Comparison of Gd(DTPA-BMA) (Omniscan) Versus Gd(HP-DO3A) (ProHance) Relative to Gadolinium Retention in Human Bone Tissue by Inductively Coupled Plasma Mass Spectroscopy

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Objective: The objective of this study was to determine the gadolinium (Gd) concentration remaining in human bone tissue after administration of standard clinical doses of 2 Gd-based contrast agents: ProHance and Omniscan.

Materials and Methods: After administration of 0.1 mmol/kg of Gd chelate to patients undergoing hip replacement surgery, bone specimens were collected and analyzed, and compared with an age-matched control population without a history of Gd chelate administration. Bone specimens were collected fresh, refrigerated, and subsequently frozen. After grinding and freeze-drying, tissue digestion was performed using Teflon bombs and concentrated nitric acid. A method for analysis of Gd in bone specimens was developed and validated using inductively coupled plasma mass spectroscopy (ICP-MS).

Results: Results were compared with a previous study using a different technique for analysis of the same tissue specimens. Tissue retention was 1.77 ± 0.704 μg Gd/g bone (n = 9) for Omniscan and 0.477 ± 0.271 μg Gd/g bone (n = 10) for ProHance measured by ICP-MS. These findings confirmed results from the previous ICP-AES study.

Conclusion: Omniscan (Gd[DTPA-BMA]) left approximately 4 times (previous study 2.5 times) more Gd behind in bone than did ProHance (Gd[HP-DO3A]).

Key Words: human bone, gadolinium retention, ICP-MS, GD(HP-DO3A), Gd(DTPA-BMA)

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The chemical structure of gadolinium (Gd) chelates used in clinical magnetic resonance imaging governs the kinetic lability of metal–ligand dissociation in vivo. Gd(DTPA-BMA), the active chelate in Omniscan, is a substituted open-chain chelate, which has lower thermodynamic stability (log Keq = 16.9, log K' [pH 7.4] = 14.9) than the macrocyclic compound Gd(HP-DO3A), the active ingredient in ProHance (log Keq = 23.8, log K' [pH 7.4] = 17.1).[1] Gd(DTPA-BMA) also has greater kinetic lability as a result of the relatively rigid and preorganized ring structure of HP-DO3A.[2,3] The fact that the Gd(DTPA-BMA) complex, but not Gd(HP-DO3A), is insufficiently stable to withstand competition from the ligand in a commonly used Ca testing kit is consistent with a weaker chelating agent and with other results reported here.[4]

Animal studies have shown increased Gd retention in free Gd repository tissues, especially bone, for the more labile Gd(DTPA-BMA) both as a chemical entity and as formulated for clinical use with 5 mol % excess DTPA-BMA.[5,6] Bone is a known natural repository for unchelated Gd and was shown to be so for injected free Gd and for Gd injected as relatively weaker chelates like $Gd(EDTA)^-$.[7] The retention of unchelated Gd ion may be important clinically, because Gd is not a naturally occurring biologic constituent and, once within the tissues of animals, persists for long periods of time.[1] It has significant toxicities, both in in vitro and in vivo experiments. For example, it is the most potent calcium antagonist known.[8–12] Gd has the potential of leeching into membranes, bone, and enzymatic structures, causing as-yet undetermined long-term consequences. Therefore, the release of Gd into the human body is of significant clinical interest, although no known long-term consequences of Gd retention have been reported.[13,14]

Only 4 human studies have attempted to validate the animal results. Weinmann and Huk analyzed surgical bone specimens (cranial) 1 to 21 days after $Gd(DTPA)^{2-}$ (Magnevist) administration using inductively coupled plasma mass spectroscopy (ICP-MS), finding 0.1 to 0.08 μg Gd/g dry weight in specimens versus <0.1 μg/g dry weight in separate untreated control specimens (ie, not statistically different).[15] Hattner reported observing spurious radiopharmaceutical ^{67}Ga scans (bone uptake) in patients receiving ^{67}Ga within 4 hours of a Magnevist clinical dose, suggesting that dechelated Gd occupied the natural Ga site in transferrin.[16] Gibby reported that dechelation of Gd(DTPA-BMA) in Omniscan but not Gd(HP-DO3A) in ProHance led to increased Zn in the patients' urine.[17] Finally, Gibby reported data on directly measured Gd in samples taken from surgical bone specimens

