Interactions between drugs and chemicals in industrial societies.
G.L. Plaa, P. du Souich, S Erill, editors.

CROSS SENSITIVITY BETWEEN ENVIRONMENTAL CHEMICALS AND DRUGS

ALAIN L. DE WECK

Institute of Clinical Immunology, Inselspital, University of Bern, Switzerland

Drugs and environmental chemicals, when interacting with the human immune system, can evoke several types of reactions: a) allergic reactions due to IgE or IgG antibodies specific for the sensitizing chemical; b) allergic reactions due to sensitized T lymphocytes; c) pseudo-allergic reactions due to non-immune mechanisms; d) secondary immune reactions occurring as a consequence of drug-induced immunomodulation or immune suppression.

Boundaries between allergic reactions due to drugs or to chemicals present in the environment increasingly tend to fade, particularly in the industrialized world where air pollution, the presence of chemical additives in foods and by topical application (e.g. fabrics) are increasingly putting us in steady contact with potentially allergenic or pseudo-allergenic chemicals. Accordingly, the topic of cross-sensitivity between environmental chemicals and drugs has become very relevant.

MAIN TYPES OF UNTOWARD SENSITIVITY TO DRUGS AND CHEMICALS

In immunology, it is almost considered as a dogma that a low molecular weight chemical (e.g. below 1000 daltons) will only induce an immune response, i.e. behave as an immunogen, when covalently conjugated to a suitable protein carrier (1,2). Indeed, many examples of sensitization to drugs acting as haptens and forming covalent bonds with proteins, either directly or through some chemically reactive derivative or metabolite, have been described (2). As candidates for autologous carrier proteins in immunogenetic drug conjugates, serum albumin appears to be the first choice, the more as direct evidence of

chemical conjugation of some drugs to serum albumin (e.g. penicillin) after administration in vivo has been presented (3). However, it appears that haptens conjugated to cell membrane proteins, especially when the cells are antigen-presenting macrophages, may be the most efficientmean to achieve sensitization and proliferation of an hapten-sensitive T cell clone (4,5). We must nevertheless consider several other possibilities by which drugs and/or environmental chemicals may induce an immune response (Table I).

TABLE I
MECHANISMS OF SENSITIZATION TO SIMPLE CHEMICALS

1. Covalent binding of haptenic structure to:	- serum protein - cell membrane
2. Non covalent binding to cell membrane	
3. Crossreaction through small antigenic epitope	
4. Generation of new autoantigenic epitopes	
5. Immunomodulation -	autoimmunity by release from suppression (breakdown from tolerance)

Non covalent binding, i.e. mere adsorption of the chemical to a protein, may also in some circumstances induce an immune response: it has recently been shown that adsorption conjugates of cyclohexidine (CHEX) with an immunogenic protein carrier cause the production of low amounts of anti-CHEX IgG antibodies (6). The production of IgE antibodies and of larger amounts of IgG requires, however, covalent CHEX conjugates (6). As will be discussed in more detail below, the size of the epitope (alias antigenic determinant) against which antibodies are formed may play a decisive role in favouring unexpected crossreactivities. Several such examples have been recently described (7-11) (Table II).

TABLE II
EXAMPLES OF CROSS REACTIONS DUE TO SMALL EPITOPES

1. Cephalosporin side chains
2. Myorelaxants and quaternary ammonium
3. Formaldehyde
4. Metals (Ni, Pt)

Of peculiar interest is the realization that chemical modification of autologous protein carriers, for example human serum albumin, may lead to the formation of new antigenic determinants from the protein carrier itself, leading to the production of autoantibodies against autologous proteins. It has already been mentioned that the bulk of penicillin molecules reacting in vivo with human serum albumin constitute "hidden determinants" which become fully accessible to immune reagents only after digestion (3). Experimental examples, such as the production of antibodies to new albumin determinants induced by conjugation with DNP (dinitophenol group) or sulfanilic acid (12) and several others (13), confirm the reality of this theoretical assumption. The presence of IgE antibodies against HSA or modified HSA in patients sensitized by platinum salts (11) or acid anhydrides (14) suggests that this mechanism is also a reality in allergy to drugs or simple chemicals. Since very different chemicals may induce similar conformational and site changes in albumin, an obvious cause of unexpected cross sensitivity following contact with unrelated drugs has been unraveled.

