Drug-Induced Anaphylaxis in Latin American Countries

Edgardo José Jares, MD[a], Carlos E. Baena-Cagnani, MD[b], Mario Sánchez-Borges, MD[c], Luis Felipe C. Ensina, MD[d], Alfredo Arias-Cruz, MD[e], Maximiliano Gómez, MD[f], Mabel Noemi Cuello, MD[g], Blanca María Morfin-Maciel, MD[h], Alicia De Falco, MD[i], Susana Barayazarra, MD[j], Jonathan A. Bernstein, MD[k], Carlos Serrano, MD[l], Silvana Monsell, MD[a], Juan Schuhl, MD[m], and Ricardo Cardona-Villa, MD[n], on behalf of "Latin America Drug Allergy Interest Group"* *Buenos Aires, Cordoba, Salta, San Juan, La Plata, Argentina; Caracas, Venezuela; São Paulo, Brazil; Monterrey, Mexico City, Mexico; Cincinnati, Ohio; Cali, Medellin, Colombia; Montevideo, Uruguay*

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

[a]Allergy Unit, CMP S.A., Libra Foundation, Buenos Aires, Argentina
[b]Centro de Investigación en Medicina Respiratoria, Faculty of Medicine, Catholic University of Cordoba, Cordoba, Argentina
[c]Allergy and Clinical Immunology Department, Centro Médico-Docente La Trinidad, Caracas, Venezuela
[d]Allergy, Immunology and Rheumatology, Federal University of São Paulo, São Paulo, Brazil
[e]Centro Regional de Alergia e Inmunología Clínica, Hospital Universitario, Monterrey, Mexico
[f]Allergy and Asthma Unit, Hospital San Bernardo, Salta, Argentina
[g]Allergy and Immunology Department, Consultorios San Juan, San Juan, Argentina
[h]Allergy, Hospital Mocel, Mexico City, Mexico
[i]Allergy and Clinical Immunology, Universidad Nacional de La Plata, La Plata, Argentina
[j]Allergy and Immunology, Nuevo Hospital San Roque, Córdoba, Argentina
[k]Department of Internal Medicine and Division of Immunology/Allergy Section, University of Cincinnati, Cincinnati, Ohio
[l]Allergy Unit, Fundación Valle del Lili, Cali, Colombia
[m]Allergy Unit, Hospital Britanico, Montevideo, Uruguay
[n]Universidad de Antioquia, Medellin, Colombia

No funding was received for this work.

Conflicts of interest: M. Gómez has received research support from GlaxoSmithKline, Novartis, Merck Sharp & Dohme, Takeda, and Stallergenes; has received lecture fees from Schering Plough; and has received travel support from Sanofi, GlaxoSmithKline, and Novartis. The rest of the authors declare that they have no relevant conflicts.

Received for publication January 12, 2015; revised April 3, 2015; accepted for publication May 4, 2015.

Available online ■■

Corresponding author: Edgardo José Jares, MD, Libra Foundation, Av. Virrey Vértiz 1784 16 A, Buenos Aires Argentina CP 1428, Argentina. E-mail: edgardo.jares@gmail.com.

* Viviana Andrea Zanacchi, Ivan Cherrez, Adolfo Salvatierra, Susana Diez, Paola Toche, Sandra González Díaz, Mara Morelo Rocha Felix, Luis Fernando Ramírez Zuloaga, Miguel Vinuesa, Ingrid Bissinger, Luis Fernando Ramírez Zuluaga, Adriana Weisz, Ada Castillo Mendez, Gregorio Mercovich, Cristina F. S. T. Piza, Antonio J. Castillo, Perla Alcaraz, Eugenia Herrera, Maria Fernanda Malaman, Galie Mimessi.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.05.012

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 AS. Dissemination of anaphylaxis guidelines among emergency department physicians should be encouraged to improve management of DIA. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)**

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