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Gadolinium determination in tissue samples by inductively coupled plasma mass spectrometry and inductively coupled plasma atomic emission spectrometry in evaluation of the action of magnetic resonance imaging contrast agents

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The quantitative determination of Gd-containing magnetic resonance imaging (MRI) contrast agents in animal tissues is performed by both ICP-AES and ICP-MS. While ICP-AES has been used to determine Gd-containing contrast agents by other workers, no published methodology has been found. An accurate and precise method using nitric acid and microwave digestion for sample preparation is described. Dosed rat tissue, blood and plasma were measured by both ICP-AES and ICP-MS. The ICP-AES method is excellent for screening Gd levels and quantitative determination of concentrations above 400 ng ml^{-1}, but it lacks the sensitivity to measure agent concentrations in low dose MRI studies. This work demonstrates that ICP-MS has the needed sensitivity to replace radiotracer methods currently used for low dose studies, while maintaining the accuracy and precision of results obtained by ICP-AES. Gadolinium detection limits in tissue were 0.04 µmol of Gd per kg of tissue, an order of magnitude lower than studies using radiotracer techniques.

Keywords: *Magnetic resonance imaging contrast agents; gadolinium; biological tissue; inductively coupled plasma atomic emission spectrometry; inductively coupled plasma mass spectrometry*

Contrast agents are used in magnetic resonance imaging (MRI) to enhance anatomical features or to distinguish tumours from benign lesions.[1,2] The majority of these agents rely on paramagnetic ions to achieve signal enhancement and contrast. The most common and the most effective ion for producing signal enhancement is Gd^{III}, because of its high magnetic moment and relaxation efficiency.[3] Gadolinium(III) is delivered after being chelated by ligands such as diethylenetriaminepentaacetate (DTPA) and linked to various structures such as protein amino groups or polymeric polylysine.[4,5] New agents are under development to help the diagnostic value of MRI procedures. There is a need for sensitive methods to analyze for the disposition of contrast agents, and therefore, gadolinium, in animal model studies of the pharmacokinetics of the agents. Quantitative comparison of tissue relaxivities of dosed and undosed tissues requires the determination of the contrast agent concentration in the tissue by either metal content determination or by use of a radiotracer.

High sensitivity measurements of the gadolinium contrast agents in tissues have been undertaken with the use of radioactive ^{153}Gd or ^{125}In.[6] This is clearly undesirable if a non-radioactive method of analysis could suffice. High sensitivity measurements are necessary in certain circumstances due to the small quantities of particular contrast agents being studied and, thus, to the limited amounts of sample available.

ICP-AES has been used for the quantitative measurement of Gd in tissue samples of animals injected with contrast agents[6,7] and in biological fluids.[8] ICP-AES has the advantage of wide linear dynamic range and good sensitivity (ng ml^{-1} level) for Gd. The sensitivity was not sufficient, however, for extremely low dose levels and very small sample sizes. The more sensitive method of ICP-MS, which has been used to determine Gd in geological materials,[9] is investigated in this work to determine if it can be used in place of preconcentration and ICP-AES and in place of radiotracer methods for very low concentrations of Gd in tissue samples. This study was carried out on samples from dosed and undosed rats with implanted mammary tumors.

Experimental

The ICP-AES instruments used in this study were a JY 138 Ultrace ICP atomic emission spectrometer and a JY 38 Plus ICP atomic emission spectrometer (both from Jobin Yvon, Edison, NJ, USA and Longjumeau, France). The JY 38Plus was equipped with a high resolution grating and dual monochromators. The ICP-MS used in this study was an Elan 6000 (Perkin-Elmer, Norwalk, CT, USA), equipped with the standard Ryton Crossflow nebulizer, rapid washout spray chamber and Pt cones. Typical operating conditions for these instruments are presented in Tables 1 and 2, but because this study was done over a two year period in an industrial laboratory, exact operating conditions on a given day may have differed from those given in the Tables. The ICP-AES instruments in particular were run with a variety of different nebulizer and spray chamber systems, depending on what the major workload for a given day happened to be (*e.g.,* V-groove nebulizer and HF-resistant sample introduction system if HF solutions were being analyzed, or glass capillary nebulizer if non-HF contain-

