

Detection of patients with multiple drug allergy syndrome by elective tolerance tests

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Background: Multiple drug allergy syndrome (MDAS) caused by antibiotics is frequently observed in allergy departments; however, risk factors for such a condition as well as the means to detect patients prone to MDAS are poorly defined.

Objective: The identification of patients prone to MDAS and the detection of risk factors for multiple antibiotic sensitivity.

Methods: Two hundred fifty-three elective oral challenges with alternative antimicrobial drugs were performed in 120 patients with histories of recent allergic reactions to antibiotics.

Results: Twenty-three (19%) subjects reacted to at least one antibiotic class. All reactions were mild and easily controlled by conventional therapy. Female sex, history of multiple antibiotic reactions, and reactions to nonsteroidal antiinflammatory drugs were the main risk factors for reactions to alternative antibiotics. To date, no patient has reported immediate adverse reactions to drugs negative on oral challenge tests but one had urticaria/angioedema on the fifth day of full dose treatment with ofloxacin.

Conclusions: Elective oral challenges with alternative antibiotics are a sensitive, specific, and safe means to detect patients with MDAS, thus sparing them more severe adverse reactions caused by full dose therapies. The recommendation to perform oral challenge tests with antibiotics just before their therapeutic use seems unnecessary and should be reconsidered.

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INTRODUCTION

Multiple drug allergy syndrome (MDAS), a clinical condition characterized by reactions to several immunologically distinct antimicrobial drugs, is frequently observed in allergy departments. Several investigators have tried to detect risk factors and clinical markers for MDAS; earlier reports found that both immediate hypersensitivity to β -lactams^{1,2} and a history of an allergic reaction to antimicrobial drugs³ are risk factors for adverse reactions to antibiotics of different classes. A recent retrospective controlled study⁴ did not disclose any difference in the prevalence of allergic reactions to non- β -lactam drugs for patients with or without penicillin allergy. This study was retrospective and

mainly based on clinical history. Since there are some patients who are prone to react to unrelated drug haptens, the detection of risk factors and identification of patients with MDAS would be helpful.

It is generally accepted that the only way to rule out antibiotic intolerance is to administer a test dose, followed by increasing increments up to the scheduled therapeutic dose, by the route used in treatment.⁵ Most guidelines recommend that, in patients who have experienced allergic drug reactions, such tests should be performed in a hospital setting and only when antimicrobial treatment is needed. The main consequences of such a policy are that hospital facilities as well as allergists and other personnel should be promptly available to perform tolerance tests. Further, patients prone to MDAS might experience severe adverse reactions to a test dose just when an antimicrobial treatment is needed.

The present study addresses some of these problems by elective evaluation of oral challenge to various classes of antimicrobial drugs in patients with clinical histories of reactions and identification of risk factors.

PATIENTS AND METHODS

Patients

All 120 patients (36 males and 84 females; mean age [SD] 39 ± 16 years, range 13 to 79) were evaluated at this allergy center between February 15, 1992, and December 31, 1996, because of recent (within the last 6 months), unequivocal, documented allergic reactions induced by antimicrobial drugs. A careful clinical history, including any previous adverse drug reaction as well as respiratory and food allergy or intolerance was recorded. One hundred patients had histories of single drug intolerance: β -lactams in 80 cases (79 amoxicillin and 1 ceftazidime), macrolides in 11, quinolones in 6, sulfonamides in 2, and rifampicin in 1. A history of multiple drug intolerance (ie, prior reactions to two or more antibiotic classes) was present in the remaining 20 patients; intolerance to two antimicrobial classes was present in 17 subjects, and to three classes in three subjects. Causative drugs in patients with multiple reactions were β -lactams (17 patients), sulfonamides (10), macrolides (9), lincomycin (3), tetracyclines (2), rifampicin (1), and nitrofurantoin (1).

