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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 [Odd'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 $\leq$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 ± 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-β1 (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,

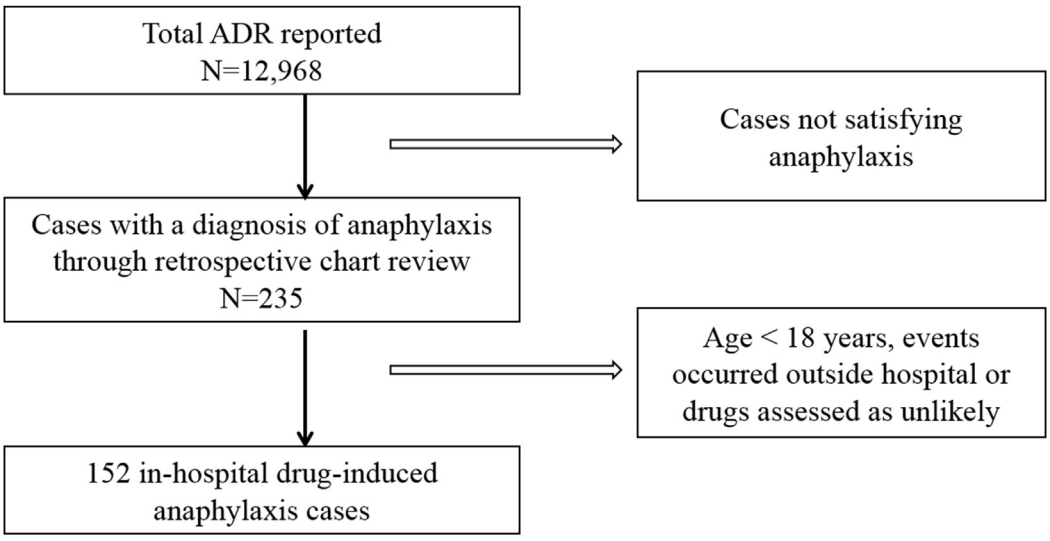

Fig. 1. Flowchart of case selection.

Table 1
Demographics of total patients with anaphylaxis and risk of anaphylactic shock.

	Total number (N = 152)	Anaphylaxis		
		Without shock (N = 50)	With shock (N = 102)	*P*-value[§]
Age (y)				0.013
Age < 50	34 (22.4)	16 (32)	18 (17.6)	
50 ≤ age < 60	44 (28.9)	14 (28)	30 (29.4)	
60 ≤ age < 70	44 (28.9)	16 (32)	28 (27.5)	
70 ≤ age	30 (19.7)	4 (8)	26 (25.5)	
Male/female				0.607
Men	71 (46.7)	25 (50)	46 (45.1)	
Female	81 (53.3)	25 (50)	56 (54.9)	
Causative drugs				
Platinum compound	48 (31.6)	24 (48)	24 (23.5)	0.002
Iodinated contrast media	46 (30.3)	4 (8)	42 (41.2)	<0.001
Aminosteroid NMBA	13 (8.6)	1 (2)	12 (11.8)	0.061
Co-morbidity				
Airway disease[†]	8 (5.3)	4 (8)	4 (3.9)	0.440
Ischemic heart disease	14 (9.2)	3 (6)	11 (10.8)	0.551
Hypertension	24 (15.8)	5 (10)	19 (18.6)	0.237
Diabetes	34 (22.4)	8 (16)	26 (25.5)	0.218
Viral hepatitis	15 (9.9)	2 (4)	13 (12.7)	0.145
Co-medication				
Statin	11 (7.2)	2 (4)	9 (8.8)	0.341
Beta-blocker	12 (7.9)	3 (6)	9 (8.8)	0.752
ACE inhibitor	3 (2.0)	2 (4)	1 (1.0)	0.252
ARBs	10 (6.6)	1 (2)	9 (8.8)	0.167
Diuretics	7 (4.6)	1 (2)	6 (5.9)	0.427
CCB	17 (11.2)	4 (8)	13 (12.7)	0.585
Aspirin, NSAID	15 (9.9)	2 (4)	13 (12.7)	0.145
PPI	9 (5.9)	3 (6)	6 (5.9)	1.000
Route of administration				0.440
Intravenous	144 (94.7)	46 (92)	98 (96.1)	
Oral	4 (2.6)	3 (6)	1 (1.0)	
Others[‡]	4 (2.6)	1 (2)	3 (2.9)	
Patients location				1.000
Inpatients	87 (57.2)	29 (58)	58 (56.9)	
Outpatients	65 (42.8)	21 (42)	44 (43.1)	

