Excipients as potential agents of anaphylaxis in vaccines: analyzing the formulations of the current authorized COVID-19 vaccines

Caballero ML, Quirce S

Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain.

Corresponding:

María Luisa Caballero

Department of Allergy

La Paz University Hospital, IdiPAZ

Paseo de la Castellana, 261. 28046 Madrid, Spain

E-mail: mlcsoto@hotmail.com

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To the editor:

The aim of this letter is to provide a brief update on the excipients as potential agents causing immediate hypersensitivity reactions (IHRs) in vaccines, with a special focus on those excipients present in the formulations of the vaccines developed so far against the current pandemic of coronavirus disease (COVID-19) produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

IHRs occurring with the administration of vaccines are frequently due to some of the excipients contained in their formulations. In some cases, a previous sensitization to any of its excipients is the cause of the reaction, as shown in a study to confirm the relation between systemic allergic reactions to vaccines and the presence of anti-gelatin IgE in children who demonstrated allergy to gelatin-containing vaccines [1]. A study described the cases of four children with IgE-mediated systemic reactions to gelatin included in a varicella vaccine, where two of the children had anaphylaxis and the other two generalized urticaria, after the vaccination [2]. Another excipient involved in the IHRs occurred with vaccines is polysorbate (PS) 80 (PS80). As example, a case of

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anaphylaxis was reported after third administration of quadrivalent human papilloma virus vaccine (Gardasil), which contains PS80 [3].

Regarding PS80, PSs are polyethylene glycol (PEG) derivatives, specifically PEG sorbitans [4]. PEGs, (H(OCH2CH2)nOH) (PubChem CID 174, https://pubchem.ncbi.nlm.nih.gov/compound/1_2-Ethanediol), are synthesized by polymerization of ethylene oxide, resulting polymers vary in chain length and molecular weight (MW). PEG and all its derivatives in addition to PSs, including PEG ethers (laureths, ceteths, ceteareths, oleths), PEG fatty acid esters (PEG laurates, dilaurates, stearates and distearates), PEG amine ethers, PEG castor oils, PEG-propylene glycol copolymers (poloxamers), and PEG soy sterols, are present as excipients in a great number of pharmaceutical products and cosmetics [4], and they have been identified as the culprit agents of an important number of reported IHRs [reviewed in 5]. On the other hand, PEGs have also been employed in polymer-based drug delivery. With the name of PEGylation is known the attaching of PEGs to systemic drugs to increase MW, prolong circulation time and shield the drug from the immune system by preventing opsonization. Thus, in terms of PEG hypersensitivity it is necessary include PEGs, the structurally similar PEG derivatives and PEGylated drugs [4].

The three COVID-19 vaccines that are being administered with Emergency Use Authorization (EUA) so far are the Pfizer-BioNTech (BNT162b2), the Moderna (mRNA-1273) and the AstraZeneca (ChAdOx1-S [recombinant]). The vaccines composition and the full list of their excipients are shown in Table I.

The COVID-19 mRNA vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2, and embedded in lipid nanoparticles (LNPs)

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(https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine). This vaccine contains PEG 2000 as potential agent causing IHRs.

The Moderna (mRNA-1273) COVID-19 vaccine contains a synthetic mRNA encoding the pre-fusion stabilized S protein of SARS-CoV-2 and formulated in LNPs (https://www.fda.gov/media/144434). This vaccine contains PEG 2000 and tromethamine (PubChem CID 6503, https://pubchem.ncbi.nlm.nih.gov/compound/2-Amino-2-hydroxymethyl-propane-1-3-diol), as potential agents causing IHRs. Tromethamine or trometamol have been recently reported as culprit of anaphylaxis occurred with a preparation of gadoteridol (Prohance), a gadolinium-based contrast agent [6].

The AstraZeneca (ChAdOx1-S [recombinant]) is based in a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 S glycoprotein, produced in genetically modified human embryonic kidney (HEK) 293 cells (https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca). This vaccine contains PS80 as potential agent causing IHRs.

As described above, two of the vaccines, Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273), are formulated in LNPs or PEGylated liposomes (PEGLip). PEGlip are artificial phospholipid vesicles that have proven to be useful in stabilizing drugs and improving their pharmacological properties [7], and in the case of these COVID-19 vaccines, this formulation in liposomes allows preserve the mRNA given its lability [8].

