Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2003;131:195–200
DOI: 10.1159/000071486

Received: July 5, 2002
Accepted after revision: April 7, 2003

Sera from Patients with Multiple Drug Allergy Syndrome Contain Circulating Histamine-Releasing Factors

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Key Words

Drug allergy · Multiple drug allergy syndrome · Antibiotics · Nonsteroidal anti-inflammatory drugs · Skin testing

Abstract

Background: A subset of drug-intolerant patients show a marked propensity to react to several chemically unrelated antibacterial drugs. This condition is termed multiple drug allergy syndrome (MDAS). The pathogenesis of MDAS is still unclear. A possible mechanism is that a nonspecific patient-related factor leading to direct histamine release from mast cells and basophils is involved. We investigated whether a patient-related facilitating factor such as the clinically unapparent presence of circulating histamine-releasing factors may represent a nonspecific mechanism underlying drug-induced histamine release in patients with MDAS. ***Methods:*** 38 otherwise healthy adults with a history of acute urticaria following the ingestion of antibacterial drugs [18 subjects with MDAS (patients) and 20 monosensitive subjects (drug-allergic controls) on the basis of both clinical history and single-blind peroral challenges with alternative substances] and 20 subjects without a history of drug allergy (normal controls) underwent an autologous serum skin test (ASST). IgE specific for β-lactams was measured in sera from 25 subjects (11 patients and 14 drug-allergic controls) with a history of amoxicillin intolerance. Sera from 13 patients and 5 drug-allergic controls (all positive on ASST) were used in the in vitro histamine release assay using basophils from 3 normal donors. ***Results:*** 17 of 18 patients (94%) versus 8 of 20 drug-allergic controls (40%) showed an unequivocal wheal-and-flare reaction on ASST ($p < 0.05$). Skin reactions were generally more intense in the patient group. In one MDAS patient, the ASST was not assessable due to dermographism. No normal control was positive on ASST. Sera from 3 of 13 patients (23%) versus 0 of 6 drug-allergic controls (not significant) induced significant histamine release from basophils of normal donors. IgE specific for β-lactams was detected in sera from 1 of 11 patients (9%) versus 5 of 14 drug-allergic controls (36%) (not significant). ***Conclusion:*** Most patients with MDAS and more than one third of subjects with a history of hypersensitivity to a single antibacterial drug were characterized by the presence of circulating histamine-releasing factors. Such factors might play a role in drug-induced adverse reactions observed in these patients.

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1018–2438/03/1313–0195$19.50/0

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Introduction

A subset of patients with a history of drug-induced skin reactions show a marked propensity to react to several chemically unrelated antibiotic and nonantibiotic drugs. This condition has been termed multiple drug allergy syndrome (MDAS) [1]. Patients with MDAS are otherwise normal, and do not report a history of spontaneous rashes or a personal or family history of atopic diseases [1]. In most cases, MDAS presents clinically as acute urticaria and/or angioedema upon ingestion of offending drugs, but different rashes, including Stevens-Johnson syndrome, anaphylaxis, serum sickness-like reactions and immune cytopenia, have also been described. Drug reactions may occur after the first administration of a particular drug class. Mechanisms underlying multiple drug reactivity are still unclear. A familial propensity for multiple drug reactions has been reported [2, 3], and a history of immediate hypersensitivity to β-lactams [3, 4] or to any antimicrobial drug [5] seems to represent a risk factor for adverse reactions to antibiotics of different classes. Moreover, a recent prospective study showed that in patients with MDAS, offending (as well as tolerated) antibacterial drugs show a great variability that does not depend on the chemical structure of the culprit agent [6]. It has been concluded that altogether, MDAS appears as a propensity to make immune responses to haptens and then to express a broad range of immune processes rather than a propensity to react to specific drug classes [1, 7]. Clearly, in patients with MDAS reacting with urticaria and/or angioedema upon ingestion of the offending drugs (who probably represent the large majority of subjects with the syndrome), the marked differences between offending compounds make an immunologic recognition of specific chemical structures (i.e. cross-reactivity) as a pathogenic mechanism unlikely, and suggest the existence of nonspecific, patient-related factors leading to histamine release from mast cells and/or basophils.

Interestingly, a link between MDAS and intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) exists in about 30% of cases [6]. Another clinical condition that is frequently characterized by multiple NSAID intolerance is chronic idiopathic urticaria [8]. Recent studies demonstrated that a high proportion (up to 60%) of patients with chronic idiopathic urticaria show a wheal-and-flare reaction upon intradermal injection of autologous serum [9, 10]. Such histamine-releasing activity has been ascribed to the presence of circulating IgG autoantibodies specific either for the high-affinity IgE receptor, FcεRI, or for IgE that would be responsible for histamine release from both basophils and mast cells [9, 11–15]. Moreover, we recently found that patients with a history of acute urticaria induced by multiple, chemically unrelated NSAIDs but without a history of chronic urticaria show a high prevalence of wheal-and-flare reaction upon intradermal injection of autologous serum [16]. In the present study, we investigated whether the clinically unapparent presence of circulating histamine-releasing factors may represent a possible nonspecific mechanism facilitating drug-induced histamine release also in patients with MDAS.

