Drug-Induced Anaphylaxis in Latin American Countries

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What is already known about this topic? Drugs are among the most common causes of anaphylaxis. Nonsteroidal anti-inflammatory drugs and antibiotics have been found as the most frequent inducers of drug-induced anaphylaxis, but there are some variations between countries.

What does this article add to our knowledge? The present study further supports nonsteroidal anti-inflammatory drugs as a main cause of drug-induced anaphylaxis and shows that anaphylaxis prophylaxis and treatment should be improved. Factors associated with drug-induced anaphylaxis may change according to the studied population.

How does this study impact current management guidelines? Dissemination of anaphylaxis guidelines among emergency department physicians in Latin American countries should be encouraged, to improve management of drug-induced anaphylaxis.

BACKGROUND: Information regarding the clinical features and management of drug-induced anaphylaxis (DIA) in Latin America is lacking.

OBJECTIVE: The objective of this study was to assess implicated medications, demographics, and treatments received for DIA in Latin American patients referred to national specialty centers for evaluation.

METHOD: A database previously used to compile information on drug-induced allergic reactions in 11 Latin American countries was used to identify and characterize patients presenting specifically with a clinical diagnosis of DIA. Information regarding clinical presentation, causative agent(s), diagnostic studies performed, treatment, and contributing factors associated with increased reaction severity was analyzed.

RESULTS: There were 1005 patients evaluated for possible drug hypersensitivity reactions during the study interval, and 264 (26.3%) met criteria for DIA. DIA was more frequent in adults and in elderly females (N = 129 [76.6%] and N = 30 [75%], respectively) compared with children and/or adolescents (N = 21 [42.9%], $P < .01$). Severe DIA was less frequent with underlying asthma (N = 22 vs 35 [38.6% vs 61.4%], $P < .05$) or atopy (N = 62 vs 71 [43% vs 59%], $P < .01$). Nonsteroidal anti-inflammatory drugs (NSAIDs) (N = 178 [57.8%]), beta-lactam antibiotics (N = 44 [14.3%]), and other antibiotics (N = 16 [5.2%]) were the most frequently implicated drug classes. Anaphylaxis was rated as severe in N = 133 (50.4%) and anaphylactic shock (AS) was present in N = 90 (34.1%). Epinephrine was only

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Abbreviations used
CV- Cardiovascular
DIA- Drug-induced anaphylaxis
DPTs- Drug provocation tests
ED- Emergency department
HDRs- Hypersensitivity drug reactions
NSAIDs- Nonsteroidal anti-inflammatory drugs
SPT- Skin prick tests
U/A- Urticaria and/or angioedema

used in N = 73 (27.6%) overall, but in N = 70 (77.8%) of patients with AS.
CONCLUSION: In Latin American patients referred for evaluation of DIA, NSAIDs and antibiotics were implicated in approximately 80% of cases. Most of these reactions were treated in the emergency department. Epinephrine was administered in only 27.6% of all cases, although more frequently for anaphylactic shock. Dissemination of anaphylaxis guidelines among emergency department physicians should be encouraged to improve management of DIA. **(J Allergy Clin Immunol Pract 2015;3:780-8)**

Key words: *Drug allergy; Epidemiology; Anaphylaxis; Epinephrine; Latin America*

Anaphylaxis is defined as "a serious life-threatening generalized or systemic hypersensitivity reaction."[1] It usually occurs suddenly after systemic exposure to an inducing substance. The diagnosis is likely when there is involvement of skin or mucosal tissue (eg, hives, angioedema), airway compromise (wheezing, dyspnea), and/or reduced blood pressure with or without associated complications (hypotonia, syncope) that is temporally related in onset (minutes to several hours) to a potential causative agent.[2] Anaphylaxis is a protean condition as it can occur without mucocutaneous involvement, with the presence of 2 of the following features: cardiovascular, respiratory and/or gastrointestinal symptoms arising shortly after exposure to a potential inciting agent.[2] Circulatory collapse and airway obstruction can be fatal.

The incidence of anaphylaxis in Europe and the United States has been estimated to range from 3 to 300 per 100,000 persons per year,[3] with a lifetime prevalence of 0.05% to 2%.[4] There have been reports that the incidence of anaphylaxis has increased in Australia, the United Kingdom, and the United States.[5-7] Mulla et al[8] reported an increase in anaphylaxis hospital discharges in New York state between 1996 and 2005, but not in Florida, suggesting that latitude may influence anaphylaxis incidence or diagnosis rates.

