Clinical Communications

Drug-induced anaphylaxis, elicitors, risk factors, and management in Latin America

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Clinical Implications

- Nonsteroidal anti-inflammatory drugs were the most frequent triggers of drug-induced anaphylaxis in Latin America, whereas antibiotics elicited faster onset and more severe reactions. An improvement was observed in epinephrine use and adherence to guidelines in the emergency department treatment of anaphylaxis in Latin America compared with our last report.

TO THE EDITOR:

Drugs are among the most frequent elicitors of anaphylaxis, especially in adults and hospitalized patients.[1] Although studies from France and Portugal found that beta-lactam antibiotics were the most frequent drug-induced anaphylaxis (DIA) elicitors,[2,3] the main drugs claimed as triggers of DIA in Latin America (LA) are nonsteroidal anti-inflammatory drugs (NSAIDs).[4] The aim of this study was, using a drug anaphylaxis–specific questionnaire, to provide new data on the clinical presentation, risk factors, and acute treatment of DIA in LA.

An online survey modified from the European Network of Drug Allergy questionnaire was used to obtain patient demographic data and the clinical features, severity, and chronology of anaphylactic reactions[5] (severity grading system and causality definitions in Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org) to implicated drugs over 2 years. In addition, acute management of the DIAs administered to patients was obtained. The results included all the patients with DIA reported to the registry between January 2017 and November 2018 by 22 allergy units from 8 LA countries. A total of 286 DIA cases were reported. The main demographic data are summarized in Table I.

Mild, moderate, severe, and fatal reactions were present in 4.20%, 59.44%, 36.01%, and 0.35% of patients, respectively. Children/adolescents, adults (18-59 years old), and elderly patients (>60 years old) experienced severe reactions in 12%, 37.17%, and 57.78% of cases, respectively (children/adolescents vs adults: $P < .001$; adults vs elderly: $P < .05$). In the unadjusted logistic regression, a 10-fold increase (odds ratio, 10.03; 95% CI, 3.55-28.33) and a 4-fold increase (odds ratio, 4.44; 95% CI, 1.80-10.93) in the chance for a severe reaction was found in elderly and adults, respectively, compared with children-adolescents. Older age has been recognized previously as a risk factor for more severe anaphylaxis.[4,6]

No significant difference in severity was found between patients with or without an allergic history (severe reactions 31.4% vs 40.3%, $P = .093$), or an asthma history (severe reactions: 30.8% vs 37.6%; $P = .354$).

Previous reaction with the implicated drug, or a drug from the same group, was present in 24.5% of patients (milder reactions, 18.6%; similar or more severe reaction 5.9%). These DIA reactions emphasize the importance of educating physicians about taking a careful history regarding previous drug-induced hypersensitivity reactions.

Oral (68.2%) and intravenous (IV) (22%) were the most common routes associated with DIAs. The IV route induced severe reactions in 48.3% of patients compared with 31.3% for the oral route ($P < .05$). In addition, drugs administered via the IV route induced quicker onset of reactions; 55.2% versus 20.6% during the first 10 minutes for the IV and oral routes, respectively ($P < .00001$). This is in accordance with other studies where patients receiving parenterally administered drugs presented more severe and faster reactions.[2,4,7]

The main inducers causing certain/probable DIA were NSAIDs (54.6%), beta-lactam antibiotics (16.6%), and non–beta-lactam antibiotics (6.4%). The predominant reactions to NSAIDS might be related to the fact that these drugs are easily obtained over the counter in most LA countries and self-medication especially with NSAIDs is very common in this region. Ibuprofen (24.3%) and metamizole (21.7%) were the most frequently implicated NSAIDs in the entire population, whereas diclofenac was the most prevalent NSAID in the elderly group (40.74%), possibly linked to their higher use for osteoarthritis. Antibiotics more frequently induced severe reactions (beta-lactams 43.4% and non–beta-lactams 44.4%) compared with NSAIDs (27.7%) ($P < .05$). Beta-lactam antibiotic reactions occurred during the 10-minute period after drug intake in 42.3% of cases compared with NSAID reactions, which occurred in 19.9% of cases during the same time period ($P < .005$). These findings might be explained by differences in the involved mechanisms. Beta-lactam–induced DIA are believed to be IgE-mediated reactions that can result in systemic reactions including vascular instability, whereas NSAID DIA are believed to be primarily related to imbalance of prostaglandins/leukotrienes production due to cyclooxygenase blocking that typically manifest as cutaneous and respiratory reactions.[8]

