Foreword

Controversial topics in drug hypersensitivity

Werner J Pichler, MD
ADR-AC, Holligenstr 91, CH-3008 Bern, Switzerland
e-mail: werner.pichler@adr-ac.ch

Drug hypersensitivity (DH) is a complex issue. The clinic is highly heterogeneous, and the mechanism are routed on both immunological and pharmacological principles. There are different approaches possible to analyse and communicate this wide field. The book on “Cutaneous Drug Hypersensitivity” edited by Bircher, Maibach, Brockow, Barbaud emphasises the practical approach and puts the optimal care for the patient in the centre (1). It is clearly intended for the physician encountering patients with suspected DH and provides practical information for specialists, but also for physicians without in-depth knowledge in pharmacology, immunology, dermatology and allergy.

The book is organized in 6 areas: starting with general aspects, clinical symptoms, diagnosis, management and DH in specific populations it concludes with 19 separate chapters devoted to DH to specific drug classes. Thus, the main aspects of DH for the clinician are covered; If one suspects a drug as elicitor for a peculiar DH one can get quickly more specific information on the particular drug/drug class, which type of DH reactions are known, how to diagnose it and the relevant cross-reactivity. Such information is helpful for the clinician, who sees patients with a particular DH only rarely and who will look for helpful advice in the management of this DH.

DH reactions are man-made diseases which can occur in every speciality of medicine. The acute care for patients with DH is often done by the physician, which has applied the drug, but he/she is rarely an allergist. Nevertheless, some basic knowledge in this field is expected from every physician using drug therapy – and the know-how to handle acute anaphylaxis is a must. On the other hand, the clinical picture of DH is often bizarre and to manage DH is often a challenge: It is difficult to gain experience in this field, as DH are rare for each drug while it is not rare as a whole. Moreover, many different factors influence the course of the disease, and diagnosis remains a crux. Thus, a presumably allergic situation may be challenging for the specialist as well. The book “Cutaneous Drug Hypersensitivity” may offer help just for such situations.

The preparation of such a book, which covers a whole area, is always a good opportunity to reflect on the field as a whole: Many aspects are covered in depths, but some controversial issues of drug hypersensitivity (DH) remain. Let`s address some of these “hot” issues.

Different DH classifications: DH are modern diseases which appeared and grew in parallel with the amount of drugs used: As discussed in chapter 4 (Bircher A: Terminology, classifications, chronology), the classification of DH is complex. This seems to be problematic, as different classifications are used in parallel and depend on the viewpoint of...
the physician or researcher: timing, Gell and Coombs, allergic - p-i – pseudo-allergic (“a-p-p”) classifications, etc. (2). One might ask, which classification is correct? But one might forget that the use of different classifications has also some advantage: it makes sense that the clinician facing the acute DH or the physician, who has to decide on the diagnostic steps, or the researcher interested in prevention may approach the patient differently and uses different classifications. The initial approach may rely on the timing of the event; If one has to decide on the diagnostic steps, the immune-mechanism (Gell & Coombs) must be considered, as it indicates which test should be used; And for the physician/researcher trying to understand the mechanism, dose dependence or cross-reactivity, the a-p-p classification may be appropriate. Thus, it is advantageous that different classifications are available and used. Most importantly, one should use a certain classification not because it is the only classification one knows, but because it is the best to help in the understanding/diagnosis/prevention of future DH in the particular case.

**Contact dermatitis as model for systemic drug hypersensitivity?** It is interesting to note that this book on “Cutaneous Drug Hypersensitivity” does not contain a chapter on contact dermatitis (CD), which is probably the most prevalent cutaneous drug hypersensitivity reaction: Why not, and what is the relationship of CD to systemic DH?

In the beginning of immunology, researchers like Karl Landsteiner were fascinated by the extraordinary specificity of the immune reactions. This specificity was elaborated using small chemicals, which were covalently bound to carrier molecules/protein (=haptens). The immune system was able to react with the hapten with high precision and small alterations of the hapten did already abrogate the serological reaction. Later, delayed, cellular reactions were described and the delayed appearing immunity to small chemicals were elaborated, which became a model for CD (3).

As the high specificity of the immune reaction (serological and cellular) was later also observed in systemic DH, it was quite logical to assume that the systemic reaction to small drugs was based on the same chemical principles as in CD: the drug given elicited DH because it or a reactive metabolite covalently bound to a carrier molecule and formed a new antigen, which elicited an immune reaction (4). This hapten-concept as basis for DH was supported by the high incidence of systemic allergic reactions to penicillin, which indeed was found to be a classical hapten (5). The example of beta-lactams, the high specificity observed in clinical cases of CD and DH, and the similar diagnosis by skin tests (patch or intradermal tests) were interpreted as proof for an identical mechanism underlying CD and DH.

