Multiple Drug Allergy Syndrome: A Distinct Clinical Entity

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Multiple drug allergy syndrome is a clinical condition characterized by a propensity to react against different, chemically unrelated antibiotic or nonantibiotic drugs. The origin of this syndrome is still elusive. This article critically examines the medical literature on multiple drug allergy syndrome, compares and discusses recent personal observations obtained in patients with intolerance to multiple antibiotic or anti-inflammatory drugs, suggests possible pathogenic mechanisms for this type of drug allergy, and reports on current personal research in this field.

Introduction

Multiple drug allergy syndrome is a clinical condition characterized by a propensity to react against different, chemically unrelated antibiotic or nonantibiotic drugs. In most cases, the syndrome presents clinically as acute urticaria, angioedema, or both upon ingestion of offending compounds; different rashes, including Stevens-Johnson syndrome, anaphylaxis, serum sickness–like reactions, and immune cytopenias have been described as well. Allergic reactions may occur after the first administration of a particular drug class. From a pathogenic point of view, with the possible exception of true allergic β-lactam–induced reactions, most drug-induced urticaria episodes characterizing multiple drug allergy syndrome should be considered pseudoallergic reactions. Pseudoallergic reactions are clinically identical to immediate-type, IgE-mediated hypersensitivity reactions but occur in the absence of any detectable immunologic mechanism. Consequently, skin tests with offending compounds and specific antibody determinations are invariably negative in these patients. Patients with multiple drug allergy syndrome are otherwise normal without a clinical history of spontaneous rashes or a personal or family history of atopic diseases.

Studies of Multiple Drug Allergy Syndrome

The observation of patients with multiple-antibiotic sensitivity is not an exceptional event (previous studies showed 1% to 5% of all drug-allergic patients to have multiple drug allergy syndrome), yet there are surprisingly few studies in the medical literature that have specifically addressed this condition. In 1966 [1], an epidemiologic survey noted for the first time that a history of prior allergic reaction to any drug was a risk factor for penicillin allergy. This observation remained totally isolated for over 20 years until congress communications by Sullivan *et al.* [2] in 1989 and Moseley and Sullivan [3] in 1991 reported that subjects with a history of allergy to β-lactam antibiotics had an approximately 10-fold higher risk of allergic reactions upon ingestion of non–β-lactam antibiotics than did the general population.

In 1991, Kamada *et al.* [4] showed the existence of multiple-antibiotic sensitivity in pediatric patients, reporting children with adverse reactions to more than three antibiotic classes; Park *et al.* [5] confirmed these findings very recently in a study of 97 children. In their 1996 retrospective study, Khoury and Warrington [6] did not find a difference in the frequency of allergic reactions to non–β-lactam antibiotics between patients with and without a clinical history of penicillin allergy. They concluded that penicillin allergy is not a risk factor for reactivity to immunochemically different drug haptens. However, in that study, 18.5% of 44 control subjects with vasomotor rhinitis experienced an allergic reaction to a non–β-lactam drug; this prevalence is much higher than would be expected in the general population, which suggests that the selection of control subjects was biased.

Personal Observations on Multiple Drug Allergy Syndrome

Multiple intolerance to antibiotics

From 1997 to 1998, a prospective study of 120 patients with a history of recent allergic skin reactions to antibiotics was carried out at the Allergy Unit of the Ospedale Caduti Bollatesi, Bollate (MI), Italy [7•]. One hundred of these patients had a history of intolerance to a single antibiotic class, and 20 had a history of intolerance to two or more antibiotic classes. These patients were referred by their family doctors, asking for safe alternative antibiotics. All of the patients underwent elective peroral challenges with alternative drugs with the aim of detecting at least two alternative antibiotic classes.

A total of 43 of 253 (17%) oral challenges elicited an urticarial reaction in 23 of 120 (19%) patients. Interest-

ingly, reactions were much more frequent among patients with a history of multiple-antibiotic intolerance (35%; relative risk [RR] = 2.8) than among patients with a history of single-drug intolerance (16%). Based on clinical history and challenge-test results, 36 of 120 (30%) patients were classified as having multiple drug allergy syndrome. The syndrome was approximately twice as frequent among female patients (29/84 [35%]) as among male patients (7/36 [19%]). Further, the prevalence of intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) showed an almost linear increase among patients intolerant to one (18%), two (35%), or more than two (47%) antibiotic classes. Patients with a history of intolerance to NSAIDs had a RR of 3.2 for developing multiple drug allergy syndrome. Female sex and a history of intolerance to NSAIDs were additive and independent risk factors for multiple-antibiotic intolerance. Whether a particular antibiotic class would be tolerated or not was unpredictable, and there was great variability among patients regarding which antibiotic classes were and were not tolerated.

