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Trace element analysis of human urine collected after administration of Gd-based MRI contrast agents: characterizing spectral interferences using inorganic mass spectrometry

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Abstract

Analysis of human urine is commonly used in biomonitoring studies to assess exposure to essential (e.g., Cu, Zn, Se) and non-essential (Pb, Cd, Pt) trace elements. These data are also used in epidemiological studies to evaluate potential associations between trace element exposure and various health outcomes within a population. Today most trace element analyses are typically performed using quadrupole-based inductively coupled plasma mass spectrometry (Q-ICP-MS). However, there is always the potential for spectral interferences with Q-ICP-MS instrumentation, especially when analyzing human specimens that may contain medications and other exogenous substances. Moreover, such xenobiotics may be unknown to the investigators.

In a recent study focusing on environmental exposures and endometriosis: Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO Study), urine specimens (n=619) were collected from participating women upon enrollment into the study or prior to surgery or pelvic magnetic resonance imaging (MRI), and analyzed for 21 trace elements by Q-ICP-MS. Here we report on some anomalous results observed for Se and Pt with elevated concentrations up to several orders of magnitude greater than what might be expected based on established reference intervals. Further investigations using Sector Field (SF-) ICP-MS instrumentation led to identification of

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doubly charged and polyatomic gadolinium (Gd) species traced to a Gd-based contrast agent that was administered to some subjects just prior to urine collection. Specifically, interferences from Gd^{2+} and several minor polyatomics were identified as interferences on all of the major isotopes of Se including ^{74}Se , ^{76}Se , ^{77}Se , ^{78}Se , ^{80}Se , and ^{82}Se . While trace amounts of Pt were present in the urine, a number of Gd-containing polyatomic species were also evident as major interferences on all isotopes of Pt (^{190}Pt , ^{192}Pt , ^{194}Pt , ^{195}Pt , ^{196}Pt , and ^{198}Pt), including Gd-chlorides, Gd-argides, and Gd-oxides. These observations underscore the importance of considering potential isobaric interferences when interpreting unusual trace element results for clinical specimens.

INTRODUCTION

Biomonitoring is the direct measurement of environmental chemicals or their metabolites in physiological specimens (e.g., blood, urine, serum, etc.) to assess internal dose.¹ When assessing human exposure to essential (e.g., Cu, Zn, Se) and non-essential (Pb, Cd, Pt) trace elements, urine is often analyzed by quadrupole-based inductively coupled plasma mass spectrometry (Q-ICP-MS). In some respects, urine may be preferred as a biomarker of recent exposure, since it is easily collected (i.e., non-invasive) and many analytes of interest for biomonitoring are easily detected. There are several advantages to using Q-ICP-MS for biomonitoring, including its high sensitivity, multi-element capability, its dynamic linear range and its high throughput for quantifying trace elements in various biological matrices. Despite these advantages, Q-ICP-MS is prone to numerous spectral interferences that may produce erroneously elevated results.

Selenium (Se) is an essential trace element that is necessary for normal enzymatic and cellular function. The main source of Se for humans is through dietary intake. There is a narrow critical physiological range for Se with detrimental health consequences being associated with both deficiency status and excessive accumulation. Diets deficient in Se may cause a form of cardiomyopathy called Keshan disease.² In recent years, dietary Se supplementation has grown in popularity due to potential cancer preventive properties.³ However, the efficacy of enhanced Se intake on human health is difficult to interpret since diets supplemented with Se have also been associated with type II diabetes.⁴ Although human sera are routinely analyzed to assess Se body burden, urine may also be a useful biomarker for assessing excessive Se intake. Urinary Se excretion reflects dietary absorption⁵ and is the main physiological elimination pathway, with greater than 50% of ingested Se excreted in urine.⁶ Concentrations of Se in human urine are quite variable with a reported reference range of 20–200 $\mu\text{g/L}$.⁷

In contrast, platinum (Pt) is a non-essential element that is known to cause platinosis,⁸ a severe asthma like reaction⁹ to hexachloroplatinate salts in some sensitive individuals. There is a growing need for Pt measurements in biological matrices due to the increased therapeutic use of Pt coordination compounds as antitumor agents.¹⁰ Although Pt containing anti-neoplastic drugs have been effective in the treatment of certain cancers, unintentional human exposure to background levels of Pt through environmental contamination from hospital effluent may be a growing area of concern.¹¹ Occupational settings and anthropogenic environmental contamination from sources such as vehicle exhaust catalysts

are also potential sources of human exposure to Pt. Many studies have used urine to assess Pt body burden. Although urine Pt is a useful biomarker of exposure, excretion and toxicity may be largely dependent upon the chemical form and route of exposure.¹² Urinary Pt levels in the population are generally very low and less than the ICP-MS detection limit, i.e., typically <10 ng/L Pt.¹³

Here we describe some select results from a recent epidemiologic study¹⁴ that included the analysis of 619 urine specimens for 21 trace elements including Se and Pt, determined by Q-ICP-MS operated in both the Standard mode and Dynamic Reaction Cell (DRC) mode. During the analysis, highly anomalous results were observed for Se and Pt that were several orders of magnitude greater than the upper limit of the population reference ranges. These observations led to an investigation of potential isobaric interferences as the reason for the anomalous Se and Pt results. Sector-Field (SF-) ICP-MS was used in both medium and high-resolution modes as part of this investigation.

