

Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging



Joanna Lukawska, MBBS^a, Deepal Mandaliya, MRPharmS^b,
A.W. Edith Chan, PhD^c, Amy Foggitt, BSc^a,
Therese Bidder, BSc^a, Jennifer Harvey, BSc^a,
Lisa Stycharczuk, DCR(R)^a, and Sotirios Bisdas, MD^{a,c}

Clinical Implications

- IgE-mediated gadolinium contrast agent allergy can be provoked by excipients such as trometamol. Some of the apparent allergic cross-reactivity between different gadolinium-based agents as well as ionic contrast media may be excipient dependent.

TO THE EDITOR:

Despite safety concerns regarding nephrogenic systemic fibrosis associated with gadolinium-based contrast agents (GBCAs),¹ from the allergy viewpoint, GBCAs continue to be regarded as safe. GBCA-associated severe acute reactions are rare and have been reported to occur at the frequency of around 0.01%,² with multiple publications indicating their likely IgE-mediated mechanism.^{3,4}

It has been suggested that at least some of the reactions to contrast agents may be due to the excipients contained in it; however, as far as we are aware, there have been no publications identifying these excipients.

We present a case of immediate allergic reaction to gadoteridol (Prohance) provoked by trometamol, an excipient contained in the product.

Our patient, a 23-year-old woman, with history of grass pollen allergy and childhood asthma, but no previous allergic reactions to medications, underwent gadoteridol (Prohance)-enhanced magnetic resonance imaging study of the brain. This was her first exposure to GBCA or indeed any contrast agent used in clinical imaging. Within a few minutes after GBCA injection she developed itching associated with impression of tightness of her throat, vomiting, shortness of breath, and facial edema.

Ten months after her index reaction with GBCA, she was seen in our drug allergy unit. Because tryptase levels were not taken during the index event and because our patient displayed no signs or symptoms of mastocytosis, baseline tryptase was not investigated. Skin tests were performed with the index GBCA—gadoteridol (Prohance)—as well as 2 other macrocyclic GBCAs—gadobutrol (Gadovist) and gadoterate meglumine (Dotarem)—in accordance with the European Academy of Allergy and Clinical Immunology (EAACI) and European Network on Drug Allergy (ENDA) guidelines.⁵ Briefly, undiluted GBCA was used for skin prick tests (SPTs); when the result was negative, it was followed by intradermal tests (IDTs) in the range of 1:1000, 1:100, and 1:10 dilution of the aforementioned commercially available GBCAs. Neat GBCA was not used for IDT because this was previously proven irritant by other

investigators⁴ and ourselves. Specifically, we observed irritant results with these 3 agents tested intradermally at 1:1 concentration in 2 out of 3 healthy volunteers.

Our patient tested negative at the SPT stage; however, she developed clear positive reactions to IDT at 1:100 with both gadoteridol (Prohance) and gadobutrol (Gadovist). She tested negative to gadoterate meglumine (Dotarem) up to 1:10 IDT concentration. Gadoteridol (Prohance) and gadobutrol (Gadovist), but not gadoterate meglumine (Dotarem), contain trometamol excipient. We therefore proceeded to skin testing with trometamol diluted to the same concentration as that contained in the index GBCA. Our patient again tested negative at the SPT stage, but developed positive reaction to trometamol 1:1000 intradermally. Ten healthy volunteers were skin tested (SPT and IDT) with trometamol up to 1:10 intradermal concentration with no evidence of irritant effect.

Although there are reports of contact dermatitis provoked by trometamol,⁶ this is the first report of likely IgE-mediated allergy to this relatively common excipient.

Trometamol/Tromethamine (C₄H₁₁NO₃), an organic amine, is used extensively as an excipient in buffer solutions in various topical as well as enteral and parenteral products. It can also be used on its own as a buffer for the treatment of severe metabolic acidosis. In the cosmetic industry, it is used as an emulsifying agent for creams and lotions. It is not clear when and how our patient became sensitized to trometamol. However, because the substance is commonly used in adhesives, coating products, fillers, putties, plasters, inks and toners, leather treatment products, lubricants, polishes, textile treatment products and dyes, as well as perfumes and fragrances, it would be very difficult to establish this. Importantly, trometamol is contained in many enteral and parenteral medications such as cotrimoxazole for infusion, Hemabate, Humalog, Keral, Menitorix, midazolam, oxaliplatin, Skudexa, and temazepam. Patients with confirmed IgE-mediated trometamol allergy should be warned of this. Our patient denied previous allergic reactions to medications and topical cosmetic products.

