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Case Report

Slow desensitization to fluconazole in woman with maculopapular exanthema

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ABSTRACT

Introduction: Desensitisation is a procedure that modifies the immune response to a pharmaceutical agent, thereby creating a transient tolerance to the drug in question. This allows the patient with an allergic reaction to continue receiving the requisite treatment without interruption. Once the desensitization process is terminated, the patient's hypersensitivity to the drug resumes. This case study presents the case of a 53-year-old woman with a personal history of kidney transplant who presents to the hospital with a lesion on the hallux of the left foot at the starting point of onychocryptosis, with a positive culture for cryptococci. The presumptive diagnosis is disseminated disease due to compatible lesions in the lungs, as indicated by computed tomography. Therefore, long-term treatment with fluconazole is recommended. During the administration of the antifungal agent, the patient developed a maculopapular rash with pruritus, which was diagnosed as a hypersensitivity reaction to the drug. Consequently, a slow desensitization procedure was performed to ensure the patient's safety and efficacy of treatment. **Objectives:** Describe a slow desensitization protocol in a patient with a non-IgE-mediated maculopapular reaction. Additionally, the medical history and clinical history of the patient, as well as the time of onset of symptoms after administration of the drug, were analyzed. Furthermore, a literature review on similar allergic reactions was conducted, and the medical and pharmacological interventions used were specified. **Material and methods:** We observed desensitization protocols in patients with a history of allergy and their subsequent monitoring. A desensitization protocol comprising 15 consecutive steps was implemented, adapted from a protocol for oral TMS in patients with HIV infection and a history of allergy to the antibiotic in question, as described by Absar et al. [11]. **Results:** The procedure was straightforward and efficacious, and thus the patient proceeded with the recommended dosage for the infectious condition. **Conclusion:** It was determined that the desensitization procedure is safe when conducted by trained medical professionals in a controlled setting.

Key words: *Cryptococcus neoformans;* transplant; hypersensitivity; disseminated infection; desensitization; fluconazole.

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RESUMEN

Introducción: La desensibilización es un procedimiento que modifica la respuesta inmune a un agente farmacológico, creando así una tolerancia transitoria al medicamento en cuestión. Esto permite que el paciente con una reacción alérgica continúe recibiendo el tratamiento necesario sin interrupción. Una vez finalizado el proceso de desensibilización, la hipersensibilidad del paciente al medicamento se reanuda. Este reporte de caso presenta el caso de una mujer de 53 años con antecedentes personales de trasplante renal que se presenta en el hospital con una lesión en el hallux del pie izquierdo en el punto inicial de onicocriptosis, con un cultivo positivo para criptococos. El diagnóstico presuntivo es una enfermedad diseminada debido a lesiones compatibles en los pulmones, como lo indica la tomografía computarizada. Por lo tanto, se recomienda un tratamiento a largo plazo con fluconazol. Durante la administración del agente antifúngico, la paciente desarrolló un exantema maculopapular con prurito, que fue diagnosticado como una reacción de hipersensibilidad al medicamento. En consecuencia, se llevó a cabo un procedimiento de desensibilización lenta para garantizar la seguridad del paciente y la eficacia del tratamiento. **Objetivos:** Describir un protocolo de desensibilización lenta en una paciente con una reacción maculopapular no mediada por IgE. Además, se analizaron los antecedentes médicos y la historia clínica de la paciente, así como el tiempo de aparición de los síntomas tras la administración del medicamento. Asimismo, se realizó una revisión de la literatura sobre reacciones alérgicas similares y se especificaron las intervenciones médicas y farmacológicas empleadas. **Material y métodos:** Observamos protocolos de desensibilización en pacientes con antecedentes de alergia y su posterior monitoreo. Se implementó un protocolo de desensibilización compuesto por 15 pasos consecutivos, adaptado de un protocolo para TMS oral en pacientes con infección por VIH y antecedentes de alergia al antibiótico en cuestión. **Resultados:** El procedimiento fue sencillo y eficaz, permitiendo así que la paciente continuara con la dosificación recomendada para la condición infecciosa. **Conclusión:** Se determinó que el procedimiento de desensibilización es seguro cuando es realizado por profesionales médicos capacitados en un entorno controlado.

Palabras clave: *Cryptococcus neoformans*; trasplante; hipersensibilidad; infección diseminada; desensibilización; fluconazol.

