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NOVELTIES IN DERMATOLOGY

Advances in the Diagnosis of Drug Eruptions☆

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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

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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.

The ease with which resident T cells ($CCR8^+/CD4^+/TCR\alpha\beta$) are stimulated via the p-i mechanism, supplemented by appropriate costimulation by the cutaneous network of antigen-presenting cells (dendritic cells, Langerhans cells), results in the activation of the defense mechanisms. The initial stimulation provides signals to keratinocytes and local endothelial cells that direct the immune reaction to the skin. The activation of lymph node T cells, which express CCR6 and other markers of ''skin homing'', occurs simultaneously. Local $CCR8^+$ T cells and recruited $CCR6^+$ cells evoke a predominantly cutaneous inflammatory response that is influenced by the profile of cytokines produced by $CCR6^+$ cells.[6]

Drug-Virus Interaction and the Risk of Skin Allergy

Cutaneous eruptions induced by drug-virus interactions, particularly those observed in adolescents with infectious mononucleosis who receive treatment with aminopenicillins, have been known for many years. The eruptions occurring in infectious mononucleosis were initially considered nonallergic phenomena, as they did not recur after remission of the acute phase of Epstein-Barr virus (EBV) infection, but were later shown to be caused by sensitization to amoxicillin and ampicillin.[12] An increased risk of cutaneous adverse drug reactions has been reported in HIV patients, in whom reactivation of other viruses (cytomegalovirus, EBV, human herpesvirus [HHV] 6) has also been observed.[13] Several studies have demonstrated a close relationship between herpes viruses and drug-induced hypersensitivity syndrome or DRESS.[14,15]

Several hypotheses have been proposed to explain this interaction. For example, it has been suggested that drug metabolism is altered by the virus; that the drug itself induces viral reactivation that causes the eruption; that the virus triggers recognition of the drug as an antigen; or that the viral infection alters the normal repression of the immune response and promotes the appearance of the eruption. According to the p-i concept, some drugs bypass the innate immune system and stimulate memory T cells by cross-reaction with peptide antigens; this may explain the high incidence of reactions associated with certain infections and autoimmune diseases. According to this argument, drug-specific TCCs carry receptors that recognize peptides; in this case, a general stimulation of T cells, as occurs in cases of herpesvirus infection, poses a risk of drug hypersensitivity reaction. Picard et al.[16] have demonstrated reactivation of viruses of the herpesvirus family (EBV, HHV-6, and HHV-7) in 76% of a series of 40 patients with DRESS induced by carbamazepine, allopurinol, or sulfamethoxazole treatment. In all patients they detected activated circulating $CD8^+$ lymphocytes that expressed ''skin homing'' markers and produced TNF-α and IF-γ. Cytokine production was higher in patients with greater visceral involvement, and expanded populations of $CD8^+$ T cells sharing the same receptor profile were detected in the blood, skin, liver, and lungs. Based on those findings, the authors proposed that the DRESS symptoms were mediated by lymphocytes directed against herpes viruses, particularly EBV.

Strikingly, a recent study described a series of cases of DRESS, grouped in an epidemic-like manner, for which the authors were unable to identify a common denominator in terms of drug class or reactivation of a particular type of virus, indicating the possibility of a common initial environmental factor that favors reactivation of a virus of the herpesvirus family and the subsequent development of the drug eruption.[17]

Genetics of Drug Reactions. MHC Restriction and Association with Specific HLA Alleles in Drug Hypersensitivity

Pharmacogenetics, the study of genetic variables that may influence individual responses to drugs, has advanced significantly in recent years. While adverse reactions are impossible to predict individually, recent studies of pharmacogenomics and the demonstration of a close relationship between the MHC class I and certain cutaneous hypersensitivity reactions to some drugs have led to significant progress towards individualized medicine.