The hapten-model in CD postulated that the chemical/drug bound by covalent links to a protein in the skin. In systemic DH (initially mostly immediate reactions) the antigen were drug-modified soluble proteins like albumin, transferrin etc. Later delayed appearing DH were recognized following ingestion of oral or parental drugs. The relevant antigen in systemic reactions was never well defined. The frequent occurrence of skin symptoms (“rashes”) during systemic DH suggested that the presumable antigen in these reactions was formed and presented in the skin and the delayed immune reactions were directed to locally available haptens or hapten-modified cells (e.g. keratinocytes); Drug induced hepatitis was
consequently seen as immune reaction to reactive drug metabolites accumulated in the liver (6).

But there are important differences between CD and DH: the clearest refers to the role of co-stimulation to mount an immune response with inflammation. CD is a localized skin reaction and, is mostly affecting the area in contact with the eliciting chemical. Local irritation is an important, dose dependent component: In CD, the contact sensitizer provides antigenicity and immunogenicity (e.g. stimulation of dendritic cells): both, interaction of the hapten with specific immune receptors as well as the activation of innate immune system are needed to start an immune reaction (7).

In DH, co-stimulation by the drug or drug metabolite was never investigated systematically and data are missing; Co-stimulation of the immune system in systemic DH might go along with symptoms of inflammation, like one observes in generalized viral infections. Co-stimulation by a systematically applied drug would therefore mean sickness/fever/fatigue. Such a reaction does not appear at the beginning of most DH and would not be acceptable. There are some DH, which show signs of inflammation in their later course (fever, fatigue), when the reaction led to inflammation. But there is no systematic “irritation/danger signals” by a systematically applied drug – not even when the patient develops a DH: Actually, patients with MPE often state that they suffer from pruritus, but do generally feel quite well with no general symptoms like fever or fatigue!

Over the last 25 years many studies have shown that drugs eliciting DH are using various pathways of immune activation. Actually, drugs stimulate T cells often by a “pharmacological” off target activity of the drug with the HLA (or TCR) structures (see below and table 1); It is not due to “antigen” formation (a hapten-protein adduct)! This difference between DH and CD becomes more and more evident: In short, CD are immune reactions to a hapten-protein antigen; DH are often pharmacological reactions stimulating the immune system, where not the drug as antigen but the drug with “off target” pharmacological activity stimulates immune mechanism. Thus, the way of immune stimulation is different – but both, CD and DH involve the specific immune system and thus show a similar high degree of molecule-related specificity.

**DH and HLA associations:** As outlined in chapter 7 (Thompson et al, pathomechanism of DH) research on DH has made big progress: allergic type IV reactions according to Gell and Coombs were dissected into type IVa-d; the p-i concept was developed, and in pseudo-allergy the MasPRGX2 was detected (2, 8). For the practitioner, the strong HLA association in some forms of DH is clinically important, as it provides a reliable tool to prevent severe DH. Table 1 provides a table of the most important HLA associations in DH (9).

In acute manifestation of DH (urticaria/anaphylaxis/angioedema) IgE-antibodies and mast cell/basophil degranulation are involved. In contrast, most delayed appearing cutaneous and systemic symptoms involve drug specific T cells. Some of these T cell reactions show an HLA-association. The background for the HLA associations is the p-i concept (= pharmacological interaction with immune receptors): The p-i concept implies that the drug binds directly to proteins of the HLA-TCR complex, both of which have highly polymorphous structures. Importantly, the drug does not bind to the presented immunogenic peptide, as in classical
hapten antigen driven reactions like CD. The drug-HLA (or drug-TCR) complex forms a new entity, which is crucial for T cell activation: The result of this p-i stimulation are exclusively T cell reactions (MPE, DRESS, SJS/TEN). Thereby, the drug may bind to various HLA alleles with distinct affinity: No clear HLA association is found, if the drug can bind to various HLA-alleles (e.g. phenytoin); But some drugs bind rather selectively to a certain HLA-allele only: Examples are abacavir to B*57:01, allopurinol/oxypurinol binding to HLA-B*58:01 etc (table 1). If the patient does not carry the incriminated HLA-allele, the drug is tolerated. Severe DH to this drug can be avoided by pre-therapeutic screening for HLA-phenotypes in a potential patient, before therapy is started; if she/he carried the HLA-allele, therapy with the HLA linked drug was not given and DH avoided. E.g. the incidence of severe DH due to B*57:01 (abacavir) and B*15:02 (carbamazepine) could be dramatically reduced: It represents one of the biggest successes of personalized medicine (10).