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removed from patients undergoing hip transplants after ProHance and Omniscan administrations. ICP-AES analysis showed that Omniscan deposited 2.5 times more Gd than ProHance.[18] However, trace levels (<2 μg Gd/g bone) were being analyzed using the ICP-AES technique, and a more sensitive method using ICP-MS could provide as much as 100 times lower quantitation limits.[19]

The study reported here was undertaken to analyze bone samples from hip replacement specimens with an eye toward confirmation of the previously reported Gibby finding. We used different samples of the original bone specimens used in the Gibby study, a GLP validated procedure, and a different, more sensitive analytical method (ICP-MS). No analytic validation data have been published to date on ICP-MS analysis of Gd in bone tissues. Therefore, complete analytic method parameters and validation data are published here. Stringent validation of the method, compliant with current ICH guidelines,[20] included determinations of range, specificity, selectivity, linearity, accuracy, precision (within run and between run), lower limit of quantitation (LLOQ), upper limit of quantitation (ULOQ), and robustness.

METHODS

Patients undergoing a total hip arthroplasty with removal of the femoral head were enrolled after informed consent. Omniscan or ProHance was injected intravenously at a dose of 0.1 mmol/kg not less than 3 days and not more than 8 days before surgery. The study was performed under the auspices of the Institutional Review Board. The bone tissues analyzed here were taken from the same surgical specimens collected in the previous ICP-AES study. Table 1 indicates the age distribution and timing of the Gd injection between the 2 groups.[18] An age-matched control population undergoing hip replacement was also obtained. The femoral heads were cut in half. Half of the surgical specimen was sent to Magnetic Research Incorporated, Provo, Utah, for ICP-AES analysis. The other half was sent to Bracco Research USA for ICP-MS analysis.

Equipment and Materials

An analytic method using an ICP-MS to measure Gd concentrations in human bone was developed and validated in collaboration with Elemental Research Inc. (North Vancouver, B.C., Canada). The study consisted of 3 analytic runs over 3 nonconsecutive days. The method was validated over the selected concentration range of Gd from the LLOQ of 0.1 μg Gd/g bone to the ULOQ of 20 μg Gd/g bone.

TABLE 1. Age Distribution and Gadolinium Timing

	Control (n = 8)	Omniscan (n = 9)	ProHance (n = 10)
Average patient age* (years)	53.3 ± 14.5†	67.6 ± 13.0	62.9 ± 9.0
Injection to bone harvest (days)*	N/A	4.3 ± 1.2	4.6 ± 1.0

*There was no significant difference between groups.
†Only includes age data from 6 controls.
N/A, not applicable.

A PE/SCIEX ELAN 6000 ICP-MS was used with RF power set at 1100 W and nebulizer gas flow at 0.9 L/min along with the corresponding ELAN software (Perkin-Elmer, Shelton, CT). Trace metal grade nitric acid (Fischer Scientific, Springfield, NJ) was used for standard and sample preparation. A Barnstead (Dubuque, IA) Nanopure UV water deionizer was used to provide >18 megaohm deionized water used in the study. Gd and terbium (Tb - internal standard) solutions were NIST traceable (SCP Science, Champlain, NY). NIST 1486 Bone Meal (NIST Standards Reference Materials Program, Gaithersburg, MD) was used to prepare spiked calibration standards, quality control (QC) samples, and blanks. Metal-free 15-mL polypropylene centrifuge tubes (Elkay, Los Angeles, CA) were used throughout the validation for samples, calibration curves, and so on. Eppendorf (Westbury, NY) and Rainin (Woburn, MA) electronic pipettors were used for volumetric dilutions. A Labconco (Kansas City, MO) Benchtop Freeze Dry Chamber 75227 was used to freeze-dry specimens.

