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Selecting chelators for heavy metals: Integrating coordination chemistry with *in vivo* decorporation (*An intra-individual proof-of-concept study*)

Abstract

Purpose: To evaluate a proof-of-concept framework for selecting chelators for retained heavy metals by integrating coordination-chemistry criteria with directly measured in vivo decorporation, using gadolinium (Gd) as the principal model metal and lead (Pb), cadmium (Cd), and mercury (Hg) as secondary comparators.

Materials and methods: A 64-year-old White male who had received 15 gadolinium-based contrast agent (GBCA) administrations between 1989 and 2014, without symptoms attributable to gadolinium toxicity, underwent four consecutive chelation administrations approximately one month apart, in the following order: oral HOPO, oral DOTA, intravenous (iv) Ca-DTPA, and oral Emeramide. The agents represented chemically distinct ligand classes and delivery characteristics. Chelator performance was interpreted using metal-ligand stability, kinetic and physiological accessibility, ability to form the complex under physiological conditions, route of administration, and directly measured change in 24-hour urinary metal elimination. For each agent, urine was collected 1–2 days before chelation and beginning within 1 hour after administration. Twenty potentially toxic metals were measured; Gd, Pb, Cd, and Hg were selected as representative metals. A threefold or greater increase from pre- to post-chelation was considered substantial.

Results: Following iv Ca-DTPA, urinary Gd increased 164-fold, Pb 14.5-fold, Cd 20-fold, and Hg 4.1-fold. Following oral HOPO, urinary Gd increased 9.4-fold and Hg 5.1-fold. Oral DOTA and oral Emeramide produced no substantial increase in elimination of the four selected metals under the tested conditions.

Conclusions: The findings support a staged method for chelator selection in which coordination chemistry identifies plausible candidates, but physiologically feasible complex formation and actual in vivo decorporation must also be demonstrated. In this enriched intra-individual model, iv Ca-DTPA produced the greatest removal of Gd, Pb, and Cd, whereas oral HOPO increased removal of Gd and Hg. The high retained-Gd burden amplified the urinary Gd signal and provided a sensitive test of the selection framework. Although Gd was the principal model metal, the methodology is potentially generalizable to other retained heavy metals and warrants evaluation in larger controlled studies.

Keywords: chelation, heavy metals, gadolinium, DTPA, coordination chemistry, decorporation

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Introduction

Selecting a chelator for a retained heavy metal is fundamentally a coordination-chemistry problem that requires biological validation. An intrinsic log stability constant describes thermodynamic favorability under defined experimental conditions, but does not by itself establish effective chelation in vivo. Rational selection should also consider conditional stability at physiological pH, donor-atom chemistry and coordination geometry, kinetic accessibility, competition from endogenous ligands, and the ability to form and retain the metal complex under physiological conditions.[1,2] Route of administration, absorption when relevant, tissue distribution, and renal or hepatobiliary elimination then determine whether favorable chemistry becomes useful decorporation.

Gadolinium provides an unusually informative model because GBCAs are deliberately engineered metal-ligand complexes whose safety depends on coordination chemistry. Chelation of retained Gd represents the reverse task: a ligand must access retained Gd, compete with its biological binding environment or capture Gd released from that environment, retain the metal during transport, and carry it to elimination. Intravenous Ca- and Zn-DTPA have increased removal of retained Gd ,[3–5] and iv DTPA has also increased urinary elimination of naturally accumulated Pb, Cd, and Hg in volunteers.[6] Gd therefore provides both a target metal and a useful model for developing a more general approach to chelator selection.

This intra-individual proof-of-concept study compared iv Ca-DTPA with oral HOPO, DOTA, and Emeramide using standardized pre- and post-chelation 24-hour urine measurements for Gd, Pb, Cd, and Hg. Multiple prior GBCA administrations created an enriched retained-Gd model intended to magnify differences among agents. The objective was not simply to rank four chelators, but to test a staged framework integrating coordination-chemistry plausibility, physiological feasibility, and directly demonstrated in vivo decorporation, thereby identifying principles and agents suitable for larger comparative studies.