METHODS

Sample Collection and Storage

Women, 18 to 44 years in age, were recruited for participation in the Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO Study), 2007–2009. The primary purpose of the ENDO Study was to assess environmental chemicals and the odds of an endometriosis diagnosis in two cohorts of women – operative and population. Complete details related to the ENDO Study design have been described elsewhere.¹⁴ Respective Institutional Review Board approvals or reliances for the conduct of the ENDO Study were obtained from the National Institute of Child Health and Human Development (NICHD), New York State Department of Health (NYSDOH), the University of Utah, and the University of California San Francisco. All women were fully consented before data or biospecimen collection.

Spot urine specimens were to be collected by protocol from women upon enrollment into the study and before surgery or Magnetic Resonance Imaging (MRI) utilizing containers determined to be free of the chemicals under study. Study participants were instructed on appropriate procedures for collection to minimize contamination potential. Urine was transferred into 2-mL Nalgene® cryovials (Thermo Fisher Scientific, Rochester, NY, USA) and stored at –20°C. Specimens were shipped frozen on dry ice to the Trace Elements Section of the Laboratory of Inorganic and Nuclear Chemistry at the New York State Department of Health's (NYSDOH) Wadsworth Center (Albany, NY, USA) for multi-element analysis. Specimens were stored at approximately –80°C until batched analysis could be arranged. All storage containers and materials used were determined to be trace element free.

Sample Preparation and Reagents

All specimens were prepared for analysis in Class II, Type A2 Biological Safety Cabinet (BSC) (The Baker Company, Sanford, MA, USA), that was validated as meeting Class 100 specifications. Specimens were sampled in a positive pressure Class 100 Clean Room (Terra Universal, Fullerton, CA, USA). Class 100 clean conditions or better for the BSC and clean

room were ensured throughout *via* periodic monitoring with a laser particle counter (Fluke Corporation, Everett, WA, USA).

Urine specimens were thawed to room temperature and diluted 1+19 for analysis with 2% (v/v) double distilled HNO₃ produced in-house using a DuoPUR sub-boiling acid still (Milestone, Shelton, CT, USA), 0.005% (v/v) Triton[®] X-100 (Sigma Ultra, Sigma-Aldrich Inc., St Louis, MO, USA) as a surfactant, and 10 µg/L Ga, Y, Rh and Ir (High-Purity Standards, Charleston, SC, USA) as internal standards in 18 MΩ•cm doubly-deionized water (DI) obtained using a NANOpure Diamond™ mixed bed deionization system (Barnstead, Waltham, MA, USA). Matrix-matched calibration curves were established using six standards prepared by serial dilution of custom multi-element stock solution (High-Purity Standards, Charleston, SC, USA) traceable to the US National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA). For each calibration standard, 500 µL of base urine was added for matrix matching purposes, along with the same reagents used to prepare patient specimens. Reagent blank samples, n=3 for each analytical run, were subtracted from each specimen result.

Aqueous solutions of Gd were prepared from a 1000 mg/L stock solution (GFS Chemicals, Powell, OH, USA) in 2% (v/v) double distilled HNO₃ and DI water. A solution containing chloride ions was prepared at a concentration of approximately 200 mmol/L from molecular biology grade NaCl (MP Biomedicals United States, Solon, OH, USA). The Gd and Cl solutions, along with select participant urine specimens, were diluted 1+19 in 2% (v/v) HNO₃ for SF-ICP-MS spectroscopic interference studies.

Instrumentation

Quadrupole-based (Q-) and sector field (SF-) ICP-MS instrumentation were utilized for analysis. Typical instrumental operating parameters are shown in Table 1.

A. Q-ICP-MS

Total elemental concentrations in urine were determined using a Perkin Elmer ELAN DRC II ICP-MS (PerkinElmer Life and Analytical Sciences, Shelton, CT, USA) with Dynamic Reaction Cell (DRC) technology. The instrument was equipped with a CETAC ASX-520 Autosampler (Omaha, NE, USA), a Meinhard[®] High Sensitivity (Type A) concentric quartz nebulizer (Meinhard Glass Products, Golden, CO), and a Quartz Cyclonic Spray Chamber. Urine specimens were analyzed for 21 trace elements using a well-validated method that has been in routine operation in the Trace Elements Laboratory since 2002. The method has been described in more detail elsewhere.¹⁵ Selenium ($m/z=78$) was determined in the DRC mode with 10% hydrogen (H₂) in argon (Ar₂) as a collision gas at a flow rate optimized at 0.3 L min⁻¹. Platinum ($m/z=195$) was determined in standard mode.

B. SF-ICP-MS

A Thermo Fisher Element 2 Sector Field (SF-) ICP-MS instrument (Thermo Fisher Scientific, Bremen, Germany) was used for more detailed interference studies. The instrument was equipped with a CETAC ASX-520 autosampler, a Conikal[®] concentric borosilicate glass nebulizer (Glass Expansion, Pocasset, MA, USA), and a quartz double

pass spray chamber (Thermo Fisher Scientific, Rochester, NY, USA). Mass spectral scans were collected in high resolution mode ($R = m/m = 10,000$) for all isotopes of Se and in medium resolution mode ($R = m/m = 4000$) for all isotopes of Pt. Instrument parameters are given in Table 1.