Method Validation

Method validation consisted of 3 analytic runs performed over 3 nonconsecutive days. Each run contained 2 calibration curves, one at the beginning and one at the end of the run, with QC samples consisting of 6 replicates of the LLOQ QC (0.1 μg Gd/g bone), 6 replicates of the low QC (0.4 μg Gd/g bone) at 4 times the LLOQ, 6 replicates of the medium range QC (2 μg Gd/g bone), and 6 replicates of the high QC (15 μg Gd/g bone) at 0.75 times the ULOQ (20 μg Gd/g bone) run between calibration curves.

The method was shown to be specific and selective for Gd. The acceptance criteria were met by measuring 10 replicates of unspiked bone meal and 3 replicates spiked at the LLOQ. The average response of the LLOQ samples (0.001006) was well above 5 times the average blank response (0.000730) and 10 times the standard deviation of the blank responses (0.00014). The spectral resolution of the mass spectrometer was also shown to be <1 atomic mass unit (amu) on each day of the validation study.

The method was shown to be robust by using one analyst to prepare the calibration curves and another to prepare the QCs.

The linearity of the method from the LLOQ of 0.1 μg Gd/g bone to the ULOQ of 20 μg Gd/g bone was demonstrated by preparing calibration curves daily by spiking digested bone meal solution with Gd stock standard. Each calibration standard was prepared by first adding a 100-μL aliquot of digested bone meal solution to a tube. An aliquot of Gd stock standard in 2% HNO_3 and an aliquot of 2% HNO_3 were then added to each tube to bring the total volume to 5 mL resulting in solutions in the range 0 to 20.0 μg Gd/g bone. Recoveries for calibration standards ranged between 93.2% and 107.6% of nominal and coefficients of determination (r^2) were >0.9999. The 3-day accuracy and precision data for the calibration standards are given in Table 2.

QC samples were prepared at 4 levels, 0.1, 0.4, 2.0, and 15.0 μg Gd/g bone, 6 replicates per level per day, by spiking 1-g aliquots of bone meal with Gd stock standard, which were then digested in 125-mL Teflon bombs. These digests were

TABLE 2. Accuracy and Precision Data for Gadolinium (Gd) Calibration Standards

	Nominal Gd Concentration (μg Gd/g bone)							
Day	**0.10**	**0.25**	**0.50**	**0.75**	**1.00**	**5.00**	**10.00**	**20.00**
1	0.11	0.25	0.48	0.76	0.99	4.97	10.03	19.95
	0.10	0.24	0.50	0.75	1.01	5.05	9.99	20.03
2	0.10	0.25	0.52	0.74	1.00	4.98	10.15	20.18
	0.11	0.23	0.49	0.75	0.99	5.03	9.85	19.82
3	0.10	0.25	0.49	0.78	1.02	4.98	9.98	20.19
	0.10	0.74*	0.49	0.74	1.02	4.97	9.95	19.90
Average	0.10	0.24	0.49	0.75	1.01	5.00	9.99	20.01
SD	0.004	0.007	0.014	0.014	0.012	0.036	0.100	0.150
%RSD	3.9	3.0	2.8	1.8	1.2	0.7	1.0	0.7
%RE	2.3	−2.2	−1.6	0.6	0.5	−0.1	−0.1	0.1
n	6	5	6	6	6	6	6	6

*Outside of acceptable limits, not included in statistics.
%RSD, percent relative standard deviation; %RE, percent relative error.

diluted to 50 mL, and 100 μL aliquots were removed from each to prepare the individual QC samples (ie, each individual digestion produced one QC sample), which were diluted to 5 mL with 2% HNO_3 for analysis.

