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Cardiac and respiratory arrest due to PEG contained in SonoVue® among others our diagnosis experience

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Abstract

Purpose of case report: Near-fatal anaphylaxis reactions after the use of SonoVue® contrast-agent can also be related to drugs and COVID-vaccines allergy due to polyethylene glycol or derivatives.

Recent findings: Knowledge of the mechanisms involved has made it possible guide the diagnosis, especially the ex-vivo diagnosis of BAT, avoiding skin tests and allowing study with other drugs such as COVID and influenza vaccines.

Summary: These cases report focuses on severe adverse reactions to SonoVue® contrast-agent and oral drugs containing PEG, emphasizing in the BAT diagnosis of allergic reactions. Basophil activation test seems to be a useful tool for the diagnosis of these high-risk allergic patients. A diagnostic pathway is suggested that, on the one hand, enables to use BAT to the involved drug and on the other hand, supports administration of subsequent drugs depending of the result of BAT to others containing PEG.

Keywords: SonoVue®, COVID-vaccines, Polyethylene glycol, Polysorbate, Allergy, BAT.

Introduction

SonoVue® (Bracco; Milan, Italy) is an enhancing-ultrasound agent that contains microbubbles with an outer layer composed of phospholipids (which contains macrogol 4000) that surrounds the sulfur hexafluoride gas inside. Sulfur hexafluoride is the active ingredient of SonoVue but macrogol -as excipient- is considered the most involved in adverse reactions induced by this

contrast. It is currently recognized that SonoVue® has a good safety profile, and the incidence of severe adverse reactions is between 0.0086% and 0.9%. Most adverse reactions reported were mild, including skin erythema, tachycardia, and palpitations. However, anaphylactic shocks and fatal reactions were scattered Ly reported and even fatal cases were documented in the literature [1-3]. It is likely that these serious reactions attributed to Macrogol are caused by an allergic reaction mediated by an IgE-mediated hypersensitivity mechanism or by a pseudo allergic mechanism attributed to C activation-related pseudo allergy-like syndrome (CARPA). Macrogol or polyethylene glycol (PEG) is a strong allergen and therefore, skin testing must be done carefully [4,5]. Specific immunoglobulin E (IgE) to Ethylene Oxide (EO), a monomer of PEG, is the only available in vitro test by CAP system (Thermo Fisher Scientific) designed for studying EO allergy.

Cross-reactivity allergic reactions have been described between macrogol/PEG and structurally related polysorbate (P) or tween [6,7].

Recently, a possible relationship between adverse reactions to m-RNA COVID vaccines containing PEG and SonoVue® have been reported [8]. In fact, the American Society of Echocardiography, has taken a consensus statement in this regard [9].

From January 2016 to December 2021, our Cardiology Department in Vitoria (Basque Country, Spain) has recorded 5 cases of severe reactions to SonoVue®, out of a total of 2,200 intravenous injections approximately. The first one was published by our group in 2017 [1] and the remaining 4 cases, have been observed in the last two years.

In addition, 2 patients with suspicion of allergy to PEG contained in oral drugs have been studied, in order to confirm cross-reactivity or co-sensitization to SonoVue®.

Case reports

Aim

To study whether Basophil Activation Test (BAT) detects sensitization to SonoVue®, COVID vaccines and other drugs that share the same or a similar excipient, in order to prevent future allergic reactions, without the need for skin testing if not strictly necessary.

Materials & Methods

Here, we present 6 patients (3 females and 3 males): the first 4 patients developed immediate severe reactions (including cardiac arrest in one of them), due to the intravenous administration of SonoVue®; and the last two patients after the intake of PEG contained in 2 different oral drugs: Omnic Cas® (macrogol 7,000,000 and 8,000) and Casen lax® (macrogol 4,000) respectively.

Patients 1-3 presented itching, erythema, hypotension, shivers, abdominal pain, dyspnea with oxygen desaturation and patient 4 presented the most severe reaction consisting of cyanosis, oral and plantar itching and subsequently cardiac arrest. Patients 5 and 6 also presented loss of consciousness and hives due to oral drugs intake and patient number 5 also associated respiratory arrest and arrhythmic tachycardia.

Epinephrine, corticosteroids, fluid therapy and antihistamines rapidly improved patients but all were admitted to the hospital for at least 24 hours and the two most severe cases, in the Intensive Care Unit.