Drug reactions experienced are summarized in Table 1. Most drugs induced urticaria/angioedema ($n = 121$), however there were 6 cases of anaphylaxis, 14 cases of Stevens Johnson syndrome, and 1 case of asthma.

Oral Challenge Tests

The goal of the study was the detection of at least two alternative, well-toler-

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Table 1. Prior Adverse Drug Reactions Reported by 120 Patients

Drug Class	U/A	Asthma	S-J	Anaphylaxis	Total (%)
β -Lactams	81	1	10	4	96 (68%)
Macrolides	16		3	1	20 (14%)
Quinolones	5			1	6 (4%)
Sulfonamides	11		1		12 (8%)
Lincomycin	3				3 (2%)
Rifampicin	2				2 (1%)
Tetracyclines	2				2 (1%)
Nitrofurantoin	1				1 (1%)
No. of reactions	121	1	14	6	142

U/A = Urticaria/angioedema and S-J = Stevens Johnson syndrome.

ated antimicrobial classes in all patients. Test doses, which were all given by the oral route, are shown in Table 2. Priority of challenges was determined by both the antimicrobial spectrum of nontolerated drug(s) and possible side effects of alternative drugs. Tolerance to macrolides and quinolones was evaluated first in most cases and other drug classes were tested as a second choice. Tolerance to sulfonamides was determined only in selected cases due to the high frequency and severity of allergic reactions to this antimicrobial class. Vancomycin and aminoglycosides were not included in the challenge panel because of the ability to induce histamine release and the need for parenteral administration, respectively.

All patients were challenged electively. Two doubling test doses were scheduled for every drug class, two hours apart; patients were carefully observed for two hours after the last dose. Only drugs that induced unequivocal reactions such as urticaria/angioedema, mucosal inflammation with

painful lesions typical of erythema multiforme, and/or asthma were considered positive. In the presence of doubtful reactions, the second test dose was delayed until necessary; alternatively the first dose was repeated after 2 weeks. Different antimicrobial classes were used for challenge at least 2 weeks apart in all cases.

Patients gave informed written consent before each session; all tests were carried out by the author, who also observed and managed adverse reactions. At the end of challenge procedures extensive explanations and detailed written recommendations were given, and patients were strongly recommended to contact the allergy center as soon as possible in event of a reaction to a new drug. Patients showing intolerance to 2 or more antibiotic classes were considered as having MDAS.

Statistical Methods

Proportions were compared by two-tailed chi square test with Yates' cor-

rection. Probability (*P*) values less than .05 were considered significant.

Relative risk for independent samples was calculated as follows:⁶

$RR = \frac{ad}{bc}$ where:

	Cases	Controls
No. with risk factor	a	b
No. without risk factor	c	d
Total	a+c	b+d

RESULTS

A total of 253 oral challenge tests were carried out: 73, 18, and 8 subjects were challenged with two, three, and four drugs, respectively. Twenty-one patients refused to undergo further evaluation after the first test (which was negative in all cases).

Results of challenge procedures are shown in Table 2. Forty-three (17%) reactions were recorded in 23 (19%) subjects. All reacted after the first test dose with mild urticaria/angioedema, which was easily controlled by conventional therapy. Reactions were more frequently observed in patients with histories of multiple antibiotic sensitivity than in those with histories of single drug intolerance (7/20 [35%] versus 16/100 [16%], respectively; $.05 < P < .1$; relative risk = 2.8). Not surprisingly in view of the study design, a much higher prevalence of reactions against second choice antibiotic than to first choice drugs were observed (Table 2). On the basis of both clinical history and challenge test results, 30% (36/120) of patients were finally considered to have multiple antibiotic sensitivity. This was more frequent in female patients (males 7/36 [19%] and females 29/84 [35%]; relative risk = 2.2). Table 3 summarizes the findings in all 19 patients intolerant to three or more antibacterial drug classes. Drug tolerance was unpredictable and showed a great variability in these subjects.

