Spurious Hypocalcemia After Gadodiamide Administration

Hypocalcemia characterized by critically low calcium levels may prompt urgent hospitalization and calcium replacement to prevent potentially life-threatening consequences. In 1995 and 1999, respectively, Normann et al and Lin et al described the interference of gadodiamide, a chelate of gadolinium, with the colorimetric assay for serum calcium resulting in spurious hypocalcemia. More recently, a retrospective study by Prince et al implicated gadodiamide as the cause of critically low calcium levels documented in hospital medical records. However, given the retrospective design of the study, this hypothesis could not be confirmed. Further studies have shown that another chelate of gadolinium, gadoversetamide, produces similar interference with calcium in the colorimetric assay. The remaining clinically available chelates, gadoteridol and gadopentetate dimeglumine, have not been associated with this phenomenon.

Current data suggest that gadolinium chelates are used in 20% to 25% of all magnetic resonance studies, a practice that is likely to result in an increase in the incidence of gadolinium-induced spurious hypocalcemia. This prediction is bolstered by the increasing number of recent reports in the literature. In 2003, Doorenbos et al noted 7 cases of false hypocalcemia after use of gadodiamide, and in 2004, Kefalas et al reported 11 cases after gadodiamide-enhanced magnetic resonance imaging in patients with cirrhosis. Although models to predict the potential effects of gadolinium on patients’ calcium levels and algorithms to minimize the laboratory reporting of false values are being developed, clinicians still need to be alert for this phenomenon.
Discussion

Gadolinium chelates are frequently used as contrast agents during magnetic resonance imaging and angiography. They are the preferred agents because they are not nephrotoxic and rarely trigger allergic reactions. Precautions in the radiology literature and in inserts accompanying appropriate laboratory reagents outline the potential interference of some gadolinium chelates with 2 commonly used laboratory reagents, arsenazo III dye and orthocresolphthalein, producing spuriously low calcium levels during colorimetric assays for serum calcium. Preliminary experience in our laboratories at Mayo indicated that one brand of arsenazo III reagent produced spuriously high results when patients had been given gadodiamide. However, the arsenzo III method on the Vitros analyzer (Ortho Diagnostics, Tarrytown, NY) does not show interference with gadodiamide.

The gadolinium ion is extremely toxic and therefore must be chelated to appropriate ligands for safe clinical use. A variety of ligands have been chelated to gadolinium, accounting for the 4 gadolinium chelates presently available—gadopentetate dimeglumine, gadoteridol, gadodiamide, and gadoversetamide. The gadolinium chelates with weaker thermodynamic stability (gadodiamide and gadoversetamide) have been shown to interfere with the reagents used in the colorimetric assay for calcium. Lin et al showed that gadodiamide undergoes displacement of the gadolinium ion from its native ligand with subsequent binding of the ion to the orthocresolphthalein complexone during the colorimetric assay using this reagent. This results in unavailability of the colorimetric reagent to interact with calcium, which itself binds with the chelate and thereby prevents the appropriate color changes characteristic of this assay. Despite the described interaction, clinical awareness of this phenomenon is lacking. Prince et al underscored this fact in their study, which showed that even in instances in which hypocalcemia had been preceded by documented gadodiamide administration, clinicians rendered treatment with either oral or intravenous calcium replacement in 43% of cases, resulting in secondary complications in some patients.

Clinician awareness of gadolinium-induced spurious hypocalcemia must improve in this era of increasing use of magnetic resonance imaging and angiography. In the study by Prince et al, this phenomenon occurred in approximately 4% of the examinations reviewed, and in more than one half of these patients (50%), calcium levels were in the critical range. However, their study may have overestimated the incidence given the presumed comorbidities in this group of hospitalized patients. Factors that affect serum concentration of the gadolinium, such as increased dose, decreased elapsed time since administration, and reduced renal function, were associated with an increased risk of false hypocalcemia. The time course for this phenomenon reportedly ranged from immediately after gadolinium infusion to more than 24 hours after administration, depending on the patient’s renal function. In patients with normal renal function, the interference disappeared within 12 hours, but in the presence of renal insufficiency, it persisted for more than 24 hours and in some instances up to several days. Additionally, the greatest errors in calcium levels were noted in patients in whom calcium levels were obtained immediately after chelate infusion and in those receiving higher doses of gadodiamide (≥0.2 mmol/kg). Data from animal studies confirm the transient nature of this phenomenon and its association with the dose of chelate administered.
Williams et al recently reported a case of a 78-year-old man with a critically low serum calcium level (5.8 mg/dL). This patient had an elevated creatinine level of 1.5 mg/dL (reference range, 0.9-1.4 mg/dL) and had initial serum calcium measured only 20 minutes after gadodiamide administration, factors that could have contributed to the critically low calcium level as measured by a colorimetric assay (see Table 1). The low serum calcium level was confirmed by repeat testing at a second laboratory, also using a colorimetric assay. However, a normal calcium level was obtained from the same specimen measured by atomic absorption spectroscopy, and a normal ionized calcium measurement was also obtained on the patient. After gadolinium studies, some groups recommend calcium measurement by ionized calcium testing (Mayo Medical Laboratories [MML] #8378 Calcium, Ionized).