Table 1 Typical ICP-AES operating conditions

Rf incident power/W	1000
Rf reflected power/W	10
Ar cooling gas flow rate/min^{-1}	14
Ar auxiliary flow rate/l min^{-1}	0.9
Ar nebulizer flow rate/l min^{-1}	0.8
Sample uptake rate/ml	1.0
Entrance slit/mm	0.02
Exit slit/mm	0.04
Monochromator	Czerny-Turner, 1 m focal length
Grating	Holographic, 2400 grooves mm^{-1}
Nebulizer	Meinhard Type C or V-groove

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ing solutions were being analyzed). The instruments were operated in such a manner as to achieve a stable plasma and a complete calibration curve, and spiked samples were run under the conditions for which data was obtained, to ensure that the samples were within the linear range of the instrument and that measurements were being made above the limit of quantitation, defined as 10 times the standard deviation of the blank.

An MDS 81D Microwave Digestion System and either 120 ml sealed digestion vessels or 7 ml inert sealed digestion vials (CEM, Matthews, NC, USA) were used in sample preparation. Nalgene disposable membrane filter units (115 ml) with 0.2 μm filters (Nalge, Rochester, NY, USA) were used to filter samples as needed. Deionized water (Type 1) was produced by a Milli-Q Reagent Water System (Millipore, Bedford, MA, USA).

Implanted rat mammary tumours were imaged by injection of the contrast agent into the rats at a dose of 0.1 mmol of Gd per kg of body mass. After intravenous injection of the test contrast agent in a rat carrying an implanted tumor, and after a suitable period of time to allow for accumulation of agent in the tumor, the animals were euthanized and various tissues were excised for analysis.

Rat tissue samples (liver, muscle, kidney, tumor) of 0.1–1.0 g wet mass were weighed accurately into 120 ml digestion vessels. Samples of 30–100 μl of plasma, whole blood, serum and the neat contrast agent were weighed accurately into the 7 ml vessels. Tissue samples were digested with 10 ml of ULTREX II concentrated nitric acid (J. T. Baker, Phillipsburg, NJ, USA), while the blood and plasma samples needed only 2 ml of acid. Tissue samples generally required 15–20 min of digestion time in the microwave, while the smaller samples took 5 min. Digestion was continued until clear, colorless or pale yellow solutions were obtained. Most of the samples were completely digested by this procedure. As needed, the solutions were filtered through the Nalgene filter units. Solutions were decanted with deionized water washing and made to volume (10, 25 or 50 ml in Class A calibrated flasks) with deionized water and acid as needed to keep the acid concentration at approximately 20% by volume. The amount of acid added to maintain approximately 20% v/v was determined by the volume of cooled digestate remaining in the vessels. This was assumed to be all acid and more nitric acid was added as needed. Spiked samples, matrix spikes consisting of 10 ml of concentrated nitric acid plus a known amount of Gd standard, and 10 ml nitric acid blanks were digested along with each set of samples in the microwave. Matrix spikes and blanks were treated exactly as samples. If, for example, liver samples required a second 10 ml of acid to complete digestion, then the spikes and blanks received the additional acid. A 1000 μg ml^{-1} solution of Gd in 2% nitric acid solution (High Purity Standards, Charleston, SC, USA) was used for spiking samples and matrix solutions. Spike concentrations ranged from 20 to 200 ng ml^{-1} Gd in the final solutions for ICP-MS, and from 0.5 to 5 μg ml^{-1} Gd for ICP-AES. In this study, no internal standards were used, as discussed below. Sample solutions were concentrated under an IR lamp as needed for determination by ICP-AES; the maximum concentration factor was 2. Solutions were diluted as needed for both techniques, maintaining an approximately 20% v/v acid matrix.

Calibration curves were prepared from 1000 μg ml^{-1} Gd in 2% nitric acid (Claritas PPT single element plasma standard, Spex, Edison, NJ, USA) by serial dilution using Class A calibrated pipettes and flasks. The working standards for ICP-AES covered a range of 0.10–20.0 μg ml^{-1} Gd in 20% nitric acid solution; the ICP-MS working standards were 5–400 ng ml^{-1} Gd in 20% nitric acid. Claritas PPT single element solutions of Fe and Ca (1000 μg ml^{-1}) were used to check ICP interferences.