Patients and Methods

Patients

Thirty-eight adult patients (8 males and 30 females; age 17–68 years, mean age 36.8 years) with an unequivocal history of acute episodes of urticaria, with or without angioedema, after taking antibacterial drugs were studied. All these subjects were otherwise healthy, and none reported spontaneous episodes of urticaria. All patients presented at this allergy center asking for safe alternative drugs. Therefore, based on the clinical history, patients underwent single-blind placebo-controlled tolerance tests with the aim of detecting at least two tolerated compounds. Clarithromycin, ciprofloxacin and doxycycline were used as representatives of macrolides, quinolones and tetracyclines, respectively. Doses and methods used in oral tolerance tests have been described elsewhere [6]. Briefly, doubling doses of the challenged drug were given 1 h apart until a therapeutically active dose was reached. Patients were kept under observation at the allergy center for at least 2 h after the last provocative dose. Only the appearance of clear-cut urticaria and/or angioedema was considered as a positive response. On the basis of both clinical history and challenge test results, 18 subjects (2 males and 16 females; mean age 37.2 years) and 20 subjects (6 males and 14 females; mean age 36.6 years) were finally classified as having MDAS (patients) or a single intolerance to antibacterial drugs (controls), respectively. Offending and tolerated drugs are shown in tables 1 and 2, respectively. Not surprisingly [6], some patients with MDAS reported intolerance to other drugs as well (table 1). The two groups did not show any difference in the prevalence of atopic diseases (4/18 vs. 5/20).

Skin Tests

Both patients and controls with single drug intolerance underwent an intradermal test with 0.05 ml of sterile, fresh autologous serum (autologous serum skin test; ASST) and with saline as negative control. Readings were taken at 20 min. Only an unequivocal wheal-and-flare formation in response to serum injection was considered as a positive reaction. The mean diameter of the wheal-and-flare reaction induced by autologous serum was expressed in millimeters. In order to assess the specificity of ASST, 20 normal subjects without a history of chronic urticaria or drug allergy underwent ASST as well.

IgE Specific for β-Lactams

Sera from 25 subjects (11 patients and 14 controls) with a history of adverse reactions induced by β-lactams (amoxicillin in most cases) underwent the detection of IgE specific for amoxicillin, ampicillin, penicillin G and penicillin V by enzyme immunoassay (UniCAP System, Pharmacia, Uppsala, Sweden). Values >0.35 kUA/l were considered positive.

Table 1. Offending compounds and IgE specific for β-lactams in patients with multiple drug allergy

Patient No.	Amoxicillin	Macrolides	Quinolones	Cotrimoxazole	Tetracyclines	Rifaximine	Lincomycin	Other offending drugs	UniCAP Pen, kUA/l
1	U	T	Uc		Uc		Tc	metisoprinole, aspirin, nimesulide	negative
2	Tc	U	Uc	Uc	Uc	Uc			negative
3	U	U	Tc	Tc	Uc		T	nomegestrol, acetylcysteine, NSAIDs	negative
4	U	U	Tc	Tc	Uc		U	aspirin	negative
5	T	U	Tc	U				NSAIDs	
6	Uc	Uc	Tc		Tc			NSAIDs	
7	U	Tc	Uc					NSAIDs	
8	U	U	U	Uc	Tc	Tc	Uc		
9	U	Uc	Uc	Tc			Tc		1.24
10	U	U	Tc					nitrofuranes	negative
11	U	U	Tc		Uc		Tc		negative
12	U	Tc	Tc		U				negative
13	U	Uc	Tc		Uc		Tc		negative
14	U	U	Tc	U					negative
15	U	Tc	Tc	U				metronidazole	negative
16	U	Uc	Tc		Tc		Uc	contrast media	
17	Tc	Tc	S	A					
18	U	Tc	Uc	Uc					negative

U = Urticaria/angioedema; A = anaphylaxis; S = stomatitis; T = tolerated; c = drug challenged.