Materials and methods

The participant was a 64-year-old White male who had received 15 GBCA administrations involving multiple linear and macrocyclic

agents between 1989 and 2014 but had experienced no symptoms attributable to gadolinium toxicity, a clinical profile consistent with Gadolinium Storage Condition.[7] This combination of high cumulative GBCA exposure and absence of symptomatic toxicity was intentionally used as an enriched, information-rich screening phenotype. The presumed larger retained-Gd pool was expected to increase the analytical signal and magnify differences among chelators. Four consecutive chelation administrations were performed approximately one month apart, in the following order: oral HOPO, oral DOTA, iv Ca-DTPA, and oral Emeramide. The interval between administrations was intended to reduce carryover from depletion of more accessible Gd reservoirs and to permit re-equilibration based on Le Chatelier's principle.[8]

For this proof-of-concept analysis, chelator performance was interpreted across three domains. First, chemical plausibility included the known metal-ligand affinity, donor set, denticity and coordination geometry, and available thermodynamic or conditional stability information. Second, physiological feasibility included kinetic accessibility, competition from endogenous ligands, route and absorption, distribution, and the ability to form the complex under physiological conditions. Third, functional validation required a measurable increase in metal elimination after chelator administration. Urinary decorporation was used as the common functional endpoint in this study; for agents with substantial hepatobiliary elimination, stool measurements would also be needed to estimate total decorporation.

HOPO is an oral medication that chelates the f-block elements of the periodic table, including Gd but in theory does not chelate any essential ions, including iron, zinc, and calcium.[9] In preclinical studies, it chelates and promotes the removal of a wide range of heavy metals from the body. These include lead, cadmium, tin, and most lanthanide and actinide elements. The reported stability constant with Gd ranges from 20.1 to 20.3.[10–12] The stability of these complexes is thought to arise from the strong bonds formed between the oxophilic Gd^{3+} center and the Lewis basic oxygen donor atoms.[13] HOPO (Fandachem, China) was administered orally at 800 mg as a powder mixed in 30 mL of extra virgin olive oil, followed by 60 mL of the same olive oil, in a fasting state.

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is a cyclen-based chelator used as a supplement, with a reported stability constant for Gd of 25.6[14,15] and a conditional stability of 19.1.[10–12] Dotarem/Clariscan uses the DOTA ligand, and DOTA-based complexes are also used in positron emission tomography and targeted cancer therapies. Importantly, the high final thermodynamic stability of a macrocyclic Gd-DOTA complex does not establish that uncomplexed DOTA will rapidly access retained Gd and form that complex in vivo; DOTA complex formation proceeds through kinetically controlled steps and intermediates.[15] DOTA (Fisher Scientific, USA) was administered orally in six capsules totaling 600 mg with 130 mL of filtered tap water in the fasting state.

The calcium (Ca) and zinc (Zn) salts of DTPA (diethylenetriaminepentaacetic acid) are chelating agents administered intravenously to treat internal contamination with actinides, including americium, curium, and plutonium.[16] DTPA has a reported thermodynamic stability of 22.46[17,18] and a conditional stability of 20.4[10–12] for Gd. As an open-chain aminopolycarboxylate, DTPA can exchange Ca or Zn for metals with greater binding affinity and form complexes that are cleared predominantly in urine. Human post-chelation urinary data provide direct evidence that iv DTPA can capture and increase elimination of retained Gd and several other metals.[3–6] Intravenous Ca-DTPA (Hameln, Germany) was administered as a 1,000-mg dose (5 mL) by rapid hand push in normal saline, approximating the standard GBCA injection rate used in MRI studies. Emeramide is a thiol-redox antioxidant and a heavy metal chelator.[19] Emeramide is created as a carboxyl benzoate compound with two cysteamine arms (located on the terminal end of Co-enzyme A). Emeramide has also been termed Oxidative Stress Relief (OSR). Presently, it is available as an Investigative New Drug (IND) in the USA. To our knowledge, thermodynamic stability and conditional stability for Gd and other heavy metals are unknown. Emeramide (Fandachem, China) was administered at 1,000 mg in 6 capsules with 30 mL of peanut butter in the fasting state.