**Identify the mechanism of DH:** Another puzzle of DH is the big heterogeneity of clinical manifestations: The main reason for this heterogeneity is the fact that different mechanism are involved in the *initiation* of the immune system activation, but that the inflammatory reaction at the *end* are similar, as the same effector cells of inflammation are involved. E.g., the eosinophilic inflammation in DRESS can involve various organs, but the hepatitis, nephritis or pneumonitis are all due to an eosinophilic inflammation.

One approach to dissect the clinical manifestations is to use classifications, which reflect different mechanism like the Gell & Coombs classification for allergic/immune reactions as well as in the a-p-p classification, which defined DH based of type and location of drug binding to proteins. On the other hand, the manifestations can look very similar, but the underlying mechanism is quite different. E.g., one cannot differentiate on clinical grounds between anaphylaxis due to IgE or a MasGRPRX2 mechanism. Both can lead to rapidly appearing anaphylaxis. And it is difficult to differentiate MPE due to DH based on hapten or p-i mechanism, and the exantheme could even be due to viral infections or due to a GVHD.

It is therefore important that the physician taking care for the patient with DH does not only define the eliciting drug/drug class, but also comes to a conclusion regarding mechanism, as this is decisive for advice on cross-reactivity, dose dependence, further prevention, or HLA linkage (2). Thus, not only the drug or drugs causing the reaction need to be identified. Also the underlying mechanism should be included in the analysis of the DH-reaction and the advice to the patient. The patient wants to know, what was the cause for my drug allergy and what do I have to avoid. An allergic or pseudo-allergic reaction to a NSAID may make a big difference for the advice, namely, to avoid all structurally similar products (in case of allergy) or avoid all products which may act similarly (in case of pseudo-allergy/intolerance).

**Acute reactions and late consequences of DH:** A further, still not well recognized aspect of DH are late reactions appearing in the *absence* of drug: The majority of DH have early-onset symptoms like urticaria, MPE, bullous exanthema, hepatitis etc., which start within minutes to weeks of treatment, depending on pre-existing immunity and mechanism. They start under therapy, but as soon as therapy is stopped, it comes normally to an rapid improvement. But there are exceptions:
a) Appearance of exanthem after drug therapy was stopped: This is well known for amoxicillin, where the therapy is tolerated for 7-10 days, but after stop of therapy, mostly on day 11-13, symptoms appear. This is puzzling since the half-life of the drugs involved is often <12 hr. Often it is possible to demonstrate a sensitization to the drug by skin testing or in vitro analysis (e.g. cytokine based LTT). The mechanism for this late manifestation is unknown; one could speculate, that the T cell reaction was started while the therapy was still ongoing, and that T cell expansion and migration to the skin occurred without antigen/drug. Or that a - transient - cross-reactivity of the drug-activated T cells with self-antigens occurred.

Other late reactions occur mainly in the frame of DHS/DRESS:

b) Viral reactivation (HHV6, CMV, EBV) occur mostly 3-6 weeks after symptoms and signs of DHS/DRESS started and drug therapy was stopped (11): The viral infections do not cause the DHS/DRESS, as often suggested, but is a late reaction in absence of drug – probably due to drug activated T cells cross-reacting with viral antigens (peptides): The original p-i stimulation led to a massive, broadly specific T cell activation, which includes T cells with specificity for herpes virus peptides (HHV6, CMV, EBV, HHV1). These activated T cells attack the virus peptide expressing cells, which leads to a transient release of virus particles with marked viremia. Symptoms are moderate; severe viral complications are rare.

c) In the frame of the massive, polyclonal p-i stimulation during DRESS, also self-peptide reactive T cells become activated; their precursor frequency is low. Nevertheless, if they are activated and encounter self-peptides, they may expand and damage self-peptide expressing cells. This leads to autoimmunity, a further late complication of DRESS, which appears in the absence of the incriminated drug.

d) Multiple drug hypersensitivity (MDH): a further consequence of p-i stimulation like DRESS or severe MPE is MDH: such patients develop an additional DHR to a structurally different drug, with the same or different clinical manifestations (12). MDH occurs in ca 20% of patients with DHS/DRESS, and can occur already at the start of DHS/DRESS (often to a combination therapy), during the initial activation, or even years after the first DHR.