Some tissue samples, particularly kidney tissue, had undigested fat remaining in the microwave digestion vessels, which separated on cooling. These solutions were filtered through 0.2 micron Nalgene disposable membrane filter units to remove the fat. The filter units were tested for adsorption and leaching of gadolinium by filtration of suitable acid blanks and standards. No problems were noted with loss or contamination. The separated fat was digested more rigorously (with a 10 + 1 mixture of ULTREX II nitric and perchloric acids to fumes of perchloric acid) on several occasions; no Gd was recovered from the fat. Based on previous experience with these filter units, an acid blank solution was filtered whenever sample solutions were filtered to ensure that no Gd was leached from different lots of filter units.

Table 2 Typical ICP-MS operating conditions

Rf power/W	1000
Dwell time/ms	50
Sweeps per replicate	20
No. of replicates	2
Total acquisition time/s	3
Acquisition mode	Peak hopping
Ar nebulizer flow rate/l min^{-1}	0.8
Sample uptake rate/ml min^{-1}	1
Ar coolant flow rate/l min^{-1}	14
Ar auxiliary flow rate/l min^{-1}	0.9
Sample and skimmer cones	Platinum

Results and discussion

The use of nitric acid alone to digest these samples, despite its inability to digest the fat, was predicated on several factors. All reported studies of MRI contrast agents in which Gd was determined in tissue stated the use of nitric acid in sample preparation without providing specific details.[3,4] Nitric acid is one of the cleanest digestion reagents available, and has the advantage of producing soluble salts of all metal elements. Nitric acid is regarded as the best acid medium for ICP-MS, since the polyatomic ions formed from hydrogen, nitrogen and oxygen already present in air and water are not increased by the presence of nitric acid.[9] The preferred digestion approach would be the use of mixed nitric and perchloric acids because the total sample is digested, but many facilities are not equipped to handle perchloric acid safely, and some facilities prohibit the use of perchloric acid. It has been our experience that the use of other reagents such as hydrogen peroxide, often used in the decomposition of biological materials, leads to significantly higher blank levels for many elements, and poor precision due to outgassing of the peroxide solutions in the peristaltic pump tubing. Solutions were made to approximately 20% nitric acid by volume because the microwave digestion of some samples, especially the neat contrast agents, did not significantly reduce the amount of nitric acid initially added (10 ml) and dilution to 50 ml final volume resulted in 20% v/v acid. The study had been designed originally for ICP-AES determination only, where a 20% acid matrix poses no analytical problem. The same solutions were then analyzed by ICP-MS to demonstrate the equivalence of the techniques for those samples which could be measured by both techniques, thereby validating the lower concentration samples, which could not be checked by ICP-AES. The Elan 6000 ICP-MS handled the 20% acid matrix with absolutely no problem, although it may be possible to achieve even better detection limits and instrument performance in solutions with less acid. While it is recommended that total dissolved solids be kept low in ICP-MS samples, to minimize space–charge effects, viscosity problems and clogging of the cones, analyses of high (10%) acid concentrations and slurries have been reported.[10] Continued analysis of concentrated acid solutions will rapidly degrade the cones, especially Ni cones,

and pitted cones can result in the formation of higher levels of interfering ions.[10] The Pt cones in the Elan 6000 showed no damage after approximately 60 h of intermittent exposure to 20% nitric acid solutions.

While ICP-AES has been used to determine Gd in tissue and biological fluid samples in support of MRI studies, no analytical details were reported.[3,4,8] The Gd emission lines at 335.862, 336.223 and 342.247 nm were investigated. The emission lines were background corrected using one point correction. Potential spectral interferences from the sample matrix were Fe and Ca.[11] The emission line at 335.862 nm had no spectral interference from Fe or Ca, but it was also the least sensitive. The other two lines showed small interferences (equivalent to < 0.3 μg ml^{-1} Gd) from 1000 μg ml^{-1} of Fe or Ca, but better sensitivity for Gd. Since the object of the study was to determine very low levels of Gd, the two more sensitive lines were used. The emission signals for a 2 μg ml^{-1} Gd solution and 1000 μg ml^{-1} solutions of Fe and Ca obtained on the JY 138 Ultrace are presented in Figs. 1 and 2.

