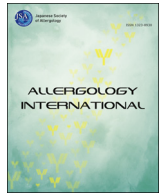




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Original article

Epidemiology of drug-induced anaphylaxis in a tertiary hospital in Korea

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ARB angiotensin receptor blocker
 COPD Chronic obstructive pulmonary disease
 NMBA neuromuscular blocking agent
 NSAID non-steroidal anti-inflammatory drug

ABSTRACT

Background: Epidemiology and risk factors of drug-induced anaphylaxis are difficult to estimate due to lack of confirmative diagnosis and under reporting. Here we report the current state of drug-induced anaphylaxis in Korea based on an in-hospital pharmacovigilance database in a tertiary hospital.

Methods: This study is a retrospective analysis of drug-induced anaphylaxis, reported to an in-hospital pharmacovigilance center in Seoul National University Hospital from June 2009 to May 2013. Anaphylaxis occurred in patients under 18 years of age or developed by medications administered from outside pharmacies or hospitals were excluded. We assessed causative drug, incidence per use of each drug and risk factors of fatal anaphylactic shock.

Results: A total of 152 in-hospital drug-induced anaphylaxis cases were reported during the study period. The single most frequently reported drug was platinum compound and the incidence of anaphylaxis and anaphylactic shock in platinum compounds users was 2.84 and 1.39 per 1000 patients use. Risk factors of anaphylactic shock among total anaphylaxis cases were identified as older age ≥ 70 years [Odds's ratio (OR), 5.86; 95% confidence interval (CI), 1.70–20.14]. The use of iodinated contrast media (OR, 6.19; 95% CI, 1.87–20.53) and aminosteroid neuromuscular blocking agent (NMBA) (OR, 12.82; 95% CI, 1.50–109.92) were also a risk factor for the development of anaphylactic shock.

Conclusions: Platinum compounds are the most commonly reported causative agents of in-hospital drug-induced anaphylaxis. Older age ≥ 70 years and drugs such as iodinated contrast media and aminosteroid NMBA are related with high risk of anaphylactic shock.

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Introduction

Anaphylaxis is a systemic allergic reaction that simultaneously exhibits fatal multi-organ symptoms as a result of the rapid release of mediators such as histamine and leukotriene. This reaction is severe and unpredictable, and sometimes may result in death due to refractory circulatory collapse.^{1,2}

The incidence of anaphylaxis varies depending on the study subjects and research design. Population-based studies have reported a 0.05–2% lifetime prevalence of anaphylaxis, and 5–40 anaphylaxis

incidences for every 100,000 person-year.^{3–6} However, one public survey reported that as many as 7.7% of the patients in the general population had answer to have an experience of anaphylaxis.⁷

Multiple studies have reported a continuous increase in the incidence of anaphylaxis.^{8,9} Several studies have identified drugs to be the most common cause of adult anaphylaxis, especially major causes of fatal anaphylaxis.^{5,7,10} A study conducted by the Portuguese Pharmacovigilance System has indicated that drug-induced anaphylaxis accounted for approximately 6% of all adverse drug reactions, and was therefore, not as rare as previously believed.¹¹

However, there are only a few epidemiological studies which focused on drug-induced anaphylaxis. A majority of the previously conducted epidemiological studies have targeted the general population or all patients who visited the hospitals including

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emergency rooms.^{10–13} Therefore, it is difficult to estimate the incidence of drug-induced anaphylaxis because the information of the total drug use is usually not available.

The aim of this study was to identify the causative agents and incidence of in-hospital drug-induced anaphylaxis in adults and evaluate the risk factors related with fatal anaphylactic shock.

Methods

Selection of patients

This study enrolled patients who had anaphylactic episodes, which were monitored by a pharmacovigilance center in the Seoul National University Hospital between June 2009 and May 2013. Spontaneous reports were made by medical personnel including physicians, nurses, and pharmacists. Periodic active surveillance based on the ICD-10 codes was also performed. Individual case safety reports were assessed by allergy specialists and defined as anaphylaxis if they satisfied the criteria of anaphylaxis.¹ Patients under 18 years old or those who had anaphylaxis occurred by medications purchased or prescribed outside the hospital were excluded. Drugs assessed as unlikely based on the WHO-UMC causality criteria were also excluded for the analysis.

If anaphylaxis occurred as a breakthrough reaction after repeated administration of the causative agents through desensitization or with premedication, only the first occurrence was included in the study.

