Editorial

Polyethylene Glycol Is a Cause of IgE-Mediated Anaphylaxis

Pedro Giavina-Bianchi, MD, PhD, and Jorge Kalil, MD, PhD *São Paulo, Brazil*

Adverse drug reactions (ADRs), the dark side of pharmacotherapy, are prevalent and may result in morbidity, hospitalization, and mortality. They account for 1% to 3% of all hospital admissions and occur in 10% to 20% of hospitalized patients, 20% of them being hypersensitivity reactions.[1] The study of ADRs is a specific field of clinical immunology and allergy that has had an impressive and solid development in the last decades. Searching the terms "adverse drug reaction" or "drug hypersensitivity" or "drug allergy" in PubMed, we observed a 30% increase in published manuscripts every 10 years since the 1990s.

Drug hypersensitivity reactions (DHRs) are a subgroup of ADRs that are unpredictable and characterized by objectively reproducible clinical manifestations, which resemble allergic reactions, initiated by exposure to a drug at a dose tolerated by normal individuals. DHRs are allergic when they are mediated by specific immune responses, involving antibodies and/or T cells.[2] DHRs are still classified according to the time elapsed from the drug administration to the reaction onset. Immediate drug hypersensitivity reactions (IDHRs) occur within 1 to 6 hours after drug exposure, often involve mast cell and basophil degranulation, and are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm, and anaphylaxis.[3]

The management of DHRs is challenging and requires training and development of specific skills. New concepts have been incorporated into our knowledge, such as direct mast cell/basophil degranulation, hapten theory, the pharmacological interaction with immune receptors (p-i) concept, the altered peptide repertoire model, the altered TCR repertoire model, the danger signal hypothesis, viral reactivation, and autoimmune mechanisms, among others.[4] As a consequence of all our learning, allergists become more decisive and essential to the proper care of patients with DHRs. Some features make the diagnosis and management of DHRs more difficult (Table I).

IDHRs to polyethylene glycol (PEG) and to structurally similar chemicals, such as polysorbates and PEG castor oils, are underrecognized and poorly understood. These substances are present in thousands of medications, cosmetics, and pharmaceutical, industrial, and food products. PEGs constitute a family of hydrophilic polymers of ethylene oxide ($H(OCH_2CH_2)_nOH$), and they are often denominated with a numerical value, which can indicate the average number of ethylene oxide units in each molecule (ie, PEG 75; term used in the cosmetic industry), or the average molecular weight (ie, PEG 3350; MW in g/mol; term used in the pharmaceutical industry). However, there are several synonyms for PEGs, such as macrogol, rendering identification and avoidance challenging.[5] Although low-MW PEGs are easily absorbed through the gastrointestinal tract and skin, most reactions are induced by high-MW (>1000 g/mol) PEGs, as we see with macrogol bowel preparations and parenteral steroid depot formulations.[5,6]

TABLE I. Difficulties in the diagnosis and management of DHRs

Most drugs act as haptens.
The culprit agent of a DHR may be the drug metabolite and not the drug itself.
The culprit agent of a DHR may be a drug excipient* and not the drug itself.
DHRs may be allergic or nonallergic.

*Drug excipient (preservative, colorant, diluent, etc).

IDHRs to PEGs may be severe and rapid in onset, and reactions are associated with PEG MW, dose, and absorption rate. As with other IDHRs, each patient would have an individual reactivity-threshold. The mechanisms involved in IDHRs to PEGs are not fully understood, but a recent review assessing 37 cases suggested that most of the reactions could be IgE-mediated. Although serum specific IgE was not detected in any case, clinical history, skin testing, and basophil histamine release and activating tests indicated an IgE-mediated mechanism.[5] One study must be highlighted, because the authors could abolish PEG-induced basophil histamine release with both patient's serum preincubation with PEG and omalizumab.[7]

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Stone et al,[8] studying 2 cases of IDHRs to PEG, further elucidated the immune mechanisms involved in these reactions. The authors, for the first time, detected serum specific IgE to PEG, confirming that at least some of these IDHRs are allergic.[8] Skin testing helped in confirming the diagnosis and to identify cross-reactivity with PEG-related compounds and thus should be included in the diagnostic algorithm.[8] The present study heightens the awareness and understanding of PEG allergy.

Clinical Immunology and Allergy Division, University of São Paulo, São Paulo, Brazil

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

Received for publication May 3, 2019; accepted for publication May 3, 2019.

Corresponding author: Pedro Giavina-Bianchi, MD, PhD, R. Prof. Artur Ramos 178 ap.211A, Jd. América, São Paulo, SP 01454 010, Brazil. E-mail: pbianchi@usp.br.

J Allergy Clin Immunol Pract 2019;7:1874-5.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

https://doi.org/10.1016/j.jaip.2019.05.001

REFERENCES

1. Ribeiro MR, Motta AA, Marcondes-Fonseca LA, Kalil-Filho J, Giavina-Bianchi P. Increase of 10% in the rate of adverse drug reactions for each drug administered in hospitalized patients. Clinics (Sao Paulo) 2018;73:e185.
2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature

Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832-6.
3. Giavina-Bianchi P, Aun MV, Kalil J. Drug-induced anaphylaxis: is it an epidemic? Curr Opin Allergy Clin Immunol 2018;18:59-65.
4. Chen CB, Abe R, Pan RY, Wang CW, Hung SI, Tsai YG, et al. An updated review of the molecular mechanisms in drug hypersensitivity. J Immunol Res 2018;2018:6431694.
5. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy 2016;46:907-22.
6. Kennard L, Rutkowski K, Mirakian R, Wagner A. Polyethylene glycol: not just a harmless excipient. J Allergy Clin Immunol Pract 2018;6:2173.
7. Wenande EC, Skov PS, Mosbech H, Poulsen LK, Garvey LH. Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: a case of probable polyethylene glycol allergy. J Allergy Clin Immunol 2013;131:1425-7.
8. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 2019;7:1533-1540.e8.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.