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An assessment of exposure to rare earth elements among patients receiving long-term parenteral nutrition

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ABSTRACT

Patients receiving long-term parenteral nutrition (PN) are exposed to potentially toxic elements, which may accumulate in bone. Bone samples collected from seven PN patients (average = 14 years) and eighteen hip/knee samples were analyzed for Al as part of a previous investigation. Yttrium was serendipitously detected in the PN bone samples, leading to the present investigation of rare earth elements (REEs). A method for quantitating fifteen REEs in digested bone was developed based on tandem ICP-MS (ICP-MS/MS) to resolve spectral interferences. The method was validated against nine biological reference materials (RMs) for which assigned values were available for most REEs. Values found in two NIST bone SRMs (1400 Bone Ash and 1486 Bone Meal) compared favorably to those reported elsewhere. Method detection limits ranged from 0.9 ng g^{-1} (Tm) to 5.8 ng g^{-1} (Y). Median REE values in the PN patient group were at least fifteen times higher than the "control" group, and exceeded all previously reported data for eleven REEs in human bones. REE content in PN bones normalized to the Earth's upper crust revealed anomalies for Gd in two patients, likely from exposure to Gd-containing contrast agents used in MRI studies. A retrospective review of the medical record for one patient revealed an almost certain case of nephrogenic systemic fibrosis, associated with Gd exposure. Analysis of two current PN formulations showed traces of REEs with relative abundances similar to those found in the PN bones, providing convincing evidence that PN solutions were the primary source of REEs in this population.

1. Introduction

Long-term parental nutrition (PN) therapy is a treatment that allows patients with chronic gastrointestinal (GI) insufficiencies (*e.g.*, extreme short bowel due to mesenteric infarction or Crohn's disease) to receive essential nutrients intravenously *via* individually formulated solutions, thereby extending and improving patient quality of life. In healthy individuals, the GI tract largely regulates the extent to which essential compounds are (or are not) absorbed, acting as a protective barrier. However, nutrient infusion leads to direct delivery into the blood compartment – irrespective of whether a constituent is essential or not, and without regard to the current body status of the substance. To address this unique issue, some toxic contaminants (*e.g.*, Pb and Al) are regulated in PN solutions. However, these patients are clearly at risk for accumulation of other contaminants present in the PN solutions.

One of the most-studied contaminants of PN solutions is Al – a bone-seeking element, ubiquitous in the environment, and a known toxicant. In addition to being a recognized cause of dialysis dementia [1], Al has been associated with metabolic bone diseases, which affect 42–100% of long-term PN patients [2–13]. In the past, a major source of Al to PN patients was a byproduct of protein hydrolysis, however this ceased when amino acid solutions replaced hydrolysates in the 1970s. In 1997, Bishop et al. compared preterm infants receiving a standard neonatal PN solution to those that received an Al-depleted PN solution and reported a significant delay in neurological function among the former [14]. In 2004, the U.S. Food and Drug Administration (FDA) issued mandates to address Al contamination in PN solutions. Despite the discontinuation of protein hydrolysate solutions, Al accumulation still occurs from contaminated salts and thus Al toxicity remains a serious concern in this group [13,15–17].

Bone is a known repository for many non-essential elements besides Al (*e.g.* Pb, Sr) [18], and access to human bone samples from a group of

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seven patients on long-term PN provided a unique opportunity to study the elemental composition in this vulnerable population. The serendipitous discovery of the element yttrium (Y) in one of the PN patient bone samples led us to ask the question: were other rare earth elements (REEs) present in these bone samples, and if so, were the levels similar to those reported for other human populations?

The REEs occur naturally in the environment, and include the group 3 elements: Yttrium (Y) and Lanthanum (La), and the thirteen elements of the lanthanide series: Cerium (Ce), Praseodymium (Pr), Neodymium (Nd), Samarium (Sm), Europium (Eu), Gadolinium (Gd), Terbium (Tb), Dysprosium (Dy), Holmium (Ho), Erbium (Er), Thulium (Tm), Ytterbium (Yb) and Lutetium (Lu). As important materials in the manufacturing of glasses, ceramics, magnets, electronics, superconductors, and lasers [19], the use of REEs in industry has increased dramatically in the last three decades. In China, REEs are added to fertilizers, reportedly to increase the yield of crops [20,21]. In medicine, La is administered orally as a phosphate binder for patients with renal impairment [22], Gd-based contrast agents are used in some MRI studies [23], and Ce has been investigated as a topical antiseptic for burn victims [24]. Clearly, industrial uses of REEs are increasing on a global scale, and their potential to affect human health is an emerging concern.

Even though the REEs are documented Ca^{2+} antagonists and have a high affinity to bind to phosphates [23], few studies have examined their accumulation in the human skeleton. Two prior studies focused on Gd accumulation following exposure to two Gd-based contrast agents [25,26]; others have measured the larger REE suite [27–29]. The determination of REEs in bone presents a major analytical challenge due to an absence of bone certified reference materials, and major interferences in inorganic mass spectrometry. The primary goals of this work were 1.) to investigate REEs in a group of seven long-term PN patients using a validated analytical method based on inorganic mass spectrometry; and 2.) to explore possible sources of REEs in the PN patients.