The accuracy of the method (as percent relative error [%RE]) was within the acceptance criteria ($\leq$15% and $\leq$20% at the LLOQ) and ranged between −1.6% and −0.6%. The LLOQ was shown to be acceptable (accuracy and precision $\leq$20%) at 0.1 μg Gd/g bone with the between-run accuracy determined as −0.8% and the precision (percent relative standard deviation [%RSD]) as 4.5%. The between-run precision of the method was calculated as 1.9%, 1.5%, and 1.7% for the low (0.4 μg/g), medium (2 μg/g), and high (15 μg/g) QCs, respectively. These values are well within the acceptance criteria of $\leq$15%. The within-run precision of the method was well within the acceptance criteria of $\leq$15% and ranged between 1.5% and 2.5% for the low QCs, between 0.6% and 1.3% for the medium QCs, and between 0.6% and 1.0% for the high QCs.

Bone Specimen Analysis

A 28-sample analytic batch was run with calibration standards in duplicate, placed at the beginning and end of the run with QC samples, also in duplicate, interspersed randomly among the samples. Each study specimen was assayed in duplicate using separate weights.

Duplicate sets of calibration standards were prepared fresh on the day of specimen digestion. A 1-g aliquot of NIST 1486 bone meal was placed in a 125-mL Teflon bomb and the digestion was carried out by first adding 5 mL of concentrated nitric acid to each bomb and placing the bombs with watch glass covers on a hot plate for 15 minutes. The bombs were then sealed and replaced on the hot plate to digest for 2 hours before removing and cooling. After being made to 50 mL, a 100-μL aliquot of the digestate was pipetted into each tube of the 2 calibration sets. Two acid blanks were prepared with no addition of bone. Aliquots of standard Gd in 2% nitric acid were pipetted into each tube to obtain 8 calibration standards ranging from 0.1 to 20 μg Gd/g bone. A calibration curve was obtained at the beginning and end of each analytic run.

A section of each of the 28 specimens was removed and set aside for laser ablation ICP-MS analysis. All specimens were stored at −20°C. Specimens to be analyzed were removed from the −20°C freezer and placed in liquid nitrogen for approximately 1 minute. The specimens were crushed in a hydraulic press at 4000 pounds per square inch and processed in a grinder for 1 minute. They were then placed in the freeze-dryer overnight.

Duplicate 1-g aliquots of each specimen were placed in 125-mL Teflon bombs and digested as previously described. A 100-μL aliquot of each specimen digestate was pipetted into an appropriately labeled tube. Each tube (samples, QCs, and calibration standards) was made to a final volume of 5 mL with 2% nitric acid. A 100-μL aliquot of 1 ppm Tb was added to each tube as the internal standard and mixed well.

A calibration equation was derived from weighted ($1/\times$) linear regression analysis carried out on the average of the 2 calibration curves generated from internal standard normalized response (ie, response at Gd divided by the response at Tb). This equation was applied to the internal standard normalized responses of the samples and QCs to obtain Gd concentrations in μg Gd/g bone.

The calibration curve had to be linear with a coefficient of determination (r^2) greater than or equal to 0.99. Points could only have been removed from the calibration curve regression calculation if there had been a documented problem with their preparation, an instrument malfunction, or the back-calculated values were not within the acceptance criteria as follows. All calibration points used in the regression had to be within 15% of the nominal value except the lowest calibration point (at 0.1 μg Gd/g bone), which had to be within 20% of the nominal value. A maximum of 3 of the 16 calibration points of the 2 curves could have been excluded from the regression calculation and at least one point had to be retained at each concentration level.

