

G. Canto

Coordinator of the
Drug Allergy Committee of
the SEAIC

Editorial

Hypersensitivity reactions to new drugs

Lhe general increase in the prevalence of allergic sensitizations observed over the last decades also encompasses the field of drug-induced immunological reactions. A number of factors have a role in this increase: greater use of drugs by the population, continuous development of new drugs, and the apparition of new diseases, such as AIDS, or of new therapeutic strategies as is the case for chemotherapeutic agents.

The investigation of drug reactions with an immunological basis has also experienced changes. The Gell and Coombs classification has been usually applied in order to explain the pathologic changes induced by drugs. However, this approach has a number of disadvantages that are mainly due to the fact that it cannot fit some of the more frequent clinical conditions caused by drugs, such as exanthema, nor some of the more severe reactions, such as the Stevens-Johnson syndrome or toxic epidermal necrolysis, nor the hypersensitivity reactions involving internal organs.

It may thus be more useful to carry out a first assessment of the reactions from a chronological point of view considering the moment of their apparition in relation to the intake of the drug, classifying them into immediate and late (or non-immediate) reactions, and then go on to the study of the mechanisms involved in a given reaction. Immediate reactions are due to an IgE antibody-mediated mechanism, as has been demonstrated in a host of publications. However, the mechanisms involved in the late reactions have been more difficult to ascertain, and they have not begun to be clarified until the '80s. In the quest to know the immunological mechanisms underlying the latter, it has been highly interesting to achieve knowledge of the modes of interaction between the antigens of the drug or of its metabolites (haptens) and the corresponding carriers; these mechanisms encompass both the drugs that are conjugated through covalent binding between the hapten and the carrier and also those that are coupled through mechanisms that are still not fully understood but which in any case evidence the capacity to induce an immunologic response.

Besides the usual recognition of the hapten-carrier complex by the T cell receptor (TcR) in the context of the Major Histocompatibility Complex (MHC) molecules, other forms of interaction between the antigen and the TcR have been observed, some of which are up to a certain point similar to what occurs in the recognition of superantigens. The clarification of the processes of hapten formation from the drug molecule and the mechanisms of recognition by the T cells, which play an essential role in the clinical and immunological characteristics of

drug reactions, and also of the induced immune response, shall render possible a better clinical and diagnostic approach to this type of reactions.

When considering which are the drugs most frequently involved in the causation of allergic reactions, our experience gives pride of place to reactions induced by antibiotics. As a whole, these represent 61% of the drug reactions studied. Among them, 59% of the cases correspond to reactions to β -lactam antibiotics, and 55% of these are reactions induced by amoxycillin.

The penicillins are the best-studied and characterised group (representing some 50% of all the papers published on this subject) because of their high and widespread use and of their capability to form stable covalent conjugates. The incidence of this group shows a receding trend, possibly because of improvements in the manufacturing processes and perhaps also because of the introduction of structures generating determinants that are less immunogenic. This diminishing trend, however, is offset by their still very high consumption.

After the penicillins, the cephalosporins are the antibiotic group that most frequently induces a selective allergic response. Allergic reactions to these antibiotics started appearing shortly after their introduction into the drug market, and from the very beginning the importance of the side chain of penicillins and cephalosporins at the time of assessing cross-reactivity was strongly considered. On the basis of this knowledge it has been possible to explain and understand the concept of cross-reactivity, which is fundamental in understanding that an individual who has developed an allergic reaction to one drug may or may not tolerate another one with a chemically related structure. In this context, one particularly complex example of cross-reactivity is that of the anticonvulsants, as molecules that are quite different may generate similar metabolites. Thus, in late reactions to hydantoin cross-reactivity to phenobarbital or to carbamazepine may exist.

Besides penicillins and cephalosporins, other antibiotics appear as responsible for allergic reactions. Aminoglycosides represent some 15% of the total number of antibiotic-caused reactions. In order of decreasing frequency they are followed by the macrolides (spiramycin being the main responsible

for sensitizations within this group), and then by the quinolones, vancomycin and the lincosamides, with progressively decreasing percentages of cases. A noteworthy observation is the reduction of the number of observed reactions caused by tetracyclines, which now represent only 1.9% of the total; this decrease is possibly due to the much lesser therapeutic use of these antibiotics in present times.

The macrolides, which are frequently used as alternative drugs to the penicillins in Gram-positive infections because of their similar antibacterial spectrum, only infrequently cause allergic reactions; however, their incidence is increasing because of increasing use. The same holds for the quinolones.

The second place in order of frequency among the various drug groups corresponds to sensitizations induced by non-steroidal antiinflammatory drugs (NSAIDs), with 30% of the total number of drug reactions. Among the NSAIDs, the first place is held by the pyrazolones (82% of all the NSAID-induced reactions), followed by the aryl-acetic derivatives (10%), the propionic derivatives (3.3%), the oxicams (2.3%), the fenamates (0.9%), acetaminophen (0.9%) and the salicylates (0.9%).

The sulfamides (sulfadiazine, sulfamethoxazole) still represent a cause of allergic sensitisation that, with some 10% of the total drug reactions, is not to be obviated.

Reactions to other groups of drugs are observed more sporadically: radiological contrast media, trimetoprim, carbamazepine, ephedrine, allopurinol, local anaesthetics not belonging to the para-amino group, benzodiazepines, calcitonin, opiates and muscle relaxants, all of them jointly representing some 8-9% of the total reactions.

The introduction of antiretroviral drugs (reverse transcriptase inhibitors, nucleoside analogues and non-analogues and protease inhibitors) for the management of HIV+ patients since 1987 has given rise in recent times to adverse reactions, with some cases of toxic epidermal necrolysis.

In the present issue of the Journal an excellent review is published of reactions induced by chemotherapeutics. This is perhaps a little-known aspect of drug allergy, and this review is thus highly useful for the recognition and diagnosis of reactions that may occur in the course of treatment with such agents.

One of the main logistic problems in relation to new drug allergy is that of the mechanism of reporting such reactions and the delay in their publication in the literature. These circumstances lead to the re-

sult that such reactions are not always considered. More streamlined mechanisms for their detection and for the spread of the information are thus required in order to facilitate diagnosis.