Q-ICP-MS Limits of Detection

Method detection limits (MDL) were calculated according to International Union of Pure and Applied Chemistry (IUPAC) guidelines.¹⁶ The MDL is defined as three times the standard deviation of concentrations measured in a base urine pool or low-level sample for a minimum of 10 independent analytical runs. The calculated MDL for Se and Pt in urine were 5 and 0.02 µg/L respectively, which incorporates a 1+19 dilution factor for urine samples. Limits of Quantitation (LOQ), defined as 10 times the calculated standard deviation, were determined for each element using the same material and analyses as those used to calculate the MDLs. The LOQ for Se and Pt in urine was 16 and 0.08 µg/L respectively.

RESULTS AND DISCUSSION

Study Results

The Trace Elements laboratory operates with repeat thresholds for elevated specimens based on information obtained from internal biomonitoring studies or from data provided by the Centers for Disease Control and Prevention related to the National Health and Nutrition Examination Survey (NHANES) studies.¹ Repeat thresholds are used within our laboratory to confirm elevated results compared to an established reference range. During the course of the ENDO Study, we were surprised to observe anomalous results for Se and Pt that were several orders of magnitude greater than the upper limit of established population reference ranges.

Figure 1 illustrates the distribution of Se (Fig 1a) and Pt (Fig 1b) values in the ENDO Study cohort. It is clear from Figure 1 that a “cluster” of participants appear to have extremely elevated results for both Se and Pt. Measured urinary Se results for the ENDO Study are shown on a log scale. From these data, we identified 38 ENDO Study participants with extremely high urinary Se that were several orders of magnitude above the laboratory’s established repeat threshold. Oddly, the same participants had elevated urinary Pt concentrations as well.

Compared to reference ranges cited in literature for Se (i.e., 20–200 µg/L),⁷ concentrations measured in the ENDO Study population ranged from below our method detection limit (MDL) to ~600 mg/L. We expected that most of the ENDO Study participants would have urinary Pt concentrations that were below our MDL, since urinary Pt is barely detectable in the US national biomonitoring study.¹ However, urine Pt concentrations for the ENDO Study ranged from non-detectable to 27.3 µg/L. These unexpected data were compared to select urinary Se and Pt concentrations for exposed populations that have been published in literature.^{17, 18} Elevated urinary Se values in the range 20–1,000 µg/L have been reported for individuals from seleniferous regions in the Midwestern US¹⁷ and Pt concentrations for

occupationally exposed individuals have been reported as 0.021–2.90 µg/L.¹⁸ It became clear from our data that extremely elevated levels of “Se” and “Pt” in urine specimens from the ENDO Study cohort were highly unusual even when compared to those reported for exposed populations, and would require further investigation.

These elevated urinary “Se” and “Pt” results triggered internal quality assurance actions within the laboratory due to the potential adverse health implications associated with such exposures. We assessed PT and EQA performance for Se and Pt during the period of time the ENDO Study analyses were conducted within the laboratory and found them all to be satisfactory. We also re-examined method accuracy for Se and Pt *via* analysis of NIST Standard Reference Materials (SRMs) 2670a Toxic Elements in Urine (Freeze-Dried) and 2668 Toxic Elements in Frozen Human Urine, and confirmed that it was acceptable. We then investigated potential spectral interferences in inorganic mass spectrometry that might explain the anomalous data.

ENDO Study and MRI Contrast Agents

The ENDO Study protocol called for a random sample of women in the operative cohort to undergo the same pelvic MRI as did all women in the population cohort who were not having surgery to inspect the pelvis for endometriosis and to assess abdominal fat distribution. By design, all MRIs were to be performed after enrollment and completion of the baseline interview, anthropometric assessment, and collection of blood and urine samples for various environmental analyses, including trace elements.

MRI is a powerful tool for visualizing soft tissues, and Gd-based contrast agents are frequently used to improve image quality. For MRI purposes, Gd is administered as a chelate, such as Gd-DTPA (diethylenetriaminepentaacetate) and Gd-DOTA (tetraazacyclododecanetetraacetic acid), to increase solubility and decrease toxicity from “free” or unbound Gd³⁺ ion.¹⁹ Once administered, approximately 90% of the chelated Gd is eliminated through urinary excretion within 24 hours¹⁹ in subjects with normal renal function. Exceptions are observed for patients with renal insufficiency where the half-life is prolonged and may exceed 30 hours.²⁰ Although Gd contrast agents have been shown to be safe in patients with normal renal function through extensive clinical trials¹⁹ and to have a low incidence of allergic-like reactions,²¹ in renal insufficiency, Gd-based agents may contribute to nephrogenic systemic fibrosis (NSF).^{19, 21_23}