The most common cause of anaphylaxis according to some studies are hypersensitivity drug reactions (HDRs)[9-13]; HDRs have also been reported to be the most frequent cause of mortality due to anaphylaxis in New Zealand[14] and Australia.[15]

There are limited data on the epidemiology of drug-induced anaphylaxis (DIA) in Latin America,[16,17] and most reports are case reports or case series focused on specific drugs or special situations such as perioperative anaphylaxis.[18] Further studies are needed to confirm the previous findings and to add new knowledge to the field.

The aims of this work were to: (1) identify the drugs most commonly implicated in DIA reported in different Latin American countries; (2) describe the clinical presentation and diagnostic testing performed to confirm DIA, and (3) describe the treatment provided to these patients.

METHODS

A cross-sectional study to assess the prevalence and characteristics of DIA was conducted using the European Network of Drug Allergy questionnaire[19] that was administered by clinicians to patients evaluated in 22 allergy units from 11 Latin American countries (Argentine, Brazil, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Mexico, Paraguay, Uruguay, and Venezuela). Detailed methodology has been previously described.[20] The study was conducted from December 2011 to July 2014. DIA was defined as a moderate or severe reaction that occurred less than 24 hours after an implicated drug administration associated with urticaria and/or angioedema (U/A), and if there were at least one of the following symptoms: respiratory (R) (cough, dysphonia, dyspnea, wheezing, rhinorrhea, sneezing, nasal obstruction), gastrointestinal (GI) (nausea/emesis, diarrhea, gastrointestinal cramps), and/or cardiovascular (CV) (tachycardia, hypotension, collapse, arrhythmia). Alternatively patients could have at least 2 of the following symptoms to meet the diagnosis of DIA: respiratory compromise, persistent gastrointestinal and/or CV symptoms.[1,21-23] Patients with angioedema, dyspnea, and dysphonia without involvement of other organ and/or system was not considered anaphylaxis (probable angioedema with upper airway involvement).

Clinical characteristics of anaphylaxis, demographics, history of previous HDRs, atopic status, physician diagnosis of asthma, and anaphylaxis treatment, including shock management and use of epinephrine, were recorded. Atopy was defined as having a physician diagnosis of allergic conjunctivitis and/or rhinitis and/or asthma, food allergy, and/or atopic dermatitis.

A causal relationship with a specific drug was implicated based on the clinical history, temporal relationship between exposure, and onset of clinical manifestations. Confirmatory diagnostic evaluation according to the patient's presentation and availability of procedures at each center (including skin prick and intracutaneous tests, provocation tests, and laboratory tests) was performed. Causal relation of the reaction to the suspected drug was categorized as certain, probable, possible, unlikely, and conditional, adapted from the World Health Organization Uppsala Monitoring Centre Causality Categories and the Argentinean Food and Drug National Agency (ANMAT).[24,25] Drugs were grouped according to an adaptation of the Anatomical Therapeutic Chemical classification of the World Health Organization Collaborating Centre for Drug Statistics Methodology.[26]

Ethical considerations

This study encouraged researchers to adhere to their standard good clinical care approach used to evaluate patients with suspected DIA at all times. No additional interventions were performed on the patients other than those deemed appropriate by the clinical investigator for the management of the DIA reaction in question at each study site.

All personal information for each patient was de-identified. In addition, all clinical information was reported anonymously and was independently linked to a code (the patient number) only known by the clinical investigator at the site responsible for each patient.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine, University Hospital of the Universidad