In vivo tests resulted in the detection of at least one tolerated antibacterial drug class in all patients except four (all included in Table 3) who refused to undergo further evaluation.

Table 2. Tolerance Tests

Class	Compound	Provocative Doses, mg		Positive	
		First	Second	Tests	(%)
Macrolides	Clarithromycin	60	125	8/99	(8%)
Quinolones	Pefloxacin	60	125	15/94	(16%)
β -Lactams	Amoxicillin	125	250	3/20	(15%)
Lincosamides	Lincomycin	125	250	9/24	(37%)
Tetracyclines	Doxycycline	25	50	7/13	(54%)
Sulfonamides	Sulfamethoxazole	100	200	1/3	(33%)
	+ trimethoprim	20	40		
Total				43/253	(17%)

Table 3. Findings in 19 Patients Intolerant to 3 or More Antibiotic Classes

No.	Antibacterial Classes*							
	Mac	Qui	Lin	Tet	Sul	β -Lac	Rif	Nit
1	H†	P	P		H	N		
2	H	P	N			H		
3	N	P	P			H		
4	H	P	P	P		N		
5	N	P	N	P		N		
6	H	N	P	P		P		
7	P	P				H		
8	N	N			H	H	H	
9	H	N	N	P		H		
10	P	P		P		H		
11	H	N		H	P	H		
12	N	P	P	H		H		H
13	P	P				H		
14	P	N	P	N		H		
15	P	P	P	N		H		
16	P	P	P	P		H		
17	N	N	H	P	H	P		
18	N	P	P	N		H		
19	H	P	N	N				

* Mac = Macrolides, Qui = quinolones, Lin = lincosamides, Tet = Tetracyclines, Sul = Sulfonamides, β -lac = β -Lactams, Rif = Rifampicin, and Nit = Nitrofurantoin.

† H = Clinical history positive, P = positive on tolerance tests, and N = negative on tolerance tests.

Thirty-five patients had histories of intolerance to other substances: antinflammatory drugs (21 aspirin and/or derivatives, 8 pyrazoles, and 1 both), contrast media (1 subject), or food additives (7 patients; 3 and 1 of these were also intolerant to nonsteroidal antinflammatory drugs and contrast media, respectively). Overall, 30 patients (25%) reported intolerance to nonsteroidal antinflammatory drugs (urticaria/angioedema in most cases, but also exfoliative dermatitis or Stevens Johnson syndrome). There was a statistically significant difference in the prevalence of intolerance to nonsteroidal antinflammatory drugs between patients intolerant to 1 or more than 1 antibiotic class (15/84 [18%] versus 15/36 [42%]; $P < .025$). The relative risk for developing multiple antibiotic sensitivity in the presence of intolerance to nonsteroidal antinflammatory drugs was 3.2. Further, the prevalence of intolerance to antinflammatory drugs impressively increased among patients intolerant to one (15/84 [18%]), two (6/17 [35%]), or more than two (9/19 [47%]) antibiotic

classes (correlation coefficient, $r = .995$; Fig 1). Female sex and intolerance to nonsteroidal antinflammatory drugs acted as independent and additive risk factors for multiple antibiotic sensitivity, since this condition was observed in 13/25 (52%) and 16/59 (27%) female patients and in 2/6 (33%) and 5/31 (16%) male patients

with and without a history of intolerance to antinflammatory drugs, respectively.

Nine patients (8%) had asthma and/or allergic rhinitis and one Hymenoptera venom allergy. The proportion of atopic patients does not differ from that observed in the general population.

None of the patients included in the present study has contacted us to report reactions to one, of the drugs tolerated on challenge tests except one patient who had severe urticaria/angioedema on the fifth day of full-dose therapy with ofloxacin.