The 4 levels of QC samples at concentrations of 0.1, 0.4, 2, and 15 μg Gd/g bone were included in the run in duplicate. QC samples had to be within 15% of nominal to be considered within tolerance, except at the LLOQ, where they

TABLE 3. Calibration Curve Data for Bone Sample Analysis

	Nominal Gadolinium Concentration (μg Gd/g bone)							
Run No.	**0.10**	**0.25**	**0.50**	**0.75**	**1.00**	**5.00**	**10.00**	**20.00**
1	0.09	0.25	0.49	0.76	1.00	4.94	9.85	19.86
2	0.11	0.24	0.52	0.77	1.01	5.07	9.93	20.31
Average	0.10	0.24	0.51	0.76	1.00	5.00	9.89	20.09
SD	0.008	0.002	0.017	0.003	0.014	0.091	0.060	0.319
%RSD	8.3	0.8	3.3	0.3	1.3	1.8	0.6	1.6
%RE	−0.7	−2.3	1.1	2.0	0.5	0.0	−1.1	0.4
n	2	2	2	2	2	2	2	2

%RSD, percent relative standard deviation; %RE, percent relative error.

had to be within 20% of nominal. At least 6 of the 8 QCs run with a batch of samples, including at least one at each concentration, had to be within tolerance for the run to be acceptable.

This study was conducted in compliance with GLP standards. A quality assurance unit reviewed the final report and determined that the report accurately reflected the raw data generated during the conduct of this study.

Results of Inductively Coupled Plasma Mass Spectroscopy

Results from the 2 calibration curves produced a regression equation of $Y = 0.004206X + 0.000076$ with a coefficient of determination of 0.999944. All calibration points were used in the regression and were within 15% of the nominal values. %RSDs were ≤8.3% and %REs were ≤±2.3%. Back-calculated Gd concentrations of the calibration standards are given in Table 3.

Calculated Gd concentrations of the QC samples are found in Table 4. All QC samples were used and were within 15% of nominal values. %RSDs were ≤2.7% and %REs were ≤±5.7%.

Calculated Gd concentrations of the 28 bone specimens are found in Table 5 and a graphic representation is presented in Figure 1 comparing Gd retention in patients dosed with Omniscan versus patients dosed with ProHance. Tissue retention was 1.77 ± 0.704 μg Gd/g bone (n = 9) for Omniscan and 0.477 ± 0.271 μg Gd/g bone (n = 10) for ProHance.

TABLE 4. Quality Control Sample Data for Bone Sample Analysis

	Nominal Gadolinium Concentration (μg Gd/g bone)			
Run No.	**0.10**	**0.40**	**2.00**	**15.00**
1	0.10	0.40	1.92	14.24
2	0.09	0.38	1.97	14.74
Average	0.09	0.39	1.95	14.49
SD	0.002	0.011	0.037	0.349
%RSD	1.8	2.7	1.9	2.4
%RE	−5.7	−2.3	−2.7	−3.4
n	2	2	2	2

%RSD, percent relative standard deviation; %RE, percent relative error.

Statistical analysis using 2 samples assuming equal variances results in $P < 0.02$, indicating that there is a significant difference between the 2 sets of data.

Laser Ablation Analysis

Laser ablation ICP-MS analysis was performed on all bone specimens to provide information on spatial distribution of Gd and a comparison to the conventional ICP-MS data. The laser data used Ca internal standard normalized Gd response for each location.

Figure 2 shows qualitatively the regions examined for each bone specimen by laser ablation ICP-MS. A 1/4-inch thick section from each bone specimen was cut using a stainless steel saw blade that had been characterized for Gd background. Each specimen was rinsed with deionized water then predried in a freeze-dryer before analysis. Data was acquired on the ICP-MS, whereas the specimen locations in Figure 2 were exposed for 30 seconds to a Nd-YAG laser operating in pulsed mode at a repetition rate of 2Hz. As a result of the sponge-like structure of the edge, middle, and center locations, the laser was continuously moved over the solid surface to avoid analyzing void regions. The movement was kept to within a 100-μm radius. Because the specimen structure at locations a, b, and c was denser, the laser beam was focused on a 15-μm region only.