Pre-chelation 24-hour urine collection (native elimination) began at 9:00 am after the overnight urination and ended at 9:00 am the following day, including the subsequent overnight urine. Samples were processed according to the testing laboratory's instructions (Doctor's Data, St. Charles, IL, USA) and shipped by 2-day delivery. The identical procedure was used for all chelators. The laboratory measured a panel of 20 metals, including Gd, Pb, Cd, and Hg, using inductively coupled plasma mass spectrometry after acid digestion. Results were reported as µg/24 h. Post-chelation collection began after the first post-chelation urination, within 1 hour after administration. The immediate post-chelation urine was excluded because it had largely formed before chelator administration. Post-chelation results were divided by native values to calculate the fold increase in elimination.

Results

The history of GBCA administration was as follows: Magnevist® (linear agent), 2 doses (0.1 mmol/kg each administration) 1989 - 1990; Omniscan® (linear agent), 3 doses (0.1 mmol/kg each administration) 1993 - 2002; Optimark® (linear agent), 1 dose (0.1 mmol/kg) 2001; MultiHance® (linear agent), 4 doses (0.1 mmol/ kg each administration) 2007- 2014; Ablavar® (linear agent), 1 dose (0.1 mmol/kg) 2009; Gadavist® (macrocycle agent), 2 doses (0.1 mmol/kg each administration) 2012, 2014; and Dotarem® (macrocycle agent), 2 doses (0.1 mmol/kg) 2013, 2014. Reasons for GBCA administration included testing new GBCA agents for adverse effects and imaging properties and testing novel organ imaging sequences or regimens. No study was performed for a diagnostic indication. No noteworthy history of other heavy metal exposures was present.

Table 1 presents the pre- and post-chelation Gd, Pb, Cd, and Hg values for the four chelators. Figure 1 provides a graphical representation. Figure 2 shows the Doctor's Data reports for pre- and post-chelation urine collections associated with iv Ca-DTPA, oral HOPO, oral DOTA, and oral Emeramide. No serious adverse effects occurred with any chelator. Prolonged gastric upset after HOPO was interpreted as secondary to the volume of olive oil consumed with the agent. There was no post-chelation heavy-metal removal flare and no heavy-metal re-equilibration flare.[5]

Table 1 The analysis of urinary elements (24-Hour Collections) was performed by ICP-Mass spectroscopy.

		Hopo	Dota	DTPA	Emeramide	Variation Hopo	Variation Dota	Variation DTPA	Variation Emeramide
Gd	Gd Pre	0.32	0.27	0.14	0.47	9.4x	0.9x	164x	0.6x
	Gd Post	3	0.24	23	0.28				
Pb	Pb Pre	0.43	0.42	0.6	0.53	0.9x	0.9x	14.5x	0.7x
	Pb Post	0.4	0.4	8.7	0.38				
Cd	Cd Pre	0.17	0.15	0.12	0.27	0.6x	0.8x	20x	0.5x
	Cd Post	0.1	0.12	2.4	0.14				
Hg	Hg Pre	0.13	0.39	0.07	0.23	5.1x	0.5x	4.1x	0.9x
	Hg Post	0.66	0.21	0.28	0.2				

Pre- and post-provocation (chelation) were reported as µg/24 h.

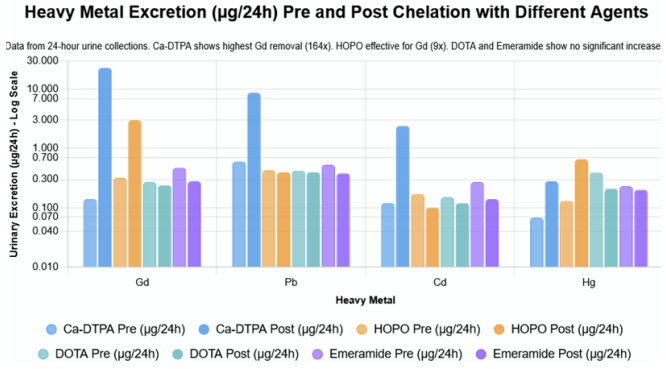

Figure 1 Heavy metal excretion (µ/24h) pre and post chelation with different agents.

The analysis of urinary elements (24-Hour Collections) was performed by ICP-Mass spectroscopy.

Pre- and post-provocation (chelation) were reported as µg/24 h.