Studies have focused primarily on HLA genotypes and their possible association with SCARs. Associations between specific HLA alleles and various severe reactions to some drugs have been described in certain population groups. Examples include HLA-B*1502 and SJS/TEN induced by carbamazepine or phenytoin, HLA-B*5801 and SJS/TEN induced by allopurinol, and HLA-B*5701 and hypersensitivity to abacavir. The relationship between the HLA-B*5701 allele and abacavir is so strong that, in some studies, screening has been shown to reduce the incidence of hypersensitivity reactions, and the FDA has recommended screening prior to the prescription of this drug. Other studies have demonstrated links between specific HLA alleles and carbamazepine-induced reactions. It has also been suggested that HLA can have a protective effect; the presence of HLA-B*0702 protects against serious adverse reactions to carbamazepine in white individuals. Whether pharmacogenetic screening can predict the risk of hypersensitivity reactions is currently being investigated, although this approach is hampered by several difficulties, including the variable prevalence of specific alleles in a given population and the lack of availability of rapid detection methods.[18–22]

The association between HLA and drug reactions could be explained by the presentation of certain peptides by a specific allele; according to the p-i concept the drug could bind to specific TCRs that would require an additional interaction with the HLA molecule that could only occur with a particular HLA allele; in the absence of that allele, the drug would be insufficient to induce immune stimulation.[7–9]

A recent study by Ko et al.[23] investigated the specific role of T cells and demonstrated, in cases of carbamazepine-induced SJS, the need for both a relevant HLA allele and a unique and relevant T cell receptor sequence, meaning that a limited number of TCCs can interact with the MCH/peptide/drug complex. These drug-specific oligoclonal $CD8^+$ T cells expand, producing cytotoxic molecules such as granulysin. While these findings represent an important advance, it remains to be determined whether they are applicable to other drugs and populations.[24]

Many issues remain to be addressed, such as the differences in the clinical presentation of the adverse reactions and the significance of cutaneous versus systemic

involvement. Because the genetic associations mentioned are neither essential nor sufficient to explain all adverse drug reactions, additional functional studies will be required for us to fully understand the relevance of this genomic approach.

Diagnosis of Adverse Drug Reactions

The diagnosis of a drug reaction requires evaluation of the patient's medical history and of the temporal relationship between drug administration and symptom onset, knowledge of the most common eruptions associated with certain drugs, and the use of reference material (e.g., databases, case descriptions). Biopsy is useful only in some cases and for certain drugs.[25] The gold standard—reintroduction or challenge with the relevant drug—is not always feasible, appropriate, or ethical.[26] Prevention, despite the aforementioned advances in pharmacogenetics, basically involves gathering information on previously documented adverse effects from the patient's medical history and the use, if possible, of alternative drugs that carry a lower risk, as there is no way to predict an adverse reaction in any given patient.

There are no validated in vivo or in vitro tests for most drug reactions. Efforts are mainly oriented towards developing diagnostic methods and preventing severe cutaneous adverse reactions.

Skin tests for drug allergies (e.g., to penicillin or anesthetics) have been well studied, but their usefulness is limited. Patch test are one of the most widely available tests to confirm the involvement of a drug in delayed-type hypersensitivity adverse skin reactions. Despite their positivity in both mild maculopapular reactions and some serious adverse reactions, patch tests are not always standardized for the study of adverse skin reactions. The advantage of patch tests is that they can be performed with any drug on an outpatient basis, given the low risk of recurrence of the drug-induced reaction. However they have the disadvantage that the test results are highly variable depending on the drug and the type of reaction observed.[27,28]

Lymphocyte activation and transformation tests are complex, are standardized only for certain drugs, and are not always sufficiently specific, while the isolation of drug-specific TCCs and studies of the profiles of the mediators involved are performed only in research laboratories.[29,30]

Granulysin is one of the possible markers of serious adverse reactions such as SJS/TEN.[31] Granulysin exhibits cytotoxic activity and plays an important role in the defense against a variety of pathogens by inducing the apoptosis of target cells via a mechanism involving caspases, primarily derived from NK cells, among other factors. Granulysin is the most potent cytotoxic molecule in the blister fluid and serum of patients with SJS/TEN, and has even been evaluated as a potential early marker of the disease. Fujita et al.[32] recently developed an immunochromatography-based strip test for the rapid detection of granulysin. This test, which is yet to be validated, would allow the distinction of SJS/TEN from other less serious drug reactions, even before the onset of widespread blistering. However, Schlapbach et al.[33] analyzed granulysin expression in cells positive for NKp46, the most selective marker of NK cells, in other reactions such as fixed drug eruption, mild maculopapular reactions, and AGEP, and concluded that the extent of epidermal damage cannot be attributed solely to granulysin and that the epidermal activation and recruitment of NKp46$^+$ cells likely play a role in determining the severity of adverse reactions.