**Diagnosis: provocation, combined evaluation:** The diagnosis of DH is still a difficult topic as the test sensitivities of available tests are not optimal: both skin test (prick, i.d., patch) and in vitro assays (BAT, lymphocyte stimulation assays, LTT) show a moderate sensitivity (30-70%) and the result depend on the drug, the clinic, time lapse since the reaction etc. (see part III, chapters 7-13). At the end, when no conclusive results are obtained, a provocation test is proposed, as mentioned in various chapters of this book.

Just as a reminder: Provocation tests are often seen as gold standard, but there are some arguments against provocation tests: a) cofactors, crucial for clinical manifestation in the acute event, are absent during provocation; b) the mechanism cannot be clarified by a provocation test, which is important for correct advice (e.g. a positive provocation to an analgesic is not informative regarding the question, whether the reaction was pseudo-allergic/intolerance or allergic); c) the patient remains sceptical against a drug, even if he/she has tolerated it during provocation; d) The procedure for provocation tests in
delayed reactions is often unclear; e) it is ethically problematic to perform a provocation test in an iatrogenic disease. Provocation tests contradict the principle “primum non nocere”, and are not recommended in severe cases, where they are most needed.

On the other hand, there is agreement that provocation tests with alternatives or when the pre-test probability for the incriminated drug is low, are clinically useful and ethically not problematic. The tolerance of an alternative drug may be reassuring for the patient and well accepted, as it helps for future therapy. And provocation tests with low pre-test probability of a reaction, are also widely accepted and even recommended. Examples are a history of past reactions to beta-lactam antibiotics at an early age: Exanthems may have appeared >20 years ago, often in childhood, and were possibly due to a coincidence of drug intake and viral infections, and this event labelled the child as beta-lactam allergic for years or even the rest of his life. The diagnosis of a permanent penicillin allergy could rarely be verified in adulthood, as skin/in vitro or provocation tests were negative; most patients tolerated a repeated treatment (delabelling). Therefore, most authors recommend direct provocation with a beta-lactam antibiotic to get rid of such a problematic and often wrong label. Only if the reaction was severe (e.g. prolonged morbidity, hospitalization) or was very acute (anaphylaxis), caution is recommended and diagnostic procedures (skin tests, in vitro tests) should be performed before provocation is considered. In the remainder, the drug allergy label should be removed and the beta-lactam can be given without further tests (13).

As provocation tests are often not possible or not recommended, one can minimize the need for a provocation test or substitute it by combining systematically all evidence for or against a DH: The questions to be answered are: is it a drug hypersensitivity? Against which drug/drugs? What mechanism is involved? By combining all factors an experienced physician can establish a reliable diagnosis in ca 70% of acute cases: The evaluation relies on a combination of clinical picture, timing and severity of the DH, detailed history/cofactors of disease manifestations, previous DH and other allergies/intolerances, knowledge of the drug`s pharmacology, of the type/time-line prior of the DH to the drug; and finally, skin and in vitro tests. Of course, this approach requires experience and requires the expertise of a specialist, and it is only possible , when a rather large armamentarium is available to proof sensitization (skin tests, LTT, BAT). The more test possibilities are available, the lower is the need for a provocation test.

In the absence of good animal models, improvement of therapy and better avoidance of DH rely on the study of such patients, who suffer from this iatrogenic and mostly unpredictable disease. The minimum we can offer as physicians, is to do our best in the management. I hope and believe that this book can help and wish the readers of this book all the best and that they find what they are looking for.

Werner J. Pichler
References


<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA allele</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>B57:01</td>
<td>HSS</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>B15:02</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td></td>
<td>A31:01</td>
<td>MPE, HSS, SJS/TEN</td>
</tr>
<tr>
<td></td>
<td>B15:11</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>B58:01</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Dapsone</td>
<td>B13:01</td>
<td>HSS</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>B15:02</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>A31:01</td>
<td>HSS</td>
</tr>
<tr>
<td></td>
<td>B15:02</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>B59:01, CW01:02</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>DRB115:01-DQB106:02</td>
<td>DILI</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>B57:01</td>
<td>DILI</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>DRB115:01</td>
<td>DILI</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>A33:03</td>
<td>DILI</td>
</tr>
<tr>
<td>Antithyroid drugs</td>
<td>B38:02-DRB108:03</td>
<td>Agranulocytosis</td>
</tr>
</tbody>
</table>