Iron and Ca were determined by ICP-AES in a variety of real sample solutions. In all cases, the concentrations were below 100 μg ml^{-1}. Therefore, no corrections were applied to the Gd concentrations determined by ICP-AES, and the excellent agreement with ICP-MS justifies this decision, since Fe and Ca will not affect the ICP-MS signals for Gd in the same manner. Both wavelengths gave comparable results in terms of accuracy and precision. Recoveries of a 2 μg ml^{-1} digested sample spike

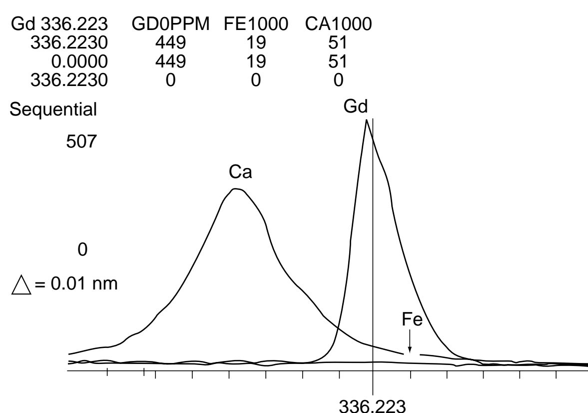

Fig. 1 Emission profile for a 2 μg ml^{-1} solution of Gd and 1000 μg ml^{-1} solutions of Fe and Ca at 336.223 nm. The Gd signal intensity is 42% higher than at 335.862 nm, with an interference from Ca which is insignificant for the purposes of this study.

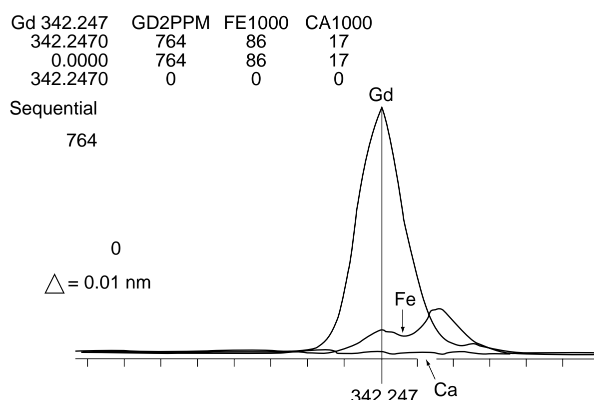

Fig. 2 Emission profile for a 2 μg ml^{-1} solution of Gd and 1000 μg ml^{-1} solutions of Fe and Ca at 342.247 nm. The Gd signal intensity is more than twice that at 335.862 nm, with an interference from Fe which is insignificant for the purposes of this study.

were 102 and 104% at the two wavelengths and average percentage relative standard deviation (RSD) for both lines was 0.8% for triplicate measurements of five sample solutions containing from 2 to 20 μg Gd ml^{-1}.

ICP-MS suffers from isobaric interferences, especially for the rare earth elements. Naturally-occurring gadolinium contains five isotopes of 15–25% abundance, which are useful for analytical measurements; 156, 158 and 160 suffer from interferences from Dy. For isotopes 156 and 158, the Dy interference is less than 0.10%. All solutions were screened for Dy and none was detected, so the 156 and 158 masses were used instead of the less sensitive 155 and 157 Gd isotopes. No matrix interferences were detected at either mass. This was ascertained by the analysis of neat contrast agents of known Gd concentration, but with very different chemical structures, both with and without digestion. As an example, duplicate digested samples of an agent were analyzed along with duplicate samples of the agent which were just diluted with 20% v/v nitric acid with no microwave digestion of the sample or solution. The Gd results for the non-digested samples were 99% of the digested samples, indicating that the Gd was rapidly and efficiently released into solution on acidification, and that the presence of the organic complexing agent in solution had no effect on the determination of Gd by ICP-MS or ICP-AES. Results at both masses and both wavelengths were accurate to 95–105% of the known Gd concentration for a variety of agents, whose exact chemical formulas are proprietary. No internal standards were used, because of the excellent precision, reproducibility and accuracy achieved without the use of internal standards, demonstrated by repeat runs of both sample and standard solutions at different times during the course of an analysis. The absolute signal for both ICP-AES and ICP-MS did not vary by more than 2% for repeat analyses of the same solutions, well within the expected instrument performance. While internal standards are routinely used in ICP-MS and other atomic spectroscopic techniques to correct for short and long term instabilities in the instrument and to correct for matrix effects such as viscosity, the results of this study indicated that these problems were not significant. The solutions were not run in the same order or using the same nebulizer type, spray chamber, gas flows or peristaltic pump rate for the two techniques. If viscosity (the only matrix effect of real concern with these samples) had been a problem, the ICP-AES and ICP-MS results should have differed significantly from each other. If the results had indicated poor precision or instrumental drift, as evidenced by changes in signal intensity with time, an internal standard would have been used to correct for these problems. In general, in trace analysis, the less one adds to the samples the better off one is, especially in the case of the rare earth elements, which are often contaminated with other members of the family.