TABLE I. Demographics of study subjects

	Overall	Children-adolescents (0-17 y)	Adults (18-59 y)	Elderly (60-93 y)	*P* value		
					Adults/children-adolescents	Elderly/children/adolescents	Elderly/adults
Patients n	264	49	175	40			
Age (y), mean	38.2	10.7	39	68.2			
Sex, n (%)							
Male	79 (29.9)	28 (57.1)	41 (23.4)	10 (25)	<.0001	<.01	.89 (ns)
Female	185 (70.1)	21 (42.9)	129 (76.6)	30 (75)			
Atopy, n (%)	144 (54.5)	28 (57.1)	104 (59.4)	12 (30)	.72 (ns)	<.01	<.001
Rhinitis, n (%)	119 (45.1)	26 (53.1)	84 (48)	9 (22.5)	.56 (ns)	<.01	<.01
Asthma, n (%)	57 (21.6)	16 (32.7)	36 (20.6)	5 (12.5)	.09 (ns)	<.05	.25 (ns)
Food allergy, n (%)	20 (7.6)	4 (8.2)	14 (8)	2 (5)	.98 (ns)	.6 (ns)	.53
Atopic dermatitis, n (%)	10 (3.9)	3 (6.1)	5 (2.9)	3 (7.5)	.23 (ns)	.8 (ns)	.15 (ns)
Hymenoptera venom allergy, n (%)	6 (2.3)	0 (0)	6 (3.4)	0 (0)			
Previous drug reactions, n (%)	101 (38.3)	21 (42.9)	65 (37.1)	15 (37.5)	.51 (ns)	.62 (ns)	.99 (ns)
Family history of allergy, n (%)	78 (29.5)	19 (38.8)	53 (30.3)	6 (15)	.22 (ns)	<.05	.06 (ns)

Autónoma de Nuevo León, Mexico. The use of informed consents was exempted due to the low risk of the study (International Regulation 45 CRF 46.117 C and article 23 of the General Health Law and Research of Mexico).

Statistical analysis

OpenEpi software was used to analyze data.[27] Nonnormally distributed quantitative variables were compared using the Mann-Whitney test and qualitative variables using the χ^2 test. All reported *P* values were based on 2-tailed tests; values less than .05 were considered statistically significant.

RESULTS

Among the 1005 HDRs evaluated in our database, there were 264 (26.3%) patients that met our diagnostic criteria for DIA. Patients with DIA had a mean age of 38.2 years (1-84) (Table I). Females more commonly experienced DIA across the adult (18-59 years old) and elderly (more than 59 years old) study populations (76.6% and 75%, respectively), whereas there was no gender predilection observed for the children and adolescent (0-17 years old) populations (adults and/or elderly vs children and/or adolescents, $P < .0001$). Patient-reported history of atopy was present in 54.5% of patients but was less frequent in elderly patients compared with children and/or adolescents and adults ($P < .01$ and $<.001$, respectively). Severe reactions were reported in 43% of atopic patients and 59% of nonatopic patients ($P < .01$). Interestingly, asthmatic patients experienced milder reactions (severe reactions: 38.6%) compared with nonasthmatic patients (severe reactions: 54.6%) ($P < .05$). A previous drug reaction history to at least one medication was present in 38.3% of patients, and a family history of allergy was present in 29.5% of patients. Of note, there were N = 97 (37%) of the cases that had received the implicated drug previously without reaction and N = 48 (18.3%) of the cases that had a previous HDR with the implicated drug and were still given that drug again. There was no difference in DIA severity between patients with a history of HDR or tolerance to the inciting drug (data not shown). Reactions to the causative agent occurred within the first hour after oral administration of the drug in 63.3% and after parenteral administration in 89.3% ($P < .0001$). The drug was administered parenteral in 36.8% of these cases.

Clinical presentation

Clinical characteristics of patients with DIA are summarized in Figure 1. The most frequent clinical presentations were U/A and respiratory symptoms (R) (86%). The most frequent R symptoms included dyspnea (73.5%), wheeze (28.8%), cough (36.7%), and dysphonia (25%); the most frequent GI symptoms were nausea vomiting (11.7%), and cramps and diarrhea (4.2%), whereas the most frequent CV symptoms were hypotension (31.8%), tachycardia (28.4%), and collapse (14.8%). Cardiovascular symptoms were more frequent in elderly patients (85%) compared with adults (45.7%) and children and/or adolescents (30.6%; $P < .00001$). Shock was present in 34.1% of patients and was more frequent in elderly patients than in adults and children and/or adolescents ($P = .01$ and .04, respectively).

Implicated drugs

A certain and probable causal relationship was attributed to drug groups as illustrated in Figure 2. The most frequently reported anaphylaxis inducers were nonsteroidal anti-inflammatory drugs (NSAIDs) in 57.8% of cases. Reactions to NSAIDSs occurred more frequently in adults compared with elderly patients ($P < .05$). The culprit NSAIDs are summarized in Figure 3. Reaction to a single NSAID from one class with tolerance to another NSAID from a different class was found in 28.1% of NSAIDs DIA patients. Beta-lactam and non−beta-lactam antibiotics were the second and third most common inducers of anaphylaxis (14.3% and 5.2%, respectively). Reactions to non−beta-lactam antibiotics were more common in elderly patients compared with adults and children and/or adolescents ($P < .05$).

