RESEARCH

Trends in Hypersensitivity Drug Reactions: More drugs, More Response Patterns, More Heterogeneity

I Doña,1 E Barrionuevo,1 N Blanca-Lopez,2 MJ Torres,1 TD Fernandez,3 C Mayorga,3 G Canto,2 M Blanca1

1Allergy Unit, Regional University Hospital of Malaga, Malaga, Spain
2Allergy Unit, Infanta Leonor Hospital, Madrid, Spain
3Research Laboratory of Allergy Diseases, Fimabis, Malaga, Spain

Abstract

Hypersensitivity drug reactions (HDRs) vary over time in frequency, drugs involved, and clinical entities. Specific reactions are mediated by IgE, other antibody isotypes (IgG or IgM), and T cells. Nonspecific HDRs include those caused by nonsteroidal anti-inflammatory drugs (NSAIDs). β-Lactams—the most important of which are amoxicillin and clavulanic acid—are involved in specific immunological mechanisms. Fluoroquinolones (mainly moxifloxacin, followed by ciprofloxacin and levofloxacin) can also induce HDRs mediated by IgE and T cells. In the case of radio contrast media, immediate reactions have decreased, while nonimmediate reactions, mediated by T cells, have increased. There has been a substantial rise in hypersensitivity reactions to antibiotics and latex in perioperative allergic reactions to anesthetics. NSAIDs are the most frequent drugs involved in HDRs. Five well-defined clinical entities, the most common of which is NSAID–induced urticaria/angioedema, have been proposed in a new consensus classification. Biological agents are proteins including antibodies that have been humanized in order to avoid adverse reactions. Reactions can be mediated by IgE or T cells or they may be due to an immunological imbalance. Chimeric antibodies are still in use and may have epitopes that are recognized by the immune system, resulting in allergic reactions.

Introduction

An adverse drug reaction (ADR) has been defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment [1]. ADRs are grouped into 2 broad categories (see Table 1): type A reactions, which are predictable, common, and related to the pharmacological actions of the drug, and type B reactions, which are unpredictable, uncommon, and usually not related to the pharmacological actions of the drug [2]. Approximately 80% of ADRs fall into the first category and include drug-induced toxicity, side effects, secondary effects, and drug interactions. Type B reactions comprise 6% to 10% of all ADRs and include drug intolerance (an undesired drug effect produced by the drug at therapeutic or subtherapeutic doses), idiosyncratic reactions (uncharacteristic reactions that are not explainable in terms of the known pharmacological actions of the drug), and hypersensitivity drug reactions (HDRs), mediated by immunological mechanisms [2-5].

It is hard to determine the true prevalence of HDRs due to difficulties in defining and identifying reactions as well as inadequate reporting mechanisms [6]. It has been estimated that HDRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients [7,8]. However, epidemiological studies of HDRs report varying results, probably related to several biases, such as differences in study populations and diagnostic criteria [5,9-14]. Moreover, drug allergy is not a static process: it varies over the years and is related to changing drug consumption patterns, the introduction of new drugs and the withdrawal of others, and the establishment of new indications [15-22].

HDRs include reactions mediated by specific and nonspecific immunological mechanisms (Table 2). Reactions in the first category may be antibody-mediated, through IgE or other antibody isotypes (drug-specific IgG or IgM antibodies), or T-cell dependent [4,23]. Those mediated by specific IgE are type I reactions and are immediate, occurring less than 1 hour after drug administration; typical clinical manifestations are urticaria and anaphylaxis. Cytotoxic (type II) and immunocomplex-mediated reactions (type III) are mediated by drug-specific, complement-fixing IgG or IgM antibodies, and classic manifestations are hemolytic anemia and serum sickness syndrome. T cell–dependent reactions (type IV) are nonimmediate and usually occur 24 to 48 hours after drug intake; maculopapular exanthema (MPE) is the most frequent reaction [4-5].

Reactions mediated by nonspecific immunological mechanisms are more heterogeneous. A majority of patients have cross-intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) [24]. Inhibition of the cyclooxygenase (COX) pathway and release of histamine and sulphidopeptide leukotrienes has been proposed as the underlying mechanism [25].

In this manuscript we analyze the major trends in the frequency and patterns of response to the drugs most frequently involved in HDRs. We have included a section devoted to biological agents because of the increasing role that these protein derivatives are playing in HDRs.