Results are n (% within group).
NMBA, neuromuscular blocking agents; ARBs, angiotensin receptor blocking agents; CCB, calcium channel blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
[†] Asthma and COPD.
[‡] Subcutaneous, intra ocular, intra articular.
[§] The univariate analysis between anaphylaxis with shock and anaphylaxis without shock by Pearson's chi-square test.

cephalosporin, or rocuronium was relatively lower in patients older than 60 (Table 3a,b).

Major clinical manifestations of anaphylaxis

Of the 152 patients subjected to this retrospective analysis, 82.2%, 75.0%, and 71.1% experienced signs and symptoms of cutaneous, respiratory, and cardiovascular system, respectively. In addition, 19.1% of the patients experienced gastrointestinal reactions.

The use of platinum compounds was predominantly associated with respiratory and gastrointestinal events but less associated with cardiovascular events (Fig. 2). The use of penicillin derivatives and cephalosporin showed similar patterns to those of platinum

Table 2
Causative drugs and causality assessment.

	Number of anaphylaxis (with shock)	Certain/probable/possible
Total patients	152 (102)	52/91/9
Chemotherapeutic agent	64 (32)	15/47/2
Platinum compound	48 (24)	14/33/1
Taxane	6 (2)	0/5/1
Monoclonal antibody	4 (3)	0/4/0
L-asparaginase	2 (1)	0/2/0
Etoposide	2 (0)	1/1/0
Antithymocyte globulin	2 (2)	0/2/0
Radiocontrast media	49 (43)	22/26/2
Iopromide	20 (18)	11/9/0
Iopamidol	8 (7)	3/4/1
Iomeprol	6 (6)	2/4/0
Iodixanol	2 (2)	1/1/0
Ioditridol	2 (2)	1/1/0
Gadolinium	3 (2)	2/1/0
Unknown (iodinated)	8 (6)	1/6/1
Antibiotics	13 (8)	4/8/1
Penicillin	6 (5)	0/6/0
Cephalosporin	5 (2)	3/1/1
Others	2 (1)	1/1/0
Neuromuscular blocking agent	14 (13)	8/3/3
Rocuronium	12 (11)	8/2/2
Others	2 (2)	0/1/1
NSAID	1 (0)	1/0/0
Others	11 (6)	2/8/1

NSAID, nonsteroidal anti-inflammatory drugs.

Table 3a
The incidence per causal drug user of anaphylaxis and anaphylactic shock.

	Total patients of drug use (N)	Anaphylaxis (N)	Anaphylactic shock (N)	Anaphylaxis rate†	Anaphylactic shock rate†
Platinum compound	16,536	47	23	2.84	1.39
Iodinated contrast media	126,133	34	32	0.27	0.25
Aminosteroid‡	88,875	12	11	0.14	0.12
Penicillin derivatives and cephalosporin, IV use	117,778	9	6	0.08	0.05

IV, intravenous.
† Rate per 1000 patients use.
‡ Rocuronium and vecuronium.

Table 3b
The incidence of anaphylaxis and anaphylactic shock per causal drug user. The incidence according to sex and age.

	Men	Women	Age < 50	50 ≤ Age < 60	60 ≤ Age < 70	70 ≤ Age
Platinum compound						
Anaphylaxis	2.70	3.07	3.89	3.61	3.64	1.64
Anaphylactic shock	1.40	1.38	1.30	1.20	1.62	1.34
Penicillin derivatives and cephalosporin, IV use						
Anaphylaxis	0.03	0.12	0.18	0.10	0.04	0.04
Anaphylactic shock	0.02	0.08	0.09	0.10	0.00	0.04
Iodinated contrast media						
Anaphylaxis	0.21	0.33	0.22	0.24	0.38	0.23
Anaphylactic shock	0.21	0.30	0.17	0.24	0.38	0.23
Aminosteroid (rocuronium and vecuronium)						
Anaphylaxis	0.13	0.14	0.26	0.25	0.05	0.04
Anaphylactic shock	0.10	0.14	0.21	0.25	0.05	0.04

Results are rate per 1000 patients use. IV, intravenous.