This work did not have an epidemiologic aim because patients and their family doctors may show a higher propensity to seek allergologic advice in the presence of a history of multiple, recurrent allergic reactions to drugs than in the case of a single episode of drug intolerance. Nonetheless, the study led to the following conclusions: 1) multiple drug allergy syndrome exists as a clinical entity; 2) there are several well-characterized risk factors for multiple-antibiotic intolerance; and 3) multiple drug allergy syndrome is related to intolerance to other drugs, namely NSAIDs.

Multiple intolerance to nonsteroidal anti-inflammatory drugs

The finding that a history of intolerance to anti-inflammatory drugs is a risk factor for multiple-antibiotic intolerance represented an intriguing link between the two completely distinct drug families and prompted us to address multiple intolerance reactions to NSAIDs as well. It is generally believed that normal subjects who experience acute urticaria after taking aspirin or other NSAIDs are monosensitive and may take other anti-inflammatory drugs with impunity, and multiple NSAID intolerance can be observed only in patients with chronic urticaria [8••]. However, clinical practice and several studies [9–15] suggest that, in subjects without a history of chronic urticaria, sensitivity to several chemically unrelated anti-inflammatory drugs may occur.

To elucidate this point, a prospective study on otherwise normal patients with a history of recent urticaria after taking NSAIDs was recently undertaken at this allergy center [16]. In this study, subjects with a history of spontaneous urticaria episodes or recurrent pruritus were carefully excluded from the investigation. Of 261 patients included, 178 (68%) had a history of single NSAID intolerance and 83 (31%) had a history of multiple NSAID intolerance. Single-blind, placebo-controlled peroral tolerance tests with alternative anti-inflammatory drugs were administered to 179 patients. The alternative drugs were acetaminophen, nimesulide, and floctafenine, which are reportedly well tolerated by patients with a history of NSAID intolerance [12–15].

Of patients historically intolerant to one NSAID, 9% did not tolerate at least one of the challenged drugs compared with 34% (RR = 5.4) of patients historically intolerant to multiple NSAIDs ($P < 0.001$). Based on clinical history and challenge-test results, 94 of 261 (36%) patients were finally classified as intolerant to chemically unrelated NSAIDs: 27 men and 67 women. As in the other multiple drug allergy syndrome study [7•], this investigation did not have epidemiologic relevance but led to the conclusion that multiple NSAID intolerance clearly exists in the absence of chronic idiopathic urticaria.

Comparison of the two multiple drug allergy studies

A comparison of the main findings of these two studies [7•,16], which were undertaken at different times and on distinct populations, reveals several impressive similarities (Table 1):

1. The high proportion of female patients confirms previous observations that drug reactions are approximately twice as frequent in females as in males [17].
2. The proportion of patients who where finally classified as having multiple drug allergy syndrome was similar.
3. In both studies, a history of multiple drug intolerance represented a significant risk factor for intolerance to an alternative, chemically unrelated drug.

Critical Evaluation of Possible Pathogenic Mechanisms of Multiple-Drug Reactivity

The pathogenic mechanisms that underlie multiple-drug reactivity are even more elusive than are those underlying pseudoallergic reactions to single drugs. Risk factors for adverse drug reactions have been traditionally classified as drug-related, therapy-related, and patient-related factors. In view of the variability and unpredictability of combinations of offending drugs, drug-related and therapy-related risk factors, which may be relevant in other conditions (*eg*, angioedema induced by angiotensin-converting enzyme inhibitors), seem to play little role in multiple drug allergies.

Among patient-related risk factors, specific human major histocompatibility gene complex (HLA) phenotypes [18–22,23•] and metabolism propensities [24–27] have been associated with a sustained immune response to certain drugs. However, HLA phenotypes cannot explain most cases of multiple drug intolerance. Similarly, a pathogenic mechanism based upon the specific immunologic recognition of the parental drugs or of their metabolic breakdown products seems unlikely in these patients considering the markedly different chemical structures of offending drugs. Along with female sex, some other as yet undefined patient-related risk factor leading to a direct, nonspecific histamine release seems to be a more reasonable explanation of the propensity for multiple-drug reactivity in these patients [28].