Hyper-sensitivitiy Drug Reactions Mediated by Specific Immunological Mechanisms

1 Immediate Reactions

1.1 β-Lactam Antibiotics

Hypersensitivity reactions induced by β-lactam antibiotics (BLs) continue to be considered the classical model of reactions mediated by specific immunological mechanisms, particularly those mediated by IgE antibodies. These antibiotics bind covalently to high-molecular-weight proteins that can later be processed and recognized by the immune system [26-28], although the details of how this occurs have not yet been fully determined [20]. BLs continue to be the most common cause of HDRs mediated by specific immunological mechanisms [29,30].

The skin is the organ most frequently involved in hypersensitivity reactions to BLs, with maculopapular, morbilliform, and urticarial rashes being the most common clinical entities. There may also, however, be systemic symptoms [10,20,30] and organ-specific responses [31].

The prevalence and incidence of allergic reactions to BLs in the general population are not well known. Early
studies reported a prevalence of allergic reactions to penicillin ranging from 0.7% to 10% of the population, with anaphylaxis occurring in 0.015% to 0.004% of cases [32]. Moreover, a considerable proportion of patients with suspected hypersensitivity to BLs have shown good tolerance in allergy studies [29,33]. This may explain the wide range of prevalence rates found in published studies, with overreporting occurring when patients are classified by clinical history only as well as underreporting of mild and severe reactions [34].

In principle, all currently available BLs can induce an HDR, as they are able to spontaneously generate immunogenic conjugates [26-28,30]. Benzylpenicillin was the first BL implicated in an HDR, followed over the years by different penicillins and cephalosporins; amoxicillin has been the most frequently involved BL since the late 1980s [23], but clavulanic acid is gaining ground, and in our experience is more relevant than major and minor determinants of benzylpenicillin [23,29,35,36]. In the largest study of HDR published so far, we analyzed variations in response to a number of drugs over a 6-year period. We observed a decrease in reactions produced by benzylpenicillin and an increase in those induced by amoxicillin and amoxicillin plus clavulanic acid [29], confirming the tendency observed since the 1980s [23]. Patterns of consumption are in part responsible for the variation in drug response and clinical entities induced [36,37].

Changes in the patterns of reactions and drugs involved in HDRs to BLs have influenced the sensitivity of diagnostic tests. The role played by major and minor determinants of benzylpenicillin has decreased, while that of amoxicillin and more recently amoxicillin plus clavulanic acid has progressively increased [17,35,38,39]. A decrease in test sensitivity has also been observed [38] and new in vitro methods, such as the basophil activation test (BAT), are gaining importance in the diagnosis of immediate allergic reactions to BLs [40].

---

Table 2. Mechanisms Involved in Hypersensitivity Drugs Reactions

<table>
<thead>
<tr>
<th>Immunological mechanism</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>![Type I Diagram]</td>
<td>![Type II Diagram]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypersensitivity reactions</th>
<th>Nonspecific immunological mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>![Nonspecific Diagram]</td>
</tr>
</tbody>
</table>

Abbreviations: Ag, antigen; APC, antigen-presenting cell; COX, cyclooxygenase; LT, leukotriene; NSAIDs, nonsteroid anti-inflammatory drugs.
1.2 Quinolones

Fluoroquinolones (FQs) can induce hypersensitivity reactions mediated by IgE and T cells. IgE-mediated reactions are more common and are severe in over 70% of cases [41]; the most frequent clinical manifestations are anaphylaxis and anaphylactic shock [41-43]. T cell–dependent reactions have been reported less often and include MPE [44,45], fixed drug eruptions [46,47], acute generalized exanthematous pustulosis [45], Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [48-50]. A considerable proportion of T-cell reactions are phototoxic [51]. The prevalence of HDRs induced by FQs has increased in the last decade [29,52,53], and FQs are now the most common non-BL antibiotic involved in HDRs [29]. Moxifloxacin, followed by ciprofloxacin and levofloxacin, is the most common FQ [41]. Moreover, moxifloxacin induces more severe reactions than other FQs [52].

We have observed an increase in the number of patients evaluated as having a clinical history compatible with hypersensitivity to FQs as well as confirmed hypersensitivity to these drugs [29]. This can be explained by both the increased prescription of FQs over the years and the introduction of moxifloxacin for therapeutic use [52]. In Spain, FQs are the second most frequently prescribed group of antibiotics, surpassed only by BLs [54]. Interestingly, patients with BL hypersensitivity are more prone to hypersensitivity to FQs mediated by specific IgE antibodies [41]. Although the reasons for this remain unknown, the fact that patients who are allergic to BLs are more likely to be prescribed FQs than those who are not is one possible explanation, although there may also be an as yet unidentified genetic predisposition.