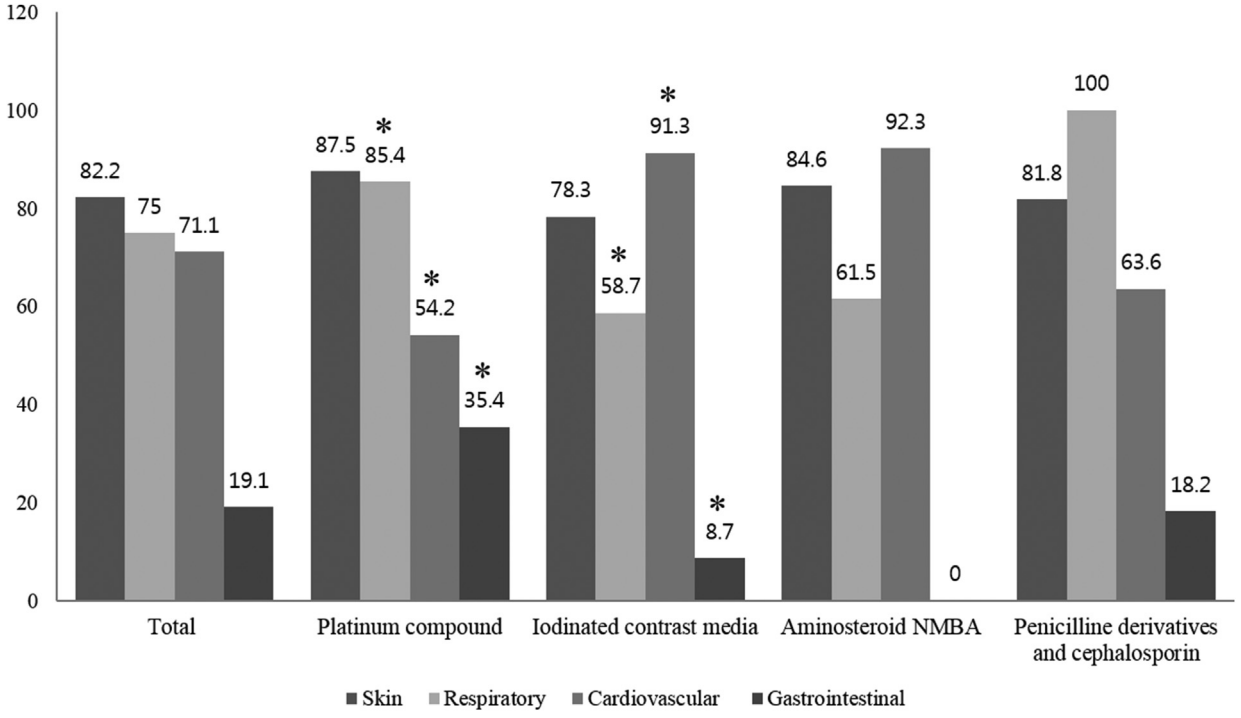

Fig. 2. Symptoms and signs of drug anaphylaxis. $^{*}p < 0.05$ compare with total patients. NMBA, neuromuscular blocking agent.

compounds. In contrast, the application of iodinated contrast media was accompanied by cardiovascular events and less associated with respiratory and gastrointestinal events; the adverse events associated with the use of aminosteroid NMBA showed a similar pattern to those shown by iodinated contrast media.

Risk factors and prognosis of anaphylactic shock

Anaphylactic shock was observed in 102 cases. The use of iodinated contrast media and NMBA was associated with significant increase of risk of hypotension. The incidence of anaphylactic

shock tended to increase with the increase in age; particularly, in patients aged 70 years or older.

Multivariate analysis identified the age (≥70 years; Odd's ratio (OR), 5.86; 95% confidence interval (CI), 1.70–20.14), and the use of iodinated contrast media (OR, 6.19; 95% CI, 1.87–20.53) and aminosteroid NMBA (OR, 12.82; 95% CI, 1.50–109.92) as risk factors for anaphylactic shock (Table 4).