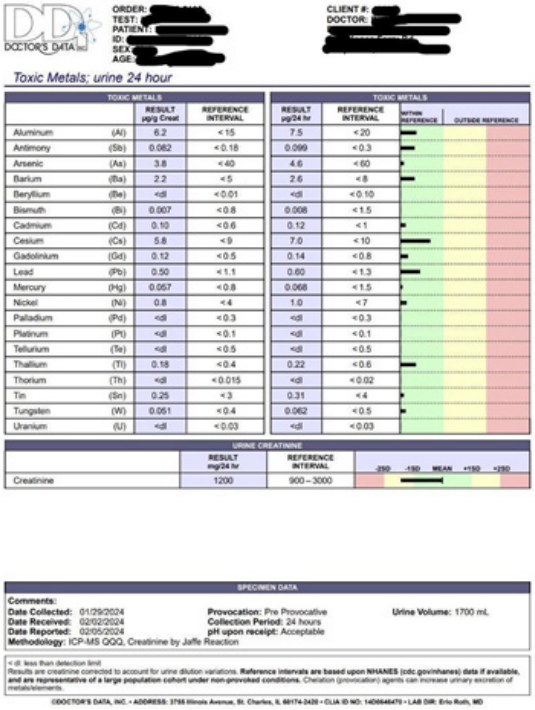

Figure 2A (Pre-provocation).

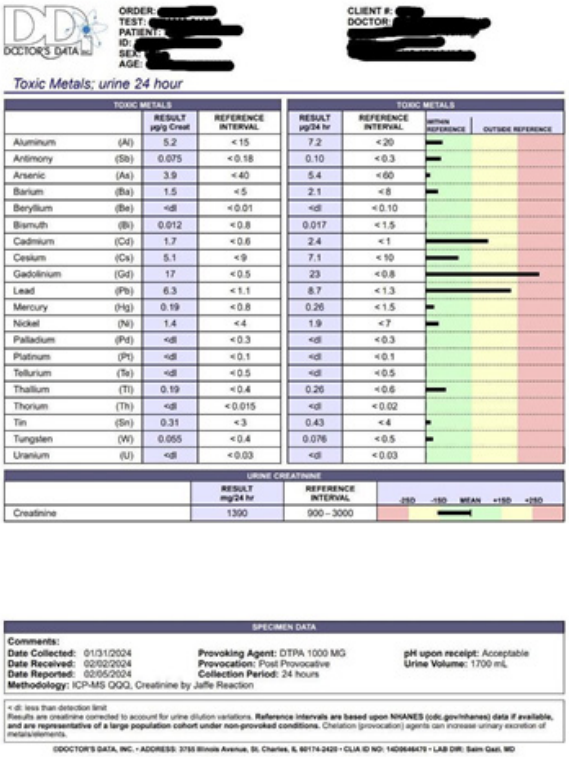

Figure 2B (Post-provocation).

Discussion

This proof-of-concept study demonstrated marked differences in metal removal among the four chelators, but its broader purpose is methodological. Iv Ca-DTPA produced by far the greatest urinary removal of Gd, Pb, and Cd and also increased Hg elimination. HOPO was the only oral agent producing substantial removal of Gd and Hg, whereas oral DOTA and Emeramide produced no substantial increase for the four selected metals. The central implication is that chemical plausibility alone is insufficient: a candidate must also demonstrate effective in vivo metal capture and elimination.

The first stage of chelator selection is coordination chemistry. Metal-ligand affinity, donor-atom matching, denticity and geometry, intrinsic and conditional stability, and kinetic behavior determine whether a candidate is chemically plausible. Stability constants are specific to individual chelator-metal pairs and should not be generalized between metals.[18] They are equilibrium descriptors measured under

defined conditions and do not represent the entire biological process. Thus, a high stability constant can narrow candidate selection but cannot alone identify the best in vivo chelator.

