INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Case Study

Excipient-Induced Hypersensitivity: A Case Study and Review

Kanish Akash Rajkumar*, Kothapalli Nagapavani , Manish Kumar S

Pharm.D Intern, Department Of Pharmacy Practice, College Of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka-560078, India.

ARTICLE INFO

Received: 26 Sep 2024
Accepted: 29 Sep 2024
Published: 13 Oct 2024

Keywords:
Drug allergy, Hypersensitivity reaction, Adverse drug reactions, Medication intolerance, Immune-mediated drug reaction.

DOI:
10.5281/zenodo.13926494

ABSTRACT

A 23-year-old female presented with a unilateral neck lump, raising suspicion of lymphoma. Empirical treatment with Brand 1 (amoxicillin/clavulanic acid) 625mg BD was given without adverse effects. However, after switching to Brand 2, the patient developed a hypersensitivity reaction, including urticaria and itching on the palms and soles. This was attributed to an excipient difference between the brands. Antibiotic therapy was stopped, and the patient was treated with methylprednisolone, levocetirizine, and calamine lotion. This case highlights the importance of excipients in hypersensitivity reactions and emphasizes the need for standardized excipient lists and labelling in the medication.

INTRODUCTION

Case presentation:

A 23-year-old female presented to the hospital with a noticeable lump on the left side of her neck. The patient reported that the lump had been gradually increasing in size over the past few weeks. She denied any associated symptoms such as fever, night sweats, weight loss, or difficulty swallowing. Her medical history was revealed, with no known allergies or chronic illnesses. She denied any recent infections or exposure to sick contacts. On physical examination, the patient appeared well-nourished and in no acute distress. Vital signs were within normal limits. Inspection of the neck revealed a single, firm, tender lump, located in the left cervical region, anterior to the sternocleidomastoid muscle. The overlying skin was intact and showed no signs of inflammation or erythema. Palpation of the lump did not elicit any fluctuance or signs of inflammation. Examination of the head, ears, eyes, nose, and throat showed no evidence of masses or lesions. Based on the investigation, lymphoma was considered as a

***Corresponding Author:** Kanish Akash Rajkumar
Address: *Pharm.D Intern, Department Of Pharmacy Practice, College Of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka-560078, India.*
Email ✉: dr.kanishakash@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

provisional diagnosis. However, in the absence of definitive clinical findings suggestive of lymphoma, the decision was made to initiate empirical treatment with broad-spectrum antibiotics before proceeding with further diagnostic investigations. The patient was prescribed a 10-day course of Brand 1 (Amoxicillin + Potassium Clavulanate 625mg) twice daily and advised to follow up after completion of the antibiotic regimen. After five days of antibiotic therapy, the patient returned to the clinic for a refill of her prescription. However, due to the unavailability of Brand 1, she was dispensed Brand 2 (Amoxicillin + Potassium Clavulanate 625mg) as an alternative. The patient reported compliance with the prescribed regimen and did not report any adverse effects initially. However, within 24 hours of starting Brand 2, the patient began to experience the sudden onset of pruritic erythematous wheals on her palms and soles, accompanied by generalized urticaria. Concerned about these new symptoms, she sought medical attention promptly. Given the temporal relationship between the initiation of Brand 2 and the onset of the urticarial rash, a diagnosis of antibiotic-induced hypersensitivity reaction was suspected. The antibiotic was discontinued immediately, and the patient was referred to a dermatologist for further evaluation and management. The dermatologist confirmed the diagnosis of antibiotic-induced urticaria and prescribed a tapering course of methylprednisolone 16 mg once daily, levocetirizine 5 mg twice daily for symptomatic relief of pruritus, and calamine lotion for topical application to alleviate skin irritation. Following initiation of this treatment regimen, the patient reported significant improvement in symptoms, with resolution of the urticarial rash and reduction in the size of the neck lump. She was advised to continue the prescribed medications as directed and to follow up with both the dermatologist and primary care physician for further monitoring and management of her condition.