Other data regarding prior exposure to PEG were suspected in most patients (4/6). In fact, patient 1 had previously received PEGylated chemotherapy; patient 2 and 3 had been exposed to SonoVue® and patient 4 suffered from gastric ulcer sclerosed 24 hours before

reaction as a compounding factor that could explain a greater passage of PEG through the digestive tract. Due to the pandemic, exposure to PEG from COVID vaccines cannot be excluded and the patients requested guidelines regarding vaccination. Patient 1 and 2, wanted to be vaccinated against COVID, patient 3 suffered from COVID infection. Patient 4 received 3 doses of Spikevax® and patients 5-6 received 2 doses of Vaxzevria® previously. Patient 1 and 6, wanted to be vaccinated against flu containing PEG- derivatives as excipients.

All cases have been studied by BAT to SonoVue® and to the available COVID vaccines at the time of the study: Pfizer/BioNTech (Comirnaty ®) and Moderna (Spikevax ®) containing PEG 2,000; Johnson- Johnson (Janssen vaccine ®) and AstraZeneca (Vaxzevria ®) containing P 80, using the discarded remnant material.

BAT was assessed in heparinized whole blood after stimulation with either SonoVue® (1/40 and 1/200) (figure 1), Comin arty® and Spikevax® at 2.5 and 0.5 µg/mL; Janssen vaccine® and Vaxzevria® at 1/40 and 1/200) and macrogol 4000 (Casen lax ®) at 1 and 0.5 mg/mL.-formyl-methionyl-leucyl-phenylalanine (fMLP) and anti-IgE antibody (Sigma-Aldrich, St. Louis, Missouri, USA) were used as positive controls. Cytofluorometric analysis of CD63+ cells on at least 300 CD123high DR dim cells were performed (FACs Cali bur, Becton-Dickinson). The test was carried out in 6 healthy individuals to exclude the ability of the SonoVue® or mRNA COVID vaccines to elicit nonspecific activation of basophils.

Depending on individual need, assessing the risk/benefit and with the approval of the patients, prick tests as it were carried out to SonoVue® (patient 1 and 2) and flu vaccines: Fluarix tetra® (P80 and octoxinol 10) and Flucelvax tetra® (traces of P80) in patient 1 and 6. Skin testing to COVID vaccines (prick 1/1 and Intradermal (ID) (1/100)) were performed in patients 1-3. More than 50 skin tests were negative as the same concentrations in other patients with suspected adverse reactions to vaccines or other drugs containing PEG in our Allergy Department.

Specific IgE to EO and baseline serum tryptase was done in all cases. Acute serum tryptase were collected in 3 cases during the reaction.

Results & Discussion

The most relevant data from the allergy study and results are summarized in Table I.

In the acute event, tryptase was elevated in all cases collected (3/3) and baseline tryptase was lower in 3 cases (see Table I). These results suggest a type I reaction of hypersensitivity or at least, a mast cell activation induced by these drugs.

Ethylene oxide has been involved as a cause of allergic reactions during dry sterilize artificial kidneys and intraoperative allergic reactions. In our report cases, specific IgE to EO was negative in all cases suggesting that this component does not contribute to the allergic response**.**

Basophil activation test (BAT) could be considered as a diagnostic tool for selected patients and selected drugs, when the test is available, particularly for patients who experienced severe reactions and when diagnosis cannot be stablished by serum-specific IgE and skin testing, in order to avoid unnecessary drug provocations tests [10]. BAT results varied accordingly to the class of the drug studied, and have promising results in immediate hypersensitivity reactions to NSAIDs (pyrazolone), neuromuscular blocking agents, beta-lactams, and platinum compounds, all examples of classical IgE-

mediated hypersensitivity drug reactions. Only one patient was not evaluable by BAT (Case 1), a common handicap that presents this technique, for this reason 3 cases induced by SonoVue® and 2 by oral drugs will be discussed below. Regarding the results of SonoVue® BATs from SonoVue® patients 2 out of 3 were positive and 2/2 induced by oral drugs. These positive results suggest an activation of basophils and possibly mast cells that results in severe anaphylactic reactions reported. One of the most surprising findings is that not only patients allergic to SonoVue® respond with BAT, but those allergic to oral drugs also did. This finding points to the possibility that patients allergic to oral PEG may have problems with severe reactions to SonoVue® even though it is the first time they receive it.