New Drug-Associated Clinical Manifestations

Cutaneous Manifestations of New Treatments for Hepatitis C

The dermatological manifestations of hepatitis C virus (HCV) infection are well known and are extensively documented in the literature, as are the adverse effects of its treatment using a combination of interferon, pegylated interferon, and ribavirin.[34,35] New antiviral agents for the treatment of HCV, including boceprevir and telaprevir, were recently approved for administration in combination with pegylated interferon and ribavirin. This triple therapy provokes a greater virologic response, with reduced treatment time in both naïve and previously treated patients, but is associated with an increased frequency of dermatological adverse effects, according to a recent review by Cacoub and coworkers.[36] Those authors also reported that in phase II/III studies of telaprevir, half of the patients experienced an eruption similar to that observed following treatment with pegylated interferon plus ribavirin; in over 90% of cases this eruption was classified as mild or moderate (grades 1 and 2) and non-progressive, and in only some cases required the withdrawal of treatment to achieve the resolution of symptoms. The management plan for these patients recommends the withdrawal of medication in cases of severe eruption (grade 3) and advises caution in cases of creeping eruption that does not correspond to any of the types of dermatitis associated with HCV treatment; SCAR should be ruled out in such cases by evaluating the appropriate criteria, or treatment immediately discontinued.[36]

Symmetrical Drug-Related Intertriginous and Flexural Exanthema

In individuals previously sensitized to an allergen through contact, systemic exposure results in the development of a condition classically termed systemic contact dermatitis. One of the most common manifestations of this condition is so-called *baboon syndrome* (BS), a term coined by Andersen et al. in 1984.[37] A subsequent study by Hausermann and coworkers[38] examined a series of 100 cases of BS, and found that about half of the patients exhibited no evidence of prior skin sensitization. For that group the authors proposed the term symmetric drug-related intertriginous and flexural exantema (SDRIFE) to describe a peculiar form of drug rash with symptoms similar to those of true BS.

Miyahara and colleagues[39] recently conducted a review of BS and described the putative mechanisms that have been implicated in this type of eruption, from delayed hypersensitivity reactions to recall phenomenon or p-i-type reactions (pharmacological interaction with immune receptors), and proposed a new classification that would include classical BS (historically equivalent to mercury exanthema), topical drug-induced BS, BS induced by systemic medications (i.e., SDRIFE), as well as BS-like patterns induced by infection and other BS-like conditions. When assessing patients with

this clinical manifestation, it should be borne in mind that a wide range of dermatoses can manifest as a symmetric intertriginous eruption, and that the number of medications implicated in systemic contact dermatitis and drug-induced BS is growing.[40]

Voriconazole-Induced Photosensitivity

Voriconazole is a broad spectrum triazole antifungal agent that is widely used in immunosuppressed patients and frequently induces adverse reactions, including an unusual form of photosensitivity that has both acute and chronic manifestations and for which the underlying mechanism is not completely understood. Reversible symptoms such as sunburn and even pseudoporphyria cutanea tarda may be observed, and cases of pigmented lesions in sun-exposed areas have recently been described, even in pediatric patients, suggesting photoaging due to chronic sun damage and a possible association with skin cancer and even melanoma.[41–44] Cowen and coworkers[43] conducted a review of voriconazole-induced photosensitization and suggested, given that this drug is frequently administered for long periods, especially in a high-risk immunosuppressed population and in outpatients, that strict prophylaxis and photoprotection measures should be implemented, particularly in patients with signs of sun damage or a history of skin cancer.