Cardiopulmonary arrest occurred in a total of 5 cases (2 cases of anticancer drug use, 1 case of gadolinium contrast media use, and 1 case each of antibiotic and NMBA use). One case related with gadolinium contrast media resulted in death despite cardiorespiratory resuscitation.

Discussion

This study analyzed the in-hospital drug-induced anaphylaxis based on reports filed at the pharmacovigilance center in the hospital. The drug profile causing anaphylaxis was different from those observed in previous population based studies. Most previous studies have reported antibiotics as the most common causative drug of drug-induced anaphylaxis, particularly, beta-lactam antibiotics which were frequently identified as the most common causative drug.[11,15,16] Other studies have also identified the usage of NSAID, radiocontrast media, and NMBA as a common cause of anaphylaxis.[17–19] The current study showed different profiles of causative drugs and it identified anticancer drugs to be the most common culprit agents of drug-induced anaphylaxis, followed by contrast media, with antibiotics and NSAIDs being reported in a relatively lower frequency. This difference in causative drugs was speculated to be a reflection of the difference in in-hospital drug use patterns of tertiary medical centers, where the use of anticancer drugs and contrast media was frequent compared to other primary or secondary referral medical institutions.

In a previous study performed in the same institute between 2000 and 2006, 14 cases of anaphylaxis were reported for each 100,000 people-year and drug was the most common cause of anaphylaxis (35.3%); the most common causative drugs were contrast media and followed by NSAIDs and antibiotics.[20] Considering that the previous analyses include cases which had been induced by medications purchased or prescribed outside hospital, the results was no match for the current study. In the current study, anticancer drugs, such as oxaliplatin, emerged as the major type of drug causing in-hospital anaphylaxis and there was an actual increase in patients receiving anticancer treatments for recent decades.

In the majority of the previously epidemiologic studies, incidences of drug-induced anaphylaxis were limited to individual drugs; in this study, we attempted a comparison of the incidence of major causative drugs. The incidence of drug-induced anaphylaxis is very rare but it showed differences depending on the type of causative drug; among these, platinum compounds showed the highest incidence rate of anaphylaxis compared to other drugs. Oxaliplatin is well known for its common hypersensitivity reaction developing in 5–25% of patients treated with[21–23]; in fact, a number of studies have reported the incidence of platinum compound-induced anaphylaxis to be higher than that caused by beta-lactam antibiotics.[22,24–26]

A large number of previous epidemiological studies have focused on penicillin-induced anaphylaxis; these have indicated an incidence and fatality rate of 0.1–0.5 cases per 1000 individuals, and 1 case per 50,000–100,000 individuals, respectively.[8,27] The incidence of penicillin derivative and cephalosporin, iodinated radiocontrast media, and NMBA-induced anaphylaxis were also reported to be approximately 0.1–0.3 cases per 1000 individuals. However, a direct comparison between drugs was difficult as the incidence for each drug was separately investigated. In this study, the incidence of anaphylaxis and anaphylactic shock induced by penicillin derivatives and cephalosporin antibiotic usage was determined to be 0.08 and 0.05 cases per 1000 individuals, respectively, which was much lower than that observed in previous reports. This might partially be attributed to the reduced usage of potential culprit drugs based on a thorough investigation of the medical history and routine performance of skin test before use of penicillin derivatives and cephalosporins by the institutional policy; intradermal test with penicillin and cephalosporins in concentrations of 10,000 U/mL and 300 μg/mL, respectively. The retrospective nature of the study seems not to affect the reliance of the result because the incidence of iodinated contrast media related anaphylaxis was not significantly different from those of previous studies, where severe and immediate hypersensitivity reactions occurred in approximately 0.02–0.04% of the patients as a result of non-ionic contrast media administration.[28,29]

A number of previous studies have reported the higher incidence of drug-induced anaphylaxis in females[8,13,30] and the results of this study also showed the higher incidence of four major drug categories related anaphylaxis in female.