An even more unexpected cause of untoward immune reactions to a drug or simple chemical might be the triggering of autoimmune phenomena where the target antigen itself may have nothing to do with the drug. Such a mechanism has been postulated in instances where autoantibodies and/or autocytotoxic T cells are found and clinical reactions observed to coincide with the administration of drugs, without evidence of an immune response against the drug itself. Indeed, it is temp-

ting to interpret in this way the observations of drug-induced toxic epidermal necrolysis (Lyell syndrome) and other bullons skin manifestations (e.g. Stevens-Johnson syndrome) (15). It is presumed in such cases that interference by the drug with suppression of autoimmunity, e.g. with suppressor T cells, leads to a breakdown of natural tolerance.

Besides immune responses themselves involving IgE or IgG antibodies and/or sensitized T lymphocytes, it is increasingly recognized that drugs or chemicals may induce in selected individuals "pseudo-allergic" reactions. These reactions are termed in this way because they rest on the same mediators and effector cells than true allergic reactions, and are therefore frequently impossible to distinguish clinically, but are not based on an immune response of the IgE or IgG type. A classical example are the intolerance reactions, manifested by asthma and/or urticaria to aspirin (ASA) and to non steroid anti-inflammatory drugs (NSAID). Operationally, and since such reactions may be induced in the same individual by a large variety of apparently chemically unrelated compounds, a broad state of crossreactivity exists. Although the mechanism of such reactions, despite intensive investigations, has remained unclear for a long time, recent studies have implicated a direct partial activation of platelets (16) leading to the liberation of arachidonic acid metabolites possibly acting as mediators.

Another possibility of apparent cross sensitivity to many apparently unrelated products is the broad range of reactions elicited by such food additives as tartrazine or sodium benzoate (17), reactions which for the most part also appear to be based upon non immune mechanisms.

ANTIBODIES AGAINST SMALL EPITOPES

It is a classical notion in immunology to state that the antibody combining site encompasses chemical structures of relatively large size, such as about three amino acids (e.g. trialanine or a whole benzylpenicilloyl group) (18). However, it is also well known that antigenic determinants (or epi-

topes) may also be smaller, e.g. of the size of a benzene ring (1,19). Some recent practical examples suggest that even much smaller chemical structures may provide sufficient hapten-antibody complementarity areas in order to elicit allergic reactions and cross reactions among compounds sharing only very minute portions of their whole chemical structure. Several years ago, we had observed cross-anaphylactic reactions in guinea pigs sensitized by various cephalosporins (8). These cross reactions could only be explained on the basis of a common group (= N-O-CH_3) present on the side chain of both cross reacting partners Cefuroxim ™ and Cefotaxim ™. A more recent example are the reactions to quaternary ammonium compounds, in which also the major epitope appears to be quaternary ammonium ions of very limited size (9,10). This may explain why a very wide range of cross-reactivities was observed in patients presenting anaphylactic reactions to quaternary ammonium myorelaxants. The IgE antibodies of such patients react with a large number of apparently unrelated molecules, where the only structural sharing is the presence of one or several quaternary ammonium ions.

The finding of very small epitopes is not a mere immunochemical curiosity; it may also explain a number of operational cross reactions to drugs following sensitization through environmental chemicals. In a recent study (10), 8 out of 32 patients presenting an immediate-type IgE-mediated allergic reaction to a quaternary ammonium myorelaxant had never been administered such drugs previously and presented their allergic accident, mostly anaphylactic shock, at their first known encounter with the drug. They must therefore have been sensitized by previous contact with other chemical compounds than the drug causing the reaction. Many compounds and drugs (e.g. myorelaxants, neuron-blocking agents, antiseptic and antiprotozoal drugs, vagolytic drugs, vasodilators, cholinesterase inactivators or inhibitors) contain quaternary ammonium ions. It is also striking that such reactions occur overwhelmingly in women, suggesting a special mode of sensitization (use of cosmetics?) rather than genetic factors, as postulated by some (10).

