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Approaches to solving gadolinium-based interference in

selenium measurement

/in Featured Articles

Selenium (Se) is an essential trace element in many biological processes. Se is measured in many sample matrices. The gold standard Se measurement method is inductively coupled plasma mass spectrometry (ICP-MS). Monitoring alternative isotopes, applying correction factors, and utilizing ICP with a triple quadrupole mass spectrometer are approaches to mitigate the interference of doubly-charged gadolinium.

Selenium background

Selenium (Se) is an essential trace element incorporated into proteins such as selenocysteine and selenomethionine [1]. There are over 30 known human selenoproteins with roles as antioxidants. Specifically, Se is a co-factor required to maintain glutathione peroxidase activity and its antioxidant function. Se is necessary for thyroid hormone activity, immune response, cancer prevention and reproductive health [2–4].

Se is present in the soil and water, and the natural dietary sources of Se include organ meats, seafood, nuts, and vegetables. Se levels in the body depend on the geographical area and dietary intake. On the one hand, marginal Se deficiency results in impaired immune function, infertility, mood disorders, inflammatory conditions, skeletal muscle dysfunction and cardiomyopathy. Severe deficiency, however, can result in Keshan disease, a cardiac disease characterized by focal myocardial necrosis and calcification. Keshan disease is prevalent in world regions characterized by Se-deficient soil. Deficiency in the US is associated with parenteral nutrition. These patients receive supplementation to raise Se levels in the blood [5]. On the other hand, Se toxicity in humans is not common, except in excess dietary intake, either through high Se-containing diets or supplement overdose. The clinical presentation of toxicity includes

garlic breath odor, hair loss, nail damage, skin conditions, nervous system disorders, poor dental health and – in extreme cases – paralysis [6–7]. The optimal range of dietary intake of Se is narrow; therefore, measuring Se concentration helps assess deficiency, toxicity and the effectiveness of replacement therapy for patients.

Preamanalytical considerations in the measurement of Se

Se is measured in whole blood, serum or plasma for short-term assessment, and hair and nail for long-term evaluation. The specimen is measured using inductively coupled plasma mass spectrometry (ICP-MS) or atomic absorption spectrometry (AAS). The measurement of metal tests requires taking preanalytical precautions. To prevent sample contamination, using a metal-free tube for sample collection and the subsequent handling of the sample (e.g. separation of serum from cellular components) is recommended. Additionally, it is advised not to collect samples for up to 4 days after administration of contrast media containing gadolinium (Gd), iodine, or barium, known to interfere with most metal tests.

Medical contrast agents for imaging may interfere with laboratory tests

Medical contrast media is known to cause analytical interference in several laboratory tests. X-ray-based imaging commonly employs organic iodine molecules (e.g. iohexol, iodixanol, ioversol) and barium sulfate. The contrast agents widely used in MRI are Gd-based (ionic, neutral, albumin-bound, or polymeric). These agents enhance the contrast of body organs or fluids during medical imaging and have contributed to the medical advancement of these techniques.

The potential impact of these agents on laboratory test results is complex. These compounds may ionize and contribute to blood osmolarity and density increase. The presence of contrast agent in the sample causes incorrect migration of gel separator above serum/plasma, causing contamination of the specimen from the cells. The presence of iodinated contrast agents can affect the accuracy of some troponin I immunoassays and capillary electrophoresis. Gd-based contrast agents also interfere with colorimetric assays. This interference is best studied and most commonly reported for calcium, although some Gd contrast agents also interfere with creatinine (Jaffe method), magnesium, angiotensin-converting enzyme and zinc, among other tests. The mechanism of interference is not well understood. Even if these analytical interferences

vary by contrast compound and assay (method and manufacturer), these laboratory tests may be highly unreliable in the presence of Gd contrast agents. The half-life of Gd is 3–4 days [8], which is the reason why samples should not be collected for at least 4 days after administration of Gd-containing contrast agents.

ICP-MS

ICP-MS is a commonly used technique for elemental analysis in clinical laboratories. Relative to other widely employed methods (e.g. AAS), ICP-MS is more sensitive, detecting concentrations down to parts per billion, and is capable of multi-elemental analysis, albeit at a higher cost. In ICP-MS, the sample is introduced in liquid form and is aerosolized in a nebulizer. Plasma, formed of argon gas coupled to an induction coil, breaks down the sample into elements and ionizes them at a very high temperature (up to 10 000 K). Then ions pass through a high vacuum region, and their elemental masses are separated using a mass analyser. Commonly, only one isotope is measured for each element of interest because the natural abundance of isotopes (isotopic fingerprint) is usually fixed in nature. Lead (Pb) is one exception, requiring to sum several isotopes because the isotope ratios of Pb vary depending on the source. Se has six natural isotopes, whereas ^{78}Se and ^{80}Se are the most common isotopes (Table 1).