Table 1. Laboratory findings in a patient with gadodiamide-induced spurious hypocalcemia.

<table>
<thead>
<tr>
<th>Analyte (reference range)</th>
<th>Specimen 1†</th>
<th>Specimen 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (8.9-10.1 mg/dL)</td>
<td>5.8‡</td>
<td>5.7,‡ 5.7,‡ 9.7§</td>
</tr>
<tr>
<td>Ionized calcium (4.65-5.3 mg/dL)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Albumin (3.5-5.0 g/dL)</td>
<td>4.0</td>
<td>ND</td>
</tr>
<tr>
<td>Creatinine (0.9-1.4 mg/dL)</td>
<td>1.5</td>
<td>ND</td>
</tr>
<tr>
<td>Bicarbonate (22-29 mEq/L)</td>
<td>25</td>
<td>ND</td>
</tr>
<tr>
<td>Parathyroid hormone (1.1-5.8 pmol/L)</td>
<td>ND</td>
<td>1.8</td>
</tr>
<tr>
<td>Phosphorous (2.5-4.5 mg/dL)</td>
<td>ND</td>
<td>3.3</td>
</tr>
</tbody>
</table>

MCJ = Mayo Clinic, Jacksonville, Fla, laboratory; MCR = Mayo Clinic, Rochester, Minn, laboratory; ND = not done.
† Specimen 1 was obtained 20 minutes after gadodiamide was administered; specimen 2 was obtained 6 hours later.
‡ Measured by colorimetric assay.
§ Measured by atomic absorption spectroscopy.

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However, treating physicians should become cognizant of the method of calcium determination and the types of gadolinium chelates used at their institutions. Use of the ionized calcium test requires a new specimen, maintained under anaerobic conditions, for accurate results. At MML, rather than redraw the patient and delay the results, the patient’s original specimen can be retested using an inductively coupled plasma-optical emission spectroscopy (ICP-OES) method. While this assay must be submitted as a special request, it eliminates the redraw, shipment, and processing delays inherent in ordering ionized calcium as a follow-up test. To order the ICP-OES assay, the physician merely needs to call Mayo Laboratory Inquiry at 800-533-1710 and request that a follow-up ICP-OES calcium test be performed on the in-house specimen. Routine serum calcium specimens are saved for 1 week. For those clients who perform serum calcium in-house, send the remainder of the abnormal specimen to MML and request the ICP-OES calcium test. Alternately, an anaerobic specimen can be submitted for #8378 Calcium, Ionized. Questions about the ICP-OES calcium test can be directed to Mayo’s Metals Laboratory.

Gadolinium-induced spurious hypocalcemia should be considered in the setting of a low calcium value, recent administration of the chelates gadodiamide or gadoversetamide, and absent clinical signs or symptoms of hypocalcemia. Clinicians should recognize that without marked hypoalbuminemia, critically low calcium levels are improbable in asymptomatic patients. Spurious hypocalcemia can be confirmed by measurement of either ionized calcium or total serum calcium determined by any spectroscopic method (such as ICP-OES). Alternatively, delaying the performance of nonurgent laboratory studies after gadolinium use will reduce the likelihood of finding spuriously low calcium levels.
Conclusion

Increasing the awareness of spurious hypocalcemia within the general medical community may reduce unnecessary extended hospitalizations, inappropriate work-ups, and potentially dangerous and unnecessary interventions, consistent with the recommendation of the Institute of Medicine’s report on patient safety. When evaluating patients for total calcium measurement following gadolinium administration, physicians must wait 48 hours before drawing the specimen. However, if a medical situation arises in which the calcium level must be assessed before the gadolinium has had time to clear, an ionized calcium test can be ordered or special arrangements can be made with MML to have the patient’s specimen tested using ICP-OES.

Adapted from Mayo Clinic Proceedings December 2005;80(12):1655-1657. References and case information omitted. The complete article is available online at URL http://www.mayoclinicproceedings.com.

Ask Us

Question: Does gadolinium administration affect tests other than calcium?