The conventional ICP-MS and center, edge, and spot c laser data resulted in 2 distinct groupings, with the Omniscan grouping higher and the ProHance grouping lower in concentration. Control specimens showed negligible Gd concentration levels. Spot a and spot b laser data were more random, perhaps as a result of the locations themselves being closer to the wet tissue/bone barrier. The middle location laser data showed an unexpectedly random distribution. This may be attributable to the more honeycomb-like structure in these regions. On average, there was a higher normalized response of Gd at spot a, although some specimens did not exhibit a greatly enhanced signal at this region relative to the other regions. No specimens exhibited a lower response at spot a than the other regions. The interior regions (spot c, edge, middle, and center) exhibited similar responses, on average, within the specimen.

The Omniscan patients averaged 1.77 ± 0.704 μg Gd/g bone using the current ICP-MS analytic method compared with 1.18 ± 0.787 μg/g bone using the previous ICP-AES

TABLE 5. Calculated Sample Concentrations for Gadolinium (Gd) in Human Bone

Sample Name	Contrast Agent	Gd Concentration (mg Gd/g bone)
209	Omniscan	2.41
209 dup	Omniscan	2.48
214	Omniscan	1.14
214 dup	Omniscan	1.16
216	ProHance	0.31
216dup	ProHance	0.30
217	Control	BQL
217 dup	Control	BQL
218	ProHance	0.28
218 dup	ProHance	0.27
219	ProHance	0.72
219 dup	ProHance	0.85
220	ProHance	0.28
220 dup	ProHance	0.32
221	ProHance	0.47
221 dup	ProHance	0.52
222	Control	BQL
222 dup	Control	BQL
223	Control	BQL
223 dup	Control	BQL
224	ProHance	0.79
224 dup	ProHance	0.78
225	ProHance	0.23
225 dup	ProHance	0.23
226	ProHance	0.88
226 dup	ProHance	1.08
227	Omniscan	1.72
227 dup	Omniscan	1.70
228	Control	BQL
228 dup	Control	BQL
229	Omniscan	12.45*
229 dup	Omniscan	12.66*
230	Control	BQL
230 dup	Control	BQL
232	Omniscan	1.71
232 dup	Omniscan	1.70
233	Omniscan	2.65
233 dup	Omniscan	2.69
235	ProHance	0.40
235 dup	ProHance	0.42
236	Omniscan	1.07
236 dup	Omniscan	1.03
237	Omniscan	0.67
237 dup	Omniscan	0.70
238	Omniscan	2.78
238 dup	Omniscan	2.59
239	Omniscan	1.74
239 dup	Omniscan	1.89
240	Control	BQL
240 dup	Control	BQL
241	ProHance	0.21
241 dup	ProHance	0.20
242	Control	BQL
242 dup	Control	BQL
243	Control	BQL
243 dup	Control	BQL

*Statistically determined to be an outlier by Q test, not included in final data analysis.

BQL, below quantitation limit.

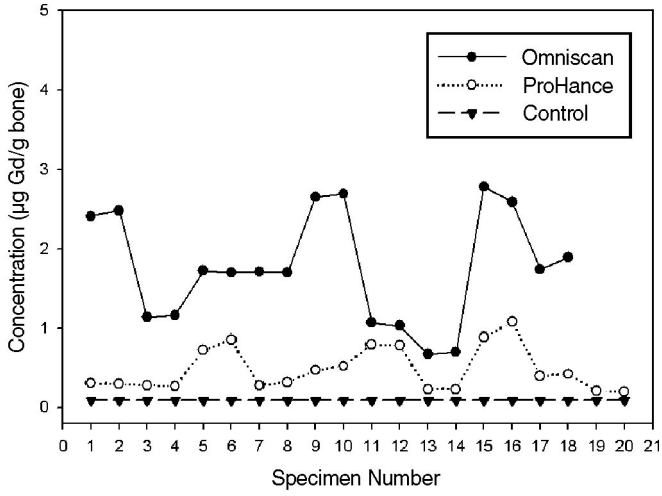


FIGURE 1. Gadolinium retention in human bone in patients dosed with Omniscan versus patients dosed with ProHance.

