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PRACTICAL DERMATOLOGY

Cutaneous Adverse Drug Reactions: How to Identify the Trigger☆

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Abstract It is estimated that 10% to 15% of medicated patients develop adverse drug reactions (ADR). Despite the high prevalence of ADR, the identification of the trigger drugs remains a medical challenge, mainly in polymedicated patients. Our goal is to update the diagnostic tools to identify enhancer drugs of type B-ADR that compromise the skin and/or mucous membranes, in order to optimize patients' follow-up and improve their quality of life. We develop the review in two stages: I- we review the pathophysiological mechanisms of the ADR; II- we developed the clinical approach for the identification of the triggering drug.

PALABRAS CLAVE
Reacciones adversas a medicamentos;
Farmacodermias;
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Interacción farmacológica de

Reacciones cutáneas adversas a medicamentos: cómo identificar el desencadenante

Resumen Entre el 10 al 15% de los pacientes medicados desarrollan reacciones adversas a medicamentos (RAM). A pesar de la alta prevalencia de RAM, la identificación del agente causal es un desafío diagnóstico y terapéutico, principalmente en pacientes que reciben múltiples medicamentos. Nuestro objetivo es actualizar los métodos de diagnóstico para identificar el fármaco desencadenante de RAM de tipo B que comprometa piel y/o mucosas, a fin de optimizar el seguimiento y la calidad de vida del paciente.

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medicamentos con receptores inmunes (CONCEPTO P-I); Pseudoalergias; Reacciones de hipersensibilidad

Desarrollamos la revisión en dos etapas: I- repasamos los mecanismos fisiopatológicos de las RAM; II- desarrollamos el abordaje clínico para la identificación del desencadenante.

Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as a response to a drug that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

The WHO classifies ADRs according to their pathophysiological mechanism from A to F. Type B reactions cannot be predicted by the drug's mechanism of action and depend on patient susceptibility. They are known as idiosyncratic reactions and may be immune-mediated or non–immune-mediated (Fig. 1).[1]

The manifestations of ADRs are very varied, and skin involvement is the most frequent. A cutaneous ADR (cADR) is defined as one that affects the skin and/or mucous membrane or adnexa.[2] cADRs are classified in different ways. Figure 2 shows the various entities according to their clinical severity (Fig. 2).

It is estimated that 10% to 15% of medicated patients develop ADRs,[3] which account for 3.5% of admissions in Europe.[4] In the United States of America, it is calculated that 197 000 people die of ADRs every year. Despite the high prevalence of ADRs, identification of the causal agent continues to hamper diagnosis.[5]

Our objective was to update the tools used to identify the trigger of type B cADRs that compromise the skin and/or mucous membranes in order to optimize follow-up and patient quality of life (see additional material in Appendix 1).

Pathophysiology of adverse drug reactions: immunological aspects

Some pathophysiological mechanisms, such as drug hypersensitivity reactions (DHRs) are well described.[6] Others, such as induction of drug-induced autoimmune syndromes (lupus erythematosus, bullous pemphigoid, and immunoglobulin [Ig] A bullous dermatosis), fixed pigmented eruption, and nonimmune anaphylaxis, are not known in detail.

Immune-mediated type B ADRs are currently classified into 3 groups[6]: DHRs or allergies, pharmacological interaction of drugs with immune receptor (P-i) reactions (independent of antigen presentation), and pseudoallergies (non–IgE-mediated anaphylaxis-type reactions).

Drug hypersensitivity reactions (Fig. 3)

DHRs affect more than 6% of the population.[5] Fig. 3

All hypersensitivity reactions commence with a sensitization stage involving the antigen, the cell that processes it and presents in its HLA (presenting cell), and the T lymphocyte that recognizes it via the T-cell receptor (TCR). The initial link between these 3 elements constitutes a trimolecular complex (HLA-antigen-TCR), which is known as the ''first signal''. This interaction leads to a series of molecular changes known as the ''second signal''. These changes determine a cellular or humoral effector response (mediated by T or B lymphocytes) and the generation of antigen-specific immunological memory. When drugs behave as antigens (or haptens), they can trigger ADRs. There are different types of hypersensitivity reactions. The Gell and Coombs classification, which was modified by Pichler,[7] summarizes the pathophysiological mechanisms of DHRs (Fig. 4). The type of reaction triggered is determined mainly by the nature of the antigen and the cytokine environment. The latter varies depending on the functional profile of the organ involved in the reaction, the route of administration of the drug, and the immunological activation status of the individual. For example, drugs with antigenic properties that are administered via the skin or mucous membrane come into contact—in both cases—with interface or border tissues that are very rich in immune cells but physiologically adapted to fulfill various functions (different functional profile). Activation of intraepithelial lymphocytes in the skin is associated with opsonization and inflammatory defense profiles, whereas the mucous membrane of the digestive tract is associated with the development of neutralization and tolerance responses via activation of type 3 helper T cells, regulatory T cells, and abundant IgA (neutralizing globulin). However, when the mucous barrier is altered and becomes inflammatory (individual immune activation status) or the patient's modulatory mechanisms fail, the patient is prone to lose peripheral tolerance and develop hypersensitivity responses. This is how an antigen that has entered the body via the digestive tract can become an allergen and induce symptoms locally or at a distance. The same occurs with the skin, for example, when the skin barrier is altered, as is the case in atopic dermatitis, and becomes more susceptible to allergic contact dermatitis (type IV-A hypersensitivity reaction).[8]

P-i concept: independence from antigen presentation (Fig. 3)

This concept can be used to explain type B ADRs that lack a sensitization stage. In these cases, it is postulated that the first signal is given by the direct interaction between HLA and the drug or between the TCR and the drug, regardless of processing and presentation by a presenting cell, thus constituting a reversible biomolecular complex, in contrast with the classic trimolecular presentation of ADRs. In P-i reactions, several theories have been put forward in the absence of an effect of the presenting cell for development