Diagnostic testing performed

Tryptase levels were determined in only 8 patients (3%). Skin prick tests (SPT) to the inciting drug or to an alternative drug with similar pharmacologic activity (n = 78) were performed in 60 patients (22.7%) with positive test results in 33 cases (41.2%). Among the 78 SPT, beta-lactams accounted for 25.6%

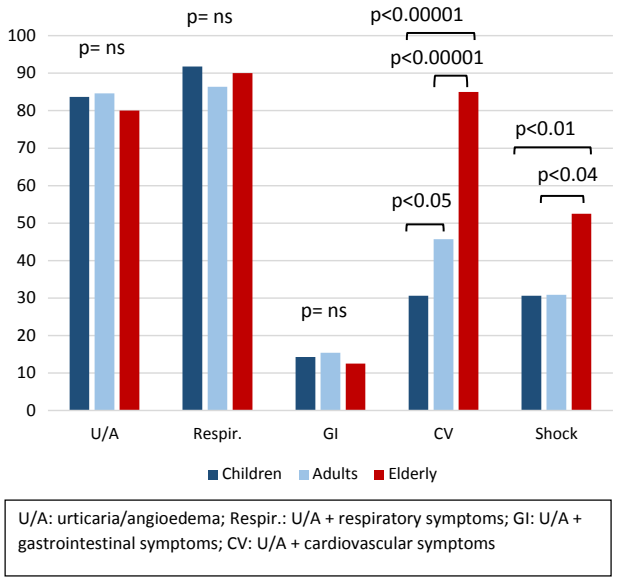

FIGURE 1. Age and clinical presentation (in percentage) of drug-induced anaphylaxis.

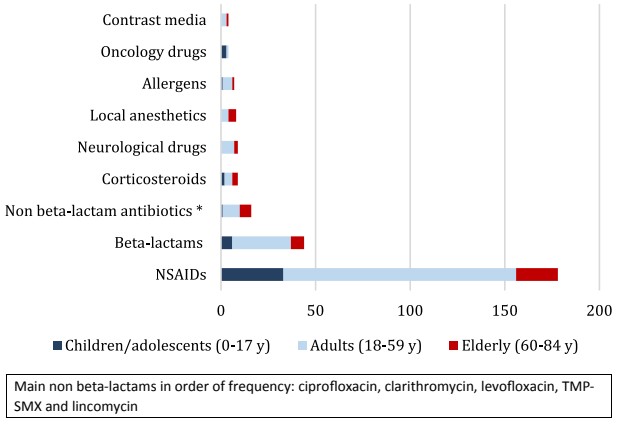

FIGURE 2. Drug groups implicated in eliciting certain and probable drug-induced anaphylaxis reactions.

(n = 20), NSAIDs 15.4% (n = 12), non–beta-lactam antibiotics 12.8% (n = 10), corticosteroids 9% (n = 7), vitamins 9% (n = 7), local anesthetics 5.1% (n = 4), muscle relaxants 5.1% (n = 4), general anesthetics 2.6% (n = 2), and others 15.4% (n = 12) (Table II).

Intracutaneous tests (n = 54) were performed in 30 patients (11.4%) and positive in 48.1% of cases (Table II).

In vitro specific IgE tests (n = 64) were performed for 33 patients (12.5%) and positive in 39.4% of cases (Table II). Specific IgE to beta-lactams were the most frequently ordered specific IgE diagnostic test (87.5%).

A basophil degranulation test (n = 29) was performed in 17 cases (6.4%), and NSAIDs (51.7%), vitamins (24.1%), corticosteroids (6.9%), and beta-lactams (6.9%) were the most frequently tested drugs. A basophil activation test (n = 18) was performed in 14 cases (13 of 14 cases in one center in Mexico) (5.3%) (Table II).