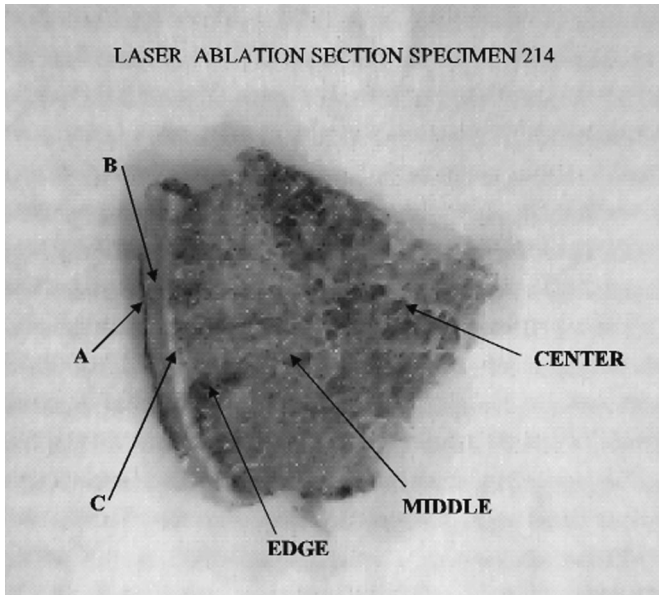


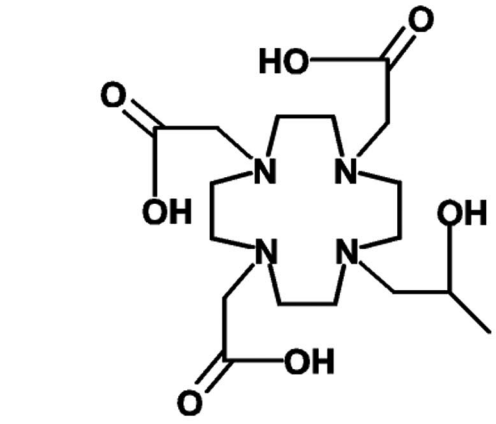
FIGURE 2. Bone sample regions examined by laser ablation inductively coupled plasma mass spectroscopy. A, Outermost edge; CENTER, innermost section (B).

analysis. ProHance patients averaged 0.477 ± 0.271 μg Gd/g bone with ICP-MS and 0.466 ± 0.387 μg/g bone with ICP-AES. This ICP-MS study finds that there is a 4-fold increase in Gd deposition in human subjects using Omniscan (Gd[DTPA-BMA]) versus ProHance (Gd[HP-DO3A]).

