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Case Report

MultiHance as a contrast alternative for Gadovist allergic patients ☆,☆☆,★,★★

Janna Malone, CPPA[a], *David Tiberi, MD*[a], *Charles Frankish, MD*[b], *Thanh Nguyen, MD*[c], *John Sinclair, MD*[d], *Shawn Malone, MD, FRCPC*[a,*]

[a] *Division of Radiation Oncology, The Ottawa Hospital, University of Ottawa, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada*
[b] *Department of Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada*
[c] *Department of Medical Imaging, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada*
[d] *Department of Neurosurgery, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada*

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ABSTRACT

The dramatic rise in the use of contrast agents for diagnostic imaging within the last decade has largely contributed to the effectiveness of MR imaging, however even with the use of prophylaxis, adverse reactions to contrast, including anaphylaxis, still occur. We describe the case of a 46-year-old female patient with a hemangiopericytoma requiring ongoing contrast MR surveillance, and a documented anaphylactic reaction to Gadovist (gadobutrol injection) despite premedication. Allergy testing was positive to intradermal undiluted Gadovist, confirming an IgE-mediated Gadovist allergy, with subsequent skin testing by prick and intradermal negative to undiluted MultiHance. She went on to receive MultiHance prior to her subsequent MRI scans without clinical reaction and without premedication, demonstrating that there may be superior alternatives to traditionally used gadolinium dyes in patients with moderate to severe reactions, and warrants further investigation into the anaphylactoid characteristics between the different gadolinium-based contrast agents.

Introduction

Between 1997 and 2006, Smith-Bindman et al. found that the use of MRI had increased by 26% per year. Over a 10-year study involving over 377,000 patients, they found that the use of MRI tripled [1]. Contrast-enhanced MRIs have improved our ability to diagnose and stage both benign and malignant tumors. Surgeons and oncologists use contrast MRIs to assist with surgical and radiotherapy planning as they provide anatomical details

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* Corresponding author.
E-mail address: SMalone@toh.ca (S. Malone).
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about soft tissue and vascular structures. In addition, contrast agents allow for perfusion imaging [4].

Gadolinium-based contrast agents (GBCAs) were introduced into clinical practice in 1998 and have been the mainstay of MR contrast imaging [4]. Gadolinium chelates can be classified based on their ionicity. In current practice, intravascular injections, including GBCAs, are almost exclusively nonionic low or iso-osmolar preparations [3]. These preparations are associated with lower rates of adverse reaction when compared to ionic or high osmolar agents. Rates of acute adverse reaction are between 0.2% and 0.7% [5] and severe reaction as infrequently as 0.04% [6]. Fatal reactions occur once in every 170,000 injections [3].

Reactions to contrast agents can be described as either physiologic or allergic in type. Classically, allergic reactions have required a sensitization exposure. Serious reactions to contrast agents are mediated by type 1 hypersensitivity reactions and can begin within minutes of an initial exposure to the substance. Basophil and mast cell degranulation in these reactions is not IgE mediated, rather, the result of direct stimulation [3]. As such severe reactions can occur without any previous exposure to the agent [3]. There are, in addition, a subset of patients who do have true IgE-mediated allergic reactions and react positive to skin testing [3]. Patients with a history of previous adverse reaction to contrast agents have a higher rate of recurrence (up to 30% after repeat exposure to contrast media) [7].

Nonemergent premedication protocols are used to reduce the frequency and/or severity of an acute allergic-like reaction to contrast agents. These protocols generally include multiple doses of corticosteroid with diphenhydramine. Studies have demonstrated that corticosteroids may provide some protection against mild, moderate, and severe reactions [8], however allergic breakthrough reactions are still documented despite the administration of corticosteroid and antihistamine premedication [9]. Typically, breakthrough reactions are similar in severity to an initial reaction [10]. Freed et al. demonstrated that a history of seafood allergy and hay fever significantly increased the likelihood of breakthrough reaction [10], whereas other studies have not found any statistically significant risk factors [11].

Patients with moderate to severe reactions to GBCAs with breakthrough reactions despite premedication are therefore left with suboptimal imaging options if no alternative contrast agent can be administered safely.

Case presentation

In 2016, a 46-year-old woman presented with a generalized tonic-clonic seizure. Imaging at the time revealed a large right parafalcine lesion. MRI with contrast (Gadovist) was administered at the time without reaction. She underwent gross total surgical resection of the lesion in April 2016 without complications. Pathology revealed a WHO 3 hemangiopericytoma. She subsequently received adjuvant radiation 6000 cGy in 30 fractions to the tumor bed using Intensity Modulated Radiotherapy.

In September 2016, she underwent contrast-enhanced (Gadovist) MR for post-treatment surveillance. Following this MRI she developed redness at the IV site as well as diffuse pruritis and urticaria for several days. This was self-limiting. At the time, she had had 3 previous contrast-enhanced MRIs with Gadovist without an adverse reaction. This was deemed a mild reaction to the Gadovist and she was followed on an ongoing basis with unenhanced MRIs. Her other known drug sensitivities include: penicillin, sulfa drugs, and dimenhydrinate. She had no history of food or shellfish allergy.

