Actas Dermosifiliogr. 2013;104(9):782–788

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

NOVELTIES IN DERMATOLOGY

Advances in the Diagnosis of Drug Eruptions☆

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Received 14 September 2012; accepted 24 November 2012
Available online 7 October 2013

KEYWORDS
Toxicoderma;
Drug reaction;
Drug hypersensitivity;
Drug eruption;
Adverse drug reaction

Abstract Drug eruptions affecting the skin or mucosas (toxicoderma) are the most common adverse effects of drugs and represent one of the more common diagnostic challenges for the dermatologist. A better understanding of the pathogenic mechanisms of drug reactions, pharmacogenetics, and pharmacoepidemiology will help us to resolve the main dilemmas and to anticipate and even prevent such reactions. Many drug eruptions are due to T cell–mediated hypersensitivity reactions that can involve activation of different proinflammatory mechanisms, which would explain the varied manifestations. Some aspects defy the classical understanding of antigen processing and presentation. New immunological hypotheses, such as the «p-i concept», have been introduced to complement the hapten theory and, at least in part, help to explain why drug reactions tend to affect the skin and why certain viral infections increase the risk of drug eruptions. In this paper we analyze these pathogenic concepts and the role of HLA genes in the susceptibility to certain severe adverse drug reactions, and also examine other advances in the diagnosis of drug eruptions. We briefly discuss a number of recently described reactions to new drugs.

PALABRAS CLAVE
Toxicodermia;
Reacción medicamentosa;
Hipersensibilidad medicamentosa;
Exantema medicamentoso;
Reacción adversa medicamentosa

Novedades en el diagnóstico de las toxicodermias

Resumen Las erupciones medicamentosas que afectan a la piel y las mucosas, o toxicodermias, se sitúan en primer lugar entre las reacciones adversas a medicamentos y suponen uno de los desafíos diagnósticos habituales para el dermatólogo. Los avances en el conocimiento de los mecanismos patogénicos implicados en las reacciones adversas a fármacos, en farmacogenética y en farmacoepidemiología, nos permitirán dar respuesta a los principales interrogantes planteados y así anticipar, e incluso prevenir, dichas reacciones.

Muchas de las toxicodermias resultan de reacciones de hipersensibilidad mediadas por células T, con activación de diferentes mecanismos pro-inflamatorios que contribuyen a su heterogeneidad clínica. Algunos aspectos desafían el concepto habitual de procesado y presentación antigénica, habiéndose planteado nuevas hipótesis, como el «concepto p-i», que complementan la teoría hapténica y que permiten explicar, al menos en parte, por ejemplo la preferencia

☆ Please cite this article as: de la Torre C, Suh Oh HJ. Novedades en el diagnóstico de las toxicodermias. Actas Dermosifiliogr. 2013;104:782–788.

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1578-2190/$ – see front matter

de la localización cutánea de las reacciones a fármacos o cómo algunas infecciones virales incrementan el riesgo de toxicodermia.

En este trabajo se realiza una revisión de estos aspectos patogénicos, del papel de los genes HLA en la predisposición a algunas reacciones adversas graves, así como de otros avances en el diagnóstico de las toxicodermias. Algunos cuadros llamativos de descripción reciente en relación con nuevas medicaciones son comentados someramente.

Introduction

Adverse drug reactions are relatively common and most frequently affect the skin. Although usually benign and self-limiting, these reactions can sometimes be serious or even fatal.[1–3] In the evaluation of drug eruptions it is essential to identify and differentiate several types of severe cutaneous adverse reactions (SCARs), which include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced systemic hypersensitivity/drug reaction with eosinophilia and systemic symptoms (DISH/DRESS), and to which acute generalized exanthematous pustulosis (AGEP) should be added. Unfortunately, current knowledge does not allow us to determine the true incidence of these adverse reactions, establish the diagnosis or causal relationship with certainty, or anticipate their appearance.[3–5]

Advances in Pathogenesis

Mechanisms of Drug Hypersensitivity and Models of T-cell Stimulation: the P-I Concept

The majority of adverse drug reactions are type A (i.e., predictable and related with the pharmacological activity of the drug). Type B reactions include the so-called idiosyncratic reactions, intolerance reactions, and immunological reactions, which are often called allergic or hypersensitivity reactions. These hypersensitivity reactions are mediated by various immune mechanisms, which determine the clinical manifestations and often are classified according to the traditional Gell and Coombs system. The majority of reactions are classified as type I (immediate) or type IV (delayed) hypersensitivity reactions.

Type IV hypersensitivity reactions require the participation of T cells that mediate the various forms of inflammation, which in turn are sub-classified into 4 categories: types IVa to IVb. To be immunogenic, and hence to be recognized by T cells, drugs must be chemically reactive (haptens) or be metabolized to form reactive compounds (prohaptens). The immune reaction begins with the stimulation of cells of the innate immune system through covalent binding to pattern-recognition receptors such as Toll-like receptors; the hapten-carrier protein complex acts as a neoantigen that can be processed and presented to T cells and can be bound by both T and B cells, triggering a humoral or cell-mediated immune response. Exclusive stimulation of T cells requires interaction with a molecule of the major histocompatibility complex (MHC).[6,7]

This hapten/pro-hapten mechanism does not however explain the clinically observed ability of some drugs to trigger hypersensitivity reactions despite being unable to undergo conjugation and transformation into neoantigens. This ability, which does not require prior sensitization, has been explained by the formulation of a new immune response hypothesis, the p-i concept (pharmacological interaction of drugs with immune receptors).[8–10] According to the p-i concept, some drugs can bind directly to specific immune receptors and thus, in certain circumstances, trigger an immune response. This mechanism, which is considered more a pharmacological interaction than an immunological reaction, is supported by several clinical observations: e.g., that some drugs can stimulate a specific immune response when administered for the first time or within an interval too short to allow metabolic transformation to a chemically reactive compound; or that certain inert substances that are incapable of forming hapten-carrier protein complexes can produce positive patch tests with a specific lymphocytic infiltrate. Moreover, this hypothesis is consistent with immunological and pharmacological findings derived mainly from studies of drug-specific T cell clones (TCCs), which do not require antigen processing or covalent binding of the antigen to the receptors; also, these TCCs can react to antigens even when antigen-presenting cells have been fixed with glutaraldehyde. The p-i hypothesis is further supported by kinetic studies of T cell activation and the observed absence of MHC restriction in TCCs.[6,8]

Drug presentation to T cells via the non-hapten route (the p-i concept) does not require covalent binding of the drug-peptide complex presented by molecules of the MHC, and is limited to certain drugs that bind in a specific and labile manner to T cell receptors (TCRs), requiring, in addition, an interaction with the MHC to fully activate T cells.[6]

According to Posadas and Pichler,[6] the p-i concept explains the preferential involvement of the skin in many of these reactions, as well as their dose dependence, and the observation that some viral diseases constitute risk factors for lymphocyte activation.

The P-I Concept and the Cutaneous Localization of Hypersensitivity Reactions

The stimulatory potential of the drug-TCR interaction depends essentially on the ability of T cells to respond to a signal of minimum intensity, such as a drug. This particularly applies to memory T cells, which have a low activation threshold compared with naïve cells. Cutaneous absorption and distribution of a drug, a lack of significant drug metabolism in the skin, and the sentinel function of some resident T cells[11] may account for the cutaneous symptoms of hypersensitivity reactions to systemic drugs.