INTRODUCTION

Cryptococcosis represents the third most common infection among transplant patients, following candidiasis and aspergillosis. The fungus of the Cryptococcus genus has a worldwide distribution. It is predominantly found in soils contaminated by bird feces, and its transmission occurs through inhalation of soil contaminated with capsulated yeasts, which are between 2 to 6 µm in diameter. It is an opportunistic disease that primarily affects individuals infected with the human immunodeficiency virus (HIV), transplant recipients, and those undergoing immunosuppressive therapy. Nevertheless, this infection also occurs in patients without HIV, with a reported incidence of 10% to 30% of cases by Silviane Bezerra Pinheiro et al. in 2021.[1] In this study, it was found that the mortality rate in these patients was high, exceeding 57.2% in 2020. The most common clinical presentation in these patients is cryptococcal meningitis. A study by Deus et al. (2022) describes that, although the main site of infection is at the pulmonary level, extrapulmonary disease is common, especially infection of the central nervous system (CNS).[2]

The treatment for disseminated cryptococcosis comprises the administration of intravenous amphotericin B in conjunction with fluorocytosine. The efficacy of fluconazole, a first-generation azole, was evaluated at 200 to 400 mg/day as an alternative treatment option, given its low toxicity profile. It is indicated for low-risk patients, such as those without neurological alterations or with a leukocyte count of less than 20 cells/ml in cerebrospinal fluid (CSF).[2] Fluconazole is a safe and well-tolerated drug; however, it can cause adverse reactions, including gastrointestinal symptoms, and, in rare cases, hypersensitivity reactions such as fixed skin rash and maculopapular exanthema. In the event of a reaction of this nature, it is imperative to discontinue the offending medication and pursue an alternative therapeutic avenue. In the event that the offending drug is irreplaceable and the type of hypersensitivity reaction allows for it, a desensitization protocol should be attempted.

Patients with chronic degenerative diseases, including but not limited to diabetes, cancer and inflammatory bowel disease, etc. Repeated exposure may result in hypersensitivity to first-line drugs. In the context of precision medicine, a more individualized approach offers the potential for the development of new tools for the management of these types of reactions. In accordance with the traditional classification system proposed by Gell and Coombs in 1963,[3] four distinct types of RHD have been identified. The first, Type I

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or immediate hypersensitivity reaction, is characterized by a rapid onset, occurring within minutes to a few hours following the interaction between the antigen (Ag) and the preformed immunoglobulin E (IgE) antibody (Ac) in individuals who have been previously sensitized. The antigen combines with two IgE antibodies bound to its membrane receptors (Fcε RI) on pre-sensitized mast cells and basophils, which results in the degranulation of vasoactive and inflammatory mediators, including histamine, tryptase, platelet-activating factor (PAF), leukotrienes, chemotactic factors, growth factors, and others.

This results in increased capillary permeability, vasodilation, glandular hypersecretion of mucus, smooth muscle spasm, and tissue infiltration of eosinophils. These reactions are accompanied by a late phase reaction, which occurs between two and four hours after contact with the antigen and is characterized by the infiltration of inflammatory cells. The symptoms of anaphylaxis include urticaria, allergic rhinitis, allergic asthma, angioedema and anaphylactic shock. An illustrative example of this type of reaction is that observed in response to beta-lactams. Type II hypersensitivity reactions are associated with a humoral cytotoxicity mechanism, which is mediated by IgG and IgM. This mechanism has the capacity to opsonize, recruit leukocytes and activate complement, thereby triggering inflammatory responses or inducing functional changes at the level of receptors. This has been observed in cases involving cell phones.[4] Cases of anemia and thrombocytopenia due to linezolid have been reported to result from this mechanism.[5,6] The case of erythema nodosum caused by oral contraceptives provides an example of a type III hypersensitivity reaction. Immune complexes are formed by the union of antigen present in the circulation with antibodies. The subsequent tissue damage will be contingent upon the sites where these immune complexes are deposited, rather than being a consequence of the origin of the triggering antigen. The formation of immune complexes activates the complement system, initiating a cascade of reactions that facilitate the migration of PMN cells and the release of lysosomal proteolytic enzymes and permeability factors from the tissues, thereby contributing to the inflammatory process.

Other drugs that are also capable of generating adverse reactions through this mechanism have been observed to manifest as serum sickness or hypersensitivity vasculitis. These include cefaclor, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin, non-steroidal anti-inflammatory drugs, diuretics and some biologicals. The type IV hypersensitivity reaction is a delayed cellular response, mediated by sensitized T lymphocytes that have been induced to produce cytokines that mediate inflammation. The sensitization phase commences upon the initial entry of the allergen into the body, whereupon it is processed by antigen-presenting cells and presented to T lymphocytes that recognize the allergen in conjunction with the molecules of the major histocompatibility complex class II. This process is facilitated by MHC II, which induces T cell differentiation towards Th1 cells, resulting in cytokine release and subsequent inflammation.