Toxicity associated with Gd contrast agents is due to the dissociation of the chelated Gd complex into the “free” metal ion and ligand. Free Gd is very toxic and accumulates in the liver and in lymph nodes.²⁴ It also accumulates in bone¹⁹ where it may become irreversibly incorporated.²⁵ For this reason it is desirable that the specific ligand used to chelate the Gd³⁺ results in a complex with a high thermodynamic stability constant that is therefore kinetically inert.²⁵ Adding to the complexity of MRI contrast agent behavior after administration, the chelate may undergo a competitive ligand reaction resulting in Gd metal ion exchange^{26, 27} with endogenous metals such as Zn. The process by which a Gd ion is exchanged by a chelate for an *in vivo* metal ion is referred to as transmetallation. These phenomena have been reported to increase human urinary excretion of zinc and copper.²⁸

MRI contrast agents have been known to interfere with several clinical analyses including a negative interference indicating apparent pseudohypocalcemia in serum²⁹ and plasma³⁰ specimens. Serum creatinine³¹ and iron³² analyses have also been undesirably impacted by Gd-based MRI contrast agent administration. In a recent report in the clinical literature, Gd was identified as an interference on Se at $m/z=78$ in a serum specimen analyzed by Q-ICP-MS.³³ While investigating an unusual high serum Se result obtained by ICP-MS, Walter³³ et al., discovered that the patient had received a Gd-based MRI contrast agent prior to the serum specimen being collected. Based on this report, we considered the possibility that administration of Gd-based MRI contrast agents might be responsible for the unusual results observed for Se, and for Pt during the ENDO Study.

To date there have been no published reports of Gd interferences observed in urine specimens analyzed by Q-ICP-MS. Thus, the ENDO Study may be considered particularly unique with regard to the large number of participants' urine specimens affected by presumed spectral interferences from an unknown source.

Based on a review of the clinical information obtained from the ENDO Study, it was found that a small number of study participants had provided urine specimens for analysis after, rather than before, undergoing an MRI. This was largely attributed to challenges in scheduling MRIs at convenient times for the participants. For other subjects, the clinical records were unclear. Therefore, we categorized the ENDO Study data for urine Se and urine Pt based on the date of participant urine collection relative to the date of MRI test as indicated in the clinical record. Figure 2 shows the urinary Se (Fig 2a) and Pt (Fig 2b) concentrations stratified by information on the timing of MRIs. These six categories include: 1) "No MRI Information" for participants that did not have MRI information available; 2) "MRI No Date" for subjects that received an MRI, but for which the MRI date in relation to urine collection was not available; 3) "Urine pre MRI" for those participants that provided urine specimens prior to having an MRI; 4) "Urine + MRI Same Day" for subjects that provided a urine specimen on the same day as undergoing an MRI; 5) "Urine 1–2 Days Post MRI" for subjects whose urine was collected 1–2 days after administration of the Gd-based MRI contrast agent; and 6) "Urine >2 Days Post MRI" for subjects that provided urine more than 2 days after having had an MRI.

Measured "Se" values are shown on a log scale in Figure 2a. It is apparent from the data that there are two distinct groups within the ENDO cohort, a grossly elevated "Se" group and an unexposed group. Urinary Pt data are shown in Figure 2b, along with the MDL for Pt. Again, it is apparent that there are two groups present within the ENDO Study, one with highly elevated urine "Pt" and, as expected, a majority of subjects with Pt levels close to the MDL. It is interesting to note that for some ENDO Study participants, elevated "Se" and "Pt" are still apparent in 1–2 Days after having undergone the MRI group. The only data irregularity or outlier is for an individual woman in the "Urine pre MRI" group with "elevated Se and Pt" levels. While this specific woman did undergo MRI after donating urine as part of the ENDO Study, it is possible that another MRI may have been performed previously with a Gd-based MRI contrast agent.

Potential Sources of Isobaric Interferences in Q-ICP-MS

The possibility of unknown isobaric or polyatomic interferences was considered as a potential explanation for unusually elevated urine Se and Pt results. Table 2 lists these interferences based on information obtained from various literature sources^{5, 10, 33, 34} and other theoretical possibilities. It is interesting to note that doubly charged Gd could interfere with all of the major isotopes of Se, except $^{82}\text{Se}^+$, which is subject to the well known $^{40}\text{Ar}_2\text{H}_2^+$ polyatomic interference. In the case of Pt, all of the isotopes are subject to spectral overlap that may be attributed to gadolinium-containing polyatomic species.

Investigating a Doubly Charged Interference from Gd^{2+} on Se using SF-ICP-MS

The determination of Se in complex biological matrices by Q-ICP-MS is an analytical challenge due to numerous potential spectral interferences. Argon based polyatomic interferences are prevalent for all the major isotopes of Se. However, the introduction of DRC technology for Q-ICP-MS has opened up new approaches for attenuating argide interferences associated with measurement of Se. For example, the argon dimer $^{40}\text{Ar}^{38}\text{Ar}^+$ that interferes with $^{78}\text{Se}^+$ can be attenuated by using 10% hydrogen (by volume) in Ar as the DRC gas.³⁵ Since $^{38}\text{Ar}^+$ has an abundance of just 0.06%, it follows that the interference will be small at $m/z=78$. According to published reports, collision processes sufficiently reduce $^{40}\text{Ar}^{38}\text{Ar}^+$ interference on the $^{78}\text{Se}^+$ isotope to negligible levels.^{35, 36} Based upon our satisfactory performance for serum and urine Se in various PT and EQA schemes, problems with Se measurements were not anticipated for the ENDO Study.