Detection limits were calculated by taking 10 measurements of the 20% nitric acid blank by both ICP-AES and ICP-MS, calculating the standard deviation, and dividing 3 times the standard deviation by the slope of the calibration curve. The detection limits reported in Table 3 are typical. They were obtained during a normal analytical run without any excessive attention to the optimization of each instrument. As described in the Experimental section, the actual operating conditions for

Table 3 Detection limits for the ICP-AES and ICP-MS measurements

	Detection limit/ng ml^{-1}	
ICP-AES—	336.223 nm	342.247 nm
JY 38Plus	58	71
JY 138 Ultrace	2	3
ICP-MS—	Gd-156	Gd-158
	0.009	0.0044

given sets of standards, samples and spikes were not the same from day-to-day, testifying to the well known efficient atomization in argon plasmas and the general robustness of the instruments used. Actual detection limits will vary depending on the condition of the instrument and the degree of optimization. The ICP-MS detection limit of 0.0090 ng ml^{-1} corresponds to approximately 6×10^{-6} μmol of Gd per g in tissue, which is very sensitive indeed. Even under low dose conditions for MRI, in which very little agent is injected, the experiment could be followed at the limit of 0.1% dose per g in tissue. For a 0.16 kg rat, the amount of Gd injected could be as little as 0.04 μmol kg^{-1}, an order of magnitude less than amounts used in radiotracer studies.[6] There is no need, therefore, to resort to radioactive Gd or other radioisotopes for sensitive Gd tissue distribution studies if ICP-MS is available.

A significant advantage of ICP-MS over ICP-AES is its extremely high sensitivity. However, solution concentrations above 200 ng ml^{-1} required long rinse times to avoid contamination of the following sample, and concentrations above 1000 ng ml^{-1} saturated the ICP-MS detector. The ICP-AES easily handles concentrations between 100 ng ml^{-1} and 500 μg ml^{-1}. The working range for ICP-MS in this study was 5–200 ng ml^{-1}, and the Elan 6000 responded linearly over that range. The working range for ICP-AES was 0.10–100 μg ml^{-1} and the JY 38 Plus responded linearly over that range. The precision is reported for duplicate readings of the same solution on each instrument in Table 4. These were randomly selected from a large data set collected over many weeks, and are truly typical of day-to-day precision. The results listed as ‘standard’ are calibration standard solutions; those marked ‘sample’ are a variety of sample solutions with the tabulated Gd concentrations rounded to match the nearest standard concentration. There was no trend in precision for standards *versus* samples. The precision for both instruments is within acceptable limits for the instruments. The notation NA in Table 4 means not applicable, and indicates that the solution concentration was too low or too high for the given instrument.

The actual rat tissue, blood and serum samples required the capabilities of both ICP-MS and ICP-AES. The blood and serum Gd concentrations were often below the detection limit of ICP-AES, while the tissue samples were often well above the saturation point for the ICP-MS. Evaporation and concentration of the solutions can be used to some effect to bring solutions into the range of the ICP-AES, and dilution can be used to lower solution concentrations into the range of the ICP-MS, but both of these manipulations are time-consuming, require more glassware and more high purity acid, thereby increasing the cost of the analysis. Most importantly, these manipulations increase the possibilities for error and for contamination of the sample. Although gadolinium is not normally considered as a contaminant easily picked up from the environment, in a laboratory working with a wide range of research materials such as ceramics and glasses that assumption may not be valid. Evaporation and concentration may lead either to increased concentrations of analyte from contamination or losses from volatilization or mechanical loss. Despite careful attention, concentration of sample solutions which had shown 100% recovery of Gd spikes prior to concentration routinely gave 85–95% recovery after a two-fold concentration step. This could have been due to loss through spattering or to sample uptake rate changes in the instrument due to changes in viscosity (too much acid in the final solutions compared with the standards) or to other unidentified matrix effects, but whatever the cause, it was desirable to eliminate the concentration step. Use of the ICP-MS with its lower detection limits permitted that.

