Allergology International 72 (2023) 580–587

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original Article

Analysis of drug-induced anaphylaxis cases using the Japanese Adverse Drug Event Report (JADER) database – secondary publication☆

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ARTICLE INFO

Article history:
Received 28 February 2023
Accepted 6 March 2023
Available online 12 April 2023

Keywords:
Adverse reaction
Anaphylaxis
Drug hypersensitivity
Epidemiology
Fatal anaphylaxis

Abbreviations:

AN	anaphylaxis
JADER	Japanese Adverse Drug Event Report database
PMDA	Pharmaceuticals and Medical Devices Agency

ABSTRACT

Background: The epidemiology of drug-induced anaphylaxis using the Japanese nationwide database has been not reported, even though drugs are a common trigger of anaphylaxis. The aim of this study was to describe the epidemiological profile of cases of drug-induced anaphylaxis, including fatal cases, using the data from the Japanese Adverse Drug Event Report database (JADER).

Methods: We extracted data regarding drug-related adverse events, between April 2004 and February 2018, published in JADER by the Pharmaceuticals and Medical Devices Agency. We analyzed cases of anaphylaxis occurring between January 2005 and December 2017. The drug classification was based on the Japanese Standard Commodity Classification.

Results: There were 16,916 cases of anaphylaxis reported during the study period. Among them, 418 fatalities were registered. The incidence of drug-induced anaphylaxis and fatal cases was 1.03 cases/year per 100,000 population and 0.03 cases/year, respectively. The most frequent causes of anaphylaxis were diagnostic agents, including X-ray contrast media (20.3%), and biological preparations, such as human blood preparations (20.1%). In fatal cases, diagnostic agents (28.7%) and antibiotic preparations (23.9%) were the most commonly associated types of drugs.

Conclusions: The frequency of drug-induced anaphylaxis and fatalities in Japan remained unchanged over the 13-year period analyzed in this study. Diagnostic agents and biological preparations were the most frequent causes of anaphylaxis; however, fatalities were most frequently caused by either diagnostic agents or antibiotic preparations.

Introduction

Anaphylaxis (AN) is defined as a hypersensitivity reaction that causes systemic allergic symptoms in multiple organs due to the invasion of allergens and can be life-threatening.[1] A situation in which AN is accompanied by a drop in blood pressure and impaired consciousness is defined as an anaphylactic shock.[1] The prevalence of AN shows an increasing trend,[2] and the global lifetime prevalence of AN is estimated to be 0.3%–5.1%, although the frequency of AN occurrence varies depending on the definition of AN, survey method, and region.[3–7] The percentage of school children in Japan with a history of AN is reportedly 0.6% in elementary school, 0.4% in junior high school, and 0.3% in high school.[8]

Foods, drugs, insect stings, and exercise have all been identified as triggers of AN.[9] Surveys of the prevalence of AN in countries other than Japan have identified drugs as a major trigger of AN.[2] In a study covering 10 European countries, 4.8% of pediatric and 22.4% of adult AN cases were caused by drugs.[10] Elsewhere, 6% of AN cases in the US[11] and 35.3% of cases in South Korea[12] are reportedly drug-induced AN. In Japan, according to the Vital Statistics collected by the Ministry of Health, Labour and Welfare, drugs were the primary cause in 323 out of 768 fatal cases (42.1%) due to anaphylactic shock reported in the 13 years from 2001 to 2013 and, therefore, the most common trigger.[8] However, little is known about changes in

☆ This article is a secondary publication of "Analysis of drug-induced anaphylaxis cases using the Japanese Adverse Drug Event Report (JADER) database" published in Arerugi [Jpn J Allergol] 2022; 71:231–241 (in Japanese).

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2023.03.006

incidence rates or details of drug classification associated with drug-induced AN in Japan, and clinical and epidemiological data from these cases remain elusive.

In Japan, drug manufacturers and medical institutions are obliged by the Pharmaceutical Affairs Law to report to the Ministry of Health, Labour and Welfare all cases suspected of being affected by side effects of drugs. The Pharmaceuticals and Medical Devices Agency (PMDA) is a public institution that handles relief for health injuries caused by drug side effects and infections through biological preparations, reviews the approval of drugs and medical devices, is responsible for the postmarketing safety information of drugs and medical devices, and serves as a contact point for reporting side effects caused by drugs. Patients can directly report such side effects to the PMDA. Information on drug side effects reported to the PMDA is published online in the Japanese Adverse Drug Event Report (JADER) database (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html).

In the current study, we aimed to analyze cases with suspected drug-induced AN based on the data published in the JADER and elucidate the actual situation of drug-induced AN in Japan.

Methods

Data extraction

In June 2018, we downloaded data on side effects that had been reported to the PMDA and published online in the JADER database. The data included sex, age, drug name (non-proprietary and trade names), route of administration, adverse event, outcome, date of occurrence of side effect/adverse event, and timing of reporting, with age being reported in 10-year categories. Reported AN cases included cases of suspected side effects of a drug; therefore, the causal relationship is unclear.