The diagnosis of immediate hypersensitivity reactions is often difficult. Skin testing is not useful because of the high number of false positives [55,56], but in vitro tests such as immunoassays and the recently developed BAT have proven to be useful [57-59]. Although the sensitivity of BAT is not optimal, it is of value given the high number of severe reactions in patients who cannot be challenged because of the risks.

2 Nonimmediate Reactions

2.1 Antibiotics

Nonimmediate reactions (NIRs) consist of a spectrum of entities that usually occur within 24 to 48 hours of drug exposure, although the time can be as short as 1 to 2 hours following an exposure period of 48 hours or more [60]. Although the most common entities are benign conditions such as MPE, followed to a lesser extent by urticaria [61], severe reactions can also occur, such as drug rash with eosinophilia and systemic symptoms (DRESS) and TEN [62]. The different clinical manifestations are explained by differences in the underlying pathophysiological mechanisms, with different T-cell populations involved in all these entities [63]. Diagnosis is often complex because of the difficulty in obtaining a reliable clinical history, the importance of identifying concomitant factors such as viral diseases, and the low sensitivity of skin and in vitro tests [64,65]. Drug provocation testing is the best and often the only procedure to confirm a causal relationship between a drug and an NIR. However, it is not generally recommended and is in fact advised against in some cases, such as generalized bullous fixed drug eruptions, acute generalized exanthematous pustulosis, SJS, TEN, DRESS/drug-induced hypersensitivity syndrome, systemic vasculitis, specific organ manifestations (blood-cytopenia, hepatitis, nephritis, pneumonitis), and drug-induced autoimmune diseases [62,63].

The true prevalence of NIRs and less severe NIRs in particular is unknown for different reasons including confusion with viral and autoimmune diseases. Moreover, linking symptoms to a particular drug can also be difficult because of the long interval between drug intake and the onset of clinical symptoms, particularly in patients who take many drugs at the same time [62].

The reported incidence for SJS/TEN is between 1.4 and 6 per million person-years [62]. Various studies of severe NIR cases have been published since the 1990s in Europe, the United States, South Asia, and the Asia Pacific [62,66,67]. Antibiotics were the most commonly implicated class of drugs in most studies: between 10.5% and 41% of patients reacted to antibiotics and sulfonamides were the most common cause of NIRs in this group of drugs [62,66]. Several studies have reported the relevance of aminopenicillins in the development of NIRs [64,67,68]. In fact, aminopenicillins are the second most important NIR-inducing antibiotic worldwide [64]. However, analysis of data from the 6-year study carried out by our group revealed a decrease in HDRs due to sulfonamides but few changes in the prevalence of BL-induced reactions [29]. BLs are thus the most common NIR-inducing antibiotics in Spain. The decrease in the consumption of sulfonamides may partly explain these findings.

3 Radio Contrast Media

NIRs to radio contrast media (RCM) have increased in the last decade, in parallel with an increase in the use of these compounds [69,70]. In the past, the high osmolarity of ionic RCM was related to a high incidence of immediate reactions [71,72] due to the nonspecific release of vasoactive mediators [73-75]. Following the introduction of nonionic low-osmolality RCM in the 1970s the incidence of immediate reactions to RCM decreased [71,72]. Conversely, NIRs have increased [29,70], to a point where they are now more common than immediate reactions [29]. A better recognition of the molecular structure of nonionic RCM by T cells may explain this.

NIRs induced by RCM are an important health problem because nearly 50% of patients with a suspected NIR to RCM are confirmed as allergic [70]. This proportion is higher than that reported for other drugs such as BLs [29,68]. The skin is the most commonly affected organ [69]. Reactions vary from mild to severe; MPE is the most frequently reported condition, followed by nonimmediate urticaria, which may be accompanied by angioedema [69,72,75].

Skin tests have a diagnostic sensitivity ranging from 43.6% to 47% [69,70]. Because of this low sensitivity, it is necessary to perform provocation tests in more than half of cases [69]. The 2 RCM most frequently involved in many places are ioxitalam and iomeprol [70], and test sensitivity depends on the contrast agent: iomeprol is more likely to induce a positive skin test, whereas for ioxitalam, drug provocation is usually needed to confirm diagnosis [69].
Trends in Drug Hypersensitivity

4 Neuromuscular Blocking Agents

Increasing attention has been paid to perioperative allergic reactions in recent decades. Depending on the underlying mechanism, these can be classified in 2 groups: reactions resulting from direct nonspecific mast cell and basophil activation [76] and IgE-dependent allergic reactions. Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions [76-80].