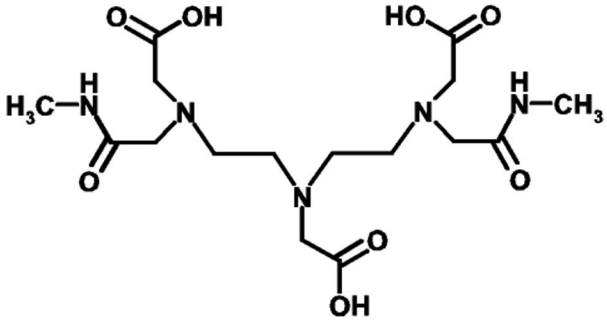
DISCUSSION

All magnetic resonance contrast agents probably dissociate in vivo to some degree. The pathway for excretion of Gd in uncertain, and its elimination is quite slow, approximately 1% per day in mice, with primary repository organs being liver, first, and then bone.[7,21] In clinical dosages, transmetallation is apparently not an acute problem, although it may cause the elevated serum Fe levels reported initially with the introduction of Magnevist. These were subsequently corrected to some extent by reformulation, adding more free ligand. However, the potential of Gd release and retention should be considered for long-term sequelae, and reasonable efforts should be made to select ligands that reduce this effect, particularly in potentially more susceptible patients such as young pediatrics, lactating or childbearing-age females, or patients with multiple sclerosis who will probably receive numerous contrast doses over time. One of the primary causes of transmetallation in vitro is the competition by other endogenously available ions such as zinc, copper, hydroxide, and phosphate that attack the chelate complex, undergoing replacement or precipitation reactions with Gd or the ligand. Some chelates such as Gd(DTPA-BMA) formulate with 5% excess calcium ligand apparently to aid in vivo stability. The rodent LD50 values of Gd(DTPA-BMA) are dramatically improved by this technique.[22] Studies with human volunteers have shown that a single dose of Omniscan removes approximately 32% of total plasma zinc (albeit a small fraction [0.09%] of the total zinc pool in the body).[17] However, with repeated high doses in subacute toxicity studies in animals, monkeys injected with Gd(DTPA-BMA) demonstrate all of the signs of zinc deficiency; including testicular atrophy, skin lesions with ulceration, and gastritis.[22]

Gd chelates are routinely compared by means of their thermodynamic or conditional equilibrium constants, kinetic lability constants under stressing conditions, selectivity of the ligands for Gd versus other endogenous metals, and in vivo animal studies that search for evidence of Gd retention. In the comparison here, we think that the primary difference may be the kinetic lability, the rate at which Gd is able to leave the chelate once complex thermodynamic conditions allow it to happen. The 2 chelating agents, DTPA-BMA and HP-DO3A, have the same number of Gd-coordinating N and O atoms (8) (Fig. 3). However, HP-DO3A is a macrocyclic compound that is quite rigidly preorganized[23] for binding Gd^{3+}. For the Gd^{3+} to break free, it must therefore simultaneously break all 4 bonds to the nitrogen atoms in the ring. On the other hand, the unsubstituted (ie, only H on the carbons between the nitrogens) linear agents like DTPA-BMA are more flexible, and modeling shows that the ligand can essentially peel away from the Gd^{3+} one donor atom at a time.[24] Thus, it is much less frequently opportune chemically for the HP-DO3A to release its Gd^{3+}, and the observed macroscopic kinetics



HP-DO3A



DTPA-BMA

FIGURE 3. Chemical structures of HP-DO3A and DTPA-BMA.

of release of Gd are far slower. The macroscopic kinetics of Gd release have not been precisely measured, but simple conditional studies in acid at pH 2 showed a half-life of 1.3 days for Gd(HP-DO3A) and <2 seconds for Gd(DTPA-BMA).[2] Also, in vitro studies of transmetallation of 18 gadolinium complexes by Zn^{2+} ion using proton relaxometry showed that bisamide derivatives such as Gd(DTPA-BMA) exhibited the highest extent of transmetallation compared with macrocyclic complexes such as Gd(HP-DO3A), which was the least susceptible to transmetallation.[25]

We have provided methodology for the GLP-validated measurement of residual trace Gd in ex vivo human bone by ICP-MS. The data reproduced the trends measured in earlier work. In the prior ICP-AES analysis, determinations were made using a partially validated, less sensitive technique. The stringently validated ICP-MS method improved accuracy (98% compared with 54%) and linearity (r^2 = 0.9999 compared with 0.8845) and significantly improved analytical rigor. Together, the 2 works suggest that Omniscan left 2 to 4 times more Gd in the bone than ProHance. Any potential risk from Gd release and long-term retention would naturally rise with higher dosage and increased frequency of use. We suggest, therefore, that this information is to be considered in certain patient populations in whom excretion of contrast is

reduced (eg, renal failure or when renal function is reduced, eg, congestive heart failure, which causes decreased renal blood flow[26]) or in patients who will receive numerous exposures to Gd chelates (eg, pediatric brain tumor, patients with multiple sclerosis) or possibly in patients in whom very little risk can be tolerated (eg, pediatrics, pregnant females).

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