Answer: Yes. Gadolinium is known to interfere with most metals tests. At the necessary levels for contrast media, gadolinium ions distort the measured concentration of the analytes of interest by direct spectral overlap, destabilize the internal standard, or overload the instrument’s detection system. If gadolinium-containing contrast media has been administered, a specimen for metals testing cannot be collected for 48 hours.
**Hepatitis New Tests Offered**

Mayo Medical Laboratories recently introduced 6 new hepatitis tests. The relevant test information is listed below.

**Hepatitis B Virus**

#87893 Hepatitis B Surface Antibody (Hepatitis B Immune Globulin Therapy) Titer, Serum

**Useful For:** Monitoring serum anti-HBs levels during intravenous or intramuscular HBIG therapy to prevent recurrence of HBV infection in liver transplant recipients

**Specimen Required:** Draw blood in a plain, red-top tube or a serum gel tube. Spin down and send 0.5 mL of serum.

**Hepatitis C Virus**

#87858 Hepatitis C Antibody for Cadaveric or Hemolyzed Specimens, Serum

**Useful For:** Screening sera of cadaveric donors of human tissue, cells, and solid organs, or hemolyzed serum specimens for HCV antibodies

**Specimen Required:** Draw blood in a plain, red-top tube or a serum gel tube. Spin down and send 1.25 mL of serum.

**Hepatitis D Virus**

#86210 Hepatitis D Antigen, Serum

**Useful For:** Diagnosis of acute HDV infection in patients with fulminant HBV infection (HDV-HBV coinfection) and patients with acute exacerbation of known chronic HBV infection (HDV-HBV superinfection)

**Specimen Required:** Draw in a plain, red-top tube(s) or a serum gel tube(s). Spin down, remove serum from clot within 24 hours, and send 2.0 mL of serum frozen in plastic vial.

#86149 Hepatitis D IgM Antibody, Serum

**Useful For:** Diagnosis of acute HDV infection in patients with HBV infection (HDV-HBV coinfection) and patients with acute exacerbation of known chronic HBV infection (HDV-HBV superinfection)

**Specimen Required:** Draw in a plain, red-top tube(s) or a serum gel tube(s). Spin down, remove serum from clot within 24 hours, and send 2.0 mL of serum frozen in a plastic vial.

**Hepatitis E Virus**

#86211 Hepatitis E IgG Antibody, Serum

**Useful For:** Diagnosis of past hepatitis E

**Specimen Required:** Draw blood in a plain, red-top tube(s) or a serum gel tube(s) from a fasting patient. **(Hemolyzed or lipemic specimen is not acceptable.)** Spin down and send 1.0 mL of serum frozen in plastic vial.

#86212 Hepatitis E IgM Antibody, Serum

**Useful For:** Diagnosing acute or recent (<6 months) hepatitis E infection

**Specimen Required:** Draw blood in a plain, red-top tube(s) or a serum gel tube(s) from a fasting patient. **(Hemolyzed or lipemic specimen is not acceptable.)** Spin down and send 1.0 mL of serum frozen in plastic vial.
Paraneoplastic Autoantibody Evaluation Change

MML’s #83380 Paraneoplastic Autoantibody Evaluation was designed to facilitate expert interpretation of autoantibody profiles in the evaluation of patients who are suspected to have paraneoplastic neurological autoimmunity. The tests that are included in this evaluation enable sensitive and efficient detection of autoantibodies directed at:

- neuronal, glial, and muscle plasma membrane ion channels
- neuronal, muscle and glial cytoplasmic antigens
- neuronal nuclear antigens that currently are encountered most frequently in patients with neurological autoimmunity initiated by systemic tumor-associated antigens (eg, in adults with lung, breast or ovarian carcinoma, thymoma or Hodgkin lymphoma, and in pediatric patients with neuroblastoma, thymoma or chondroblastoma, and sometimes with other cancers).

These antibodies usually do not occur in isolation, but as a group whose profile is predictive of a specific cancer type, rather than a specific neurologic syndrome. Thus, the tests are always performed in algorithmic fashion, and reflex tests are done as dictated by the individual patient’s emerging autoantibody profile. Some of these autoantibodies are encountered in the context of graft-versus-host disease, or as a complication of D-penicillamine therapy.

Recently, the test algorithm was changed to:

- Include automatic reflexing to #83107 CRMP-5-IgG Western Blot (performed at an additional charge) when acetylcholine receptor (AChR) ganglionic neuronal antibody is ≥0.03. This reflex has been added because AChR ganglionic neuronal antibody is a recognized marker of thymoma and lung carcinoma, for which CRMP-5-IgG also serves as a sensitive confirmatory marker.
- Discontinue reflexing to paraneoplastic autoantibody Western blot (using native neuronal proteins), except when a particular neuronal nuclear or cytoplasmic autoantibody is suspected in the initial immunofluorescence screening, or when coexisting nonorgan-specific autoantibodies preclude accurate immunofluorescence interpretation. The currently optimized immunofluorescence assay is a more sensitive test than the paraneoplastic autoantibody Western blot, eliminating the need for the reflex.