Doubly charged species are not generally problematic for the measurement of $^{78}\text{Se}^+$ by Q-ICP-MS, and the $^{138}\text{Ba}^{2+}/^{138}\text{Ba}^+$ ratio is typically optimized to be less than 2%, since Ba is a good indicator of doubly charged ion formation due to its low second ionization potential.³⁷ Previous studies of doubly charged ions (M^{2+}) indicate that those elements with second ionization potentials that are below that of Ar (i.e., 15.76 eV) are likely to become doubly ionized.³⁸ With a second ionization potential of 12.09 eV, Gd is a good candidate for M^{2+} production that could affect Se measurements at $m/z=78$.

Walter³³ et al., has previously noted an interference on $^{78}\text{Se}^+$ when an elevated measurement was observed in a clinical serum specimen. The resultant investigation indicated that doubly charged species present from administration of a Gd-based MRI contrast agent may have caused an isobaric interference and hence, an erroneously elevated serum $^{78}\text{Se}^+$ value. In order to explore the source of interference in the serum specimen, the authors added an aqueous Gd solution to archived EQA scheme samples with Se target values established by inter-laboratory comparison. An observed increase in the measured Se values following addition of Gd confirmed the $^{156}\text{Gd}^{2+}$ interference on $^{78}\text{Se}^+$. With access to sector field (SF) instrumentation, we are able to explore the $^{156}\text{Gd}^{2+}$ interference on $^{78}\text{Se}^+$ in more detail for an aqueous Gd solution and a clinical urine specimen from the ENDO Study.

In Figure 3, a mass scan is shown of an aqueous solution containing 1 mg/L Gd (dashed line) and a participant urine specimen (solid line), measured in high-resolution mode ($R = m/m = 10,000$) by SF-ICP-MS. A small peak identified as $^{78}\text{Se}^+$ ($m/z=77.92$), is clearly evident in the urine specimen and is consistent with expected levels in humans. A peak that

may be attributed to a combination of $^{40}\text{Ar}^{38}\text{Ar}^+$, $^{78}\text{Kr}^+$, and $^{62}\text{Ni}^{16}\text{O}^+$ is observed for both the urine specimen and the aqueous solution. The large peak at $m/z=77.96$ is doubly charged $^{156}\text{Gd}^{2+}$ and confirms the presence of large amounts of the contrast agent in the participant's urine specimen. For the participant urine, an unidentified peak appears in the mass scan at $m/z=77.95$, and a signal at this mass is not observed for the aqueous solution. The analyte signal at $m/z=77.95$ is therefore presumably due to an endogenous matrix component that is only present in the participant urine.

Given the doubly charged interference observed at $m/z=78$, we elected to investigate potential interferences on each of the other isotopes of Se. However, to accomplish this using the limited residual volume of participant urine available to us required collection of fewer data points per scan. Figure 4(a–f) shows the SF-ICP-MS scans in high resolution for a second participant urine (solid line) compared to 1 mg/L $\text{Gd}_{(\text{aq})}$ solution (dashed line) for each of the 6 isotopes for Se: ^{74}Se , ^{76}Se , ^{77}Se , ^{78}Se , ^{80}Se , and ^{82}Se .

As expected, doubly charged Gd ions were confirmed in the second participant urine specimen by comparison to a 1 mg/L aqueous Gd solution, and are observed for all isotopes of Se except for $^{74}\text{Se}^+$ and $^{82}\text{Se}^+$. Interesting additional features were observed for many of the Se isotopes when explored in high resolution by SF-ICP-MS. For $^{74}\text{Se}^+$ (Fig 4a) an identified peak that is barely detectable occurs at $m/z=73.920$ that may be an endogenous matrix component in the study participant's specimen and $^{74}\text{Se}^+$ is apparent at $m/z=73.922$. In Figure 4a, a small peak is visible for the $\text{Gd}_{(\text{aq})}$ solution at $m/z=73.930$ that may be $^{36}\text{Ar}^{38}\text{Ar}^+$. By contrast, a peak observed at $m/z=73.932$ in the participant urine specimen could be the species $^{37}\text{Cl}_2^+$. The well-characterized argon dimer interferences were observed for $^{76}\text{Se}^+$ (Fig 4b, $^{36}\text{Ar}^{40}\text{Ar}^+$), $^{78}\text{Se}^+$ (Fig 4d, $^{38}\text{Ar}^{40}\text{Ar}^+$), and $^{80}\text{Se}^+$ (Fig 4e, $^{40}\text{Ar}^{40}\text{Ar}^+$). Additional polyatomic interferences can also be discerned under high resolution for $^{77}\text{Se}^+$ (Fig 4c, $^{36}\text{Ar}^{40}\text{ArH}^+$), and $^{82}\text{Se}^+$ (Fig 4f, $^{40}\text{Ar}^{40}\text{ArH}_2^+$). Argon interferences cannot be resolved from other potential interferences, such as nickel oxides, even in high-resolution. For example, the argon dimers observed for $^{76}\text{Se}^+$ (Fig 4b) and $^{78}\text{Se}^+$ (Fig 4d) may also include $^{60}\text{Ni}^{16}\text{O}^+$ ($m/z=75.930$) and $^{62}\text{Ni}^{16}\text{O}^+$ ($m/z=77.923$). Potential contributions from krypton (i.e., $^{78}\text{Kr}^+$ and $^{82}\text{Kr}^+$) due to contamination of liquid Ar supplies are identified in Figs. 4d and 4e, however these have not been confirmed independently. Additional peaks visible in the mass scans have been tentatively attributed to various chloride and oxide species. These include $^{37}\text{Cl}^{40}\text{Ar}^+$ on $^{77}\text{Se}^+$ (Fig 4c) and $^{66}\text{Zn}^{16}\text{O}^+$ on $^{82}\text{Se}^+$ (Fig 4f).