The true incidence of perioperative reactions is unknown [81]. Figures vary, probably reflecting differences in clinical practice and reporting systems across countries. The estimated incidence of all immune- and nonimmune-mediated immediate hypersensitivity reactions is 1 in 5000 to 13 000 anesthetic procedures [81-84], with anaphylaxis occurring in an estimated 1 in 10 000 to 1 in 20 000 cases [85-88].

However, the general view is that immediate-type hypersensitivity reactions are largely underreported. This observation has been confirmed in the largest cohort of patients available in the literature, with a higher incidence (100.6 [range, 76.2-125.3] per million procedures) of allergic reactions than previously reported [81]. Different populations show different patterns of sensitization [77,85-87,89,90]. Neuromuscular blocking agents (NMBAs) are the most common cause of perioperative reactions in France [78,79] with an incidence of 1 in 6500. However, IgE-mediated reactions involving NMBAs seem to be less frequent in Denmark, Sweden, and the United States [76,85]. In earlier studies, up to 70% of anaphylaxis episodes were reported to be caused by NMBAs [77,88]. However, changes in etiological patterns of anaphylaxis during anesthesia have occurred in the last 20 years, alongside changes in usage of anesthetic agents, with greater co-administration of other drugs such as antibiotics and analgesics and an increase in latency. Studies from France and the United Kingdom over the last decade suggest a substantial rise in anaphylaxis due to antibiotics or latex during anesthesia. According to some studies, NMBAs may account for 50% of all cases of anaphylaxis during anesthesia, with 20% due to latex and 15% due to antibiotics [77,86,87].

Within the NMBAs, suxamethonium was previously shown to be the most common cause of anaphylaxis (43% of all NMA reactions in France in 1990-1991) [77,85-88], but changing patterns of drug use have led to an increase in cases due to other agents, particularly atracurium, rocuronium, and cisatracurium. Pancuronium and cisatracurium are associated with the lowest incidence of allergic reactions during anesthesia [77,86-88]. It has been suggested that the lower incidence of cisatracurium allergy may have been due to underestimation, because positive skin tests have been mistakenly assumed to be due to nonspecific histamine release [81]. In fact, 20% to 50% of adverse reactions to NMBAs are considered to result from direct nonspecific mast cell and basophil activation [85-87]. A high incidence of allergy to rocuronium in Norway and France has been reported (26% of NMBAs) [78,82-86,89]. This may be the result of biased reporting of adverse effects of new drugs [90] or differences in the influence of environmental factors or genotypic differences [91]. More information is needed from large epidemiological studies.

5 Hypersensitivity Reactions by Other Mechanisms: Cross-Intolerance

Although many drugs can induce the release of histamine or other mediators through nonspecific immunological mechanisms, in recent years growing attention has been given to NSAIDs. The increasing global use [92] has resulted in this group of drugs being responsible for many adverse drug effects, including hypersensitivity reactions [93,94]. In fact, NSAIDs are now the most common class of drugs involved in HDRs [29,33,95,96].

Two groups of reactions have been identified. The first is cross-intolerance (CI) [8,24], where the proposed mechanism is the inhibition of the COX enzyme and the release of histamine and sulphidopeptide leukotrienes [25]. This can be caused by more than one chemically unrelated NSAID. The second group is formed by selective reactions (SRs); these involve a response to a single drug and patients have good tolerance to other chemically unrelated NSAIDs [97-100]. The first group of reactions is the most common and in our experience accounts for more than 75% of cases [24]. These 2 major groups can be subdivided into 5 subtypes, as presented in Table 3. This is the recent proposed classification for NSAIDs according to the interest group of the European Network of Drug Allergy [101]. Further subclassification providing more phenotypes has been proposed [102].

CI to NSAIDs may affect the skin and/or the respiratory airways [9,25,103]. Early studies of NSAID hypersensitivity reactions focused on respiratory airway involvement, including asthma and/or rhinitis and nasal polyposis [25,103,104]. However, skin is the most common organ affected in both CI and SR groups [24]. Two cutaneous conditions have been described: acute urticaria/angioedema in the absence of a history indicative of chronic spontaneous urticaria, called NSAID–induced urticaria/angioedema (NIUA), and reaggravation of pre-existing chronic spontaneous urticaria, called NSAID–exacerbated cutaneous disease (NECD) [101]. Although most studies focusing on CI with skin involvement have been carried out in NECD patients, NIUA is more common [24]. There are controversies concerning the natural course of NIUA, with some authors indicating that it can progress to NECD [105,106]. One recent study of a large group of patients with NIUA followed for 12 years showed that 6% developed chronic spontaneous urticaria, a similar rate to the control group [107].