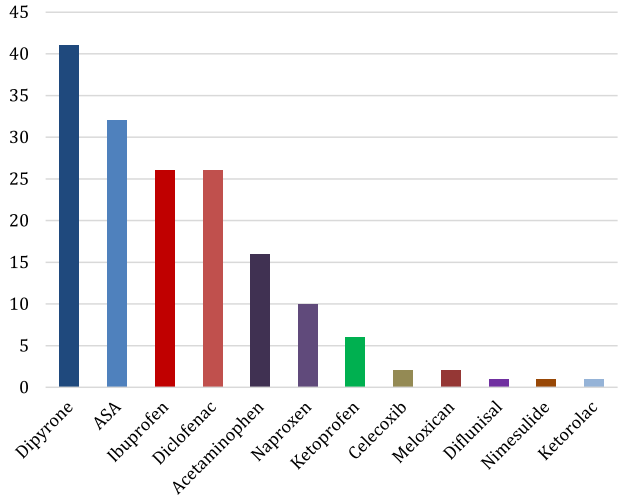

FIGURE 3. Nonsteroidal anti-inflammatory drugs implicated in drug-induced anaphylaxis.

Provocation tests (n = 149) (Table II) were performed in 113 cases (42.8%) with NSAIDs (63.7%), beta-lactams (8%), and non–beta-lactam antibiotics (7.4%) being the most frequently challenged drugs. More than half of the challenges (53.1%) were conducted with an alternative drug rather than the suspected drug to provide a safer alternative treatment for the patient (eg, etoricoxib in a patient with DIA induced by diclofenac). More than one suspected drug was present in 44.2% of the patients who underwent drug provocation. Provocation testing was positive in 31.5% of cases.

Treatment

The majority of patients 206 (78%) were treated in the emergency department (ED); 23 (8.7%) were hospitalized (9 patients admitted from ED), and 9 (3.5%) of them required admission to the intensive care unit. Treatment was administered by an allergist in 26 patients (9.8%) and by a general practitioner in 5 cases (1.9%). Reactions went untreated in 7 patients (2.7%) and patients self-medicated in 6 cases (2.3%). The treatments used for anaphylaxis are illustrated in Figure 4. Corticosteroids (72.7%) and antihistamines (75.8%) were the most frequent prescribed therapies. Epinephrine was used in only 27.6% of patients. Epinephrine was administrated in 39.2% of patients experiencing CV symptoms compared with 15.2% of cases when these symptoms were absent ($P < .00001$) but was administered in 77.8% of patients experiencing intravascular collapse. Elderly patients received epinephrine more frequently than adults ($P < .01$) and children and/or adolescents ($P < .05$).

DISCUSSION

This study is an extension of an earlier study that reported the prevalence and characteristics of HDRs evaluated and treated at 22 medical centers located in 11 Latin American countries.[20] The focus of this analysis was to specifically assess patients experiencing DIA.[21] Similar to previous studies, we found a predominance of DIA reactions in adult and elderly female patients and not in children and/or adolescent patients.[16,28-30] Other investigators have reported similar findings in DIA associated with perioperative anaphylaxis.[18]

TABLE II. Diagnostic test performed

	Prick test		Intracutaneous test		Specific IgE		BDT		BAT		Provocation test	
	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos
Beta-lactams												
Amoxicillin	4	6	2	3	14	3				1	3	1
Penicillin G	4	2	2	2	15	5		1		1	1	3
Penicillin V					12	1						
Minor determinants	2		2									
Major determinants	2		2									1
Ampicillin				1	2	2				1		1
Cephalosporin*			1	4	2			1			2	
No beta-lactams												
Clarithromycin	4			1							4	1
Lincomycin		2		2						2		2
Ciprofloxacin			1								1	
Levofloxacin	2			1							1	
Clindamycin	1										1	
Nalidixic acid		1									1	
NSAIDs												
Dipyrone	6		2	1	2			3			3	2
Acetaminophen		2		2	1			3		1	10	5
Diclofenac		2					2	2		2		6
Ketoprofen	1									1		
Aspirin		1			1		1	1		2	11	8
Ibuprofen					1			3		1		4
Meloxicam										1	23	2
Other NSAIDs†										1	20	1
Local anesthetics												
Lidocaine	2	1	1			2		1			4	1
Bupivacaine	1			1								
Muscle relaxants												
Succinylcholine			1									
Rocuronium	1		2	1								
Atracurium	1	1										
Vecuronium	1											
General anesthetics												
Propofol	1	1	1									
Vitamins												
Thiamine	1	1		1							2	1
Pyridoxine		1		1			1	1			1	
Cyanocobalamin	1	3	1	1			1	4			2	1
Corticosteroids												
Dexamethasone	1		1									
Metilprednisone		2	1					1				
Betamethasone		1	1							1	3	
Fluticasone		1						1				1
Others	9	5	6	5		1	2		2	1	9	6