Another possible and practical consequence of immune responses directed agianst relatively small epitopes is the fact that numerous drug/chemical molecules may then become functionally "bivalent", i.e. react simultaneously with two different antibody molecules recognizing the same small epitope on two different portions of the drug's structure. Particularly efficient in this respect may be, in the quaternary ammonium series, suxamethonium (Fig. 1)

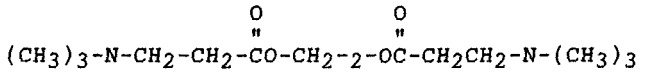


Fig. 1 Suxamethonium

or in another context cyclohexidine (Fig. 2),

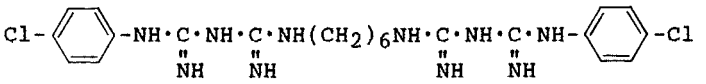


Fig. 2 Chlorhexidine

which appear to be "mirror"molecules in which the reactive epitopes are separated by 6 or more Angströms (10). This is important because such bivalent molecules may, in an patient possessing IgE antibodies of the same specificity, efficiently bridge the IgE molecules on the mast cell surface, without prior conjugation to a carrier. As well known (2) and described with similar synthetic bivalent haptens more than 30 years ago (20), bridging of IgE on the effector cell surface by bi- or multivalent antigen is the first triggering event leading to mediator release. It is therefore understandable that such mirror compounds, like suxamethonium (10) or cyclohexidine (21) are efficient anaphylactogens in man. The possi-

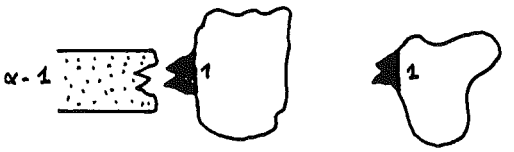
bility and perspective that contact with chemicals in a trivial context (e.g. cyclohexidine is a topical disinfectant) may lead to sensitization and subsequent immediate allergic reaction upon first encounter with a drug sharing small epitopes should definitely be kept in mind.

SEVERAL TYPES OF CROSS-REACTIONS

From an immunological point of view, several types of cross-reactions may be visualized (Fig. 3).

MOLECULAR AND IMMUNOLOGICAL BASIS FOR CROSS REACTIONS

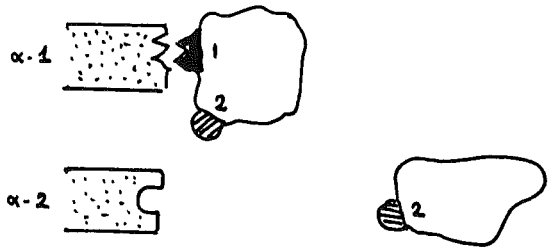
1. Monoclonal response to single epitope



Very small epitopes increase the chance of unexpected cross reactions

Antibody Immunogen Crossreacting antigen

2. Polyclonal response to complex immunogen



Antibodies Immunogen Crossreacting antigen

3. Polyclonal activation of immune response (e.g. LPS)

Fig. 3

The same epitope may be present on very different compounds; this is the situation illustrated by the small epitopes we have discussed above and which is at best ascertained when using a monoclonal antibody against the incriminated epitope. In most instances, however, operational cross reactivity rests on the fact that most in vivo immune responses are polyclonal and involve several antibodies recognizing different epitopes (Fig. 3, 2). If the same epitope is located on very different antigenic compounds, the range of cross reactivities may become quite large and unexpected. Cross-reactivity may also be induced by non specific polyclonal activation, e.g. by bacterial endotoxins. In such a case also, an apparent sensitization to many different allergens may lead to cross reactions and immediate reactions, even against allergens with which no previous contact has taken place.

