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Original Article

Anaphylactic reaction to dapsone: case report

Reação Anafilática a Dapsona: Relato de caso

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ABSTRACT

Dapsone is an antibiotic capable of inhibiting the synthesis of folic acid in bacteria and producing a bacteriostatic effect. Adverse reactions have already been recorded with the use of this medication. The objective of this study was to describe the case of a patient who developed an anaphylactic reaction after administration of dapsone, review the literature on the subject and apply algorithms to assess causality. Anaphylaxis is an immediate hypersensitivity reaction that can potentially be fatal. This is the first case report of anaphylactic reaction to dapsone described in the literature based on research carried out by the authors in databases.

Keywords: Pharmacovigilance; Adverse Reaction; Anaphylaxis.

RESUMO

A dapsona é um antibiótico capaz de inibir a síntese de ácido fólico nas bactérias e produzir um efeito bacteriostático. Reações adversas já foram registradas com o uso deste medicamento. O objetivo deste estudo foi descrever o caso de uma paciente que desenvolveu reação anafilática após a administração da dapsona, revisar a literatura sobre o tema e aplicar algoritmos para avaliação da causalidade. A anafilaxia é uma reação de hipersensibilidade imediata que pode ser potencialmente fatal. Este é o primeiro relato de caso de reação anafilática a dapsona descrito na literatura a partir das pesquisas realizadas pelos autores nas bases de dados.

Palavras-chave: Farmacovigilância; Reação Adversa; Anafilaxia.

Introduction

Dapsone is an antibiotic of the sulfone class that exhibits bacteriostatic and anti-inflammatory activity. It is commonly used for the treatment of leprosy, Pneumocystis sp. pneumonia, and dermatological diseases.[1] Despite its benefits, its use is associated with the occurrence of adverse reactions such as mild methemoglobinemia, hemolytic anemia, neutropenia, agranulocytosis, increased serum transaminases, and headache.[2,3]

According to the World Health Organization, an adverse drug reaction is defined as a harmful and undesirable reaction that occurs after exposure to a medication at usual doses, aimed at preventing, treating, or diagnosing a disease or modifying a biological function.[4]

The objective of this study was to describe the first case reported in the literature of an adverse reaction in which the patient developed an anaphylactic reaction after the administration of dapsone, review the literature on the subject, and apply algorithms to assess causality.

Case report

A 27-year-old woman with Systemic Lupus Erythematosus (SLE), diagnosed in 2014, with no prior history of adverse drug reactions (ADRs), presented with blistering lesions on the face, back, abdomen, and upper limbs. She sought outpatient care with the rheumatology team of a University Hospital in Salvador, Bahia, and was prescribed dapsone. She used the medication for 30 days, after which she reported malaise, severe dysuria, and fever. She discontinued the medication on her own and subsequently improved.

Three weeks after discontinuation, she was admitted to the hospital for renal and skin biopsies due to worsening of hyperchromic and blistering facial lesions and proteinuria of 1.1 g in 24 hours. The medical team decided to reintroduce dapsone at 50 mg/day. One hour after administration, the patient developed nonspecific malaise, nausea, dyspnea without desaturation, dizziness upon ambulation, and chest pain.

At the time of the ADR, her capillary blood glucose was 103 mg/dL, blood pressure 80/49 mmHg, heart rate 136 bpm, and axillary temperature 38.0°C. Volume expansion with 500 mL of 0.9% sodium chloride was initiated. Despite the intervention, her condition worsened, presenting with bilateral conjunctival hyperemia and facial flushing, raising suspicion of an anaphylactic reaction.

Management included discontinuation of the suspected drug, administration of intravenous hydrocortisone 200 mg, intramuscular promethazine 25 mg, and intramuscular adrenaline 0.5 mg. The patient showed clinical improvement, with complete resolution within 24 hours after the interventions. She remained hospitalized for an additional six days for evaluation of the underlying disease. The case was reported to the hospital pharmacovigilance center and, after validation, presented in a clinical session.