For Se isotopes where doubly charged Gd interferences were expected, $^{76}\text{Se}^+$, $^{77}\text{Se}^+$, $^{78}\text{Se}^+$, and $^{80}\text{Se}^+$ (Fig 4b–e), these species are clearly evident and confirmed using an aqueous Gd solution. Indeed the relative intensities observed in the participant urine for each of the four Gd^{2+} isotopes matching the major Se isotopes, closely match the natural abundance for Gd (Table 3).

Investigating Gd-based polyatomic interferences on Pt using SF-ICP-MS

Figure 5 shows a mass scan from 194.85 to 195.00 amu of an aqueous solution containing 1 mg/L Gd (dashed line) and a participant urine specimen (solid line), measured in medium-resolution mode ($R = m/m = 4,000$) by SF-ICP-MS. A distinct peak, identified as $^{195}\text{Pt}^+$ ($m/z=194.96$), is evident in the participant urine specimen, and is consistent with very low

background levels of Pt found in human urine. Analysis of the aqueous Gd solution (i.e., without Pt) under medium resolution shows a small peak at $m/z=194.89$, which could be assigned as one or more GdAr species, e.g., $^{155}\text{Gd}^{40}\text{Ar}^+$ and $^{157}\text{Gd}^{38}\text{Ar}^+$. By contrast, the presence of a much larger peak at $m/z=194.89$ in the participant urine suggests some other species might be present, and thus further investigation was undertaken with a second participant urine. In this follow up investigation, we explored potential interferences on each of the isotopes of Pt: ^{190}Pt , ^{192}Pt , ^{194}Pt , ^{195}Pt , ^{196}Pt , and ^{198}Pt , as we had done with Se.

Fig 6 (a–f) shows SF-ICP-MS scans (in medium resolution) that were obtained for each of the following: a participant urine; 10 mg/L Gd; 100 mg/L Gd; and 100 mg/L Gd + 10 mmol/L NaCl, to identify select polyatomic species. Note the NaCl concentration was selected to match human urine following dilution.

Trace amounts of Pt are clearly evident in the participant urine at all of the isotopes of Pt (Fig 6c–f), except $^{190}\text{Pt}^+$ and $^{192}\text{Pt}^+$, which are <1% relative abundance. It is interesting to note that a number of Gd-containing polyatomic species are present at all isotopes of Pt. Potential polyatomic species were identified using the “Interferences Workshop” feature in the Element2 software. For example, Fig 6c shows the mass scan in the region of $m/z=194$, under medium resolution. A peak is clearly visible $m/z=193.89$ in the participant urine but it is absent in both the 10 mg/L and 100 mg/L Gd solutions. Since this peak cannot be due to a $^{154}\text{Gd}^{40}\text{Ar}^+$ species, the only other possibility is that it must be another Gd polyatomic, perhaps GdCl. Adding sufficient Cl to the 100 mg/L Gd_(aq) solution to match that found in typical human urine provided convincing evidence that the peak at $m/z=193.89$ must be due to a $^{157}\text{Gd}^{37}\text{Cl}^+$ species. Indeed, other GdCl species could well be causing interferences on $^{190}\text{Pt}^+$, $^{192}\text{Pt}^+$, and $^{196}\text{Pt}^+$ (Fig 6a,b,e). For $^{195}\text{Pt}^+$, the interference is an unresolved mixture of several Gd argide species and $^{160}\text{Gd}^{35}\text{Cl}^+$. For $^{196}\text{Pt}^+$, there is a potential interference from $^{158}\text{Gd}^{35}\text{ClH}_3^+$. Additional interferences identified by the Element2 program included gadolinium oxide species (GdO). Evidence for a GdO species was obtained by comparing 10 mg/L to 100 mg/L Gd_(aq). Potential interferences include: $^{158}\text{Gd}^{16}\text{O}_2^+$ on ^{190}Pt ; $^{160}\text{Gd}^{16}\text{O}_2^+$ on ^{192}Pt ; and $^{160}\text{Gd}^{16}\text{O}_2\text{H}_2^+$ on ^{194}Pt . Many of the Gd-containing polyatomic species identified under medium resolution, would remain unresolved even under high-resolution.

Polyatomic interference production in an argon plasma, as is the case with GdAr species, is likely to be instrument specific.³⁹ The precise mechanism for polyatomic species formation in ICP-MS is still unclear. Ion extraction investigations propose formation of argides and oxides in the region between sampler and skimmer cones due to collisions or in the sheath in the inner boundary layer of the sampler cone.³⁷ If this is the case, then these interferences might be attenuated with the use of DRC technology.