Table 1. Comparison of antibiotic and NSAID multiple drug allergy studies

	Antibiotic trial*	NSAID trial†
Patients, *n*	120	261
Men, *n* (%)	36 (30)	78 (30)
Women, *n* (%)	84 (70)	183 (70)
Mean age, *y*	39	42
Positive challenges / total challenges		
In patients with a history of single drug allergy, *n* (%)	16/100 (16)	11/126 (9)
In patients with a history of multiple drug allergy, *n* (%)	7/20 (35)	18/53 (34)
Patients finally classified with MDAS		
Total, *n* (%)	36/120 (30)	94/261 (36)
Proportion of total who were men, *n* (%)	7/36 (19)	27/94 (29)
Proportion of total who were women, *n* (%)	29/36 (81)	67/94 (71)

*Asero [7•].
†Asero [16].
MDAS—multiple drug allergy syndrome; NSAID—nonsteroidal anti-inflammatory drug.

Current Personal Research

It is well known that chronic idiopathic urticaria is a clinical condition that may be characterized by multiple-drug reactivity; indeed, approximately 30% of patients with this skin disorder may experience acute and severe exacerbation of their disease following the ingestion of different NSAIDs [29]. This prevalence is surprisingly similar to that of patients intolerant to multiple drugs in both of our previous studies [7•,16]; moreover, chronic urticaria is characterized by a markedly higher prevalence in women. Recent studies by distinct groups of scientists have demonstrated that a high proportion of patients with chronic idiopathic urticaria show a wheal and flare reaction upon intradermal injection of autologous serum. Further, the sera of urticaria patients frequently contain autoantibodies directed against IgE or the high-affinity IgE receptor, FcεRI, that can induce histamine release from basophils from normal donors and human mast cells in vitro [30–36]. It was recently shown that the sera from chronic urticaria patients may induce de novo sulfidoleukotriene production by leukocyte suspensions [37•]. On a molar basis, sulfidoleukotrienes are approximately 100 times more potent than histamine in inducing wheal and flare reactions [38].

These findings in patients with chronic urticaria prompted us to perform autologous serum skin tests on some patients with multiple drug allergy (either the antibiotic or the anti-inflammatory type) to assess their "autoreactivity." Some patients intolerant to single drugs were tested as were subjects with no history of drug intolerance. Surprisingly, all eight patients intolerant to multiple drugs who were included in this very preliminary investigation showed an extremely strong wheal and flare reaction upon the injection of autologous serum. However, two of 10 (20%) patients intolerant to single drugs were also positive to an autologous serum skin test, whereas no reactivity was observed among 20 atopic subjects without a history of drug intolerance.

We have very recently begun to assess the histamine-releasing activity of sera from these autoreactive multiple-drug-allergic patients by the basophil histamine release assay. Preliminary results show that the sera from patients intolerant to multiple drugs show little or no ability to induce significant histamine release from basophils of normal blood donors, suggesting that in these patients autoreactivity is not caused by functional circulating autoantibodies directed against IgE or FcεRI. Thus, patients with multiple-drug reactivity (to NSAIDs, antibiotics, or both) seem to show the same in vivo and in vitro responses as patients with so-called type II chronic urticaria [33] but without suffering from spontaneous urticaria. Type II chronic urticaria has been associated with an as yet uncharacterized 30 kDa histamine-releasing factor that is specific for mast cells but is not able to induce degranulation of normal basophils. We are now trying to confirm these very preliminary observations on a larger number of patients to assess the histamine-releasing activity of the sera from these patients on animal and human mast cells and to study the main features of their cultured basophils. These studies might shed new light on the mysterious world of pseudoallergic drug reactions. Certainly, these preliminary observations raise a number of questions:

1. Why is spontaneous chronic urticaria not present in patients showing such an intense wheal and flare reaction upon intradermal injection of 0.05 mL of autologous serum?
2. Is autoreactivity the pathogenic mechanism underlying multiple drug intolerance; if so, how can drugs that are so chemically different amplify patients' propensity to autoreact?
3. Do offending drugs have common activity on human mast cells and basophils?
4. Why do tolerated and offending drugs differ from one patient to another?
5. Is histamine always the main chemical mediator of drug-induced urticaria?

Conclusions

Multiple drug allergy syndrome is probably a distinct clinical entity characterized by a common, nonspecific pathogenic mechanism. The histamine-releasing (or possibly sulfidoleukotriene-releasing) properties of sera from patients with a history of intolerance to several chemically unrelated drugs—clearly demonstrated by the intense wheal and flare reaction following intradermal injection of autologous serum—might represent, at least in part, the common background of multiple-drug reactivity. The reasons why tolerated and offending drugs show a marked variability from one patient to another remain unclear as do the mechanisms by which offending drugs enhance the underlying autoreactivity leading to acute histamine (or leukotriene) release.

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