Levamisole-Induced Vasculopathy

One of the most striking drug eruptions described recently is vasculopathy induced by levamisole-contaminated cocaine. First reported in 2010,[45,46] this condition presents with a characteristic pattern of retiform purpura and ecchymoses with necrosis, mainly affecting the pinna, nose, and cheeks and, less commonly, the trunk and extremities. Histopathology reveals microvascular thrombosis with or without leukocytoclastic vasculitis, and there is associated neutropenia. Given the widespread use of levamisole as a cutting agent in cocaine due its stimulatory effects and cocaine-like appearance, and the widespread distribution of this drug, it is important to consider this condition in the differential diagnosis of vasculitis and vasculopathies.

Secondary Cutaneous Effects of New Cancer Therapies

Anticancer treatments frequently cause side effects and adverse skin reactions. In addition to cytotoxic drugs, the advances in the understanding of the mechanisms of oncogenesis have led to the development of new immune therapies and specific cancer therapies directed against certain molecules (targeted therapies). The use of these compounds is associated with several different more-or-less specific and relatively frequent cutaneous adverse effects, which sometimes correlate with tumor response, and although occasionally severe, do not usually require treatment withdrawal. These reactions are most commonly induced by epidermal growth factor receptor inhibitors and stabilizers of the mitotic spindle (taxanes).[47,48]

One of the most striking aspects of targeted cancer therapies is the development of skin tumors in patients treated with kinase inhibitors such as sorafenib. These tumors fall within the spectrum of keratinocyte cancers (actinic keratoses, keratoacanthomas, squamous cell carcinoma, and even basal cell carcinoma) and are characterized by a good prognosis and even regression after discontinuation of sorafenib treatment. The use of vemurafenib, a BRAF inhibitor, was recently approved for the treatment of unresectable or metastatic melanoma with a BRAF V600E mutation, and the development of both keratoacanthomas and squamous cell carcinoma have been observed in patients treated with this drug. The proposed hypothesis is that RAF inhibitors induce the activation of mitogen-activated protein kinases (MAPK) in cells that do not carry the BRAF mutation, such as keratinocytes, resulting in keratinocyte proliferation. In tumors of patients treated with RAF inhibitors, the mutational profile (i.e., RAS mutations) supports a mechanism of tumor induction with accelerated lesion growth caused by activation of the MAPK pathway.[49–53]

Another notable aspect of the cutaneous adverse effects of cancer therapy is the existence of a group of reactions characterized by painful erythematous-edematous lesions, which can be blistering and sometimes self-limiting, located mainly on the hands, feet, elbows, knees, pinnae, and intertriginous zones, often with lesion overlap. These disorders have been described in recent decades and are referred to by several different terms (erythrodysesthesia, acral erythrodysesthesia, acral erythema, hand-foot syndrome, chemotherapy-induced acral erythema, intertriginous eruption associated with chemotherapy, neutrophilic eccrine hidradenitis, chemotherapy-associated eccrine syringometaplasia, and epidermal dysmaturation) based on the clinical morphology, location, symptoms, or histological characteristics of the lesions.[54–59] Bolognia and coworkers[60] proposed the term *toxic erythema of chemotherapy* for this apparently heterogeneous group of disorders, given that a spectrum with overlapping clinical and histological manifestations, and even drug triggers, can be demonstrated. Those authors argue that this inclusive term defines and characterizes a type of identifiable reaction, eliminates potentially confusing terminology (e.g., syringometaplasia, epidermal dysmaturation), indicates the nature of the condition, excludes infectious or allergic processes, and alerts the clinician to the fact that the condition is associated with chemotherapy and can resolve and recur during the same therapeutic regimen. Moreover, this term facilitates understanding between different specialists involved in the identification and management of this condition.

Ethical Responsibilities

Protection of persons and animals. The authors declare that no experiments were performed on humans or animals during the course of this study.

Data confidentiality. The authors declare that they have followed the protocols of their place of work pertaining to the publication of patient data and that all patients included

in the study were appropriately informed and provided written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in this article. This document is in the possession of the corresponding author.

Conflict of Interest

The authors declare that they have no conflict of interest.

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