CONCLUSIONS

Our data suggest that administration of Gd-based MRI contrast agents are associated with major spectral interferences for the determination of Se and Pt in urine by Q-ICP-MS. The specific interferences were characterized using SF-ICP-MS by analyzing urine specimens obtained from 2 study subjects, who had received a Gd-chelate contrast agent. For each of

the Se isotopes, we also analyzed a solution containing 1 mg/L Gd and, for the Pt isotopes, we analyzed solutions containing 10 mg/L Gd, 100 mg/L Gd, and 100 mg/L Gd_(aq) supplemented with Cl. The large amount of Gd present in some of the ENDO Study participants' specimens was sufficient to result in erroneously elevated values for urinary Se, measured at $m/z=78$, and urinary Pt, measured at $m/z=195$ using Q-ICP-MS.

SF-ICP-MS can be used in high and medium-resolution modes to resolve the Gd-based interferences from $^{78}\text{Se}^+$ and $^{195}\text{Pt}^+$. It may be reasonable to employ SF-ICP-MS instrumentation for some purposes when Gd based interferences are suspected in a study population; however, use of SF-ICP-MS may be cost prohibitive for large-scale epidemiological and biomonitoring studies.

A spectral interference caused by $^{156}\text{Gd}^+$ was previously reported when analyzing a serum specimen for Se at $m/z=78$;³³ however, to our knowledge the observations reported herein are the first to document Gd interferences in urine specimens, and first to identify GdAr, GdCl, and GdO as interferences on Pt. Data from this study are particularly unique with regard to the number of participants' specimens affected by the Gd interferences.

The prevalence of interferences in argon plasma from medical formulations when analyzing biomonitoring study specimens may increase as Gd-based contrast agents become more widely used and new formulations make their way into common usage. This study serves as a cautionary reminder of the importance of maintaining effective communication between the analytical, medical, and epidemiological team members regarding strict adherence to study protocols in human biomonitoring studies.

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Fig. 1. Distribution of (a) Se and (b) Pt results for participants in the ENDO Study, 2007–2009 population (n=619).

Fig. 2.

Urinary (a) Se and (b) Pt concentrations by timing of MRI, ENDO Study. Horizontal lines indicate the calculated geometric mean.

Fig. 3.
SF-ICP-MS mass scan of a patient urine specimen and an aqueous Gd solution (1 mg/L),
under high resolution ($R = m / \Delta m = 10,000$). Number of samples per mass range = 200.

Fig. 4.

(a–f) SF-ICP-MS mass scans of a patient urine specimen (—) and an aqueous 1 mg/L Gd solution (---), under high resolution ($R = m/m = 10,000$). Mass scans are shown for (a) ^{74}Se , (b) ^{76}Se , (c) ^{77}Se , (d) ^{78}Se , (e) ^{80}Se , and (f) ^{82}Se . Number of samples per mass range = 200.

Fig. 5. SF-ICP-MS mass scan of a patient urine specimen and an aqueous Gd solution (1 mg/L), under medium resolution ($R = m/m = 4000$). Number of samples per mass range = 100.

Fig. 6. (a-f) SF-ICP-MS of a 100 mg L⁻¹ aqueous Gd solution containing approximately 10 mmol L⁻¹ NaCl (—), a participant urine specimen (—), a 100mg L⁻¹ aqueous Gd solution (—), and a 10 mg L⁻¹ aqueous Gd solution (—). Mass scans are shown for (a) ¹⁹⁰Pt, (b) ¹⁹²Pt, (c) ¹⁹⁴Pt, (d) ¹⁹⁵Pt, (e) ¹⁹⁶Pt, (f) ¹⁹⁸Pt. Number of samples per mass range = 100.

Table 1

Typical ICP-MS instrumental operating parameters.

	Q-ICP-MS	SF-ICP-MS
Instrument	ELAN DRCII ICP-MS	Thermo Element 2
RF Power	1300 Watts	1245 Watts
Plasma gas	15 L min ⁻¹	15 L min ⁻¹
Auxiliary gas	1.2 L min ⁻¹	1.1 L min ⁻¹
Nebulizer gas	0.9 L min ⁻¹	0.98 L min ⁻¹
Nebulizer	Meinhard concentric	GE Conikal concentric
Spray chamber	Quartz cyclonic baffled	Quartz double pass
Cones	Nickel	Nickel
Data acquisition	Peak hopping	Scanning (Escan)
Sweeps per reading	3	3–10
Replicates per reading	3	3
Dwell time	500 ms	20 ms per sample
Scan mode	-	Mass accuracy
Detection mode	Both	Both
Oxide ratio	3% (¹⁴⁰ Ce ¹⁶ O ⁺ / ¹⁴⁰ Ce ⁺)	0.6% (¹³⁷ Ba ¹⁶ O ⁺ / ¹³⁷ Ba ⁺)
Doubly-charged ratio	1.2% (¹³⁸ Ba ²⁺ / ¹³⁸ Ba ⁺)	3% (¹³⁷ Ba ²⁺ / ¹³⁷ Ba ⁺)

Table 2

Selenium and platinum isotopes, natural abundance and potential spectral interferences in Q-ICP-MS.