Most patients received glucocorticoids (80.1%) and antihistamines (80.4%). Epinephrine was administrated in 49.6% of cases, intramuscularly 41.6% and subcutaneously 8% of cases

TABLE I. Demographic data of all questionnaire respondents

Characteristic	Overall (N = 286)	Children-adolescents (0-17 y) (n = 50)	Adults (18-83 y) (n = 236)	*P* value adults/children-adolescents
N	286	50	236	
Age (y), median	37 (24-52)	11.0 (8-14)	41.0 (31-56)	<.001†
Sex, %				
Male	35.7	58.0	30.9	<.000*
Female	64.3	42.0	69.1	
Allergic background, %	47.9	66.0	44.1	<.005*
Rhinitis, %	36.7	52.0	33.5	<.014*
Asthma, %	18.2	36	14.4	<.000*
Food allergy, %	6.3	8.0	5.9	NS
Atopic dermatitis, %	4.9	12.0	3.4	<.010*
Hymenoptera venom allergy, %	3.8	14.0	1.7	<.000*
Latex allergy %	1.7	2.0	1.7	NS
Previous drug reactions, %	32.5	26.0	33.9	NS
Family history of allergy, %	28.7	48.0	24.6	<.007*

NS, Nonsignificant.
*$P < .05$, χ^2.
†$P < .05$, Mann-Whitney *U* test.

