Anaphylactic Reactions with Three Non-Related Drugs (Gadoteridol, Paclitaxel, Bevacizumab) In a Patient with Severe Comorbidities

González-Bravo L[1], Laiseca García J[1], Alonso-Díaz-de-Durana MD[1], Nieto Nieto A[1], Álvarez-Twose I[2], Tejedor Alonso MA[1], Alfaya Arias T[1]

[1]Allergy Unit. Hospital Universitario Fundación Alcorcón, Madrid

[2]Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast), Hospital Virgen del Valle, Toledo

Each named author states their contribution in all four requirements approved by the International Committee of Medical Journal Editors (ICMJE)

Corresponding author

Lucía González Bravo

Allergy Unit, Hospital Universitario Fundación Alcorcón

Calle Budapest 1, 28922, Alcorcon, Madrid, Spain

Email: luciagonzalezb92@gmail.com

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0729

© 2021 Esmon Publicidad

Key words: Anaphylaxis. Chemotherapy. Monoclonal antibodies. Excipients. Multiple drug hypersensitivity syndrome.

Palabras clave: Anafilaxia. Quimioterapia. Anticuerpos monoclonales. Excipientes. Síndrome de hipersensibilidad a múltiples fármacos.

Multiple Drug Hypersensitivity Syndrome (MDHS) confirmed with a positive allergy study is unusual. A few cases have been described in literature, mainly related to delayed reactions while immediate ImmunoglobulinE(IgE)-mediated cases are exceptional[1]. We describe a case of MDHS where all episodes were immediate reactions.

A 66 year-old woman without a history of allergic diseases, but suffering a high-grade ovarian and fallopian tube carcinoma, high blood pressure, and anky losing spondylitis treated with prednisone-5mg and an angiotensin-II-receptor-blocker, experienced an anaphylactic shock (skin and respiratory involvement, hypotension, Glasgow score 3) immediately after the first administration of Gadoteridol during a magnetic resonance imaging, requiring admission in the intensive care unit.

One month later, after the infusion of 5mL of Paclitaxel during her first chemotherapy cycle, she had an immediate, severe anaphylaxis (skin and digestive involvement, hypotension) requiring antihistamines, corticosteroids, intravenous fluid and oxygen treatment. The remaining drugs (Carboplatin and Bevacizumab) were administered the following day without complications.

During the second chemotherapy cycle, she presented a new anaphylactic episode 3 minutes after starting Bevacizumab infusion, consisting of facial and palmar itching erythema, abdominal pain, nausea/vomiting and dyspnea (baseline $SatO_2$88%), recovering after antihistamines, corticosteroids and oxygen treatment. The patient tolerated Carboplatin the following day.

We carried out an allergy workup including a basal serum tryptase (4µg/L), a total IgE value (44UI/mL), skin prick tests (SPT) to aeroallergens and hazelnut (negatives) and skin tests (ST) to Gadoteric Acid, Gadoteridol, Paclitaxel and Bevacizumab, which were positive for Gadoteridol in SPT and Paclitaxel in intradermal test (IDT) (Table 1).

 © 2021 Esmon Publicidad
doi: 10.18176/jiaci.0729

Accepted Article

Because Paclitaxel was the most effective option for the patient´s carcinoma, desensitization with premedication (corticosteroids and antihistamines) was programmed. During the first desensitization session, 2 minutes after starting the first step (calculated dose administered of 1.7mcg), she presented an anaphylactic episode with skin, digestive and respiratory involvement, requiring epinephrine. Serum tryptase increased up to 22.8µg/L2 hours after the symptom's onset, with further decrease to 3.39µg/L in 24hours.

Paclitaxel treatment was discontinued after a risks-benefits analysis by her oncologist and allergist. The oncologist scheduled an alternative chemotherapy regimen with Gemcitabine and Carboplatin which was administered during six chemotherapy cycles without complications, followed by surgery resulting in patient´s carcinoma remission.

We tried to find an explanation to these four severe anaphylaxis.

Firstly, we considered the possibility of a clonal mast cell activation disorder (cMCAD) as a subjacent cause. We calculated the Spanish Network on Mastocytosis (REMA)score of each reaction obtaining negative values in all episodes except for that related with Gadoteridol(+2) indicating a high risk of cMCAD and the need for further mast cell clonality studies[2]. According to REMA recommendations, a peripheral blood sample was sent to the Spanish Mastocytosis Reference Center (CLMast), for the study of the D816V KIT mutation by allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR). This mutation wasn´t detected.

Secondly, we considered a potential sensitization to excipients as the cause of reactions to different non-related drugs. We reviewed each of the three involved drugs composition, but we did not find a common excipient. However, Cremophor EL® (CrEL; Macrogolglycerol-Ricinoleate), contained in Paclitaxel, has been described as a cause of IgE-mediated allergic reactions due to Polyethylene glycol (Macrogol) included in CrEL. In addition, cross-reactivity between CrEL and Polysorbate contained in Bevacizumab has been described[3]. Consequently, SPT were carried out with Polyethylene glycol and Polysorbate with negative results (Table 1). Therefore, we reasonably discarded sensitization to excipients as cause of the reactions to non-related drugs.

Finally, a MDHS was suspected in our patient. MDHS has been described in literature as a rare entity (prevalence of 0.6-2.5%) that involves a positive allergy study to ≥2

© 2021 Esmon Publicidad
doi: 10.18176/jiaci.0729

Accepted Article

chemically different drugs, being more frequent (10-18%) in severe delayed skin reactions such DRESS[1].