At present, type IV reactions are classified according to the effector cell involved and the corresponding cytokines into the following categories: a) Type IVa reactions are characterized by the activation of the Th1 profile, with macrophages and INF-γ, TNF-α serving as the effector cells. b) Type IVb reactions, on the other hand, are typified by the activation of the Th2 profile, with eosinophil effector cells and the release of cytokines such as interleukins IL-5, IL-4 and IL-13. c) Type IVc reactions in this instance, the effector cells are cytotoxic T lymphocytes, which result in the release of granzymes B and perforins.

Finally, type IVd is characterized by the involvement of neutrophils as effector cells, accompanied by the release of the chemokine CXCL8 and the granulocyte-macrophage colony-stimulating factor (GM-CSF).[7,8] Severe reactions to immunological medications are included in the category of delayed hypersensitivity mechanisms. This group encompasses a range of drug-induced cutaneous reactions, including skin rashes, erythema morbilliformis, fixed eruptions associated with drugs such as sulfonamides, beta-lactams, anticonvulsants, and more severe forms of dermatitis, such as drug sensitivity reaction with eosinophilia and systemic symptoms (DRESS) and necrolysis. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and other conditions such as drug-induced vasculitis/pemphigoid.

New methodologies for a more comprehensive understanding of drug hypersensitivity entail the characterization of reactions according to phenotype, endotype, and biomarkers.[4] A novel approach to this classification was proposed by Mariana C. Castells et al. in 2017.[9]

Immediate reactions, defined as those occurring within one to six hours of drug administration, represent a distinct category of drug-induced responses. This phenotype typically encompasses the IgE-mediated endotype of mast cell activation, driven by epitope-specific IgE with mast cells serving as the primary effectors. Other endotypes include direct complement activation, drug-hypersensitivity reactions (DHR) mediated by cyclooxygenase-1 inhibition, which are referred to as aspirin-exacerbated respiratory disease (AERD), and aspirin-exacerbated skin disease. Additionally,

reactions may occur due to certain components of medications, such as tetrahydroisoquinoline (THIQ). The signals are transmitted via the G protein-coupled receptor (Mrgp X2), which has the capacity to induce the release of histamine through the activation of mast cells. It has been documented that symptoms such as fever, chills, and abdominal discomfort have manifested during DHRs in response to the administration of monoclonal medications, oxaliplatin, and taxanes. Such reactions, designated as "cytokine storm reactions," are mediated by the release of proinflammatory cytokines that activate macrophages and other immune cells with FcγR receptors. Regarding type IV or late reactions, they manifest in a more heterogeneous manner and occur several days or weeks following administration of the drug in question. The symptoms are mediated by T cells, manifesting as maculopapular rash or late urticaria, and may also affect other organs, including the liver, lungs, and kidneys. Additionally, hematological alterations may occur. Severe cutaneous drug reactions (SCAR) encompass AGEP, DRESS, Sweet's syndrome (SSJ), and neutrophilic eruption with telangiectasias (NET). These have a distinct clinical presentation and can potentially be life-threatening if appropriate treatment is not promptly initiated.

Desensitization is a procedure that induces a temporary state of hyporesponsiveness/tolerance by gradually increasing suboptimal doses of the offending drug. It is performed under close medical surveillance and its immunological basis consists of achieving temporary tolerance by reducing the reactivity of the effector cells of the immune system such as mast cells and basophils and increasing regulatory cells (Treg cells) avoiding the presentation of immediate reactions. Desensitization protocols have been developed that are used in patients with allergic reactions to antibiotics such as penicillin, chemotherapeutic and biological agents, insulins, sulfonamides, and many other drugs.[10] In cases where the offending medication is essential and no satisfactory alternative exists or is available, the possibility of desensitization should always be considered. Desensitization treatment may be indicated in cases where there is a compelling need for a particular medication or prophylaxis, where the medication is irreplaceable, is more effective than alternative treatments, has a unique mechanism of action, or where the potential benefit outweighs the risks. Absolute contraindications include a serious or life-threatening reaction, such as a severe cutaneous adverse reaction (SCAR), or a severe general symptom, such as fever, chills, nausea, pain, a severe headache, dyspnea, hypertension or hypotension with or without end-organ involvement. Additionally, contraindications include a drug-induced autoimmune disorder. Relative contraindications include anaphylaxis, age, pre-existing liver or kidney involvement, autoimmune disorders, patients with unstable heart disease, any simultaneous treatment that could interfere in the event of anaphylaxis, and uncontrolled asthma. The case of a female patient presenting with a rash is presented. The patient was diagnosed with late-onset maculopapular disease, for which a slow desensitization procedure was indicated.

