

GUEST EDITORIAL

When Drugs Make Patients Worse

The skin is the most common target of adverse drug reactions. For commonly used agents such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics (aminopenicillins, sulfonamides) and antiepileptics, more than 1%, perhaps even more than 5%, of patients using these drugs for the first time may develop a skin eruption. According to the World Health Organisation definition, about 2% of all skin reactions are considered "serious ... if it results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening". It has been estimated that one out of every 1000 hospitalized patients experiences a serious cutaneous drug reaction.

Dealing with drug reactions is becoming one of the main activities of dermatologists, at least of hospital-based dermatologists. Drug reactions are occurring more and more frequently, with new entities being described every month. Each new drug that is introduced, especially in oncology, brings with it new types of reactions. The evolution and prognosis of each of these clinicopathological entities can be benign or potentially lethal. When dealing with cutaneous drug reactions, all too frequently physicians label the different clinicopathological entities under the common "package" of "cutaneous drug reaction" or "hypersensitivity reaction". In fact, the mechanisms are different, the prognoses are different, the therapeutic measures are different, although they all share the common necessity to withdraw the drug in question.

In this issue, of *Acta Dermato-Venereologica*, Kruse et al. (p. 183) report on reactions caused by COX 2 inhibitors. These reactions are thought to be provoked by a pharmacological mechanism completely different from the usual "hypersensitivity" phenomenon of immune-mediated reactions. In fact, they found that the same kind of reaction was provoked by non-chemically related drugs; they also demonstrated that selectivity of these new anti-inflammatory drugs was not sufficient to prevent the recurrence of intolerance reactions in patients who had previously experienced reactions to the "classical" NSAIDs. The reason explaining why only a minority of patients are intolerant to NSAIDs while the mechanism is thought to be a pharmacological one remains unknown.

Immune-mediated reactions are the most frequent types: morbilliform or maculopapular rash, acute exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (also called "hypersensitivity syndrome" – an ambiguous term that is best avoided) and the spectrum of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are well-known examples of these immune-mediated reactions. In this issue, Chi Keung Yeung et al. (p. 179) report on 16 patients with SJS–TEN and emphasize the role of widely prescribed drugs such as Allopurinol.

Recent advances in our understanding of the mechanisms of these reactions have enabled us to differentiate between several clinicopathological entities and to ban the generic term "hypersensitivity reactions".

Fifteen years ago it was hypothesized that patients suffering from severe drug reactions (hepatitis and/or cutaneous reactions) were exposed to increasing amounts of reactive (oxidative) metabolites because of a decreased production of normal soluble non-toxic metabolites and also because of a diminished ability to detoxify the reactive metabolites. This hypothesis has been supported by evidence from drug-induced

hepatitis, but does not fit with what is observed for drug eruptions. In several series of studies, no significant association was found with a slow acetylation phenotype or epoxide hydrolase defect. Initial reports claiming that patients with AIDS suffered from glutathione depletion were not confirmed by further studies. Furthermore, immune reactions caused by drugs with non-reactive metabolites (minocyclines) have been observed. On the other hand, most T-lymphocyte clones derived from patients with prior reactions to sulfamethoxazole (SMX) recognized the parent drug only and not the metabolites (Schnyder et al.). These results suggest that SMX itself has a more important role than its reactive metabolites in initiating the immunologic reaction that results in eruption. Studies of these clones have demonstrated that drugs differed from common peptidic antigens by their ability to stimulate T cells in several ways, including an original non-covalent link with major histocompatibility complex molecules on the surface of antigen-presenting cells. Different drug reactive clones produce different cytokines *in vitro*. This probably contributes to different clinical expressions of the reaction.

Concerning SJS and TEN, it has been demonstrated that the widespread apoptosis of keratinocytes, which causes detachment of large layers of epidermis, was mediated by several cytokines: Fas and TNF- α . Recent studies, however, have confirmed prior observations that other mediators of apoptosis, e.g. perforin-granzyme, were also involved in the mechanisms of skin lesions of TEN. Many activated CD8 T-lymphocytes were found in the blister fluid that accumulated under the necrotic epidermis. These cells shared the phenotypic markers of natural killer cells and of cytotoxic T cells. They also expressed a membrane marker (CLA) allowing homing of lymphocytes in the skin. It therefore seems probable that several pathways may be activated at the same time and that some additive effect leads to destruction of the epidermis.

These new insights into the pathophysiological mechanisms of immune-mediated cutaneous drug reactions open up a new field of knowledge in cutaneous immunity. They may also enable us to find new approaches to rationally designed, specific treatment of drug reactions.

LITERATURE

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