

Original Article

A Predictive Model for the Diagnosis of Allergic Drug Reactions According to the Medical History

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What is already known about this topic? The clinical history is essential when deciding whether to submit patients to controlled drug exposures. Such testing is necessary to rule out sensitization but can be costly and has some risks.

What does this article add to our knowledge? A simple, easy-to-use mathematical model is useful in evaluating potential drug reactions using only the medical history.

How does this study impact current management guidelines? It adds a diagnostic method that estimates the probability of an adverse drug reaction in numerical terms. This may reduce uncertainty about the use of drugs such as penicillin or nonsteroidal anti-inflammatory drugs.

BACKGROUND: Quantification of the risk of an allergic drug reaction through the medical history is essential in clinical decision making. However, in normal clinical practice, this evaluation is generally entirely subjective.

OBJECTIVE: The objective of this study was to construct a mathematical model to predict the risk of allergic drug reactions using the data collected in the medical history.

METHODS: A total of 696 active principles, corresponding to 466 patients aged more than 14 years attending the Allergy Service of the University Hospital of Salamanca, were included. Simple binary logistic regression was used to determine associations between variables from the medical history and the final diagnosis, to construct a predictive model.

RESULTS: Variables useful in predicting a final diagnosis of allergic drug reaction were age, sex, drug class, number of active principles, time to the reaction, number of doses, clinical presentation suggestive of allergic disease, and time to medical consultation. True adverse drug reactions were estimated to occur in 20% of active principles. However, possible allergic reactions could only be ruled out in 52.2%.

CONCLUSIONS: The use of mathematical models could greatly improve the discriminatory capacity of the medical history. Both

the overdiagnosis and underdiagnosis of allergic drug reactions should be considered a public health problem. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: Allergic drug reaction; Drug hypersensitivity; Diagnosis; Predictive model; Penicillin; Analgesics; Medical history

INTRODUCTION

Allergic drug reactions (ADR) are the third most common reason for consultation in allergy services.¹ Epidemiological data are imprecise. Globally, ADR affect 10%-20% of hospitalized patients and up to 7% of outpatients.² However, this might be an underestimate due to underreporting, or an overestimate due to unexplained reactions often being classified as "allergic."³ This carries risks for the patient. On the one hand, the possibility of anaphylactic shock: 13% of cases are due to drug allergies.⁴ On the other hand, the use of therapies that are not first choice treatments and are usually more expensive⁵ have more side effects and an increased risk of treatment failure.⁶⁻¹⁰ ADR also increase the costs of medical care because of the increased use of emergency services, hospitalizations¹⁰ suspension of tests,^{6,7} and extended hospital stays.^{8,10}

Assessment by an allergy specialist is crucial because it allows a diagnosis to be reached in some cases and allergies to be ruled out in most patients. Complementary tests include skin tests and laboratory analysis. However, the sensitivity of these diagnostic methods is not optimal, and, in any case, the definitive test to establish or exclude the diagnosis is a controlled exposure test.¹¹ This may be expensive, time consuming, and potentially dangerous, but is usually necessary, as no sensitization to the drug involved is found in two-thirds of patients with suspected ADR.¹¹

Quantification of the risk of ADR by the medical history is vital to decision making by the allergy consultant, and to provide

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication November 4, 2014; revised October 4, 2015; accepted for publication November 4, 2015.

Available online ■ ■ ■

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.11.003>

Abbreviations used

ADR- Allergic drug reactions

NSAID- nonsteroidal anti-inflammatory drug

SD- Standard deviation

criteria for other physicians to refer the case to a specialist. It may also allow an estimate of the accuracy of suspected diagnoses.

The main objective of this study was to develop a predictive model for the diagnosis of ADR by analysis of all variables routinely collected by the medical history.

METHODS

A retrospective cohort study was performed by the review of the medical history. All patients aged more than 14 years studied for suspected ADR between January 1 and December 31, 2010, at the University Hospital of Salamanca, which provides care to approximately 353,000 persons, were included. Written informed consent was obtained from all patients. Data were entered into a Microsoft Excel database and dissociated to ensure that no patient could be identified.