CLINICAL CASE

A 53-year-old female patient with a personal medical history of end-stage renal failure (ESRD) secondary to bilateral polycystic kidney disease, diagnosed at 17 years of age, denies a history of allergy. Received an unrelated unilateral kidney transplant in 2021 without other surgical complications. It did not present any complications, until in the year 2023, suffered active kidney rejection In July 2023, the patient was admitted to the hospital due to an area of phlogosis and local erythema on the left leg with an entrance due to onychocryptosis in the hallux. This was classified as a severe skin and soft tissue infection (STI), and treatment was initiated with intravenous antibiotics. Skin and soft tissue cultures show positive results for capsulated yeasts compatible with cryptococcosis, so in order to rule out disseminated infection in the context of an immunocompromised patient, lumbar puncture (LP) is performed to detect polysaccharide capsular antigen (CrAg) in CSF, and microscopy with Indian ink, which is negative. The antibiotic was discontinued and intravenous induction treatment with liposomal amphotericin B was started. A computed axial tomography (CT) scan of the thorax was conducted, which revealed the presence of isolated nodular images with ground glass in the region of the right lower lobe of the lung. This was interpreted as indicative of an infectious etiology. A decision was made to administer liposomal amphotericin B for a period of 15 days, followed by a 14-day course of oral fluconazole. Two days after treatment with fungicides, the patient developed a rash comprising reddish maculopapular lesions distributed asymmetrically, with a predilection for the trunk and abdomen. This was primarily related to liposomal Amphotericin B, so treatment was suspended and continued only with intravenous fluconazole. The administration of hydrocortisone in conjunction with diphenhydramine was indicated for the purpose of alleviating the symptoms, with an adequate clinical response. Following a two-day course of fluconazole, the patient once again exhibited a pruritic maculopapular rash (MPE) on the trunk, without evidence of mucosal or systemic involvement. It was decided that the intravenous fluconazole should be switched to an oral route, due to the suspicion that the reaction was related

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to the method of administration and excipients. The eruption persists with the EMP, which worsens with each oral administration of fluconazole. Consequently, a consultation is held with the dermatology service of the hospital, which determines the definitive diagnosis to be simple pharmacoderma secondary to fluconazole. The treatment is then suspended. Subsequently, a consultation was requested from the allergy service for evaluation. In light of the patient's development of a maculopapular rash without systemic involvement, coupled with the unfeasibility of conducting skin tests given the patient's concurrent antihistamine and steroid treatment, and the absence of superior therapeutic alternatives for the underlying infection, a decision was made to pursue a slow desensitization protocol to oral fluconazole. The procedure was conducted in 15 consecutive steps, with the dose gradually increased until the desired level was reached. The treatment was well tolerated, and the patient did not experience any adverse reactions (Table 1).

Table 1. Slow desensitization protocol table to oral fluconazole adapted from protocol for TMS[11]

DAY	STEPS	SOLUTION	CONCENTRATION	DOSE	TOTAL (mg)
1	1	TO	1mg	0.2ml	0.2
2	2	TO	1mg	0.4ml	0.4
3	3	TO	1mg	0.8ml	0.8
4	4	TO	1mg	1.6ml	1.6
5	5	TO	1mg	3.2ml	3.2
6	6	TO	1mg	6.4ml	6.4
7	7	b	10mg	1.0ml	10
8	8	b	10mg	2.0ml	twenty
9	9	b	10mg	4.0ml	40
10	10	c	50 mg (comp or syrup)	1	fifty
11	11	c	50 mg (comp or syrup)	2	100
12	12	c	50 mg (comp or syrup)	3	150
13	13	c	200 mg (comp)	1	200
14	14	c	100 mg (comp)	3	300
15	15	c	200 mg (comp)	2	400

