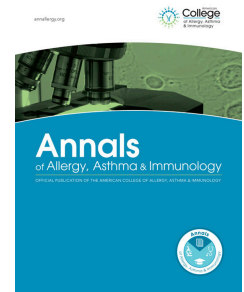


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Gadolinium induced anaphylaxis with positive skin tests

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Title page

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Gadolinium is a heavy metal element with paramagnetic properties used as contrast in Magnetic Resonance Imaging (MRI) studies. There are nine types of gadolinium-based contrast agents (GBCAs), that may be classified as ionic or nonionic and linear or macrocyclic.¹ Hypersensitivity reactions (HSR) to GBCAs are uncommon (0.004 to 0.7%), but anaphylaxis (0.001 to 0.01%²) and fatalities have occurred. These less frequent acute reactions were once considered non-immunological. However, there are few case reports implicating an IgE-dependent allergic mechanism.³⁻⁵ We present a case of a patient who developed anaphylaxis to gadobenate documented through positive skin tests (ST).

A 40-year-old woman with a history of essential hypertension and chronic urticaria developed facial urticaria, flushing, angioedema, and presyncope within minutes of a gadobenate meglumine-based MRI for a suspected breast cancer. The procedure was canceled and her condition improved after treatment with IM diphenhydramine. Tryptase was not obtained. Six-weeks later she was referred to our Allergy clinic for evaluation as an MRI-guided biopsy was necessary to establish the diagnosis of breast cancer. We performed undiluted skin prick tests (SPT) all GBCAs available at our institution (gadobenate dimeglumine 529 mg/mL; gadoterate meglumine 376.9 mg/mL; gadobutrol 604.72 mg/mL, gadodiamide 287 mg/mL, and gadoxetate disodium 181.43 mg/mL) and intradermal testing (ID) using 10-fold dilutions (1:1000 – 1:10) if SPT was negative. ~~the suspected GBCA and four other~~. SPT was positive to undiluted gadobenate dimeglumine 529 mg/mL and gadoterate meglumine 376.9 mg/mL (Figure 1). The alternative GBCAs were negative (gadobutrol 604.72 mg/mL, gadodiamide 287 mg/mL, and gadoxetate

disodium ~~181.43 mg/mL~~ on SPT and ID. Baseline tryptase was within normal limits (2.7; ref <11.5 ng/mL). Additionally, SPT to undiluted gadobenate and gadoterate meglumine were negative in four healthy volunteers. We performed a graded dose provocation test (DPT) to gadobutrol (10% dose; monitor for 30 minutes followed by rest of the dose and monitored for one hour) without adverse reactions and tolerated the agent in a subsequent MRI-guided breast biopsy. The patient was instructed to avoid gadobenate dimeglumine and gadoterate meglumine.

Gadobenate dimeglumine is a linear ionic GBCA.¹ It has been reported that the incidence of immediate HSR is higher with linear ionic agents than with nonionic agents, occurring in 0.22% of patients receiving ionic radiocontrast media. Gadobenate dimeglumine has been identified as the GBCA with the highest incidence of immediate HSR.⁶ Risk factors for HSR to contrast media include female sex, previous HSR to other contrast media, atopic disease, history of a prior allergic reaction, drug allergy, and age 20-29 or >55.⁶⁻⁸

The management of a patient who requires radiocontrast media with a history of a prior immediate HSR includes:⁶ 1) Determination of study necessity; 2) ensuring the patient understands the risks; 3) ensure proper hydration; 4) use a nonionic, iso-osmolar radiocontrast media (if available), and 5) use of a pretreatment regimen. ~~However, since premedication has not been proven to reduce the incidence of moderate or severe reactions or reaction-related deaths, and has limited supporting evidence of efficacy in~~

~~high-risk patients, ST may provide a safe and reliable alternative to premedication when~~
~~other contrast media options are available.~~ There is evidence that pre-medication for
severe reactors to iodinated contrast media is beneficial.⁹ The mechanism of GBCAs-
induced HSR has not been completely elucidated, but the presence of positive ST in
individuals who have developed anaphylaxis, provides a strong argument for the presence
of GBCA-specific IgE. ST should be performed 1-6 months after an acute HSR to a GBCA.
Prick (undiluted) and intradermal (1:1000, 1:100 and 1:10) tests should be utilized to
assess for true allergy to the GBCA and cross-reactivity to other contrast agents. ST
specificity has been reported between 96% and 100% in patients with HSR to contrast
media.⁷ We therefore recommend a subsequent graded DPT to GBCAs with negative ST to
identify an alternative agent.

There are a few reports that used a ST protocol after an immediate HSR to GBCAs. Galera
et al.³ reported two patients who developed anaphylactic shock after the first exposure to
gadoteridol and gadobenate dimeglumine and determined that a 1:10 dilution of the
original concentration is the nonirritant threshold. Chiriac et al.⁴ reported a series of
GBCAs ST results of 27 patients over 5 years with a compatible clinical history of GBCA
hypersensitivity. All patients were re-challenged after negative ST. Upon re-exposure
during a new MRI, eleven patients tolerated the GBCA to which they had negative ST.

We utilized SPT and ID to assess for immediate HSR to gadobenate dimeglumine.
Furthermore, ST revealed a possible cross-reactivity to gadoterate meglumine, a

65 macrocyclic ionic GBCA. Subsequent graded DPT helped identify gadobutrol as a safe
66 agent, which the patient tolerated in a later MRI-guided biopsy.

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Figure 1. Left forearm showing skin testing to multiple gadolinium-based contrast media. Skin prick testing was positive to undiluted gadobenate and gadoterate meglumine.