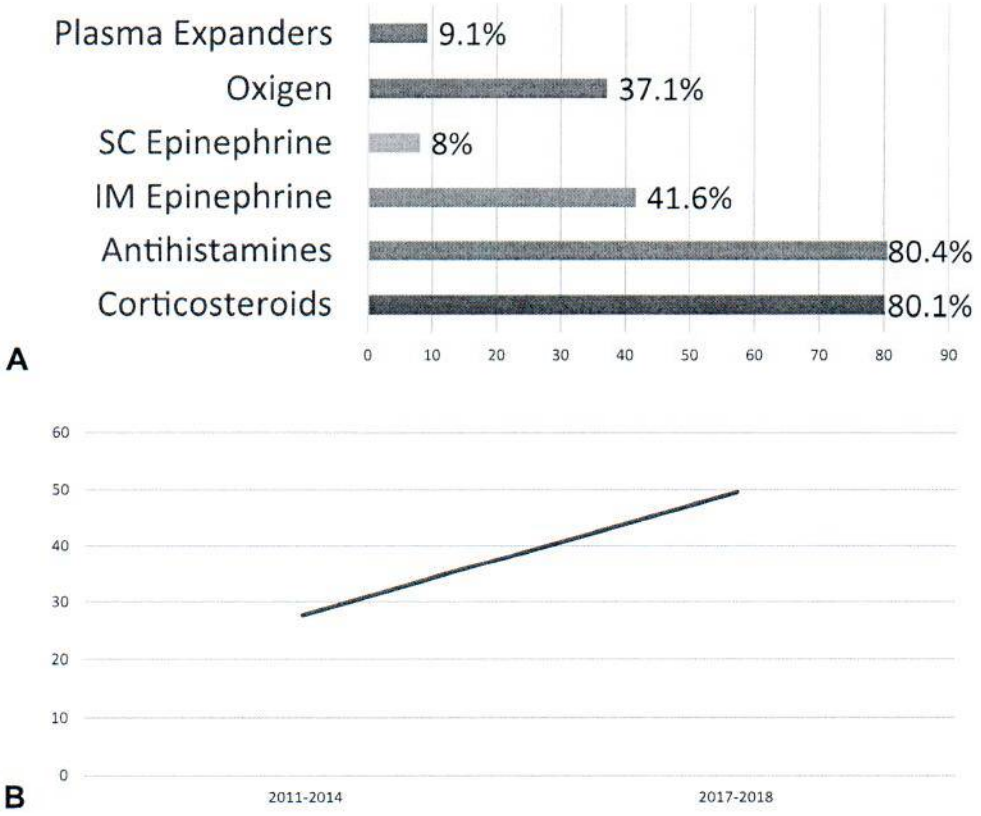

FIGURE 1. (**A**) Acute treatment of anaphylaxis. (**B**) Change in epinephrine use in Latin America from 2011-2014 (Jares et al[4]) to 2017-2018. *SC*, Subcutaneous; *IM*, intramuscular.

(Figure 1, *A*). Intramuscular epinephrine is the cornerstone of anaphylaxis treatment,[9] but its use has remained low in different parts of the world. In a previous study on DIA in LA, we found that epinephrine was used only in 27.6% of cases.[4] (Figure 1, *B*). We speculate that the use of epinephrine in these situations is improving with continued education and awareness. Glucocorticoids are used in most of the patients with DIA, in spite of the lack of evidence supporting its effectiveness.

Biphasic anaphylaxis was present in 11 patients (3.84%). Severe reactions were present in 45.45% of patients with biphasic and 36% with nonbiphasic anaphylaxis ($P = .53$, nonsignificant). The biphasic group received epinephrine in 27.27% of cases and systemic glucocorticoids in 90.90% of cases during the early phase response. This is in contrast to the nonbiphasic group that received epinephrine in 50.91% ($P = .14$, nonsignificant) of cases and systemic glucocorticoids in 80% ($P = .41$, nonsignificant) of cases. Although not significant, this trend for reduced biphasic reactions in those patients treated with epinephrine early on is consistent with reports suggesting that epinephrine is more effective than systemic glucocorticoids at preventing biphasic reactions.[10]

This study has a number of strengths because it is a large DIA population from LA using a validated questionnaire survey. Furthermore, clinical evaluations were performed in Allergy Units, permitting a more accurate trigger diagnosis.

However, limitations include lack of generalizability because patients were from Allergy Units, and their management may not reflect care provided in General Medicine Units. Furthermore, this was a retrospective descriptive questionnaire study that has inherent reporting bias.

In summary, this study found that NSAIDs were the most frequent triggers of DIA in LA, whereas antibiotics elicited faster onset and more severe reactions. Epinephrine was used in almost half the patients with DIA, mostly by the intramuscular route, demonstrating improved adherence to guidelines in the ED treatment of anaphylaxis since our last survey.

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TABLE E1. Severity criteria[E1]

SEVERE (hypoxia, hypotension, or neurologic compromise) Cyanosis or $SpO_2 < 92\%$ at any stage, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence
MODERATE (features suggesting respiratory, cardiovascular, or gastrointestinal involvement) Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
MILD (skin and subcutaneous tissues only) including generalized erythema, urticaria, periorbital edema, or angioedema

TABLE E2. Causality criteria[E2]

CERTAIN
• Event or laboratory test abnormality, with plausible time relationship to drug intake
• Cannot be explained by disease or other drugs
• Response to withdrawal plausible (pharmacologically, pathologically)
• Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon)
• Rechallenge satisfactory, if necessary
PROBABLE/LIKELY
• Event or laboratory test abnormality, with reasonable time relationship to drug intake
• Unlikely to be attributed to disease or other drugs
• Response to withdrawal clinically reasonable
• Rechallenge not required
POSSIBLE
• Event or laboratory test abnormality, with reasonable time relationship to drug intake
• Could also be explained by disease or other drugs
• Information on drug withdrawal may be lacking or unclear
UNLIKELY
• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
• Disease or other drugs provide plausible explanations
CONDITIONAL/Unclassified
• Event or laboratory test abnormality
• More data for proper assessment needed, or
• Additional data under examination
UNASSESSABLE/UNCLASSIFIABLE: Report suggesting an adverse reaction
• Cannot be judged because information is insufficient or contradictory
• Data cannot be supplemented or verified

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