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CORRESPONDENCE

Other excipients than PEG might cause serious hypersensitivity reactions in COVID-19 vaccines

To the Editor,

The availability of new vaccines against SARS-CoV-2 brings promising opportunities to prevent people from getting infected and developing COVID-19. As with other drugs, vaccines can cause adverse drug reactions (ADRs). Although generally the ADRs to vaccines are mild and serious reactions are very rare,[1] anaphylactic reactions were reported after administration of COVID-19 vaccines.[2] Cabanillas et al provide valuable background information that these anaphylactic reactions might be caused by polyethylene glycols (PEGs) that are part of lipid nanoparticles (LNPs) of mRNA-vaccines.[2] We agree that PEGylated liposomes are one of the possible excipients responsible for anaphylaxis. Given the little experience so far with the use of PEGs in vaccines, focus on PEGs is easy to understand. However, in this letter we would like to suggest that other excipients in the new COVID-19 vaccines might also be the cause of anaphylaxis or serious hypersensitivity reactions.

The mRNA-vaccines are composed of LNPs stabilized by buffers, ions and sucrose. The adenovirus-based AstraZeneca vaccine is stabilized by a combination of excipients including a buffer/oxidation inhibitor (histidine), non-ionic surfactant (polysorbate 80) and a metal-ion chelator ethylenediaminetetraacetic acid (EDTA).[3] Table 1 lists the excipients of the vaccines currently used in the European

TABLE 1 Excipients in the COVID-19 vaccines Comirnaty, Moderna, and AstraZeneca and their functions

Type of excipient	Excipient[a]	Vaccine
Lipid nanoparticles: stability and transport of mRNA		
PEGylated lipids[b]	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)	Comirnaty
	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)	Moderna
Phospholipids[c]	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)	Comirnaty, Moderna
Lipids	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)	Comirnaty
	Lipid SM-102 (patented ionizable lipid)	Moderna
	Cholesterol	Comirnaty, Moderna
Buffer: Stability of lipid nanoparticles/radical oxidation inhibition		
Phosphate buffer	Potassium dihydrogen phosphate/disodium phosphate dehydrate	Comirnaty
Tromethamol[b]	Tromethamol/tromethamol hydrochloride	Moderna
Acetic acid/acetate	Acetic acid/sodium acetate trihydrate	Moderna
Histidine	L-histidine/L-histidine hydrochloride monohydrate	AstraZeneca
Other stabilizers: Ionic strength, surfactant, metal-ion chelates		
	Potassium chloride	Comirnaty
	Sodium chloride	Comirnaty, AstraZeneca
	Magnesium chloride hexahydrate	AstraZeneca
	Ethanol	AstraZeneca
	Disodium edetate dihydrate (EDTA)[b]	AstraZeneca
	Polysorbate 80[b]	AstraZeneca
Thermostabilization	Sucrose	Comirnaty, Moderna, AstraZeneca

[a] Excipients according to SmPC published on the EMA website (Comirnaty and Moderna) and the information for UK recipients on COVID 19 Vaccine AstraZeneca (Updated 7 January 2021) on the UK governmental website.

[b] Serious hypersensitivity reactions have been related to the substance.[5,6]

[c] No hypersensitivity reactions have been reported, yet reactions to other phospholipids in pollen were described.[4]

Union and the United Kingdom. There are examples of phospholipids in pollen that were involved in hypersensitivity reactions.[4] Both the Comirnaty and Moderna vaccine contain distearoylphosphatidylcholine (DSPC), a phospholipid that is part of the LNPs. Although no anaphylaxis or other allergic reactions to DSPC have been described, it should be considered as a potential allergen. Moreover, the Moderna vaccine contains tromethamol as buffer. One case report was published with anaphylaxis to tromethamol as excipient in an intravenously administered radio contrast agent.[5] In addition to the PEGylated liposomes, these two excipients should be considered as potential allergens.

So far, anaphylaxis has not been reported after administration of the AstraZeneca vaccine that has been used in the United Kingdom since January 4th. Also this vaccine contains excipients that were related to systemic hypersensitivity reactions, and these should be considered in case patients develop serious reactions after exposure. The AstraZeneca vaccine contains polysorbate 80 and EDTA as potential allergens. Cabanillas described how polysorbates might cause anaphylaxis and that cross-reactivity between polysorbates and PEGs is likely given the shared chemical moiety.[2] Allergic reactions to EDTA are generally limited, but might include systemic reactions. Russo described a patient with a systemic allergic reaction to EDTA in local anaesthetic and radiocontrast media.[6] As far as we know, other excipients of the current COVID-19 vaccines have not been associated with serious reactions.

To analyse potential hypersensitivity reactions in patients, skin tests for the vaccine and its excipients should be performed. If test results are negative, the vaccine can be administered under 30-min observation. The observation period is needed, as false negative results for skin tests are possible. Also, suspected individuals can receive the vaccine in graded doses, with adrenaline ready for emergency management. If positive, an alternative vaccine without the suspected excipient can be given under observation. An alternative vaccine may also be considered in case of shortage of vaccines or logistic issues. Allergologic work-up with the vaccine components should be performed before vaccination.

We conclude that in case of serious hypersensitivity reactions, also excipients other than PEG should be evaluated as causative agents. Healthcare professionals should be made aware of these risks, evaluate previous allergies before vaccination and inform patients well. Given the low risk, and the positive risk-benefit balance, there is no reason to avoid vaccines. We suggest that any patient with a possible vaccine-associated, serious hypersensitivity reaction in the past should be thoroughly evaluated by means of an allergologic work-up.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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