In relation to excipients, it is important to highlight two points to take account before the administration of any vaccine or medication in general. First, it has been reported IHRs with unrelated products due to a common excipient [5]. As example, the case of a patient who suffered anaphylaxis after the intake of a laxative solution during bowel

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preparation and reactions after the application of a sunscreen and with the use of a toothpaste, all of which were PEG-containing products [9]. Second, the possibility of cross-reactivity between PEGs and all of their derivatives [4]. These facts reinforce the importance of check all the excipients that could be present in the formulation of a vaccine, as well as consider in which other products could be contained, including medications, foods or cosmetics, in order to perform an exhaustive search of possible antecedents of hypersensitivity [10].

As conclusion, excipients contained in vaccines, some of which are present in the novel SARS-CoV-2 vaccines authorized so far, can give rise to hypersensitivity reactions. A thorough clinical history should be obtained in patients with a previous history of allergic reactions to vaccines or excipients contained in medications and cosmetics, as well as an appropriate allergological assessment, in order to prevent sudden hypersensitivity reactions to vaccination.

Specific financial sources have not been received or used for this study.

Conflicts of Interest:

Dr. Quirce reports personal fees and non-financial support from GSK, AstraZeneca, Sanofi, Novartis, Mundipharma, Teva and Allergy Therapeutics, outside the submitted work.

Dr. Caballero has not conflict of interest to declare.

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References

1. Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. J Allergy Clin Immunol. 1996;98:1058-61.

2. Sakaguchi M, Yamanaka T, Ikeda K, Sano Y, Fujita H, Miura T, et al. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. J Allergy Clin Immunol. 1997;99:263-4.

3. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. BMJ Case Rep. 2012;2012.

4. Wenande E, Garvey L. Immediate-type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy. 2016;46:907-22.

5. Caballero ML, Quirce S. Immediate hypersensitivity reactions caused by drug excipients: A Literature Review. J Investig Allergol Clin Immunol. 2020;30:86-100.

6. Lukawska J, Mandaliya D, Chan AWE, Foggitt A, Bidder T, Harvey J, et al. Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging. J Allergy Clin Immunol Pract. 2019;7:1086-7.

7. Zamboni WC. Concept and clinical evaluation of carrier-mediated anticancer agents. Oncologist. 2008;13:248-260.

8. Kim H, Park Y, Lee JB. Self-assembled Messenger RNA Nanoparticles (mRNA-NPs) for Efficient Gene Expression Sci Rep. 2015;5:12737.

9. Shah S, Prematta T, Adkinson NF, Ishmael FT. Hypersensitivity to polyethylene glycols. J Clin Pharmacol. 2013;53:352-5.

10. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current

Evidence and Approach. J Allergy Clin Immunol Pract. 2020 Dec 31:S2213-2198(20)31411-2.

Table 1. Composition of the three COVID-19 vaccines that are being administered with Emergency Use Authorization (EUA) so far.

Pfizer-BioNTech (BNT162b2)	**Moderna (mRNA-1273)**	**AstraZeneca (ChAdOx1-S [recombinant])**
mRNA encoding the viral spike (S) protein of SARS-CoV-2 virus	Synthetic m (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus	Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein
ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate)	Lipid SM-102	L-Histidine
ALC-0159 = 2-[(**polyethylene glycol)-2000**]-N,N-ditetradecylacetamide	1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000 [**PEG2000**-DMG]	L-Histidine hydrochloride monohydrate
1,2-Distearoyl-sn-glycero-3-phosphocholine	cholesterol	magnesium chloride hexahydrate
cholesterol	1,2-distearoyl-snglycero-3-phosphocholine [DSPC]	**polysorbate 80**
potassium chloride	**tromethamine**	ethanol
potassium dihydrogen phosphate	tromethamine hydrochloride	sucrose
sodium chloride	acetic acid	sodium chloride
disodium hydrogen phosphate dihydrate	sodium acetate	disodium edetate dihydrate
sucrose	sucrose	

Excipients marked in bold are potential agents for immediate hypersensitivity reactions, as they have been involved in previously reported reactions.

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