In recent years, the increased consumption of propionic acid derivatives has resulted in increasing reports of adverse effects to these compounds, including gastrointestinal symptoms, renal failure, acute myocardial infarction, heart failure [108,109], and hypersensitivity reactions [24,29,94,110].

An analysis of the drugs involved in NSAID-induced HDRs over the last 30 years showed that in the period 1980 to 1990, pyrazolones and acetylsalicylic acid (ASA) were the drugs most frequently involved in hypersensitivity reactions to NSAIDs; in the period 1991 to 2000, ASA was the most frequent whilst pyrazolones decreased; and in the period 2001 to 2010, propionic acid derivatives were the most frequent, with ASA in second place and pyrazolones in last place. These changes may partly reflect the changing consumption patterns of each NSAID over time [24,29].
When we compared drugs involved in both CIs and SRs, pyrazolones remained the most frequent drug involved in SRs [24]. The reasons for this are unclear but may be related to a lower capacity of propionic acid derivatives to induce an IgE-mediated response; pyrazolones, by contrast, may have a chemical structure that is better recognized by the immune system, and therefore more likely to induce a response.

### 6 Hypersensitivity Reactions to Biological Agents

In this section we will consider monoclonal antibodies (mAbs) and protein derivatives, which collectively are known as biological agents. Biologics have a great impact in medicine, providing an unlimited source of therapeutic agents and representing more than 30% of all licensed products [111]. The first agents to be introduced were cytokine immunomodulatory biologies, followed by antibody-based immunomodulatory molecules [112]. So far, more than 180 new biologics have been registered [111,112] and more are currently being investigated in clinical trials [113]. Some of these new agents are antibody drug conjugates that can potentially induce allergic drug reactions [114]. The first therapeutic mAbs were mouse antibodies; these were immunogenic and produced a large number of adverse effects [112]. This problem has been tackled by replacing the murine sequences with their human counterparts [111], significantly reducing the adverse reactions [115,116]. Three major groups of mAbs are in use: chimeric antibodies (-ximab), humanized antibodies (-zumab), and human antibodies (-zumab). Chimeric antibodies are still the most widely used mAbs and therefore adverse reactions are expected to occur [117]. mAbs are used in transplantation, oncology, and autoimmunity, cardiovascular, and infectious diseases. More recent applications include virus and toxin-neutralizing antibody fragments that can replace treatment with serum-derived polyclonal antibodies. In the future fully humanized mAbs will be available for a wide variety of indications [111].

Adverse effects can be caused by the suppression of the immune response, leading to decreased resistance to infectious agents or tumor cells. In other instances mAbs can enhance the immune response by stimulating immune cells, inducing autoimmune [111,112]. Because they are immunogenic [117], they can also induce adverse effects through immunological mechanisms. The hypersensitivity reactions fall within the 4 categories reported by Gell and Coombs [4]. IgE-dependent reactions to basiliximab [118], infliximab [119], and cetuximab [120] have been reported, although other mAbs may also induce these reactions. There are other instances where immediate reactions have been reported but no clear evidence exists for an IgE-mediated mechanism [121-123]. Type II cytotoxic reactions have been mainly reported for blood components, such as platelets [124] and red blood cells [125]. In these cases cytotoxic antibodies are produced. Type III mediated reactions have also been reported [126-128], although evidence of the circulating immunocomplexes responsible for these reactions is still lacking. Type IV T-cell reactions such as SJS [129] and drug-induced reactions [130,131] have also been reported. Direct proof of the presence of a T-cell infiltrate in the skin, together with the presence of activated CD4+ and CD8+ cells and positive lymphocyte stimulation to infliximab, has been reported by our group [130]. Other adverse reactions may mimic those induced by the classical mechanisms of Gell and Coombs, but they are associated with immune deregulation rather than a specific immunological mechanism.

In summary, biologics represent a new group of agents with intriguing perspectives for allergologists in terms of hypersensitivity reactions.
Acknowledgments

We thank James Perkins for revising the English of the manuscript.

Funding

The review was funded in part by the Instituto de Salud Carlos III-Thematic Networks of Cooperative Research Centers RIRAAF (RD07/0064) co-funded by the European Regional Development Fund.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Germany: differences in reporting rates between individual anaphylaxis in spontaneous adverse drug reaction reports in

García-Campos J, Gomez F, Rondón C, Blanca M. Hypersensitivity reactions to fluoroquinolones: analysis of the

Delacourt C, Scheinmann P, De Blic J. Allergy to betalactam in P


**Miguel Blanca**

Servicio de Alergología, Hospital Civil
29009 Malaga, Spain
E-mail: mblancago@gmail.com