Increased risk of GBCA-mediated allergic reaction in patients with previous reaction to GBCA is well documented and has been estimated to be 8 times higher than in GBCA-naïve patients.⁷ Equally, increased risk of allergic reactions to GBCA in patients with suspected hypersensitivity to iodinated contrast medium (IOM) has also been described. The first published report of likely allergic reaction to GBCA, back in 1990, involved a patient who suffered previous suspected hypersensitivity reaction with IOM.⁸ Out of the 36 patients with adverse reactions to GBCAs analyzed by Murphy et al,² 4 subjects had a history of adverse reaction to IOM.

GBCAs and IOM are structurally dissimilar and therefore unlikely to lead to IgE-mediated cross-reactivity. We therefore postulate that some of the apparent cross-reactivity reactions may be excipient dependent. Several of the commonly used IOMs such as niopam (Iopamidol), visipaque (Iodixanol), and omnipaque (Iohexol) contain trometamol.

In patients with previous hypersensitivity reactions to GBCA, an alternative GBCA is de facto chosen.² Our recommendation is however to perform skin testing with the index agent as well as

available GBCA alternatives. If future requirement for IOM is anticipated, we would also recommend skin testing with available IOMs. We postulate that some of these reactions, according to previous studies^{3,4} and our results, are IgE-mediated. However, in view of the scarcity of Drug Allergy Services,⁹ this thorough approach may not always be possible. Accounting for this limitation, we endorse in patients with known hypersensitivity to GBCA (if an unenhanced magnetic resonance imaging scan is not diagnostically useful) an alternative GBCA with a different excipient to be chosen. Equally, in patients with known hypersensitivity to IOM and when allergy opinion and skin testing are not available, GBCA containing different excipient to the one present in the index IOM should be injected. These recommendations underscore the importance of clear documentation of GBCA and IOM allergic reactions by radiologists and radiographers in terms of not only signs, symptoms, and severity but also providing details of the used agent such as GBCA class, commercial drug name, and manufacturer.

^aUniversity College London Hospitals NHS Foundation Trust, London, United Kingdom

^bNottingham University Hospital NHS Trust, Nottingham, United Kingdom

^cUniversity College London, London, United Kingdom

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 23, 2018; revised August 25, 2018; accepted for publication August 28, 2018.

Available online September 11, 2018.

Corresponding author: Joanna Lukawska, MBBS, Royal National Ear Nose and Throat Hospital, Department of Specialist Allergy and Clinical Immunology, 330 Grays Inn Rd, London WC1X 8DA, UK. E-mail: Joanna.lukawska@nhs.net.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.08.035>

REFERENCES

1. Broome DR, Girquis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR* 2007;188:586-92.
2. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. *AJR* 1996;167:847-9.
3. Bianchi L, Hansel K, Marietti R, Tramontana M, Stingeni L. Anaphylaxis after first exposure to gadoterate meglumine: a case report and literature review. *J Allergy Clin Immunol Pract* 2018;6:2124-6.
4. Galera C, Pur Ozygit L, Caviglioli S, Bousquet PJ, Demoly P. Gadoteridol-induced anaphylaxis — not a class allergy. *Allergy* 2010;65:132-4.
5. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
6. Singh M, Winhoven SM, Beck MH. Contact sensitivity to octyldodecanol and trometamol in an anti-itch cream. *Contact Dermatitis* 2007;56:289-90.
7. Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA. Clinical safety of gadopentetate dimeglumine. *Radiology* 1995;196:439-43.
8. Lufkin RB. Severe anaphylactoid reaction to GD-DTPA. *Radiology* 1990;176:879.
9. Warren AM, Malhi R, Jani Y, Corrigan C, Walker D, et al. Prevalence of reported drug allergy and its impact on beta lactam use with financial and health implications. *Arch Asthma Allergy Immunol* 2017;1:028-35.