Note: The Western blot assay using recombinant human CRMP-5 is more sensitive than immunofluorescence for detecting CRMP-5-IgG. In follow-up of patients already known to be seropositive for CRMP-5-IgG in this laboratory, #83107 CRMP-5-IgG Western Blot is automatically performed. As well, if the IFA pattern suggests CRMP-5, #83107 CRMP-5-IgG Western Blot is automatically performed. The #83107 CRMP-5-IgG Western Blot is highly recommended for evaluating patients with subacute unexplained basal ganglionic disorders (chorea/Parkinsonism/hemi-ballismus), cranial neuropathies (particularly loss of vision, smell or taste), myelopathies, and radiculoplexopathies.

The revised algorithm is on page 7.
Reflex testing for #83380 Paraneoplastic Autoantibody Evaluation, Serum

If Calcium Channel Antibody P/Q-Type or N-Type >20

If Ach Receptor (muscle) Binding Antibody is ≥0.03 or Striational Antibody is ≥1:60

If Ach Receptor Modulating Antibody is ≥40% loss

#83107 CRMP-5-IgG Western Blot is performed at an additional charge.

#83108 Paraneoplastic Autoantibody W blot is performed at an additional charge.

#83378 Ach Receptor (Muscle) Modulating Ab is performed at an additional charge.

If Ach Receptor (Muscle) Modulating Antibody is ≥40% loss or Mayo's laboratory has requested a second specimen

#83379 Ach Receptor (Muscle) Blocking Ab is performed at an additional charge.

Immunofluorescence (IFA)

#83381 Anti-Neuronal Nuclear Ab, Type 1
#83382 Anti-Neuronal Nuclear Ab, Type 2
#83137 Anti-Neuronal Nuclear Ab, Type 3
#83383 Purkinje Cell Cytoplasmic Ab Type 1
#83138 Purkinje Cell Cytoplasmic Ab Type 2
#83076 Purkinje Cell Cytoplasmic Ab Type Tr
#83386 Amphiphysin Ab
#83077 CRMP-5-IgG

ELISA

#8746 Striational (Striated Muscle) Ab

Radioimmunoprecipitation

#81185 Calcium Channel Ab, P/Q-Type
#81184 Calcium Channel Ab, N-Type
#8338 Ach Receptor (Muscle) Binding Ab
#84321 AChR Ganglionic Neuronal Ab
**Upcoming Education Conferences . . .**

**13th International Surgical Pathology Symposium**  
May 2–5, 2006  
Hotel Maggior Consiglio • Treviso, Italy

**Integration Through Community Laboratory Insourcing**  
May 3–5, 2006  
Disney Coronado Springs Resort • Orlando, FL

**Bleeding and Thrombosing Diseases - Wet Workshop**  
August 2, 2006  
The Kahler Grand Hotel • Rochester, MN

**Bleeding and Thrombosing Diseases Conference**  
August 3–4, 2006  
The Kahler Grand Hotel • Rochester, MN

**Practical Surgical Pathology**  
September 14–16, 2006  
Siebens Building • Mayo Clinic, Rochester, MN

**State-of-the-Art Thrombophilia**  
September 21–23, 2006  
Siebens Building • Mayo Clinic, Rochester, MN

**Quality Phlebotomy: Back to the Basics**  
October 2, 2006  
Hilton Dallas/Park Cities • Dallas, TX

**Practical Spirometry**  
October 12–13, 2006  
Radisson Hotel & Suites • Chicago, IL

**Real-Time PCR for the Clinical Microbiology Laboratory**  
October 26–27, 2006  
Siebens Building • Mayo Clinic, Rochester, MN

**Practical Spirometry**  
November 14–15, 2006  
Siebens Building • Mayo Clinic, Rochester, MN

**Interactive Satellite Programs . . .**

**The Laboratory Approach to the Child With Possible Immunodeficiency**  
May 24, 2006  
Presenter:  Thomas G. Boyce, MD

**Genomics and Proteomics: An Update**  
September 12, 2006  
Presenter:  David B. Schowalter, MD, PhD

**An Approach to Evaluation of Bleeding Disorders**  
October 3, 2006  
Presenter:  Rajiv K. Pruthi, MBBS

**Update on Contemporary Pain Management of the Patient with Cancer**  
November 14, 2006  
Presenters:  Marc A. Huntoon, MD  
Toby N. Weingarten, MD

**Update on Cardiovascular Markers**  
December 12, 2006  
Presenter:  Allan S. Jaffe, MD

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