Analysis cases

Of the cases with suspected drug side effects reported to the PMDA between April 1, 2004, and February 28, 2018, we included those for which the adverse event was anaphylactic reactions (i.e., anaphylactic shock, AN-like shock, anaphylactic reaction, AN-like reaction, anaphylactic transfusion reaction). The analyzed cases were limited to those for which the event occurred between January 1, 2005 and December 31, 2017, to allow the comparison of annual incidence rates. Cases with missing data on sex, age, drug classification, and outcome were excluded from the analysis.

Analysis method

We analyzed the data set in terms of the frequency of fatal cases, year-on-year changes in the number of cases, age/sex distribution of cases, number of incidences according to the drug classification, number of incidences according to the drug classification, and route of administration. Year-on-year changes in the number of cases were analyzed based on the time of disease onset. The frequency of AN cases was calculated per population of 100,000 people, with the population being based on the confirmed figure published in the Vital Statistics by the Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/toukei/list/81-1.html). The drug classification followed the Standard Commodity Classification for Japan, with the exception that antibiotic preparations were categorized based on the List of Antimicrobial Drug Abbreviations of the Japanese Society of Chemotherapy (https://www.chemotherapy.or.jp/uploads/files/publications/glossary_jjs_ryakugo.pdf). Drug names were those with more than 100 AN cases and more than 5 fatal cases were reported for a single drug. Patients aged $\leq$19 years were defined as pediatric cases, whereas those $\geq$20 years were defined as adult cases.

Ethical considerations

This study was planned in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the study design was approved by the ethics committee of Sagamihara National Hospital (Approval No. 151004, dated October 22, 2015). As the data used for this study contained no personal information, it was not necessary to obtain informed consent from the study subjects. We notified the PMDA about the use of their data and that the information obtained by our analysis will be published.

Results

Analysis cases

Of the 513,764 cases with suspected side effects of drugs, 20,525 cases (4.0%) involved AN reactions as the adverse event. We analyzed a total of 16,916 cases, excluding 2430 cases for which data on sex, age, outcome, or drug classification were missing and 1179 cases that were reported outside of the analysis timeframe, from 2005 to 2017 (Fig. 1). Of the analyzed cases, 418 were fatalities (2.5%).

The male-to-female ratio was 1.03:1 for all AN cases and 1.68:1 for cases resulting in fatal cases. Regarding the age classification, 1784 cases (10.5%) were pediatric and 15,132 cases (89.5%) were adult. In terms of adult age groups by decade, cases of patients in their 60s were the most common, with 3799 cases (22.5%), followed by those in their 70s, 3557 cases (21.0%), and 50s, 2318 cases (13.7%). The 418 fatal cases comprised 9 pediatric (2.2%) and 409 adult (97.8%) cases. In terms of age group, fatal cases were found most frequently in patients in their 70s, with 132 cases (31.6%), followed by those in their 60s, 106 cases (25.4%), and 80s, 82 cases (19.6%).

Changes in AN and fatal an cases over time

Between 2005 and 2017, the number of cases with AN varied between 1154 and 1423 cases/year, with an increasing trend between 2005 and 2011, and a decreasing trend thereafter, except for 2015. In the same period, the number of fatal cases varied between 19 and 49 cases/year, and the ratio of fatal cases to AN cases by year varied between 1.6% and 3.8%.

The frequency of AN cases per population of 100,000 varied between 0.91 and 1.13 cases/year (on average, 1.03 cases/year; Fig. 2). From 2005 to 2011, there was a trend toward increases in AN cases per 100,000 people, with the figure in 2011 being 1.2 times higher than that in 2005. Except for 2015, this figure tended to decrease afterward, and by 2017, the frequency was similar to that in 2005. The frequency of fatal cases per population of 100,000 varied between 0.02 and 0.04 cases/year (on average, 0.03 cases/year). Apart from 2013, this frequency varied between 0.02 and 0.03 cases/year for the period from 2005 to 2017. The figure in 2013 was 0.04 cases/year, which was 1.3-fold higher than that in 2005.

Numbers of AN incidences and mortality rates by drug classification

Drug-induced AN was caused by diagnostic agents including X-ray contrast agents, 3428 cases (20.3%), followed by biological preparations including human blood preparations, 3405 cases (20.1%); antineoplastic agents, 2147 cases (12.7%); antibiotic preparations, 2103 cases (12.4%); and other agents affecting metabolism including antidotes, 1241 cases (7.3%) (Table 1). In adults, drug-