Regarding the COVID vaccines BAT results, 4 out of 5 were positive, two from SonoVue® patients and two from oral drug patients. Again, the possibility that patients allergic to PEG by SonoVue® may react with another PEG containing- drugs such as vaccines is highlighted. New sources of exposure to PEG, such as COVID vaccines and chemotherapy, have been able to contribute to the increase in cases registered in the last two years.

Skin tests performed on 4 patients were positive in 1/3 cases to COVID vaccines, 1/2 cases to flu vaccines and negative to SonoVue® in the 2 cases done.

The first patient with a non-evaluable BAT, had a negative cross-reactivity study and therefore, an anaphylactoid reaction or CARPA was suspected [2]. He tolerated vaccines without PEG, containing P80 and octoxinol 10 with antihistamine pre-treatment.

Due to the results of the study realized and due to Janssen® and flu vaccines do not contain PEG as such, they were preferably recommended in patients with these severe reactions to SonoVue® or oral PEG-containing drugs. Three out of 4 patients induced by SonoVue® tolerated Janssen® (2) and flu vaccine (2).

BATs with SonoVue® were positive in 3/4 evaluable patients. In the cases where COVID or flu vaccine tests were done (4/6), two positive results were obtained, confirmed by BAT to COVID vaccines.

In addition, in the 2 cases with severe allergy to oral drugs, both presented positive BAT results to SonoVue® and COVID vaccines containing PEG. Once again, these results suggest that patients sensitized to oral high molecular weight PEG show some cross-reactivity with other PEG-containing drugs. These findings had not been previously described in PEG-sensitized patients from chemotherapy. Therefore, in these severe cases, the use of PEG-containing drugs seems at least controversial.

Allergy to PEG has been increasingly reported in recent years and patients diagnosed with allergy to this excipient generally experience recurrent systemic reactions with several types of drugs. Various characteristics of the cases studied have led to consider PEG as a hidden allergen in drugs. In the PEG allergy study, the complexity of its management is combined due to the severity of the symptoms and the risk of skin tests. Intradermal test should be systematically avoided or performed with caution, especially in patients with comorbid conditions or history of severe reaction [11].

Conclusions

These are the first cases of severe reactions due to SonoVue® studied by BAT to this contrast, showing usefulness for the diagnosis and prevention of possible subsequent allergic reactions against other treatments that contain the same or similar excipients.

BATs with SonoVue® and COVID vaccines seem to be useful due to positive evaluable results obtained (8/10). A

diagnostic pathway is suggested that, on the one hand, allows the necessary precautions to be taken in people with a history of severe allergy of the cardiorespiratory arrest type, and, on the other hand, supports the administration of subsequent doses of COVID or flu vaccines according to these results.

The data suggest that there may be co-sensitization to different PEGs present in oral drugs, SonoVue® and vaccines and cross-reactivity in the cases due to macrogol 4,000 contained in SonoVue® and Casen lax®. Anaphylactoid reactions can also occur and Epinephrine is essential in the treatment and resolution of all cases.

Surprisingly, in cases with severe allergy to oral drugs due to PEG, BAT seems to be useful not only in diagnosis, but also in the additional SonoVue® and COVID vaccines- BAT study suggesting cross-reactivity and caution in its use.

Not only allergists should be aware of possible serious reactions to SonoVue®, but also other specialists due to new sources of sensitization and the increased use.