Discussion

Anaphylaxis is an immediate hypersensitivity reaction, potentially severe, that develops within seconds to minutes, rarely hours later, and usually following exposure to an agent (medications, drugs, venoms, foods, physical factors, and other substances).[5,6] In its clinical presentation, symptoms may vary from mild to severe, and in some cases may resolve spontaneously due to the endogenous production of mediators.[7,8]

The anaphylactic reaction involves pathophysiological mechanisms that may or may not be related to the immune system.[5] Reactions involving immune system activation can be mediated by immunoglobulin E, immunoglobulins G, and complement activation by immune complexes, all culminating in mast cell and basophil degranulation with the release of biochemical mediators and other substances responsible for the entire symptomatology characteristic of anaphylaxis. Prior sensitization to an agent may result in more severe clinical manifestations upon re-exposure due to antibody production.[9]

In cases of non-immunologically mediated reactions, the causative agent directly stimulates the reaction mechanisms without the need for prior sensitization. In some cases, it is not possible to determine the mechanism related to the reaction and, therefore, these are called idiopathic.[9]

Tabela 1. Medicamentos em uso pela paciente.

MEDICATIONS	PERIOD OF USE	
	Start	end
Hydroxychloroquine 400 mg PO/day	2015	Ongoing treatment
Prednisone 60 mg PO/day	2015	Ongoing treatment
Mycophenolate mofetil 2 g PO/day	19/09/2023	Ongoing treatment
Dapsone 50 mg PO/day	08/2023	09/2023
Dapsone 50 mg PO/day	04/11/2023	11/04/2023
Losartan 50 mg PO/day	03/2023	Ongoing treatment
Calcium carbonate 1250 mg (Ca^{2+} = 500 mg) + vitamin D 400 IU PO/day	2015	Ongoing treatment
Ferrous sulfate 40 mg PO once daily	08/2023	Ongoing treatment

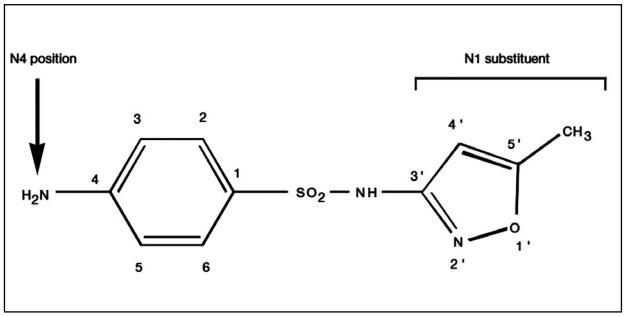
Legend: PO - per oral; Ca - calcium; IU - international units.

In the World Health Organization global database of adverse drug reactions, VigiAccess, there are reports of 10 cases of anaphylactic reaction and 4 of anaphylactoid reactions associated with the use of dapsone. In PubMed, Virtual Health Library, and Embase databases of studies published up to June 2024 using the strategy ("hypersensitivity reaction" OR "anaphylactic reaction" OR anaphylaxis OR "Anaphylactoid Reaction") AND Dapsone, no articles specifically addressing dapsone-induced anaphylactic reactions were identified.

Lorenz, Wozel, and Scchmitt[10] conducted a review study on hypersensitivity reactions to dapsone, in which they identified 97 case reports and 17 observational studies. Of the 336 patients included, none presented an anaphylactic reaction. Hypersensitivity symptoms began on average 28 days after exposure (ranging from 6 hours to 21 weeks, data from 166 patients), and recovery occurred after 6 days to several months. In the patients described, fever, cutaneous signs, and mucosal involvement accounted for 96.6% (281/291), 92% (276/291), and 44.6% (58/130), respectively. Hepatitis occurred in 81.9% of the 298 reported cases, and lymphadenopathy was reported in 73.7% of 270 patients.