DISCUSSION:

Amoxicillin-clavulanate is widely used in emergency departments and primary care settings across the nation, it is predominantly safe and well-tolerated in the general populace, with the predominant adverse effects encompassing mild gastrointestinal manifestations and dermatological reactions[1]. However, our patient did not exhibit such reactions attributable to the active ingredients. If the dermatological reactions had stemmed from the active ingredients, patients would likely have experienced skin allergies while consuming brand 1 tablets. Thus, there is a suspicion that the allergy might have been induced by the excipients utilized in the drug formulation, given the variability of excipient composition among different manufacturers, notwithstanding the active ingredients. The prevailing assumption often links reactions solely to the active ingredient, which holds true for numerous drugs and drug classes. Nevertheless, it's imperative to recognize that excipients also possess allergenic potential. Excipients are necessary as a support to the active ingredients in drugs, vaccines and other products and they contribute to their stability, preservation, pharmacokinetics, bioavailability, appearance and acceptability[3]. Allergic reactions to excipients can contribute to multidrug allergies, potentially resulting in unforeseen severe reactions if not properly considered[2]. Both companies were contacted via email to notify them about the induced allergy and requested information regarding the excipient composition. However, due to the lack of response to the emails, we performed the study using "AMOXICILLIN AND CLAVULANATE POTASSIUM tablet, film coated" as the search term in the NLM drug database to evaluate the excipient composition of 23 distinct brands of amoxicillin and clavulanate (625mg and 1.2g). The excipients listed in the

NLM drug database were compared with those identified in five research studies[24-28] ,investigating excipients known to induce allergies in drug formulations. Shared excipients found in the studies and the NLM database were chosen for a detailed examination and comparison. The excipients commonly shared across research studies and the NLM database include magnesium stearate, polyethylene glycol, propylene glycol, and crosspovidone. Magnesium stearate is a lubricant widely used in pharmaceutical formulations to aid in the manufacturing process and prevent sticking. Polyethylene glycol and propylene glycol are both commonly used as solvents or vehicles in drug formulations. Crosspovidone is a disintegrant that helps tablets to break apart and dissolve quickly when ingested. PEG (polyethylene glycol) and povidone, both polymers, are commonly used in pharmaceutical formulations, where PEG, with a presence in 36.03% of medications, and povidone, found in 35.80% of formulations[23]. Magnesium stearate is found in various food supplements, confectionery, chewing gum, herbs, spices, and baking products, highest concentrations are in cocoa butter (chocolate), butter, and shea butter. Additionally, it serves as a common inactive component in manufacturing pharmaceutical tablets, capsules, and powders[7,8]. In a study, urticaria was reported with a formulation containing magnesium stearate[4]. Further, A 28-year-old woman developed urticarial symptoms due to an allergic reaction to magnesium stearate[5]. A 58-year-old woman developed urticaria from four anti-diabetic drugs, each containing magnesium stearate as an excipient[6]. Upon inquiry, the patient denied any allergic reactions to butter and butter products, thereby excluding it as a potential cause. Polyethylene glycol (PEG), also known as macrogol, is commonly used as an inactive additive in various medications, healthcare products, cosmetics, and food items to provide bulk or stabilization[9]. Recent concerns about allergic reactions to COVID vaccines have intensified interest in excipients like polyethylene glycol derivatives (PEGs)[2]. Despite its generally low toxicity and inert nature, there has been a growing number of documented cases of immediate-type hypersensitivity reactions to PEG over the past two decades, some of which have been severe. PEG 6000 has been implicated in Immediate Hypersensitivity Reactions (IHRs) across various medications, including European formulations of penicillin antibiotics and effervescing medications[18]. Notably, a fatal incident was reported involving PEG-induced anaphylaxis after the administration of a glucocorticoid injection containing PEG to a 24-year-old man who had previously experienced urticaria from similar injections [11]. Additionally, six cases of acute hypersensitivity reactions to PEG have been recorded, predominantly in females with an average age of 36.4 years. Initially, some patients were suspected of having allergies to nonsteroidal anti-inflammatory drugs, while others had histories of chronic spontaneous urticaria and angioedema[9]. A study found that severe hypersensitivity reactions to hidden compounds like macrogol might not be sufficiently diagnosed. There has been an observed increase in immediate-type hypersensitivity reactions to PEG. It's crucial to raise awareness about PEG's allergenic properties and ensure precise product labelling to reduce the risk of PEG-induced hypersensitivity reactions[10]. A review of 37 documented instances of immediate hypersensitivity reactions to PEG spanning from January 1977 to April 2016 further underscores the importance of understanding and managing such reactions[12].