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Abbreviations

PEG: polyethylene glycol

IgE: immunoglobulin E

EO: Ethylene Oxide

P: polysorbate

BAT: Basophil Activation Test

fMLP: N-formyl-methionyl-leucyl-phenylalanine

ID: Intradermal

ANAS: antinuclear antibodies

Anti TPO: thyroperoxidase antibodies

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Legend Tables

Table 1: Patient characteristics

Patient / drug	1 SonoV®	2 SonoV®	3 SonoV®	4 SonoV®	5 Omnic Cas®	6 Casen®
Age (y)/ Sex	54 ♀	55 ♂	73 ♂	64 ♀	89 ♂	62 ♀
Acute tryptase	Nd	13.1 - 5.3	Nd	14.10	23.4	Nd
Baseline tryptase	2.1	5.5	8.64	8.3	12.3	3.08
BAT Sono V® (%)	Ne	+ 12	+ 27	-	+ 15.3	+ 13.2
BAT PEG/P80 vaccines (%)	Ne	+ 8.7 Pf + 9.6 Mo + 10.3 Jo - AZ	- Mo - Jo	+ 15.2 Pf + 11.1 Mo + 12.5 Jo - AZ	+ 30.8 Pf + 28.4 Mo Jo	+ 61.9 Pf + 64.9 Mo + 24.1 AZ + 14.8 Jo - Flua
Prick SonoV® Casen®	-	-	Nd	Nd	Nd	Nd
Positive skin tests PEG/P80 vaccines	-	+ ID Pf®:9x8 Mo®:8x8	-	Nd	Nd	+ Prick Flua® Flucel®
Alternative vaccine tolerated	Jo®* Flua®*	Jo®	Flua®	-	-	-

Table I abbreviations: y, years; Nd, Not done; BAT, Basophil Activation Test; Ne, Not evaluable; PEG, Polyethylene glycol; P80, Polisorbate 80; ID, intradermal; Pf, Pfizer vaccine; Mo, Moderna vaccine; Jo Johnson- Johnson; AZ, AstraZeneca vaccine; Fluarix®, Fluarix tetra vaccine®; Flucelvax®, Flucelvax tetra vaccine

* Antihistamine pretreatment was performed 2 hours before vaccination. Skin tests: mm; Tryptase µg/L (range 0,00-11,50)

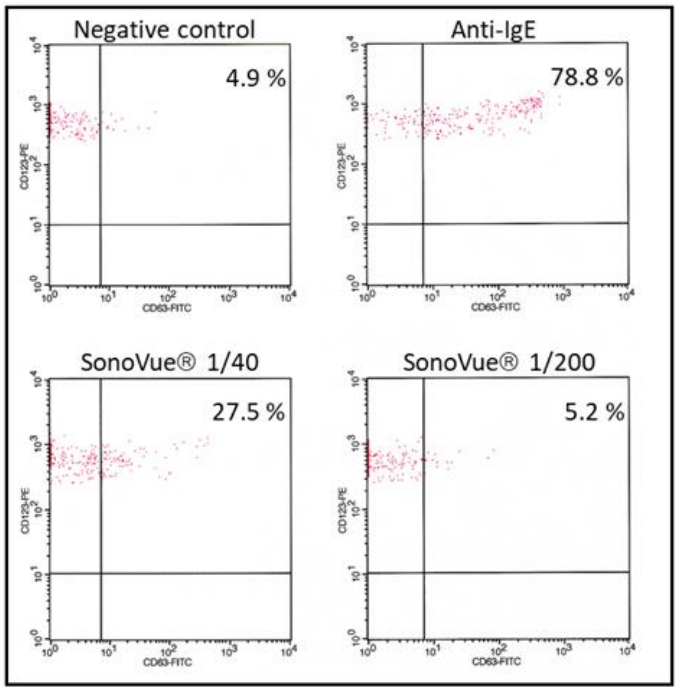

Figure 1: Patient 3 SonoVue® Basophil Activation Test images.

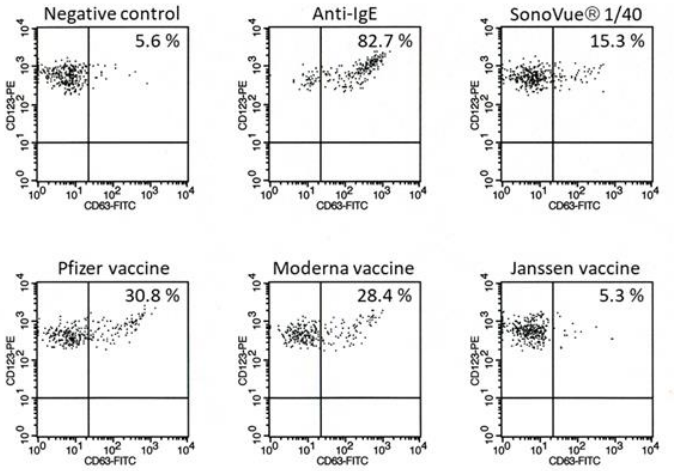

Figure 2. Patient 5 Basophil Activation Test images.

Figure 2: Patient 5 SonoVue® and COVID vaccines Basophil Activation Test images