Basophil Histamine Release Assay

Sera from 13 patients with MDAS and from 5 controls (all positive on ASST) underwent the basophil histamine release assay (HRA). Leukocyte suspensions from 3 normal donors were prepared by dextran sedimentation of peripheral venous blood, anticoagulated with 0.01 *M* EDTA, and mixed with 6% dextran in saline solution (Solplex 70, Sifra, Verona, Italy) and 30 m*M* dextrose (Sigma Chemical, St. Louis, Mo., USA). The cells were allowed to settle for 60–90 min at room temperature, according to Lichtenstein and Osler [17]. The leukocyte-rich plasma was aspirated and centrifuged at 300 *g* for 15 min at 4°C, and the cell button was washed twice in Tyrode's buffer, pH 7.4, containing (in m*M*): 140 NaCl, 5.5 dextrose, 2.7 KCl, 0.36 NaH_2PO_4 and 12 $NaHCO_3$.

Leukocytes (with about 7×10^4 basophils) were then resuspended in 100-μl volumes of Tyrode's buffer with 1.8 m*M* $CaCl_2$ and 0.5 m*M* $MgCl_2$, and incubated with 100 μl of each serum under examination, making a final volume of 200 μl. After incubation for 40 min at 37°C, the reaction was stopped by addition of 800 μl of ice-cold buffer solution and centrifugation at 1,000 *g* for 10 min at 4°C. After centrifugation, the supernatants were aspirated and analyzed for histamine concentration. Histamine was measured by radioimmunoassay using a commercially available kit (Immunotech, Marseille, France). Spontaneous histamine release was evaluated by measuring the histamine concentration in the supernatant of unstimulated cells incubated for 40 min at 37°C.

Total histamine content was obtained by heating the cells at 85°C for 40 min. Net histamine release was calculated as the percentage of the total histamine content, after subtraction of spontaneous release. A 5% release cutoff value was used. All sera were tested with basophils from all 3 normal donors. As a control, basophils were stimulated with an optimal dose (100 μg/ml) of goat polyclonal anti-human IgE. Anti-IgE induced 48.2, 60.6 and 20% histamine release from basophils of the 3 donors, respectively. The highest histamine release result obtained in each patient was considered for the analysis.

Table 2. Offending drugs and IgE specific for β-lactams in controls with single drug allergy

Control No.	Amoxicillin	Cephalosporins	Macrolides	Quinolones	UniCAP Pen, kUA/l
1	U		Tc	Tc	
2	U		Tc	Tc	
3	U		T	Tc	negative
4	A		T		
5	U		Tc	Tc	
6	U		Tc	Tc	2.39
7	U		Tc		negative
8	U		Tc	Tc	negative
9	A		T	T	2.54
10	U		Tc	Tc	negative
11	U		Tc	Tc	negative
12	U		Tc	Tc	3.21
13	U		Tc	Tc	negative
14	U		Tc	Tc	negative
15		U	Tc	Tc	negative
16	U			Tc	1.56
17	Tc		U	Tc	
18	U		Tc	Tc	
19	U		Tc	Tc	negative
20	U		Tc	Tc	4.71

U = Urticaria/angioedema; A = anaphylaxis; T = tolerated; c = drug challenged.

Statistical Methods

Proportions were compared by χ^2 test with Yates' correction. Probability (p) values less than 0.05 were considered significant.

Results

Skin Tests

17 of 18 patients (94%) showed a clear-cut wheal-and-flare reaction on ASST (table 3). The mean diameter of the wheal and flare reaction exceeded 25 mm in most cases. The remaining patient was positive on ASST as well, but this result was not considered valuable due to dermatographism (the intradermal injection of saline induced a wheal-and-flare reaction). 8 of 20 controls (40%) with a single drug allergy showed a wheal-and-flare reaction on ASST (table 3); in most cases, the skin reaction was less intense than in patients. The prevalence of positive ASST was significantly higher in patients than in drug-allergic controls ($p < 0.05$). None of 20 normal controls was positive on ASST. The intradermal injection of saline did not induce a skin reaction in any subject except in a single patient (see above).

In vitro Tests

Sera from 3 of 13 patients (23%) and 0 of 6 controls, all positive on ASST, induced significant histamine release from basophils of normal donors (not significant; table 3). IgE specific for β-lactams was detected in sera from 1 of 11 patients (9%) and from 5 of 14 controls (36%). Due to the small number of patients tested, this difference did not reach statistical significance. The only patient showing circulating IgE to β-lactams did not tolerate either macrolides or quinolones on oral challenge tests (table 1).

Table 3. In vivo and in vitro histamine-releasing activity of sera from patients and controls

Subject No.	Patients		Controls	
	ASST, mm	HRA, %	ASST, mm	HRA, %
1	>25	negative	negative	
2	10	12.9	negative	
3	>25	negative	15	negative
4	>25	negative	negative	
5	DG		negative	
6	10		15	negative
7	>25		10	negative
8	15	7.7	15	negative
9	>25	6.3	negative	
10	>25	negative	15	negative
11	>25	negative	negative	
12	>25	negative	negative	
13	>25	negative	negative	
14	15	negative	negative	
15	>25	negative	10	
16	10		negative	
17	>25		negative	
18	15	negative	10	
19			negative	
20			10	

ASST values represent the mean diameter of wheal and flare.
DG = Dermatographism.

