Original Article

Nonsteroidal Anti-Inflammatory Drugs are Major Causes of Drug-Induced Anaphylaxis

Marcelo Vivolo Aun, MD[a], Miguel Blanca, MD, PhD[b], Laila Sabino Garro, MD, PhD[a], Marisa Rosimeire Ribeiro, MD[a], Jorge Kalil, MD, PhD[a], Antonio Abilio Motta, MD, PhD[a], Mariana Castells, MD, PhD[c], and Pedro Giavina-Bianchi, MD, PhD[a] *São Paulo, Brazil; Malaga, Spain; and Boston, Mass*

What is already known about this topic? Drugs are responsible for 40% to 60% of anaphylactic reactions treated in the emergency department.

What does this article add to our knowledge? Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis, and they are prescribed to many patients despite a history of a previous reaction.

How does this study impact current management guidelines? This study raises awareness of nonsteroidal anti-inflammatory drug anaphylaxis, which can improve the prevention, diagnosis, and treatment of these reactions.

BACKGROUND: Drugs are responsible for 40% to 60% of anaphylactic reactions treated in the emergency department. A global research agenda to address uncertainties in anaphylaxis includes studies that identify factors associated with morbidity and mortality.

OBJECTIVE: The present study investigated drug-induced anaphylaxis, etiologies, aggravating factors, and treatment.

METHODS: A total of 806 patients with adverse drug reactions were screened, and those who had a clinical diagnosis of anaphylaxis were included in the study. Clinical and demographic characteristics of anaphylaxis were described, including etiologies, pathophysiologic mechanisms involved in the reactions, and a personal history of atopy and asthma. Factors associated with disease severity also were identified.

RESULTS: Anaphylaxis was diagnosed in 117 patients (14.5%). The etiologies were defined in 76% of the cases, nonsteroidal anti-inflammatory drugs being the most frequent. Seventy-eight patients (66.7%) reported a previous reaction to the drug involved in the current reaction or to a drug from the same class and/or group. Epinephrine was used to treat 34.2% of patients who presented with anaphylaxis, and 40.8% of those with anaphylactic reactions with cardiovascular involvement. IgE-mediated reactions were associated with greater severity, manifested by the rates of cardiovascular dysfunction, hospitalization, and use of epinephrine.

CONCLUSIONS: The prevalence of anaphylaxis is high in patients who seek medical assistance for drug reactions, but its diagnosis is missed in emergency services, and adrenaline is underused. Drugs were prescribed to many patients despite a history of previous reaction. Nonsteroidal anti-inflammatory drugs were implicated in most cases of anaphylaxis induced by drugs, and IgE-mediated reactions were less frequent but more severe. **(J Allergy Clin Immunol Pract 2014;■:■-■)**

Key words: *Anaphylaxis; Hypertensively reaction; Nonsteroidal anti-inflammatory drugs; Adverse drug reaction; Epinephrine; IgE mediated*

Hypersensitivity reactions (HSR) induced by drugs are a subgroup of adverse drug reactions (ADR) that are unexpected and characterized by objectively reproducible symptoms or signs initiated by exposure to a drug at a dose tolerated by normal individuals.[1] Immediate reactions, those that occur within the first hour after drug exposure, are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm, and anaphylaxis.[1-4] Anaphylaxis is defined as a serious, life-threatening HSR that is rapid in onset.[1] It can be considered a syndrome, and its diagnosis is based primarily on a detailed clinical history with recognition of patterns.[4] Criteria have been developed in an attempt to make the diagnosis more accurate and reliable, and the severity of systemic reactions has been classified from grade I (mild reaction) to V (death).[4,5] The prevalence of anaphylaxis is not well known, with an estimated overall incidence that ranges from 3 to 50 per 100,000 person years, with a lifetime prevalence of 0.05% to 2%.[6] Drugs are responsible for 40% to 60% of the

[a]Department of Clinical Immunology and Allergy, University of São Paulo School of Medicine, São Paulo, Brazil
[b]Allergy Service, Hospital Civil, Malaga, Spain
[c]Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass
No funding was received for this work.
Conflicts of interest: M. Castells has received consultancy fees from Merck and Sanofi; is employed by Brigham and Women's Hospital; has a pending grant from National Institutes of Health Desensitization; has received royalties from UpToDate; has received travel support from the American Academy of Allergy, Asthma, and Immunology Board of Directors. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication January 6, 2014; revised March 21, 2014; accepted for publication March 27, 2014.
Corresponding author: Pedro Giavina-Bianchi, MD, PhD, Clinical Immunology and Allergy Division, University of São Paulo School of Medicine, Av Dr Enéas de Carvalho Aguiar, 255, 8° andar, CEP 05403-900, Cerqueira César - São Paulo - SP – Brazil. E-mail: pbianchi@usp.br or marcelovivoloaun@gmail.com.
2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2014.03.014

Abbreviations used
ADR- Adverse drug reaction
ENDA- European Network on Drug Allergy
HSR- Hypersensitivity drug reaction
ICU- Intensive care unit
NMBA- Neuromuscular blocking agent
NSAID- Nonsteroidal anti-inflammatory drug

reactions treated in the emergency department.[6,7] However, the rate of anaphylaxis induced by different classes of drugs is unknown. Although anaphylaxis is a potentially fatal medical emergency whose treatment is based on intramuscular epinephrine, this medication is often not used, which is associated with an increased mortality rate.[4,8,9]