BAT, Basophil activation test; *BDT*, basophil degranulation test; *NSAIDs*, nonsteroidal anti-inflammatory drugs.
*Cephalosporin: cefuroxime, ceftriaxone, cefotaxime, cefazoline.
†Other NSAIDs: etoricoxib, ketorolac, nimesulide, celecoxib, naproxene, lysine clonixinate.

The present study did not identify any specific host risk factors for DIA. On the contrary, asthmatic and atopic patients in this study presented with less severe DIA reactions. In contrast to our findings, González Pérez et al[12] found a 2-fold and 3.3-fold greater risk of anaphylaxis in nonsevere and severe asthmatics, respectively, compared with patients without asthma. They also found that atopic dermatitis was associated with a significantly greater risk of anaphylaxis within their no asthma cohort study group. Other studies also reported that asthma, especially if severe or uncontrolled, was a risk factor for having more severe anaphylactic reactions.[31,32]

However, Banerji et al,[33] in a retrospective analysis of 716 patients with a visit to an ED and/or hospitalization for DIA, found that patients with asthma, allergic rhinitis, and eczema

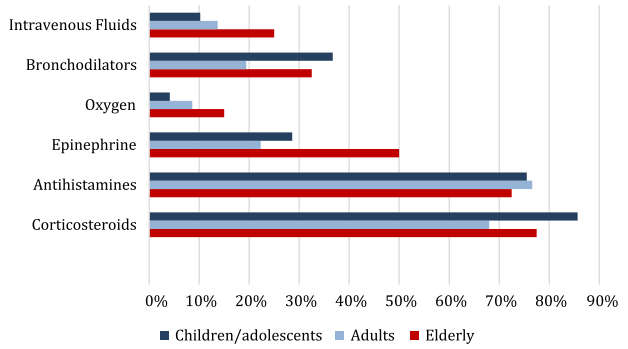

FIGURE 4. Treatments used to manage drug-induced anaphylaxis.

compared with patients without these conditions did not differ with respect to the severity of the reaction, location of treatment (ED vs hospital inpatient), or their management. Aun et al[16] investigated 117 patients with DIA and found a high frequency of atopy and asthma in their population, but the personal history of atopy and asthma was not associated with severity of the drug reaction. Faria et al[30] also found in their study of 313 patients with DIA that atopy and asthma were not risk factors for anaphylaxis. Therefore, given our findings and those of several other independent investigators, the presumption that atopic predisposition contributes to a more severe allergic drug reaction[34,35] requires further investigation to better understand host risk factors for HDRs and more specifically DIA.

More than 15% of the patients in this study experienced a previous HDR with the same drug. Aun et al found that a greater proportion of previous reactions were to the drug involved in the current reaction or to a drug from the same class and/or group.[16] These preventable severe DIA reactions emphasize the importance of educating physicians about avoiding the use medications previously reported by their patients to elicit an HDR.

Similar to what has been reported by other authors,[12,16,17,30] we found that cutaneous and respiratory symptoms were the most common manifestations of DIA and that more than 45% of the patients had cardiovascular involvement that was more prevalent in elderly patients compared with children and/or adolescents and adult groups. Park et al[36] found that elderly patients with anaphylaxis presenting with symptoms of cyanosis, syncope, and dizziness were at increased risk for the development of shock. In an Australian study that investigated death from anaphylaxis,[15] most DIA deaths occurred in patients between the ages 55 and 85 years. This observation may be explained by a number of underlying factors, including concomitant poorly controlled cardiovascular and respiratory disease and the use of concurrent medications such as angiotensin converting enzyme inhibitors and β-adrenergic blockers all of which can increase the patient's susceptibility to more severe DIA reactions.[21-23,37-40] As patients were evaluated after they experienced DIA to be included in this study, there were no deaths reported.