The second stage is physiological feasibility. A ligand must reach the relevant reservoir, gain kinetic access to the metal, compete with endogenous ligands, form the new complex within a biologically relevant time, retain the metal during transport, and reach an elimination pathway. These requirements are summarized by the phrase "ability to form the complex under physiological conditions." DOTA illustrates the distinction: although Gd-DOTA has very high thermodynamic stability, oral DOTA produced no substantial increase in urinary Gd under the formulation and dose tested. This does not establish intrinsic inability to bind Gd; gastrointestinal delivery, distribution, kinetic accessibility, or slow complex-formation kinetics may have limited performance. In contrast, iv Ca-DTPA increased urinary Gd 164-fold, while HOPO produced a smaller but clear Gd signal.

The third stage is functional validation by decorporation. Increased excretion after chelator administration shows that the sequence of access, binding, transport, and elimination has occurred. Standardized pre- and post-chelation 24-hour urine collections provide a practical integrated endpoint for predominantly renally eliminated complexes and avoid reliance on a single serum concentration. Urinary decorporation does not equal total-body burden and does not quantify the fraction removed from durable reservoirs, but it directly tests whether a candidate increases elimination under the studied conditions. Agents with substantial hepatobiliary elimination would also require fecal measurements.

Gadolinium is particularly useful for establishing this framework because exposure can often be reconstructed from known GBCA administrations and GBCA science already demonstrates the importance of metal-ligand stability and kinetics. The framework itself is not Gd-specific. Pb, Cd, Hg, actinides, and other metals differ in donor preferences, oxidation states, tissue reservoirs, endogenous competitors, and elimination pathways. Consistent with this metal specificity, Ca-DTPA generated the largest signals for Gd, Pb, and Cd, whereas HOPO generated the strongest Hg signal among the oral agents. Chelator selection should therefore proceed metal by metal rather than assuming that one chelator is optimal for all metals.

Safety is integral to this approach. Chelation may produce decorporation, redistribution without elimination, or subsequent re-equilibration. A chelator with insufficient affinity or kinetic persistence could transiently mobilize a metal and release it before elimination. This parallels GBCA design, in which the ligand must retain Gd during distribution and elimination;[13,20] lower-stability Gd complexes are more prone to Gd release, with relevance to nephrogenic systemic fibrosis and tissue deposition.[21–27] Decorporation requires the mirror image: capture retained metal, maintain the complex during transport, and minimize rerelease. EDTA was not included because early GBCA work demonstrated lower stability of Gd-EDTA than Gd-DTPA and related ligands.[28,29] Other candidates lacking sufficient coordination-chemistry assurance were likewise excluded from this asymptomatic volunteer study to reduce redistribution risk.

A further methodological point is enrichment of an initial comparative population for the property being measured. Subjects with little retained Gd may show only small post-chelation changes, obscuring differences among agents. The participant had received 15 prior GBCAs without Gd-attributable symptoms, consistent with Gadolinium Storage Condition,[7] and therefore provided an information-rich model for detecting a removal signal. Larger early-phase studies could similarly favor asymptomatic volunteers with multiple prior GBCA administrations before extending testing to individuals with lower retained-Gd burdens. Controlled volunteer DTPA studies have already demonstrated feasibility for naturally accumulated Pb, Cd, and Hg.[6]

The principal limitation is the single-participant, intra-individual design. Results apply only to the doses, formulations, routes, and timing tested and do not establish population-level efficacy. Failure of oral DOTA or Emeramide to increase Gd elimination does not prove that either compound is intrinsically ineffective; absorption, formulation, dose, kinetic accessibility, or physiological complex formation may have limited performance. The high cumulative GBCA exposure also means that the magnitude of Gd removal should not be extrapolated to individuals with fewer administrations, although this enrichment was advantageous for screening. A single post-chelation collection is not a measure of total-body burden and reflects only the accessible metal pool at that time. Larger studies should evaluate interindividual variability, dose-response, repeated dosing, route and formulation, longer-term reservoir depletion, and clinical outcomes.

This study supports a staged strategy for chelator evaluation:[1] use coordination chemistry to identify plausible metal-ligand pairs;[2] determine whether the candidate can access the metal and form a durable complex under physiological conditions; and[3] demonstrate actual in vivo decorporation before larger efficacy studies. Gd provides a sensitive proof-of-concept model, but the logic is potentially applicable to other heavy metals. The results therefore support a more rigorous method of chelator selection rather than a universal hierarchy of chelators.

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Conflict of interest

Authors declare that there is no conflict of interest.

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