More trivial, but not less impportant in clinical terms, may be the cross sensitivities arising when structurally similar or identical compounds are used on the one hand as drugs and are present on the other hand in our environment. A few examples are given in Table III. The case of quaternary ammonium compounds has already been discussed above. A recent problem is that of patients subjected to a vertebral disk nucleolysis with chymopapain and who develop anaphylactic reactions. Over 1% of the normal population appears to possess IgE antibodies to papain and has apparently been sensitized by previous contact (foods? meat tenderizers?).

TABLE III
SOME EXAMPLES OF "CROSS-REACTIONS" BETWEEN ENVIRONMENTAL CHEMICALS AND DRUGS

Environmental		Drug
Quaternary amonnium compounds	-	myorelaxants (Suxamethonium)
Yellow DC * 11 (paints, plastic)	-	Quinoleine Yellow (dyestuff in foods)
Sodium benzoate	-	Parabens (drugs)
Tartrazine - aminopyrazolone	-	Pyrazolones
Papain (meat tenderizer)	-	Chymopapain (nucleolysis)

CONCLUSIONS AND SUMMARY

Several mechanisms may lead to cross sensitivity between drugs and environmental chemicals. In some cases, the cross reactivity rests on molecular similitudes (e.g. sharing of antigenic epitopes) facilitating interaction with the same antibodies. In other cases, cross sensitivity may occur in operational terms only and reflects merely the distribution of the implicated drugs or environmental chemicals interacting with a rather polyclonal and polyspecific immune response. Cross sensitivities are also encountered in the frame of non immune "pseudo allergic" reactions. Improved knowledge about and continuous surveillance of cross-sensitivities should contribute in decreasing their incidence.

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DISCUSSION - Cross sensitivity between environmental chemicals and drugs.

P.G. Watanabe

Concerning the possibility that sensitization to simple chemicals may occur without covalent binding to cell membranes, how can you exclude that this binding is taking place, albeit in amounts too low to be detected?

A.L. de Weck

Well it is difficult to make sure that there is absolutely no covalent binding, but it seems that this is not a necessary step for the production of low amounts of anti-chlorhexidine IgG antibodies, for example.

T. Wieland

What are the conditions of the penicilliloylation of proteins? Have experiments been done in vitro to show that penicillin will bind covalently to proteins?

A.L. de Weck

Oh! yes, very many. Penicillin binds in several ways, but essentially either directly by opening of the betalactam ring reacting with amino groups or indirectly through very highly reactive derivatives like penicillenic acid.

G. Zbinden

Are there in vitro or in vivo protein binding studies that show good potential for the prediction of the sensitizing properties of new chemicals?

A.L. de Weck

In a very crude fashion, yes. If a chemical can easily bind covalently with proteins it has a chance to be a good sensitizer, but the great majority of drugs do not show this kind of binding. In the case of drugs, one could, and probably should do first a crude screening, such as that provided by in vitro conjugation studies or relatively easy experiments in vivo. However, one should be very careful in their interpretation and the results should probably not be used to decide on the future of the

compound. Penicillin may not have passed these tests and, more recently, I saw data on two cephalosporins that pointed to a high antigenic potential that never materialized in clinical use.

J.V. Castell

Does the form of administration play any significant role on the incidence of drug sensitization?

A.L. de Weck

Yes, and I can give an example. Some time ago we were struck by the fact that many patients developped neutropenia about 12 to 17 days after starting treatment with high doses of penicillin. An interesting feature was that IgG antibodies and lymphocyte sensitization could be detected in these patients, but also in those that were treated with the same doses of penicillin and that did not develop neutropenia. Furthermore, hemolytic anemia which is associated with penicillin IgG antibodies was not detected. Upon further investigation, it was discovered that many of these patients received the antibiotic in two daily i.v. infusions and that a number of highly reactive derivatives were being formed in vitro. When the therapeutic regime was changed and freshly prepared solutions of penicillin were given by direct intravenous injection the problem of neutropenia completely disappeared.