The positive ST to Paclitaxel and Gadoteridol found, suggest an IgE-mediated mechanism as cause of the immediate reactions. Immediate hypersensitivity is uncommon in MDHS. In a recent retrospective study[1]including>9000 patients with a suggestive history of drug allergy, only 45 patients were confirmed to have a MDHS, and exceptionally in 10 patients all the reactions were immediate.

In consequence, we report a patient who has suffered four severe anaphylaxis after administration of three different non-related drugs (Gadoteridol, Paclitaxel, Bevacizumab) that are uncommon causes of anaphylaxis.

The prevalence of immediate reactions to magnetic resonance contrast media ranges from 0.04 to 2.2%, and anaphylactic shock represents around 0.004–0.01% of cases [4].Both high osmolality-related complement activation and IgE-mediated mechanism have been involved in the pathogenesis of these reactions[4].

Paclitaxel immediate hypersensitivity reactions (HSRs) occur in <10% of premedicated patients, usually present with flushing, back or abdominal pain and respiratory symptoms, mostly after first dose[5-7]and being atopy described as a risk factor[6,7]. It has been postulated that the yew tree[5-7]and hazelnut tree pollen(and hazelnuts)[6] are potential sources of first exposure and sensitization to Taxanes molecules, although reactions are generally attributed to surfactants used in Paclitaxel formulation (CrEL) through complement activation[5-7]. ST seems to be an useful tool, being positive to Paclitaxelin 10-70% of cases[5,6,8] or to CrEL[3] suggesting an IgE-mediated mechanism. Despite desensitization using a 3-bag-12step-protocol has a very high rate of efficacy and safety[6,7], a severe reaction happened with a minimum dose of drug.

Infusion reactions to Bevacizumab are rare (<6.1%)[7,9]. It has been recently published the first case of anaphylaxis due to Bevacizumab[9], being this one the second case reported so far. Patients with cancer and chronic inflammatory diseases treated with monoclonal antibodies and antineoplastic agents, are susceptible to experience immediate reactions to these drugs[7].These reactions may be due to different mechanisms than those included in the classical *Gell and Coombs* classification of HSRs. In consequence, it has been suggested that different underlying

Accepted Article

© 2021 Esmon Publicidad
doi: 10.18176/jiaci.0729

endotypes/phenotypes might be involved in the development of immediate reactions to these drugs[7,10].

In summary, we describe a case report of MDHS with three non-related drugs, presenting as immediate anaphylaxis.

Studies that explain the susceptibility to develop MDHS are lacking. It´s necessary to investigate and clarify the predisposing mechanisms of this rare condition, that is exceptional for immediate reactions.

Conflicts of interest

Any author has any conflict of interest.

Funding

The authors declare that no funding was received for the present study.

Accepted Article

References

1. Landry Q, Zhang S, Ferrando L, Bourrain JL, Demoly P, Chiriac AM. Multiple Drug Hypersensitivity Syndrome in a Large Database. J Allergy Clin Immunol Pract. 2020;8:258-66.
2. Alvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol. 2010;125:1269-78.
3. Caballero ML, Quirce S. Immediate Hypersensitivity Reactions Caused by Drug Excipients: A Literature Review. J Investig Allergol Clin Immunol 2020;30:86-100.
4. Rosado A, Gonzalez-Moreno A, Privitera-Torres M, Tejedor-Alonso MA. Anaphylaxis Induced by Magnetic Resonance Imaging (MRI) Contrast Media. Curr Treat Options Allergy. 2020;7:32–42.
5. Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, Cernadas J, et al. Role of Skin Tests in the Diagnosis of Immediate Hypersensitivity Reactions to Taxanes: Results of a Multicenter Study. J Allergy Clin Immunol Pract. 2019;7:990-7.

 © 2021 Esmon Publicidad
doi: 10.18176/jiaci.0729

6. Picard M. Management of Hypersensitivity Reactions to Taxanes. Immunol Allergy Clin North Am. 2017;37:679-93.

7. Castells M. Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: The Role of Desensitizations. Front Immunol. 2017;8:1472.

8. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A, Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization. Allergy. 2015;70:784-94.

9. Gonzalez-Diaz SN, Villarreal-Gonzalez RV, De Lira-Quezada CE, Rocha-Silva GK, Oyervides-Juarez VM, Vidal-Gutierrez O. Desensitization Protocol to Atezolizumab and Bevacizumab after Severe Anaphylaxis in the Treatment of Lung Adenocarcinoma. J Investig Allergol Clin Immunol. 2021;31.

10. Jimenez-Rodriguez TW, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy. 2018;11:121-42.

Table legend

Table 1. Skin tests to drugs and excipients

	SPT 1/10	SPT 1/1	IDT 1/1000	IDT 1/100	IDT 1/10
Gadoteric Acid (279.3mg/mL)	-	-	-	-	-
Gadoteridol (279.3mg/mL)	+ (6mmwheal)	NP	NP	NP	NP
Paclitaxel (6mg/mL)	NP	-	NP	-	+ (8mm wheal)
Bevacizumab (25mg/mL)	-	-	-	-	-
Polyethylene glycol 1500 (0.5gr/mL)	NP	-	NP	NP	NP
Polyethylene glycol 3350 (0.5gr/mL)	NP	-	NP	NP	NP
Polyethylene glycol 4000 (0.5gr/mL)	NP	-	NP	NP	NP
Polysorbate 80 (1gr/mL)	NP	-	NP	NP	NP
SPT: skin prick test; IDT: intradermal test; NP: not performed.					

Accepted Article

© 2021 Esmon Publicidad