Two authors assessed and consensually agreed all variables in the medical history that may be useful for the diagnosis of ADR according to previous studies, protocols, and recommendations.¹² The variables finally included were sex, age at the time of reaction, relatives with allergic diseases, personal history of allergic disease, personal history of drug allergy, chronic disease, chronic treatment, skin tests to aeroallergens (pollen, mites, dander, mold), skin test to food allergens (flour, egg, milk, fish, fruit, nuts, legumes), IgE total value higher or lower than the IgE median of 60 found in our sample (IgE60), number of drugs assessed, time to assessment, referring service, emergency department visits, hospitalization, specific drug to be assessed, route of administration, number of doses, clinical manifestations, duration of episode, latency period between exposure and reaction, number of episodes, and previous tolerance (Table I). Candidate variables for inclusion in the multivariate regression model were sex and age, which are routinely included,¹³ and variables in Table I with a value of $P < .25$ in the univariate analysis.¹³

Various categories may be established.¹ *Confirmed diagnosis*: when skin tests, specific IgE test, or controlled exposure to the drug are positive. *Diagnosis ruled out*: when the controlled exposure test is negative. *Suspected diagnosis*: suspected according to the medical history but no controlled exposure test is performed. An alternative drug is usually tested. Nonsteroidal anti-inflammatory drugs (NSAIDs) often result in idiosyncratic reactions that are clinically very similar to allergic reactions.¹⁴ Therefore, 2 further categories can be established. *Confirmed diagnosis of idiosyncratic reaction*: when there is a positive oral controlled exposure test to aspirin. *Suspected diagnosis of idiosyncratic reaction*: suspected according to the medical history, but no controlled challenge test is performed.¹¹

Statistical analysis

Descriptive variables were analyzed using means and percentages to determine the characteristics of the sample. Binary logistic regression was used to establish possible relationships between the variables contained in the medical history and the final diagnosis to construct a predictive model.¹⁵ The dependent variable was diagnosis confirmed and/or ruled out. Suspected diagnoses and idiosyncratic reactions to NSAIDs were eliminated from the analysis. The statistical study was performed using the SPSS version 21

statistical package. Recommendations on data analysis were followed.^{13,15}

RESULTS

Between January 1 and December 31, 2010, 466 patients were tested for ADR. More than 1 suspected active principle was studied in 57.7% of patients. Therefore, 696 active principles were initially studied. A total of 50 patients, representing 70 active principles (10%), abandoned testing because of the large number of medical visits required (mean of 4 visits, with 84% of patients requiring 3 or more visits). Therefore, 626 active principles, representing 416 patients, were finally included in the analysis. The maximum number of active principles studied in 1 patient was 5. A total of 70.7% of the active principles involved were in female patients and 29.3% in males. The mean number of drugs did not differ significantly according to sex ($P = .15$, t -test for means).

The mean age at consultation was 48 years, and standard deviation (SD) 17.7. The distribution was normal (Kolmogorov-Smirnov test, $P = .37$). The mean age at presentation of the reaction was 42 years (SD, 18.11), with a normal distribution (Kolmogorov-Smirnov test, $P = 0.44$). The age range was less than 12 months to 89 years. A total of 68.8% of patients were referred from primary health care.

Of the 626 active principles finally evaluated, ADR was ruled out in 58.1% and confirmed in 13.4%, whereas 26.4% remained as suspected. In the remaining 2.1% of cases, a diagnosis of idiosyncratic reactions to NSAIDs was made and confirmed by a controlled exposure test.

With respect to the type of drug, 244 (39%) were NSAIDs, 172 (27.5%) β -lactam antibiotics, and 210 (33.5%) other drug classes (other antibiotics 11.4%, anesthetics 3.5%, corticosteroids 2.9%, opiates 2%, proton pump inhibitors 1.6%, radiocontrast agents 0.4%, and other drug classes 11.8%).

Table II shows the diagnoses assigned according to pharmacological class. In the case of NSAIDs, of the 114 suspected cases, 50 corresponded to ADR and 64 to idiosyncrasies. β -Lactams were the drug class with the most confirmed ADR, and NSAIDs the drug class with the highest sum of confirmed and suspected diagnoses and, therefore, the class with the highest rate of contraindications to their use.

Table III shows the classification of the final diagnosis of the clinical presentations.

To establish associations between the variables included in the medical history and the final diagnosis, simple logistic regression (a single independent variable) was applied to each variable.¹³ Candidate variables identified in the first step were IgE median60, number of drugs, time before medical consultation, emergency department visits, drug group, clinical presentation suggestive of allergy, duration of the episode, latency period, and number of doses. Variables not associated with the final diagnosis in the first step were personal or family histories, chronic disease, the number of active treatments, the results of skin tests for aeroallergens and food allergens, the referring medical service, the route of administration, previous tolerance, or the number of episodes.

Of the multivariable models tested, that shown in Table IV was considered the simplest and most useful. After adjustment, IgE median60, emergency department visits, and duration of the episode were not considered significant with respect to the final

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