NSAIDs were the most frequently implicated group of drugs involved with DIA in adults, the elderly, and children and/or adolescents, which is in agreement with reports from other studies conducted in Latin America[16,17,41] and other regions of the world.[42-44] However, these findings are discordant with other reports by investigators,[12,15,30,45-47] who found that NSAIDs were the second most common cause of DIA after antibiotics. Dipyrone, of the pyrazolone class of NSAIDs, was the most likely group to elicit DIA followed by aspirin, ibuprofen, and diclofenac. This is similar to what was reported by Aun et al[16] (dipyrone, aspirin, and diclofenac), and as stated by Kowalski et al[48] in their review of NSAIDs hypersensitivity, whereas other investigators[30,47,49] found a lower causality of DIA for dipyrone that may represent regional differences in NSAID availability and/or consumption. A review on NSAID-induced anaphylaxis has been recently published.[50] The increased prevalence of NSAIDs inducing DIA in our study is not surprising given the fact these drugs are easily obtained over the counter in drugstores in most Latin American countries. Moreover, the prevalence of self-medication especially with NSAIDs in children and/or adolescents and young adults is very high in this region.[51,52]

Similar to previous reports,[30,47] selective NSAID anaphylaxis accounted roughly for one-third of all NSAID anaphylaxis cases. Renaudin et al[47] found that 27% of the patients with severe anaphylaxis induced by NSAIDs were selective reactors, with one-third of these reactions attributed to unknown or uncertain mechanisms.

Increased serum tryptase levels can support the clinical diagnosis of anaphylaxis from insect stings, and injected medications especially in those patients who become hypotensive; however, levels are often within normal limits in patients with anaphylaxis triggered by foods and in patients who are normotensive. Overall, the correlation between acute serum tryptase levels and the severity of anaphylaxis and/or systemic reactions is weak, and the sensitivity of serum tryptase in patients who present to the ED with acute allergic reactions is low.[53-55] Serum tryptase levels were determined in only 8 patients (3%) enrolled in this study, and we have them informed only as positive or negative. The underutilization of this diagnostic test[1,56] may be due to its poor predictive value and the unavailability of this test in EDs.

Participating physicians in this study generally preferred drug provocation tests (DPTs) over other diagnostic approaches. Drug provocation testing was performed in more than 40% of cases primarily to NSAIDs, and slightly more than 30% of DPT elicited positive reactions. The small percentage of positive provocation tests might be related to the fact that slightly more than half of DPTs were performed with a different drug from that involved in the DIA. Concern about patient safety in this group of serious HDRs may explain this finding, which was usually done to offer an alternative therapeutic option for the patient. Additionally, more than 40% of the patients challenged had more than one suspected drug reactions that could have further lowered the percentage of total positive results for provocation testing. Different DPT procedures were used in different centers, and this fact emphasized the need of standardized procedures for assessing immediate and delayed type drug hypersensitivity reactions in Latin America.

Epinephrine is considered the first drug of choice for the treatment of moderate-to-severe anaphylaxis. In contrast with current recommendations,[1,21-23,55] epinephrine was used in less than 30% of anaphylactic reactions and in approximately 40% of cases when there was CV involvement. Elderly patients received epinephrine more frequently that was probably related to this group having a greater degree of CV involvement.

In general, anaphylaxis is underrecognized and undertreated in the United States,[57] Latin America,[16] and other regions of the world.[11] The use of corticosteroids and antihistamines in each study for which data are available[57] was notably higher compared with rates of epinephrine use, even when the diagnosis of

anaphylaxis was made at the time of treatment. This raises concerns as to whether clinicians are knowledgeable about epinephrine being the treatment of choice for DIA and that corticosteroids and antihistamines are not recommended as first-line therapies for anaphylaxis. The low frequency of epinephrine use in anaphylaxis treatment is common in studies from Latin America[16,17] as well as other regions of the world.[11,33] In the study by Banerji et al,[33] only 8% of patients with DIA treated in the ED received epinephrine. Other investigators reported a higher rate of epinephrine use for DIA (Faria et al,[30] 47%, and Pumphrey et al[58] 62%). Droste and Narayan[59] found that a high proportion of hospital physicians were not knowledgeable regarding current recommendations for anaphylaxis treatment. Because most of these reactions are typically treated in EDs, dissemination of anaphylaxis guidelines in this group of physicians should be encouraged.[55]

The strengths of this study are the use of a validated standardized clinical questionnaire[19] in addition to the specific procedures used by each participating center to confirm the diagnosis of HDRs. Furthermore, the limited time frame from the drug reaction to its reporting (1 year) minimized the potential for recall bias.

