Title: Anaphylaxis to trometamol excipient in gadolinium based contrast agents for clinical imaging.

Authors:

Joanna Lukawska MBBS[1], Deepal Mandaliya MRPharmS[2], A.W. Edith Chan PhD[3], Amy Foggitt BSc[1], Therese Bidder BSc[1], Jennifer Harvey BSc[1], Lisa Stycharczuk DCR(R)[1], Sotirios Bisdas MD[1,3]

[1] University College London Hospitals NHS Foundation Trust, London, UK

[2] Nottingham University Hospital NHS Trust, Nottingham, UK

[3] University College London, London, UK

Conflict of interest disclosure statement

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Keywords: drug allergy, gadolinium, trometamol, excipient, contrast media

Corresponding author: Dr Joanna Lukawska

Corresponding Author Mailing Address:

Royal National Ear Nose and Throat Hospital, Department of Specialist Allergy and Clinical Immunology, 330 Grays Inn Road, London WC1X 8DA, UK

Email: Joanna.lukawska@nhs.net

Telephone: 00447886596340

To The Editor:

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

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 female, with history of grass pollen allergy and childhood asthma, but no prior allergic reactions to medications, underwent gadoteridol (Prohance®) enhanced MRI 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 oedema.

Ten months after her index reaction with GBCA, she was seen in our drug allergy unit. As tryptase levels were not taken during the index event and as 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 two other macrocyclic GBCAs: gadobutrol (Gadovist®) and gadoterate meglumine (Dotarem®) in accordance with the EAACI-ENDA guidelines.[5] Briefly, undiluted GBCA was used for skin prick tests (SPTs); when 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 wasn't used for IDT as this was previously proven irritant by other investigators [4] 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 SPT stage, however, she developed clear positive reactions to IDT at 1:100 with both gadoteridol (Prohance®) as well as 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 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 tromatemol,[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 sensitised to trometamol. However, as the substance is commonly utilised 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: Co-trimoxazole 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 prior allergic reactions to medications and topical cosmetic products.

Increased risk of GBCA-mediated allergic reaction in patients with previous reaction of 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 IOM (iodinated contrast medium) 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 analysed by Murphy et al, 4 subjects had previous history of adverse reaction to IOM.[2]

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®), Omnipaque (Iohexol®) contain trometamol.

In patients with prior hypersensitivity reactions to GBCA an alternative GBCA is de facto chosen.[2] Our recommendation is however to perform skin testing with 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 MRI 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 index IOM should be injected. These recommendations underscore the importance of clear documentation of GBCA and IOM allergic reactions by radiologists and radiographers not only in terms of signs, symptoms and severity but also providing details of the used agent such as GBCA class, commercial drug name, and manufacturer.

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; 188:586–592.
2. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR 1996; 167:847–849.
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 Mar in press.

4. Galera C, Pur Ozygit L, Cavigioli S, Bousquet PJ, Demoly P. Gadoteridol-inducedanaphylaxis – not a class allergy. Allergy 2010; 65: 132–134.
5. Brockow K, Garvey LH, Aberer W, et al. 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: 289-290.
7. Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA. Clinical safety of gadopentetate dimeglumine. Radiology 1995; 196: 439–443
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: 028-035

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.

167

168

169