Propylene Glycol, a small molecule, functions as both an emollient and an emulsifier and is prevalent in cosmetics, medications, and food products. Despite its diverse applications, it holds

the unfortunate distinction of being the most frequently cited excipient in Drug Hypersensitivity Reactions (DHRs). Consequently, it was designated as the Allergen of the Year for 2018 by the American Contact Dermatitis Society[13]. A retrospective study determined that topical antibiotics containing propylene glycol are one of the factors contributing to acute contact dermatitis[14]. A research study by Mayo Clinic found that Propylene glycol is linked to allergic and irritant patch test reactions, with higher concentrations correlating with heightened reactions[17], However, a 2005 study indicated that PG exhibits a low likelihood of sensitization, with minimal risk of sensitization on intact skin[15], a finding consistent with a more recent study conducted in 2023[16]. Crosspovidone is a commonly used tablet disintegrant[19]. Allergic reactions to povidone are infrequent but have been observed with a rising incidence, where a study documented Povidone anaphylaxis triggered by chemically unrelated medications and unexplained exposures[3]. Additional instances of anaphylactic reactions following ingestion of flubendazole suspension[20] and acetaminophen-containing tablets [21,22] were reported. Although drug allergies are typically attributed to the active components, excipients can play a crucial role in adverse reactions, as seen in this patient's experience. This highlights the need for a more thorough examination of excipient profiles during drug formulation and patient management. To ensure better clinical outcomes, physicians should consider not only the therapeutic agents but also the accompanying excipients when evaluating unexplained allergic reactions. By promoting more precise excipient labelling and fostering awareness of their allergenic potential, healthcare providers can enhance diagnosis, prevention, and patient safety in cases of drug hypersensitivity.

CONCLUSION:

The extensive array of reported cases and scholarly literature detailing instances of anaphylaxis originating from excipients underscores the imperative of including a comprehensive list of all excipients in medication formulations within the package insert. This practice not only eliminates the need for direct inquiries to manufacturers regarding excipient composition but also aids in advancing research on excipient-induced allergies. Standardized labelling of preparations and excipient nomenclature could streamline the identification of allergic reactions and facilitate the implementation of effective avoidance strategies to prevent future incidents in sensitized patients.

CONTRIBUTOR ROLES TAXONOMY (CREDIT):

Kanish Akash Rajkumar – Conceptualization, Investigation, Methodology, Data curation, Supervision, Project administration, Validation, Writing – Original Draft, Writing – Review & Editing

Nagapavani Kothapalli - Conceptualization, Investigation, Formal Analysis, Validation, Data curation Writing – Original Draft, Writing – Review & Editing

Manish Kumar S - Conceptualization, Investigation, Formal Analysis, Validation, Data curation Writing – Original Draft, Writing – Review & Editing

ACKNOWLEDGEMENT:

We would like to extend our gratitude to the patient for giving his consent for us to write this report.

CONFLICT OF INTEREST:

The authors declare no conflict of interest

REFERENCE:

1. Principi N, Petropulacos K, Esposito S. Genetic Variations and Antibiotic-Related Adverse Events. Pharmaceuticals. 2024 Mar 2;17(3):331.

2. Venturini Díaz M, Vidal Oribe I, D'Elia Torrence D, Hernández Alfonso P, Alarcón Gallardo E. New challenges in drug allergy: the resurgence of excipients. Current Treatment Options in Allergy. 2022 Sep;9(3):273-91.
3. Bruusgaard-Mouritsen MA, Nasser S, Garvey LH, Krantz MS, Stone CA. Anaphylaxis to excipients in current clinical practice: evaluation and management. Immunology and Allergy Clinics. 2022 May 1;42(2):239-67.
4. Kutlu A, Ucar R, Aydin E, Arslan S, Calıskaner AZ. Could aluminum be a new hidden allergen in type 1 hypersensitivity reactions when used as a drug additive?. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 2016 Jun 3;33(3):243-5.
5. Tammaro AB, Abruzzese C, Narcisi A, Cortesi G, Persechino F, Parisella FR, Persechino S. Magnesium stearate: an underestimated allergen. Journal of Biological Regulators and Homeostatic Agents. 2012 Oct 1;26(4):783-4.
6. Al Masri D, Fleifel M, Hirbli K. Fixed drug eruption secondary to four anti-diabetic medications: an unusual case of polysensitivity. Cureus. 2021 Oct;13(10).
7. Hobbs CA, Saigo K, Koyanagi M, Hayashi SM. Magnesium stearate, a widely-used food additive, exhibits a lack of in vitro and in vivo genotoxic potential. Toxicology reports. 2017 Jan 1;4:554-9.
8. Stearic Acid. In: Baumann L. eds. Cosmeceuticals and Cosmetic Ingredients. McGraw-Hill Education; 2015. Accessed March 23, 2024. https://dermatology.mhmedical.com/content.aspx?bookid=2812&sectionid=244978561
9. Cox F, Khalib K, Conlon N. PEG that reaction: a case series of allergy to polyethylene glycol. The Journal of Clinical Pharmacology. 2021 Jun;61(6):832-5.
10. Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. Allergy, Asthma & Clinical Immunology. 2016 Dec;12:1-3.
11. Roseingrave L. Verdict of medical misadventure in case of fatal allergic reaction. The Irish Times Available at . 2017 https://www.irishtimes.com/news/crime-and-law/courts/coroner. scourt/verdict-ofmedicalmisadventure-in-case-of-fatal-allergic-reaction-1.3324937.
12. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. Clinical & Experimental Allergy. 2016 Jul;46(7):907-22.
13. McGowan MA, Scheman A, Jacob SE. Propylene glycol in contact dermatitis a systematic review. Dermatitis. 2018 Feb 1;29(1):6-12.
14. Choi C, Vafaei-Nodeh S, Phillips J, de Gannes G. Approach to allergic contact dermatitis caused by topical medicaments. Canadian Family Physician. 2021 Jun 1;67(6):414-9.
15. Lessmann H, Schnuch A, Geier J, Uter W. Skin-sensitizing and irritant properties of propylene glycol: Data analysis of a multicentre surveillance network (IVDK*) and review of the literature. Contact dermatitis. 2005 Nov;53(5):247-59.
16. Pemberton MA, Kimber I. Propylene glycol, skin sensitisation and allergic contact dermatitis: A scientific and regulatory conundrum. Regulatory Toxicology and Pharmacology. 2023 Feb 1;138:105341.
17. Lalla SC, Nguyen H, Chaudhry H, Killian JM, Drage LA, Davis MD, Yiannias JA, Hall MR. Patch testing to propylene glycol: the Mayo Clinic experience. Dermatitis. 2018 Aug 1;29(4):200-5.

18. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone Jr CA. Hidden dangers: recognizing excipients as potential causes of drug and vaccine hypersensitivity reactions. The Journal of Allergy and Clinical Immunology: In Practice. 2021 Aug 1;9(8):2968-82.
19. Hiew TN, Johan NA, Desai PM, Chua SM, Loh ZH, Heng PW. Effect of moisture sorption on the performance of crospovidone. International journal of pharmaceutics. 2016 Nov 30;514(1):322-31.
20. Rönnau AC, Wulferink M, Gleichmann E, Unver E, Ruzicka T, Krutmann J, Grewe M. Anaphylaxis to polyvinylpyrrolidone in an analgesic preparation. British Journal of Dermatology. 2000 Nov 1;143(5):1055-8.
21. Pedrosa C, Costa H, Oliveira G, Romariz J, Praça F. Anaphylaxis to povidone in a child. Pediatric allergy and immunology. 2005 Jun;16(4):361-2.
22. Bergendorff O, Hansson C. Urticaria and anaphylaxis to povidone in a paracetamol preparation. Journal of the European Academy of Dermatology and Venereology: JEADV. 2007 Apr 1;21(4):573-4.
23. Reker D, Blum SM, Steiger C, Anger KE, Sommer JM, Fanikos J, Traverso G. "Inactive" ingredients in oral medications. Science translational medicine. 2019 Mar 13;11(483):eaau6753.
24. Bruusgaard-Mouritsen MA, Nasser S, Garvey LH, Krantz MS, Stone CA. Anaphylaxis to excipients in current clinical practice: evaluation and management. Immunology and Allergy Clinics. 2022 May 1;42(2):239-67.
25. Kaushik AY, Tiwari AK, Gaur A. Role of excipients and polymeric advancements in preparation of floating drug delivery systems. International journal of pharmaceutical investigation. 2015 Jan;5(1):1.
26. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone Jr CA. Hidden dangers: recognizing excipients as potential causes of drug and vaccine hypersensitivity reactions. The Journal of Allergy and Clinical Immunology: In Practice. 2021 Aug 1;9(8):2968-82.
27. Pfützner W. Anaphylaxis to drug excipients. Allergo Journal International. 2022 Jul;31(5):137-40.
28. Venturini Díaz M, Vidal Oribe I, D'Elia Torrence D, Hernández Alfonso P, Alarcón Gallardo E. New challenges in drug allergy: the resurgence of excipients. Current Treatment Options in Allergy. 2022 Sep;9(3):273-91.

HOW TO CITE: Kanish Akash Rajkumar , Kothapalli Nagapavani , Manish Kumar S. , Excipient-Induced Hypersensitivity: A Case Study and Review, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 10, 744-749. https://doi.org/10.5281/zenodo.13926494