A limitation of this study is that only patients referred to an allergist were assessed and enrolled. In the study of Banerji et al,[33] in the United States, the authors found that only 14% of the patients had any allergist and/or immunologist follow-up in the subsequent year, even after having an episode of DIA requiring treatment in the ED or hospitalization. There is also a potential for population bias as well as treatment and reporting differences between sites. Therefore, the present findings may not be truly generalizable as the population analyzed may not reflect the true incidence or prevalence of DIA across all medical communities in Latin America. Furthermore, there was no comparative control group used in this analysis. It is also likely that only the most severe and/or complex cases were referred to an allergy clinic further contributing to selection bias. Interestingly, Banerji et al[33] found that patients presenting with DIA and a concomitant allergic condition were more likely to see an allergist or immunologist compared with DIA patients without a concomitant allergic condition.

In summary, this study identified patients with DIA using a validated and standardized questionnaire in 11 Latin American countries and describes the main features of diagnostic testing and treatment performed by the participating centers. In patients with DIA in Latin America, NSAIDs and antibiotics were implicated in approximately 80% of cases. Most of these reactions were treated in the ED. Epinephrine was administered in only 27.6% of all cases, although more frequently for anaphylactic shock. The results of this study emphasize the need to improve dissemination and implementation of anaphylaxis guidelines to primary care and ED physicians in Latin American countries.

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IN MEMORIAM: CARLOS E. BAENA-CAGNANI

One of the authors of this study, Carlos E. Baena-Cagnani died suddenly celebrating the beginning of 2015 with his children and grandchildren in Ascochinga, Province of Cordoba, Argentina. This location had significant symbolic value to Carlos as it was where he frequently met with his colleagues in an atmosphere of friendship and camaraderie to plan regional, national, and international scientific meetings that would disseminate advances in scientific research for the specialty of allergy-immunology. He was an avid supporter of education and training of younger physicians and scientists, inspiring many of his colleagues to become actively involved in the development of original scientific research.

Carlos was a very hard worker from the time he began his career as an allergy fellow at the University of Navarra in Pamplona, Spain, under the mentorship of the late

Dr. Alberto Oehling. At that time, many diseases in our specialty were empirically managed; however, Carlos recognized very early on the importance of advocating for scientific evidence-based approaches in treating asthma and allergic rhinitis. His passion for evidence-based medicine, although sometimes misunderstood, was infectious and was instrumental in changing the public perception of allergy and immunology in Argentina and throughout Latin America.

In his organizational and scientific endeavors, Carlos worked with major thought leaders in our specialty, such as Gunnar Johansson, Jean Bousquet, and Allen Kaplan, emphasizing personal knowledge and friendship with each colleague. Carlos was highly regarded for his academic aptitude, passion, and energy, as well as his collegial skills, and as a result became a dear friend to many. He was a prolific writer of many scientific articles in peer-reviewed journals and chapters in allergy-immunology textbooks. Carlos left an indelible imprint transforming and modernizing the scientific societies that he chaired, including the Argentinean Association of Allergy and Clinical Immunology, the Latin American Society of Allergy Asthma and Immunology, the World Allergy Organization (WAO), and most recently, the Global Asthma Association (Interasma), whose mission includes bringing scientific knowledge and advances in care to allergists and/or immunologists working in underserved countries of the world who are not able to readily travel to international meetings. Carlos became an ambassador for all of the above societies all over the world. His tireless efforts were instrumental in drawing international recognition of allergy-clinical immunology in Argentina and throughout Latin America.

As a former rugby player, Carlos always emphasized that outcomes depend on teamwork, where all partners are critical for success. He worshiped friendship and was a lover of the arts, especially music, and sports.

Carlos's absence has left an irreplaceable void in our lives and is a great loss to our specialty. His giant personality will be greatly missed, but his memory has invoked in all of us the desire to continue to promote and develop the educational and/or scientific initiatives that he passionately embraced. Carlos had a unique personality: charismatic, vibrant, generous, and always in favor of collegiality and cooperation. We all will miss him and his passion for research, education, and dissemination of scientific knowledge.

Edgardo J. Jares, MD
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