A comparison of results from rat samples measured by both ICP-AES and ICP-MS is presented in Table 5. The notation ND in Table 5 means not detected. The accuracy of the digestion method was assessed by the digestion and analysis of a variety of neat contrast agents with known Gd concentrations, by digestion of replicate tissue samples and by evaluation of spike recoveries from matrix solutions and spiked samples. Results were within 5% of the known value for the neat agents and spiked solutions, indicating that any matrix effects due to viscosity, other elements present in the samples, total salt content of the solutions and so on, all of which affect both ICP-AES and ICP-MS, but to different extent, were compensated for by simple matrix-matching of the standards for approximate acid concentration. The replicate tissue samples were randomly sectioned pieces of tumor or liver from a larger piece of tissue. The results reported in Table 5 are on an ‘as is’ or wet mass basis. The moisture content may be variable and the tissue pieces may be inhomogeneous in other respects, such as the fat content or connective tissue content. The replicates are within 15% of the average Gd concentration in the tissue and are not considered to be significantly different for the purposes of this study. MRI images of tissue containing Gd do not show uniform contrast enhancement, and in fact the Gd may not be uniformly distributed in a given organ. For accurate bulk concentration

Table 4 Typical short term method precision

Gd concentration	ICP-AES RSD (%) (n = 2)	ICP-MS RSD (%) (n = 2)
4 ng ml^{-1} (Standard)	NA	6.0
10 ng ml^{-1} (Standard)	NA	2.0
50 ng ml^{-1} (Standard)	NA	0.68
50 ng ml^{-1} (Sample)	NA	1.04
75 ng ml^{-1} (Sample)	7.5	1.00
100 ng ml^{-1} (Standard)	1.10	0.52
250 ng ml^{-1} (Sample)	0.40	1.29
500 ng ml^{-1} (Standard)	1.20	0.93
500 ng ml^{-1} (Sample)	1.30	0.25
1000 ng ml^{-1} (Standard)	1.50	NA
2000 ng ml^{-1} (Sample)	0.63	NA
10 μg ml^{-1} (Standard)	1.20	NA
20 μg ml^{-1} (Standard)	0.40	NA

Table 5 Gd concentrations in rat tissue, blood, serum and plasma: method comparison

Sample	ICP-AES Gd/μg g^{-1}	ICP-MS Gd/μg g^{-1}
Tissue	14.3	14.0
Tissue 1A (replicate)*	13.1	13.2
Tissue 2	132	132
Tissue 2A (replicate)	112	110
Tissue 3	1.80	1.65
Tissue 3A (replicate)	1.47	1.55
Tissue 4	1.16	1.11
Tissue 5	1.62	1.54
BSP† 1	32.7	29.4
BSP 2	9.41	9.42
BSP 3	ND	3.97
BSP 4	21.5	23.1
BSP 5	83.9	83.5
BSP 6	ND	0.80
BSP 7	ND	0.44
BSP 8	ND	0.99
BSP 9	107	102
BSP 10	37.5	33.8
BP 10A (replicate)	36.5	34.2
BSP 11	106	106
BSP 12	69.5	72.5

* Replicate = digestion replicate of a second aliquot (solid or liquid) of the sample. † BSP = whole blood, serum or plasma.

measurements of Gd in a given tissue, homogenization and/or drying to a constant mass should be performed prior to taking aliquots.

Conclusion

Evaluation of MRI agents containing gadolinium is efficiently performed by both ICP-AES and ICP-MS, but the significantly higher sensitivity of ICP-MS is absolutely required for accurate pharmacokinetic studies. The optimal situation is to have both instruments available, so that solutions may be screened rapidly by ICP-AES, and those solutions with appropriate concentrations measured quantitatively, while solutions below the detection limit of the ICP-AES are measured by ICP-MS without the danger of saturating the detector or contaminating the system and subsequent samples with excessively high concentrations of analyte.

Both instruments were run under normal operating conditions for the torches, nebulizers and spray chambers used and both were capable of measuring solutions containing 20% v/v nitric acid with good precision. The digestion method described resulted in accurate Gd determinations in tissues treated with a variety of MRI agents, as well as in the neat constrast agents.

No interferences were found for Gd in rat tissues digested with nitric acid. The ICP-AES is more robust in terms of its wide linear dynamic range and its ability to handle wide variations in analyte concentrations without extended washing periods. Detection limits for Gd on the JY 138 Ultrace were significantly lower than those found using the JY 38Plus. The ICP-MS is invaluable for its sensitivity, which will permit very low level studies to be performed, replacing the requirement for radiotracers. The Elan 6000 proved to be a very sensitive, highly stable instrument, which eliminated the need for internal standards in this study.

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