The literature search was expanded to the class of sulfones and sulfonamides in order to identify articles that related these drugs, which share a similar molecular structure, with immediate hypersensitivity reactions. Brackett, Singh, and Harleen[11] observed that type I allergic reactions to sulfonamide antibiotics appear to be directed by the molecular substituents N1 and possibly N4 of these agents (Figure 1):

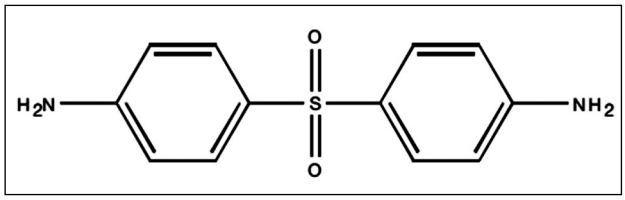
Figure 1. Medications used by the patient.



Source: Brackett, Singh and Harleen, 2004.

By comparing the molecules of sulfamethoxazole and dapsone, both present the arylamine ring at the N4 position (Figure 2), which may therefore be the structure responsible for triggering the anaphylactic reaction in the patient under investigation.[12]

Figura 2. Chemical structure of Dapsone



Source: Brackett, Singh and Harleen, 2004.

Anaphylaxis was described in a 19-year-old man recently diagnosed with dermatomyositis, who had started using prednisone and sulfamethoxazole-trimethoprim for Pneumocystis pneumonia prophylaxis. After two days, he developed fever (38.3°C), hypotension (78/42 mmHg), tachycardia (120 bpm), erythematous reticular lesions, and T-wave inversions. Management included administration of epinephrine, discontinuation of sulfamethoxazole-trimethoprim, and subsequent transfer to the intensive care unit for fluid replacement and clinical stabilization.[12]

Thus, reports exist of reactions similar to that observed in the patient, with a drug that has a structure similar to dapsone.[12 13] Concomitantly, by evaluating the temporal onset of the reaction after exposure and the recovery process, the association with dapsone administration is highly suggestive. Furthermore, it was considered that the patient experienced a positive re-exposure to the drug, leading to progression and development of a severe reaction.

In the evaluation of alternative causes, the underlying disease was ruled out, since the acute onset of symptoms (nonspecific malaise, nausea, dyspnea, dizziness after ambulation, hypotension, rash, and chest pain) and rapid recovery were not compatible with the patient's baseline condition. Moreover, there were no changes in the treatment of the disease that could justify symptom improvement. Reports exist in the literature of anaphylactic and anaphylactoid reactions related to the concomitant medications (Table 1); however, all of them continued to be used after symptom resolution without the occurrence of new adverse events.

For causality assessment, the Naranjo algorithm and the Roussel Uclaf Causality Assessment Method (RUCAM) were applied, yielding results classified as definite and probable, respectively. The reaction was categorized as Category A in the European Union causality scale and as Certain or Proven in the World Health Organization (WHO) causality assessment. It was identified as a type B reaction, not dose-related.

According to the Naranjo algorithm, a reaction is classified as definite when there is a reasonable temporal sequence from drug administration, recurrence upon re-exposure, and when the clinical presentation cannot reasonably be explained by the patient's underlying condition.[14] The WHO and European Union algorithms follow the same rationale as Naranjo, therefore providing the maximum score for causality.[15]

Regarding the RUCAM algorithm, the absence of prior information in package inserts or in the literature about dapsone causing such a reaction affected the scoring, resulting in a classification of probable rather than highly probable.[16]

Conclusion

The application of the algorithms demonstrated a causal relationship between the administration of the medication and the onset of the reaction. Therefore, based on the temporal relationship, scientific evidence, and observed manifestations, it is possible to conclude that the anaphylactic reaction was caused by Dapsone. Severe reaction, type B.

Authors' Contributions

LBS, LACBN, GQA, ACBN: Conception and design, or analysis and interpretation of data;
LBS, LACBN, GQA, LMSA: Drafting of the article or critical revision of its intellectual content;
LBS, LACBS, GQA, LMSA, GBNCS, ACBN: Final approval of the version to be published;
LBS, LACBN, GQA, LMSA, GBNCS, ACBN: Responsibility for all aspects of the text in ensuring the accuracy and integrity of any part of the work.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the data described in this article.

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Data Availability Statement

All data relevant to the study are included in the article.

Responsible

Lindemberg Assunção Costa.

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