Medication use is different according to ages. Polypharmacy is very common in the elderly and this may partly contribute to the increase in the absolute number of drug-induced anaphylaxis in the elderly.[31] On the contrary, the results of this study revealed the incidence of anaphylaxis and anaphylactic shock per drug use was not higher in elderly patients; this result may be associated with a reduced atopic tendency in the elderly.

This study evaluate the risk factors of anaphylactic shock among patients with anaphylaxis and determined the age (70 years or older) and the use of causative drugs (iodinated radiocontrast media and NMBA), to be significant risk factors of anaphylactic shock. Previous studies have reported older age to be a risk factor related to severe anaphylaxis; infants, pregnancy, and adolescent age were also reported to be risk factors that increased the severity of anaphylaxis.[1,32,33] This study targeted adults 18 years or older; therefore, this study included no information on infants and youths. However, the increase in age in adults resulted in a corresponding increase in the severity of anaphylaxis, with the risk increasing greatly in patients who were 70 years or older. Although the incidence of anaphylaxis did not increase with age, the severity of anaphylactic reactions was higher in elderly patients. Comorbidities such as diabetes, hypertension and other cardiovascular disease and the use of related medication might contribute to the progression of anaphylaxis to shock or cardiac arrest.

Among the causative drugs, the use of iodinated contrast media and NMBA were found to increase the risk of anaphylactic shock. Although this could be attributed to the nature of the drugs

Table 4
Multivariate logistic regression analysis: risk factors of anaphylactic shock.

	Odd ratio (95% CI)	*P* value
Age		
Age ≥70 year	5.86 (1.70–20.14)	0.005
Sex (male)	0.99 (0.44–2.23)	0.972
Causative drug		
Platinum compound	0.73 (0.30–1.77)	0.486
Iodinated contrast media	6.19 (1.87–20.53)	0.003
NMBA	12.82 (1.50–109.92)	0.020
Co-morbidity		
Viral hepatitis	3.48 (0.63–19.18)	0.152
Co-medication		
Angiotensin receptor blocker	1.27 (0.13–12.87)	0.838
Aspirin, NSAID	1.45 (0.24–8.62)	0.686

NMBA, neuromuscular blocking agents; NSAID, nonsteroidal anti-inflammatory drugs.

themselves, the infusion rate could be considered as a contributing factor. Drugs such as iodinated contrast media and NMBA are usually administered as intravenous bolus while most anticancer drugs are slowly injected for dozens of minutes to several hours via dilution in normal saline or dextrose solution. These differences in drug use patterns might be considered to affect the risk of anaphylactic shock. Although previous reports have correlated the route of administration of drugs to the severity of anaphylaxis, no significant such difference based on the route of administration was observed in this study because a majority of the drugs were administered via injected. In addition, some reports have indicated accompanying diseases, such as lung (asthma or COPD) and cardiac diseases, and mast cell disorder, and the drugs, such as beta-blockers, ACE inhibitors, and proton pump inhibitors, to be risk factors of severe anaphylaxis.[1,32,33] This study evaluated hypertension, diabetes, viral hepatitis, aspirin/NSAID, and angiotensin receptor blockers as accompanying diseases and drugs increasing the risk of anaphylactic shock. However, these differences were not statistically significant.

This study has some limitations. First, this study was based on the spontaneous reports made by medical staff and active surveillance for anaphylaxis based on the ICD-10, the incidence of drug-related anaphylaxis might have been rather underestimated than overrated. Second, symptoms related with NMBA-induced anaphylaxis could be underestimated since patients were unable to communicate under general anesthesia. In order to overcome these limitations and estimate more accurate incidence of drug related anaphylaxis, a large scale prospective study is needed.

In conclusion, this study revealed the recent status of in-hospital drug-induced anaphylaxis and identified anticancer drugs and contrast media to be the most common causative agents in a tertiary medical center. In addition, contrast media administration, neuromuscular blocking agent usage, and older age were identified as major risk factors of anaphylactic shock. Therefore, the vulnerable group with risk factors should be subjected to active drug monitoring and sufficient preventive measures.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HKP and HRK designed the study and wrote the manuscript. MGK performed the statistical analysis and interpretation of the results. MSY, JWJ and SHC contributed to data collection and revised the manuscript.

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