DISCUSSION

There are few case reports or desensitization protocols described for adverse reactions to fluconazole. In 1996, Craig et al described a fluconazole desensitization protocol in an HIV-positive patient with cryptococcal meningitis who developed a pruritic rash in the armpits in addition to hypereosinophilia. Subsequently, dyspnoea and tachycardia were also observed. In this case, a protocol for trimethoprim/sulfamethoxazole (TMS) described by Absar et al. was employed, with the patient tolerating the entire procedure without clinical complications.[11,12] In a further case report published in 2008, Randolph and colleagues describe the rapid desensitization of a patient with a bone and soft tissue infection caused by cryptococcus. This was achieved in just eight hours, following the administration of the second dose of fluconazole, which had resulted in the development of a pruritic erythematous maculopapular rash. The procedure was completed without any clinical complications, and the patient was subsequently discharged without any adverse effects or complications.[13] The third case reported was that of a 76-year-old patient with a history of class IV IgA nephropathy with hematogenous and CSF dissemination of cryptococcus (cryptococcal meningitis) who, 15 days

after commencing treatment with fluconazole, presented with a generalized pruritic rash that originated in the abdomen and subsequently disseminated throughout the body. Following the hypothesis of a delayed hypersensitivity reaction to fluconazole, the drug was suspended, resulting in an improvement in the skin lesions. In light of the crucial role the drug played in the treatment plan, a rapid intravenous desensitisation procedure was conducted prior to the administration of antihistamines.[14] It is crucial for the planning of the study and treatment of hypersensitivity reactions to provide an accurate description of the morphology of the lesions and the chronology of the administration of the drug and the onset of symptoms. This should be done by considering the route of administration, the role of drug metabolites, and other additional factors that may affect the speed or progression of the reaction.[15] In the case of the patient, a comprehensive review of the complete medical history of all the administered medications and their chronological relationship with the onset of symptoms, as well as the route of administration and the duration of treatment, should have been conducted. A comprehensive assessment of the presenting signs and symptoms, the characteristics of the lesions, their topography and the manner of their progression was conducted. The mucous membranes of the mouth, eyes and genitals were examined, as well as the search for signs of severity, including laboratory parameters. The patient exhibited a maculopapular rash, without evidence of mucosal involvement, and laboratory studies demonstrated normal parameters for her underlying pathology. The patient began to present symptoms seven days after the commencement of antifungal therapy, which comprised amphotericin B and fluconazole. Initially, amphotericin B was suspected as the causative agent, and the drug was therefore discontinued. However, when the reaction persisted and the itching and rash worsened with each intake of fluconazole, the diagnostic suspicion was directed towards fluconazole. Despite the existence of a substantial corpus of literature and desensitisation protocols in the context of immediate reactions, this is not the case for non-immediate reactions. In this latter category, there is no common consensus on the indication and implementation of desensitisation protocols. In cases of immediate IgE-dependent reactions, it is established that glucocorticoids are ineffective in preventing the activation of mast cells and that antihistamines are only capable of masking the early signs of an allergic reaction. Furthermore, they are unable to prevent the onset of severe reactions during the course of treatment. In contrast, this phenomenon does not occur in immediate reactions whose pathophysiology is not IgE-dependent. This is exemplified by monoclonal drugs, which can benefit from the use of premedication. In the case of the patient, it was decided that performing skin tests would be contraindicated due to the administration of antihistamines and immunosuppressive treatment, which can result in false negative results. Consider desensitization since the offending medication was essential for the treatment of disseminated cryptococcosis and there were no other appropriate alternatives in a transplant patient. Desensitization is indicated when the treatment with the offending drug is more effective than other pharmacological alternatives, when the reaction is not serious and is well documented clinically, when the benefits of the drug outweigh the risk and when no alternative drug is available that does not present cross-reactivity. It has been demonstrated that in cases of non-IgE-mediated reactions, such as the maculopapular reaction presented by the patient, the desensitization procedure can be performed without contraindications. This is not the case in severe DHR. In the EAACI guidelines from 2014 and 2018, experts confirm that desensitization in delayed DHR is only indicated for fixed eruptions or uncomplicated exanthems, as was the case for the patient.[15,4]

CONCLUSION

Desensitization is a key procedure for the secure reintroduction of allergenic medications to the patient, thereby enabling the continuation of primary treatment for the underlying disease. The procedure is safe when conducted in a controlled setting by highly trained healthcare professionals in collaboration with other specialties, thereby ensuring a multidisciplinary approach. The patient's risk profile, comorbidities and established treatments must be considered and an appropriate protocol followed. At present, further experience is required to define the specific steps to be followed. It is also evident that future research processes must be conducted to establish standardized protocols for non-severe late-type allergic reactions.

CONFLICT OF INTEREST

There are no conflicts of interest.

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