On follow-up noncontrast MRI in November of 2016, there was found to be increased T2 signal at the surgical bed and an epidural fluid collection with mass-effect. This was clinically accompanied by left leg paresthesia and weakness. In December 2016, she underwent surgery with a right parietal craniotomy with temporalis flap for a right CSF leak/epidural hygroma and removal of right parietal radiation necrosis. She has no postoperative complications or deficits.

The patient continued to be followed throughout 2017 with unenhanced MR imaging. However, it was deemed by her neurosurgeon and neuroradiologist as suboptimal imaging of her WHO grade 3 hemangiopericytoma. As a result a premedicated contrast-enhanced MRI scan was performed in December 2017. She was given Prednisone 50 mg at 13 hours, 7 hours, and 1 hour prior to contrast media injection as well as Benadryl 50 mg 1 hour prior to injection. After 30 minutes postcontrast injection, the patient developed facial swelling, pruritis, generalized hives, and a rash on the neck. She was treated with epinephrine 0.3 cc IM $\times$ 2 at a 1 hour interval and Benadryl 50 mg po q 6 hours. Her symptoms improved while under observation in the emergency department. She was discharged on the evening of her MRI with outpatient diphenhydramine.

Subsequent to the patients' reaction, she was referred to an allergist for assessment of sensitivity to other gadolinium preparations. She underwent prick skin testing which was negative to Gadovist (Gadobutrol). Her intradermal skin testing was positive to Gadovist (5-mm wheal). Three weeks later, she was tested for Multihance (Gadobenate dimeglumine). Prick skin testing was negative. Intradermal testing was negative to 1:1000, 1:100, 1:10, and negative to undiluted solution. She was deemed tolerant to MultiHance.

The patient underwent enhanced MR imaging use MultiHance in May 2018. She tolerated this well without adverse reaction and subsequently received a second contrast-enhanced MRI using MultiHance in December 2018 without premedication. She again tolerated this well without adverse reaction.

Discussion

There are inherent risks with using a contrast agent for MR imaging. By using a nonionic, low or iso-osmolar GBCAs, the risks of adverse reaction and side effects are minimized [3]. Nonetheless, contrast-induced nephrotoxicity, hypersensitivity reactions, contrast-induced thyroid dysfunction, and contrast-induced nephropathy known complications associated with contrast media [12].

Table 1 – A property comparison of gadobutrol to gadobenate dimeglumine [15–18].

Property	Gadobutrol	Gadobenate dimeglumine
Ionicity	Non ionic	Linear ionic
Osmolality	1.603 osmol/kg @ 37°C	1.970 osmol/kg @ 37°C
Viscosity	4.96 mPa s @ 37°C	5.3 mPa s @ 37°C
Solubility	Water soluble, hydrophilic	Water soluble, hydrophilic
pH	6.6-8.0	6.5-7.5
Molecular weight	604.72 g/mol	1058.2 g/mol
Relaxivity (r_1)	5.2 L/mmol/s	6.3 L/mmol/s
Half life	1.33-2.13 h	1.17-2.02 h
Excretion	Renal, 1.1-1.7 mL/(min•kg)	Predominantly renal, up to 4% biliary
Preservatives	None	None

Certain factors are associated with an increased likelihood of having an adverse reaction to contrast media. From a hypersensitivity or allergy perspective, these include but are not limited to previous anaphylactoid reaction to contrast material, asthma, food or medication allergies, and hay fever [2]. Those who develop anaphylactoid reactions to gadolinium may still require ongoing use of contrast media due to the nature of their underlying disease. This poses an issue for clinicians who are trying to balance adverse contrast reactions to adequate imaging of an underlying pathology.

Allergy literature has shown that cases of anaphylaxis to gadolinium may show monosensitization to one of the gadolinium preparations and negative responses to other preparations [13]. However, the predictive value of skin testing is not well established [14]. Allergy testing may provide another avenue for investigation for clinicians requiring contrast-enhanced MR imaging in patients with gadolinium hypersensitivity.

What differentiates the GBCAs such that one may be well tolerated whereas another may cause anaphylaxis? In our case, the patient experienced a document IgE-mediated allergy to Gadobutrol, but tolerated Gadobenate dimeglumine. A comparison of the 2 compounds can be seen in Table 1.

It is difficult to ascertain what characteristics or components of a contrast injection will result in a reaction in 1 patient and not another. As previously stated, typically nonionic GBCAs have the lowest documented rate of reaction [3]. However, our patient represents a case of hypersensitivity to a nonionic contrast dye, but tolerance to a higher osmolality, linear ionic chelate with verified allergy testing for both agents.

Conclusion

This case demonstrates a nonconventional alternative solution for patients with contrast allergies whose underlying pathology requires contrast-enhanced magnetic resonance imaging. Allergy testing allowed for optimal surveillance imaging in our patient with a malignant brain tumor. Further research into predictive factors of both gadolinium agents and patients would be of clinical value.

Declarations

- Consent for publication was obtained from the patient.
- The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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