DISCUSSION

Elective in vivo oral challenge tests with alternative antimicrobial drugs revealed unexpected reactions in many (19%) subjects with histories of antibiotic allergy. These patients avoided more severe reactions that might have been caused by full dose therapy or, alternatively, mild reactions induced by challenge in the presence of bacterial infections.

One of the main concerns with elective challenge tests has been that similar procedures may "sensitize" to the substances under investigation. Several lines of evidence seem to rule out this possibility. First, all 43 reactions observed in this study took place after the first dose was given, which suggests that oral challenge tests simply

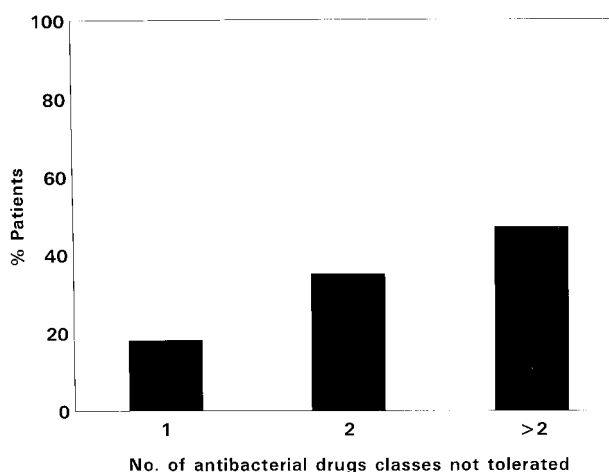


Figure 1. Prevalence of intolerance to nonsteroidal antinflammatory drugs in 120 patients with antibiotic allergy.

identified pre-existing "sensitization"; moreover, notably, some of these reactions were induced by drugs that had probably never previously been taken.

Second, to date only one patient has contacted us to report a reaction to a drug tolerated on in vivo tests. This woman experienced urticaria/angioedema after five days of full-dose therapy with quinolones. Such a reaction would not have been prevented by a tolerance test performed just before the start of antibacterial treatment, as recommended in most guidelines. More than 5 years have passed since tolerance tests were first performed, and several other patients probably have taken recommended antibiotics on at least one occasion.

Third, since it is generally accepted that pathogenetic mechanisms of most drug allergies are not immunologic, "sensitization" caused by tolerance tests is not likely. At present, there is no evidence that elective test doses may induce intolerance to the substances tested.

The study confirmed the observation that drug reactions are twice as frequent in females as in males,⁷ and we also showed that females are more prone to MDAS.

Unlike some previous reports^{1,8} atopy did not represent a significant risk factor for antibacterial drug intolerance in this population.

A history of intolerance to both antiinflammatory drugs and food additives was much more frequent in patients included in this study than in the general population.^{5,9} This finding indirectly confirms previous observations of an increased rate of acetaminophen or nimesulfide intolerance among aspirin-intolerant patients who had histories of antibacterial drug intolerance.⁸ Clinical data suggest that

certain subjects are prone to react to chemically unrelated substances such as antibacterial drugs, nonsteroidal antiinflammatory drugs, food additives, and probably others. The higher rate of positive challenge tests among patients with histories of multiple antibiotic allergy in this study supports this view. An immunologic pathogenesis seems unlikely in patients with MDAS; as previously suggested for patients with intolerance to multiple food additives,¹⁰ reactions might occur via common nonspecific mechanisms that lead to direct mediator release.

This study shows that MDAS is rather frequent. Female sex, history of intolerance to more than one antibacterial drug class, and history of intolerance to antiinflammatory drugs are risk factors for intolerance to alternative antibiotics. Elective oral challenge tests are sensitive, not particularly hazardous, and result in the detection of at least one tolerated antibiotic class in most cases. This offers physicians the means to treat patients with MDAS more safely. In view of these findings, patients with clinical histories of antibiotic allergy could be offered elective oral challenge tests with alternative antibacterial drugs.

The recommendation to perform tolerance tests only when antibacterial treatment is needed seems unnecessary and should be reconsidered.

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