Similar to many other laboratory techniques, ICP-MS has its drawbacks. The methodology is affected by interferences from the sample matrix, solvent medium, plasma gas, entrained atmospheric gases and many other sources. In general, interferences in ICP-MS are classified into three main groups: spectral, non-spectral and others [10]. For spectral interferences, the presence of isobaric, doubly-charged, and polyatomic ions with the same m/z ratio of the element of the interest could falsely elevate the measured concentration. Another spectral interference arises when a large adjacent peak from a neighbouring high-abundance isotope overlaps with the peak of the low-abundance isotope of interest. The larger peak will 'tail' into the smaller peak, causing an analytical error. The second interference group comprises interferences caused by matrix effects, space-charged effects, and physical interferences from the instrument. The matrix-induced signal variation could lead to either signal enhancements or suppressions, and it is affected by the mass of both the analyte and the matrix elements. On the other hand, space-charge effects are instrument and tuning condition-dependent. It arises when a net charge imbalance is caused by an excess of positive ions in the beam extracted from the ICP. Interferences caused by the build-up of matrix elements in the nebulizer and sampling orifices and deposition in the torch and

ion lens stack are some of the common examples of physical interferences. Last but not least, the third interference category comprises interferences resulting from contamination effects during sample storage, transportation, and preparation, and memory effects during sample nebulization and analysis. These effects can cause cross-contamination between samples and lead to inaccurate analysis [10].

Approaches to solving Gd-based interference in Se measurement

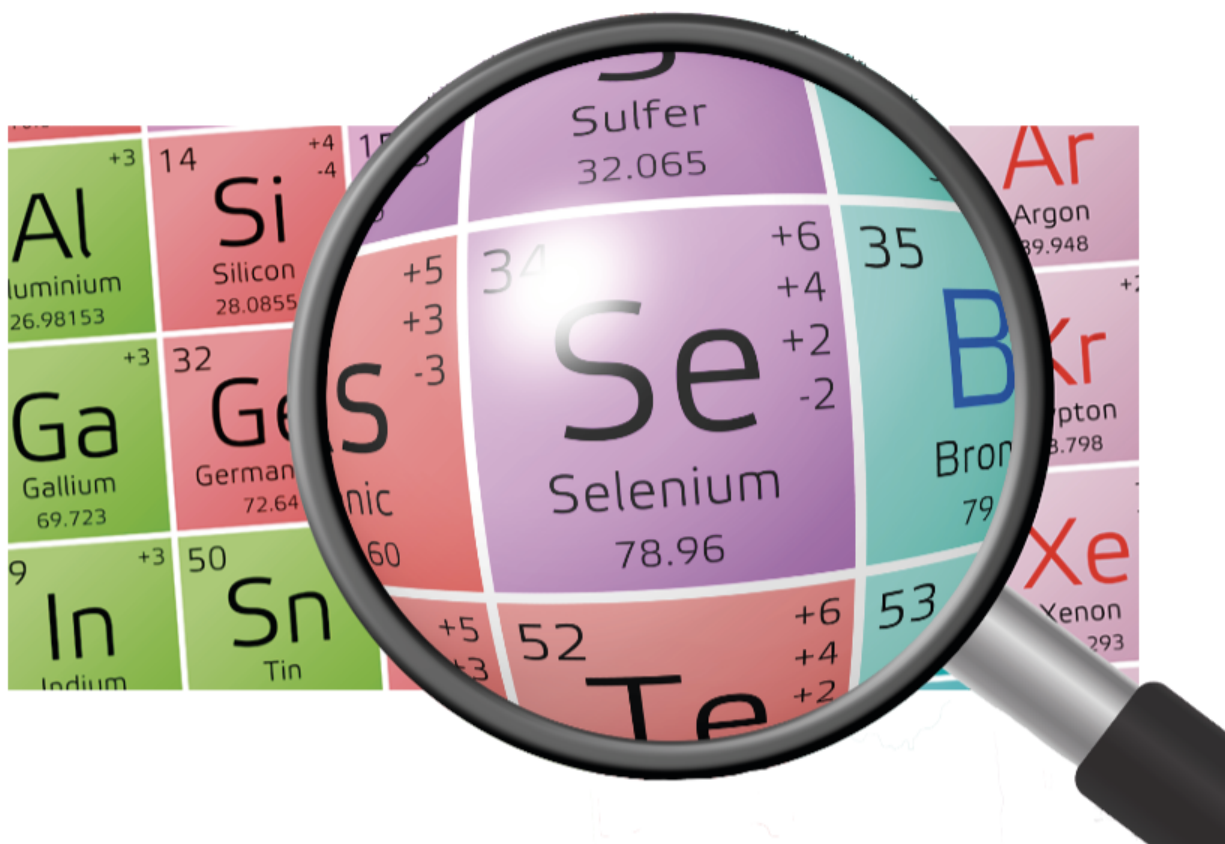
Gd-based contrast agents are often present at high concentrations in biological samples and interfere with several elements by ICP-MS. Gd interferes with elemental analysis, mainly Se, by double charge interference. $^{156}\text{Gd}^{2+}$ interferes in assays utilizing the ^{78}Se isotope. Under ICP conditions, Gd undergoes a double charge state. $^{156}\text{Gd}^{2+}$ results in a mass-to-charge identification of 78, indistinguishable from $^{78}\text{Se}^+$. When a sample is collected for Se soon after receiving Gd-based contrast, there may be a falsely elevated result for Se, proportional to the concentration of Gd. Very high levels of Se usually trigger suspicion of an erroneous result. High Gd concentrations in the range of 5000 $\mu\text{g/L}$ and 500 000 $\mu\text{g/L}$ have over a 6-fold increase in Se concentrations. A reference laboratory reported receiving samples with Gd concentrations of up to 160 000 $\mu\text{g/L}$. Unexpectedly high Se concentrations often trigger the identification of false elevations in Se due to doubly-charged Gd. Accordingly, the typical reported case in the literature consists of an elevated Se concentration in serum/blood, commonly above 1000 $\mu\text{g/L}$ (standard upper reference interval limit is approximately 200 $\mu\text{g/L}$), in a patient evaluated for deficiency and with no symptoms of Se toxicity. The investigation often requires reviewing the medical history for imaging studies using contrast in recent days before sample collection – the collection of another sample at least 4 days after Gd-contrast administration should follow. Laboratories may opt for screening for Gd in all elemental determinations that may be affected and establishing acceptability thresholds for Gd concentrations at which the laboratory should cancel the test. Laboratories have also developed alternative ways to overcome this double charge interference. Se measurement by AAS is unaffected by this interference, although referral laboratories most commonly use ICP-MS. One group developed a Se method that monitors ^{82}Se . It demonstrated good comparability with a ^{78}Se method, unaffected by double charge Gd [11]. ^{82}Se should not be used as the sole isotope to monitor Se due to potential interference from polyatomic $^{81}\text{Br}^{1}\text{H}$. Also, ^{82}Se has a lower natural abundance than ^{78}Se and may suffer from lower sensitivity. Another group developed a method for monitoring m/z of 78 and 78.5 to measure ^{78}Se and

