excretion of 20 toxic metals (aluminum, arsenic, barium, beryllium, bismuth, cadmium, lead, gadolinium, mercury, nickel, platinum, palladium, antimony, tin, thallium, cesium, tellurium, thorium, tungsten and uranium) at baseline (spontaneous metal excretion), after a TACT placebo infusion, and after a TACT active (edetate disodium-based) infusion (Lamas et al., 2012). The placebo and TACT infusions were administered on consecutive days. Arsenic levels represent total non-speciated arsenic. All patients provided written informed consent and an institutional review board approved the final protocol and provided ongoing oversight. This study was performed under a US Food and Drug Administration Investigational New Drug (IND) application.

Patients were recruited from outpatient cardiology clinics. Inclusion and exclusion criteria precisely mimicked the TACT criteria (Appendix), as the purpose of this study was to assess the effect of the infusions on TACT-eligible patients. Participants were at least 50 years of age with a history of myocardial infarction at least 6 weeks prior to enrollment and serum creatinine $\leq$ 2.0 mg/dL. Patients were excluded if they had a platelet count less than 100,000/mm^3, a recent heart failure hospitalization, a recent coronary or carotid revascularization or a planned revascularization procedure. Cigarette smoking in the previous 3 months, prior chelation therapy (within 5 years), abnormal liver function and diseases of copper, iron or calcium metabolism were also exclusion criteria. A complete list of inclusion and exclusion criteria has been published (Lamas et al., 2012) and is reproduced in the Supplementary table.

The edetate disodium based infusion consisted of up to 3 g of Na_2-EDTA, 2 g of magnesium chloride, 100 mg of procaine HCL, 2500 U of unfractionated heparin, 7 g of ascorbate, 2 mEq KCl, 840 mg sodium bicarbonate, 250 mg of pantothenic acid, 100 mg of thiamine, and 100 mg of pyridoxine. The vitamin and other components of the edetate disodium-based solution developed organically in the complementary and alternative medicine community, and were used in TACT to reflect typical practice (Lamas et al., 2012). All components were mixed with sterile water to a volume of 500 mL. The placebo infusion consisted of 500 mL of normal saline with 1.2% dextrose. All infusions were administered over 3 h.

Blood counts, lipid profile, hemoglobin A1c and creatinine concentrations were measured in venous blood in all participants before the first urine collection. Urine samples were collected in trace metal free containers provided by the metals laboratory and sent to Doctor's Data Inc, (St. Charles IL), for elemental testing. Urine samples were tested for creatinine using a kinetic modification of the Jaffe procedure on a Beckman Coulter AU680. Samples were prepared for elemental analysis by diluting the sample in dilute nitric acid, based on creatinine concentration (Shah et al., 2012). The urine sample was analyzed for trace elements using an Inductively Coupled Plasma – Mass Spectrometer (ICP-MS; Perkin Elmer Elan DRCII). Elemental concentrations are reported controlled for creatinine concentration. Quality was assured by measuring three levels of Bio-rad controls and in-house spiked samples.

A 3-day study protocol was followed. On day 1, patients were asked to collect all overnight urine. On day 2, patients were given the placebo infusion and asked to collect post-infusion urine for 6 h. On day 3, patients were given the TACT active infusion and post-infusion urine was also collected for 6 h. For baseline urine collections, patients were instructed to collect all urine from 10:00 p.m. on day 1–6:00 a.m. on day 2, so that the morning void prior to placebo infusion was the final pre-infusion collection. For urine collections after placebo or edetate disodium infusions (days 2 and 3, respectively), patients were instructed to collect all urine for 6 h after receiving the infusion.

Self-reported metal exposure, smoking status, food frequency, occupational history, drinking water source, housing and hobbies were collected via questionnaire (see Supplementary information). Patients were enrolled at Mount Sinai Medical Center in Miami Beach, FL and all lived within easy driving distance of Miami Beach. Telephone follow-up was conducted one week after active chelation infusion to assess patient condition and record any adverse events.

2.1. Statistical methods

Urinary metal levels were expressed as μg metal/g of creatinine. Values under the limit of detection were replaced by the lower limit of detection provided by the laboratory (Appendix: Supplementary table) divided by the square root of two. Logarithmic transformation was applied given the skewed distribution of metals. Geometric means and their 95% confidence intervals (CI) were calculated. Spearman's rank test was used to investigate correlations within and between metals in baseline and/or post EDTA urine. Non-parametric tests (Wilcoxon rank test, Kruskal-Wallis Test) were used to compare urinary levels of metals before and after treatment with placebo or edetate disodium infusions, and to test the association of lifestyle with baseline and post-infusion urinary metal levels. Given the small sample size, only unadjusted comparisons were calculated. The Supplementary figure shows the distribution of metals in baseline and post EDTA urine after log transformation.

3. Results

3.1. Patient characteristics

We enrolled 26 adult male (Table 1), mostly Hispanic (73%) patients who lived a median 16 miles (IQR 13) away from the main campus of Mount Sinai Medical center in Miami Beach. Mean (SD) urinary creatinine was 79 (26) at baseline, 87 (39) post-placebo and 81 (38) mg/dl post-EDTA ($P > 0.05$, for all comparisons), respectively. No

Table 1
Baseline characteristics[a].

Age (years)	65 (9)
History of diabetes (%)	50
Smoking history (%)	58
Prior CABG (%)	50
Prior PCI (%)	65
LVEF %[c]	45 (12)
Serum creatinine (mg/dl)	0.95 (0.31)
eCrCl[b] (mL/min)	105 (49)
HbA1c %	6.8 (1.9)
Total cholesterol	170 (53)

[a] Results represent mean (SD) unless otherwise indicated.
[b] Cockcroft-Gault method.
[c] Last left ventricular ejection fraction (LVEF) known.