2. Experimental

2.1. Human bone sample collection

Bone samples were collected at autopsy from seven long-term PN patients with approval from the Albany Medical College (AMC) Institutional Review Board (IRB), and archived at −80 °C. Trabecular bone samples were collected from all seven patients; in addition, a cortical bone sample was harvested from Patient 2. Characteristics of the patients have been previously described [17,30], and are summarized in Table 1. The patients had received PN for between 2 and 21 years (average = 14 years) and were managed by the home PN program at AMC throughout their treatment. For comparison purposes, trabecular bone samples were collected from eighteen age-comparable subjects, following hip/knee replacement surgery carried out at AMC; none of these “control” subjects had GI or renal impairments. All bone samples were de-identified before being transferred to the Wadsworth Center, New York State Department of Health (NYS DOH) for trace element measurements. Analysis of the bone samples was considered exempt by the NYS DOH IRB under category 4 of the pertinent U.S. federal regulations.

2.2. Instrumentation

Analysis of previously digested bone samples was conducted using an Agilent 8800 inductively coupled plasma tandem mass spectrometer (ICP-MS/MS), also referred to as a triple quadrupole (QQQ)-ICP-MS, (Agilent Technologies, New Castle, DE), equipped with an octopole reaction system (ORS) situated between two mass analyzing quadrupoles. A 200-μL min^{-1} MicroMist nebulizer (Glass Expansion, Pocasset, MA) and a Peltier cooled (2 °C) Scott double-pass spray chamber (Agilent Technologies, New Castle, DE) were used. Operating conditions for the ICP-MS/MS instrument and acquisition parameters for the REEs are listed in Table 2. Specific REE isotopes were selected so as to avoid the many isobaric interferences that can affect these elements, and to minimize potential polyatomic interferences *i.e.*, rare earth oxides. Gas mode settings were selected based on gas flow studies and were optimized for the fewest number of tune modes (n = 3) to minimize the acquisition time. Method performance parameters are summarized in Table 2.

2.3. Reagents and standards

A 100-mg L^{-1} multielement REE standard solution (GFS Chemicals, Inc., Columbus, OH, USA), traceable to the National Institute of Standards and Technology, (NIST) was used to calibrate the ICP-MS/MS instrument. An intermediate stock and the calibration standards were prepared fresh for each analysis in Nalgene polypropylene volumetric flasks (Thermo Fisher Scientific, Rochester, NY) and stored in 15-mL polypropylene conical centrifuge tubes (Thermo Fisher Scientific, Rochester, NY). The intermediate stock was prepared by diluting the REE standard stock solution 1 + 99. Eight working calibration standards ranging in concentration from 0.1 μg L^{-1} to 100 μg L^{-1} were prepared by diluting the intermediate stock solution appropriately. Matrix-matched calibration standards were prepared by combining the REE working standards with an aliquot of acid-digested bone reference material (NYS RM 05-04 Lead in Caprine Bone, Wadsworth Center, Albany, NY, USA), and diluting 1 + 24 with a reagent solution containing 2% (v/v) HNO_3, 1 μg L^{-1} Ir as an internal standard (single elements stock, GFS Chemicals, Inc., Columbus, OH, USA) and 0.005% (v/v) Triton X-100 (Baker Analyzed, Phillipsburg, NJ). The reagent solution was stored in acid-washed 2-L fluorinated ethylene propylene containers (GFS Chemicals, Inc., Columbus, OH, USA). All HNO_3 used in this work was double distilled in-house from reagent grade acid using a DuoPUR Sub-boiling point Distillation System (Milestone Inc., Shelton, CT). Double de-ionized (DDI) (> 18 MΩ cm) water was produced using a NANOpure DIamond UV/UF water system (Barnstead International, Dubuque, IA).

2.4. Preparation of bone samples and reference materials

Preparation of the bone samples was adapted from a previously established procedure for trace element measurements in human bone [31], and was described previously [17]. Briefly, adhering tissue was removed from the bones using an ultra-pure tantalum knife. Bone samples were soaked overnight in 30% (v/v) H_2O_2 to remove blood

Table 1
Brief clinical description of the seven long-term PN patients.

Patient	Years Receiving PN	Age at Death	Diagnosis Leading to PN	Other Medical Notes
1	2	38	Bowel Ischemia	Liver Failure
2	10	72	Bowel Ischemia	Broncho pneumonia, kidney failure
3	12	29	Bowel Ischemia	Suspected opiate overdose, recurrent catheter sepsis, osteomyelitis
4	20	69	Bowel Ischemia	Catheter sepsis, chronic renal disease
5	20	77	Crohn’s disease	Cardiomypathy, congestive heart failure, hypertension
6	20	60	Crohn’s disease	Catheter sepsis, kidney failure
7	21	69	Crohn’s disease	Broncho pneumonia, cirrhosis, hepatitis C