Anaphylaxis may be allergic or nonallergic.[1] Allergic reactions are those that involve specific immunologic mechanisms, which may be IgE- or non-IgE–mediated. With IgE-mediated reactions, appropriate drug conjugates bind to high-affinity IgE receptors on mast cells and basophils, which activate these cells and triggers the release of mediators such as histamine, tryptase, leukotrienes, and prostaglandins. Penicillins and neuromuscular blocking agents are considered the main causes of IgE-mediated anaphylactic drug reactions.[10-12] Nonallergic anaphylaxis occurs without specific immune response and includes several mechanisms, such as activation of the complement system with production of anaphylatoxins, generation of arachidonic acid metabolites, and direct activation of mast cells.[1,13] Nonsteroidal anti-inflammatory drugs (NSAID) and iodinated contrast agents are common causes of nonallergic anaphylaxis.[14,15] A global research agenda in anaphylaxis includes studies that identify factors associated with morbidity and mortality.[4,16] The present study assesses drug-induced anaphylaxis in a population referred to a specialized service in ADRs, which emphasizes the culprit drugs, aggravating factors, and treatment.

METHODS

This was an observational study of 806 patients, who were evaluated at the division of clinical immunology and allergy of a tertiary university hospital for presenting HSRs induced by drugs, from January 2006 to June 2012. A specific ADR questionnaire adapted from the ENDA (European Network on Drug Allergy) was used, and patients with a diagnosis of anaphylaxis were included and followed up for at least 6 months (Figure 1).[17] The reactions that met at least 1 of the 3 criteria described in the World Allergy Organization guidelines were considered anaphylactic.[4] The protocol was approved by our institutional review board, and all the patients signed the study consent form. Clinical characteristics of anaphylaxis, demographics, history of previous ADRs, atopy, asthma, and use of epinephrine were registered. Atopy was defined as a history of allergic conjunctivitis and/or rhinitis and/or asthma, food allergy, and/or atopic dermatitis.

The culprit agents were identified based on clinical history, relationship between exposure and onset of clinical manifestations, and diagnostic tests. Because latex allergy must be considered in the differential diagnosis of drug allergy, patients who presented with latex allergy were included in the study. According to the clinical history, *in vivo* and *in vitro* tests were performed. We conducted skin prick and intradermal tests to antibiotics, neuromuscular blocking agents (NMBA), hypnotics, opioids, local anesthetics, and latex, as recommended.[18,19] Serum-specific IgE (ImmunoCAP Pharmacia Diagnostics, Uppsala, Sweden) for latex and β-lactam antibiotics (penicillin, amoxicillin, and ampicillin) were performed when these agents were involved in the reactions. Drug provocation tests were done when indicated according to ENDA protocols.[20-22]

Regarding NSAID reactions, the diagnoses were made based on clinical history and were confirmed by challenge tests when needed. Cross reaction with NSAIDs was identified in the same way. Anaphylactic reactions were classified as allergic (IgE mediated) and nonallergic, according to the pathophysiologic mechanism. In those reactions defined as allergic, an IgE mechanism was confirmed by skin tests or serum-specific IgE. Anaphylaxis triggered by different classes of non–chemically related NSAIDs were defined as nonallergic.[15] Reactions triggered by unknown mechanisms in which specific IgE could not be detected were considered reactions with an undetermined mechanism.

Severity of anaphylaxis was graded from grade II (mild reaction) to grade IV (severe reaction) according to the Systemic Reaction Grading System of the World Allergy Organization, in which an anaphylactic reaction is at least grade II.[5] This system of classification is as follows: grade I, cutaneous or conjunctival or mild upper respiratory manifestation; grade II, involvement of 2 organ systems of grade I or of gastrointestinal or mild lower respiratory manifestation; grade III, moderate upper and/or lower respiratory manifestation; grade IV, severe upper and/or lower respiratory or cardiovascular manifestation; grade V, death. Reactions with cardiovascular dysfunction were those that presented as hypotension with or without loss of consciousness. Admission to the emergency department, hospitalization, admission to the intensive care unit, and tracheal intubation or tracheostomy also were assessed. Severity of anaphylaxis was analyzed in relation to age, sex, pathophysiologic mechanisms involved in the reactions, and personal history of atopy and asthma. Features of allergic and nonallergic reactions were compared.

Statistical analysis

Categorical variables were expressed as absolute (n) and relative (%) frequency, and were analyzed by the Pearson χ^2 test or the Fisher exact test, whenever appropriate. The level of significance was set at $P \leq .05$. All data were analyzed by using the Statistical Program for Social Sciences (SPSS for Windows 19.0; SPSS, IBM Corp, Armonk, NY).

RESULTS

We evaluated 806 patients with a history of HSR, of whom 117 (14.5%) met clinical criteria for anaphylaxis (Figure 1). Patients age ranged from 2 to 70 years (mean [SD] 38.6 ± 14.5 years), 81% (n = 95) were female patients, and the vast majority had not been previously diagnosed as having anaphylaxis. Epidemiologic and clinical features, and the agents involved in the reactions are described in Table I. There was no difference in severity of anaphylaxis in relation to age or sex (data not shown). Mucocutaneous manifestations, including urticaria, rash, itching, and oropharyngeal angioedema, were the most frequent, reported by 88% of patients, followed by respiratory symptoms (Figure 2). Anaphylaxis with cardiovascular dysfunction, a grade IV reaction, was reported by 49 patients (41.9%). Epinephrine was used to treat 34.2% of all the patients and 40.8% of those with anaphylaxis with cardiovascular involvement. The frequencies of atopy