Discussion

Mechanisms underlying immediate pseudoallergic adverse drug reactions have long been a matter of debate. Apart from single cases of allergy to macrolides [18, 19], tetracyclines [20], quinolones [21] and other antibacterial drugs [22, 23], in most instances, immunological mechanisms have not been detected. More than 90% of our patients with MDAS showed an unequivocal wheal-and-flare reaction upon injection of autologous serum in the absence of any skin reactivity to saline, a finding that strongly suggests the presence of circulating histamine-releasing factors. The proportion of patients with MDAS positive on ASST is even greater than that we previously observed in patients with chronic idiopathic urticaria (about 60%) [10]. Interestingly, 40% of controls with single drug hypersensitivity were also positive on ASST. Since each of these subjects was submitted to a small number of tolerance tests, it cannot be excluded that some MDAS patients may have been misgrouped as single drug reactors. A follow-up study is in progress to ascertain whether such controls with single drug intolerance will show some propensity to react to drugs other than those challenged. A nonspecific role of bradykinin or C5a generated during the clotting process [24] in causing the wheal-and-flare reaction upon injection of autologous serum was ruled out by the absence of any positive ASST among 20 subjects without a history of drug allergy. It is conceivable that circulating histamine-releasing factors may contribute to urticaria episodes following the ingestion of chemically unrelated compounds that are observed in MDAS. The nature of factors responsible for positive ASST is still unclear. Studies of chronic idiopathic urticaria concluded that histamine release is caused by circulating IgG autoantibodies specific either for the high-affinity IgE receptor, FcεRI, or for IgE [9, 11–15], but the clinical significance of such autoantibodies has recently been questioned after it was found that IgG-depleted sera from urticaria patients are still able to induce wheal-and-flare reactions on ASST [25]. Such findings, along with the marked discrepancy between positive ASST and positive HRA that has been observed both in this study and in previous studies of chronic urticaria [10], suggest the possible involvement of mast cell-specific histamine-releasing factors of a different nature [26].

Most patients positive for the detection of penicillin-specific IgE belonged to the monosensitive control group. Although variability in the time from the last amoxicillin-induced reaction may have played a relevant role in RAST results, this finding might suggest that a significant proportion of amoxicillin reactors in the control group were truly allergic to penicillins, whereas most of those in the patient group had possibly experienced non-immune-mediated (pseudoallergic) reactions. The only MDAS patient whose serum contained penicillin-specific IgE reacted to two chemically unrelated drugs, namely clarithromycin and ciprofloxacin, on oral challenges. Theoretically, the 'autoreactivity' observed in most patients with MDAS might represent a risk factor for intolerance to drugs other than antibiotics as well. In effect, interestingly, some patients had a history of urticaria after taking a number of other compounds, including NSAIDs, acetaminophen, nomegestrol, acetylcysteine, iodinated contrast media, metisoprinole (an antiviral agent), metronidazole and nitrofuranes (table 1). These observations indirectly confirm the conclusions of previous studies showing a high propensity to MDAS among patients with a history of allergy to β-lactams [3, 5], or an association between allergic reactions to NSAID and to antibacterial drugs [4, 6, 27, 28]. In the presence of an underlying condition facilitating histamine release, a history of prior drug allergy would certainly represent a risk factor for nonspecific hypersensitivity reactions induced by other compounds. Obviously, several

aspects remain elusive. For instance, the reason why only certain drugs seem able to induce histamine release from basophils and/or mast cells in single patients, or which kind of interactions occur between offending drugs (or some of their metabolic breakdown products), histamine-releasing factors and mast cells and/or basophils. In this sense, our observations do not exclude the coexistence of other pathogenic mechanisms. For instance, a role played by dyes and/or preservatives cannot be excluded. Moreover, the group of Baldo [29–31] recently suggested IgE recognition of N-alkyl groups or primary amino groups as a mechanism for multiple drug allergies. Another interesting question regards the absence of clinically evident chronic urticaria in patients showing a strongly positive ASST. One reasonable hypothesis might be that circulating histamine-releasing factors themselves do not induce sufficient histamine release to cause clinically relevant urticaria and that a further nonspecific trigger (the offending drug) would be needed to cause a massive histamine release from both mast cells and basophils in these subjects. A long-term follow-up study on patients with a history of single and multiple hypersensitivity to NSAIDs was recently carried out by one of us and showed that chronic urticaria occurs in a relevant proportion of these subjects [32]. A similar propensity to develop chronic urticaria cannot be excluded in patients with MDAS.

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