another double charge Gd, $^{157}\text{Gd}^{2+}$. Then, they used a mathematical correction to account for the contributions of $^{156}\text{Gd}^{2+}$ based on the known relative isotopic abundance of $^{157}\text{Gd}^{2+}$ and $^{156}\text{Gd}^{2+}$. This approach demonstrated adequate Se recovery when Gd was present at concentrations up to 20 000 $\mu\text{g}/\text{L}$ [12]. One last approach to accurately quantitate Se in the presence of Gd consists of using ICP with a triple quadrupole and O₂ mass shift. In this method, Q1 filters a target m/z ratio, 78 for the case of Se, before introduction into Q2. The Q2 facilitates the addition of a reaction or a collision gas. Q3 filters the desired analyte, either the original mass or the reaction product with O₂, depending on which is the desired analyte. For example, a method can use O₂ to react with Se⁺ to form SeO⁺, The Q3 the filters a mass of 94 (sum of 78 and 16) to only detect Se [9,13].

Summary and future perspectives

The use of contrast media for imaging studies is widespread in healthcare. Several contrast-based agents can interfere with laboratory tests using immunoassay, colorimetric and ICP-MS methodologies. Although the elimination half-life of these compounds is less than 2 hours, a slower elimination rate follows after, and a blood collection days after administration of contrast agents is the safer option. This precaution requires healthcare professionals to be aware of the contrast-agent administration and the impact on laboratory tests. Healthcare institutions could develop electronic tools to prevent sample collection in these situations. For example, an automated alert could trigger after laboratory tests are ordered, alerting a clinician that the patient received a contrast agent and to preferably wait for collection of specific tests such as highly impacted tests (e.g. calcium and elements by ICP-MS).

In the case of elemental testing, laboratories should consider developing approaches to quantitatively detect contrast agents in samples and validating acceptability criteria. The detection of contrast agents has the potential to cause test cancellations. Although it is not feasible to characterize all the possible interfering contrast agents and the extent of interference, laboratories may be able to eliminate some interferences by employing techniques such as ICP-triple MS.



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The authors

Ruhan Wei PhD and Dr Jessica M. Colón-Franco* PhD
Laboratory Medicine, Cleveland Clinic, Cleveland,
OH 44106, USA

*Corresponding author

E-mail: Colonj3@ccf.org

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