Isotope	Abundance (%)	Potential interferences
$^{74}\text{Se}^+$	0.89	$^{37}\text{Cl}_2^+ \text{ } ^{36}\text{Ar}^{38}\text{Ar}^+$, $^{40}\text{Ar}^{34}\text{S}^+$, $^{38}\text{Ar}^{36}\text{S}^+$
$^{76}\text{Se}^+$	9.36	$^{152}\text{Gd}^{2+40}\text{Ar}^{36}\text{Ar}^+$, $^{38}\text{Ar}_2^+$, $^{40}\text{Ar}^{36}\text{S}^+$, $^{31}\text{P}_2^{14}\text{N}^+$, $^{60}\text{Ni}^{16}\text{O}^+$
$^{77}\text{Se}^+$	7.63	$^{154}\text{Gd}^{2+40}\text{Ar}^{37}\text{Cl}^+$, $^{40}\text{Ar}^{36}\text{Ar}^1\text{H}^+$, $^{38}\text{Ar}_2^1\text{H}^+$
$^{78}\text{Se}^+$	23.8	$^{156}\text{Gd}^{2+40}\text{Ar}^{38}\text{Ar}^+$, $^{38}\text{Ar}^{40}\text{Ca}^+$, $^{31}\text{P}_2^{16}\text{O}^+$
$^{80}\text{Se}^+$	49.6	$^{160}\text{Gd}^{2+40}\text{Ar}_2^+$, $^{64}\text{Zn}^{16}\text{O}^+$, $^{32}\text{S}^{16}\text{O}_3^+$
$^{82}\text{Se}^+$	8.73	$^{40}\text{Ar}_2^1\text{H}_2^+$, $^{12}\text{C}^{35}\text{Cl}_2^+$, $^{34}\text{S}^{16}\text{O}_3^+$, $^{82}\text{Kr}^+$, $^1\text{H}^8\text{Br}^+$
$^{190}\text{Pt}^+$	0.01	$^{152}\text{Gd}^{38}\text{Ar}^+$, $^{154}\text{Gd}^{36}\text{Ar}^+$, $^{174}\text{Yb}^{16}\text{O}^+$
$^{192}\text{Pt}^+$	0.79	$^{152}\text{Gd}^{40}\text{Ar}^+$, $^{154}\text{Gd}^{38}\text{Ar}^+$, $^{156}\text{Gd}^{36}\text{Ar}^+$, $^{176}\text{Yb}^{16}\text{O}^+$, $^{176}\text{Hf}^{16}\text{O}^+$
$^{194}\text{Pt}^+$	32.9	$^{154}\text{Gd}^{40}\text{Ar}^+$, $^{156}\text{Gd}^{38}\text{Ar}^+$, $^{158}\text{Gd}^{36}\text{Ar}^+$, $^{178}\text{Hf}^{16}\text{O}^+$, $^{177}\text{Hf}^{17}\text{O}^+$, $^{176}\text{Hf}^{18}\text{O}^+$, $^{176}\text{Yb}^{18}\text{O}^+$, $^{176}\text{Lu}^{18}\text{O}^+$
$^{195}\text{Pt}^+$	33.8	$^{155}\text{Gd}^{40}\text{Ar}^+$, $^{157}\text{Gd}^{38}\text{Ar}^+$, $^{179}\text{Hf}^{16}\text{O}^+$, $^{178}\text{Hf}^{17}\text{O}^+$, $^{177}\text{Hf}^{18}\text{O}^+$
$^{196}\text{Pt}^+$	25.3	$^{156}\text{Gd}^{40}\text{Ar}^+$, $^{158}\text{Gd}^{38}\text{Ar}^+$, $^{160}\text{Gd}^{36}\text{Ar}^+$, $^{178}\text{Hf}^{16}\text{O}^+$
$^{198}\text{Pt}^+$	7.20	$^{158}\text{Gd}^{40}\text{Ar}^+$, $^{160}\text{Gd}^{38}\text{Ar}^+$, $^{198}\text{Hg}^+$

Table 3

Measured Gd species in a participant urine specimen.

Se Isotope	Interfering Gd Isotope	Gd ²⁺ m/z	Observed mean m/z	Gd natural % abundance	Gd calculated* % abundance	Observed Intensity mean cps
⁷⁴ Se	---	---	---	---	---	---
⁷⁶ Se	¹⁵² Gd ²⁺	75.960	75.959	0.2	0.2	10578
⁷⁷ Se	¹⁵⁴ Gd ²⁺	76.960	76.960	2.18	2.14	111113
⁷⁸ Se	¹⁵⁶ Gd ²⁺	77.961	77.960	20.47	20.85	1079141
⁸⁰ Se	¹⁶⁰ Gd ²⁺	79.964	79.963	21.86	---	1131897
⁸² Se	---	---	---	---	---	---

Se: Selenium

Gd: Gadolinium

m/z: mass to charge

Cps: Counts per second

The observed masses and intensities are calculated as mean values (n=3).

* Relative intensities normalized to Gd-160 = 21.86.