Patient variables, including characteristics, treatment, and severity of drug-induced anaphylaxis

The basic demographic information (age, gender, body mass index, patient's location, etc.), information on causative drugs (type of drugs, route of administration), clinical manifestation of anaphylaxis (symptoms of the skin, and respiratory, circulatory, and gastrointestinal systems), prognosis (death, cardiopulmonary arrest), accompanying diseases, and drugs used by the patients in combination were investigated through a retrospective chart review. Anaphylactic shock was defined as the decrease in systolic blood pressure to ≤ 90 mmHg, or more than 30% reduction from basal blood pressure after drug administration.

Evaluation of causative drugs, incidence per drug use, and risk factors of anaphylactic shock

Causality between the drugs and the occurrence of anaphylaxis was evaluated by two allergy specialists based on the WHO-UMC causality criteria. This method classified the causality into four categories (certain, probable, possible, and unlikely) based on the temporal relationship between drug use and adverse reaction, pharmacological and symptomatological novelty of drug, possibility of being caused by accompanying diseases or other drugs, and response after dechallenge or rechallenge of corresponding drug.¹⁴ In cases where the usage of platinum compounds, penicillin derivatives and cephalosporin, iodinated contrast media, and aminosteroid neuromuscular blocking agent (NMBA) resulted in anaphylactic episodes (that occurred in over 10 cases), incidence was defined as the reported number of anaphylaxis patients per 1000 corresponding drug users in the hospital during the study period. The denominator, the total numbers of each drug users, were attained based on the numbers of all patients who were prescribed the corresponding drugs at least once during the study period. After obtaining IRB approval for this research, all the electronic records of prescription during the study period were

extracted in order to verify the total number of patients who received each drug.

Statistical analysis

All statistical analyses were performed using the SPSS version 21.0 software platform (SPSS Inc., Chicago, IL, USA). All measured values were expressed as mean \pm standard deviation or percentage. The variables were compared by univariate analysis, using the *t*-test, Pearson's chi-square test, and Fisher's exact test. Multivariate analysis was performed on the variables that demonstrated a *p*-value < 0.2 by univariate analysis in addition to the age and gender; these included causative drugs, viral hepatitis, and drugs used in combination (angiotensin receptor blocker (ARB), aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs)). *P*-values less than 0.05 were considered to be statistically significant.

Results

Characteristics of the patients with drug-induced anaphylaxis

A total of 12,968 adverse drug reaction cases were collected based on spontaneous reports submitted during the study period and anaphylaxis cases were 235 (1.81%). Among these, in-hospital anaphylaxis cases were 152 (Fig. 1).

The causality evaluation of causative drugs determined 52, 91, and 9 cases as "certain", "probable" and "possible" cases, respectively. The mean age of occurrence of anaphylaxis was 57.59 ± 13.55 years. The age distributions of the patients were as follows: < 50 years in 34 cases (22.4%), ≥ 50 and < 60 years in 44 cases (28.9%), ≥ 60 years and < 70 years in 44 cases (28.9%), and ≥ 70 years in 30 cases (19.7%). Males and females comprised of 46.7% (71) and 53.3% (81) of the cases (Table 1). The route of administration was intravenous in 94.7% of cases. Of the total 152 patients, 87 (57.2%) were inpatients admitted in the hospital and 65 (42.8%) were outpatients who visited the hospital for undergoing chemotherapy or procedure (Table 1).

Causative drugs for drug-induced anaphylaxis

Anti-cancer drugs were the major causative agents of the in-hospital anaphylaxis cases (64; 42.1%). Among anti-cancer drugs, oxaliplatin, a platinum compound, was the most common, followed by taxane and monoclonal antibodies. The second most commonly reported drug was radiocontrast media (49; 32.2%) followed by beta-lactam antibiotics and NMBA (Table 2). Among NMBA, rocuronium accounted for 85.7%. Other minor causative drugs included vitamin K and filgrastim (two cases for each), and ibuprofen, tramadol, terlipressin, ramipril, heparin, famotidine, intra-ocular fluorescein, and intra-articular transforming growth factor- $\beta 1$ (one case for each).

Incidence per use of four major causative drugs

The incidence of drug-induced anaphylaxis was highest in platinum users as 2.84 for every 1000 use, followed by iodinated contrast media, aminosteroid NMBA, and penicillin derivatives and cephalosporin users (0.27, 0.14, and 0.08 for every 1000 use, respectively). The incidence of anaphylactic shock was also highest in platinum compounds users (1.39 individuals per 1000 use).

Among cases related with these four major causative drugs related anaphylaxis cases, the proportion of female was higher compared to male patients. Comparing by on the age, the incidence of anaphylaxis related with the use of penicillin derivatives,

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