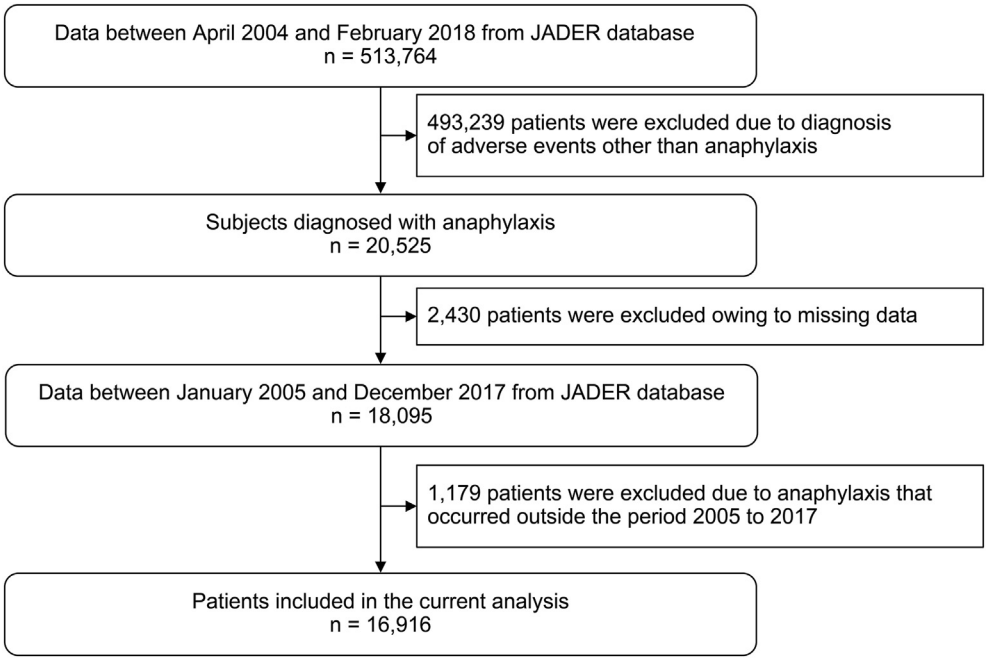

Fig. 1. Flow diagram of this study.

induced AN was caused by: diagnostic agents, 3361 cases (22.2%); biological preparations, 2663 cases (17.6%); antineoplastic agents, 2067 cases (13.7%); antibiotic preparations, 1838 cases (12.1%); and other agents affecting metabolism, 1164 cases (7.7%). In children, drug-induced AN was caused by: biological preparations, 742 cases (41.6%); antibiotic preparations, 265 cases (14.9%); chemotherapeutics, 130 cases (7.3%); agents affecting the central nervous system including anesthetics, 99 cases (5.5%); and antineoplastic agents, 80 cases (4.5%).

Death was caused by diagnostic agents, 120 cases (28.7%), followed by antibiotic preparations, 100 cases (23.9%); and antineoplastic agents, 50 cases (12.0%). In adults, death was caused by: diagnostic agents, 118 cases (28.9%); antibiotic preparations, 98 cases (24.0%); antineoplastic agents, 50 cases (12.2%); biological preparations, 34 cases (8.3%); and other agents affecting metabolism, 29 cases (7.1%). The breakdown of the nine pediatric cases revealed that two cases each were related to diagnostic agents, biological preparations, antibiotic preparations, and agents affecting digestive organs, whereas one case was related to chemotherapeutics.

The mortality rate by drug classification was highest for antibiotic preparations, accounting for 4.8% of fatal cases (100/2103 cases), followed by diagnostic agents, 3.5% (120/3428 cases); agents affecting the peripheral nervous system, 3.2% (17/526 cases); agents affecting the central nervous system, 2.4% (20/834 cases);

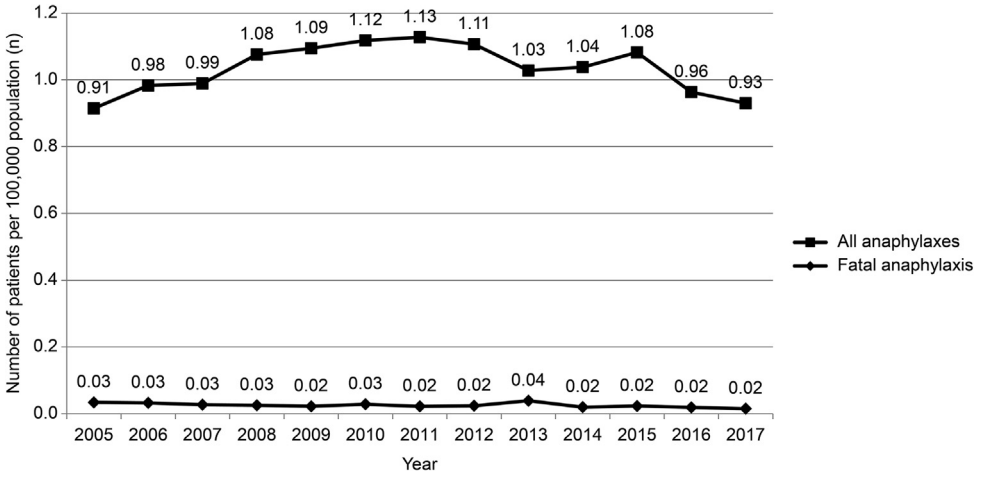

Fig. 2. Time trends for the occurrence of anaphylaxis and anaphylaxis-related fatal cases from 2005 to 2017. All data are presented as cases per 100,000 people. All anaphylaxis cases include both anaphylaxis cases (black boxes) and anaphylaxis-related fatalities (black triangles).

Table 1
Frequency of anaphylaxis based on drug classification.

Number of patients (n)	All anaphylaxis			Fatal anaphylaxis			% of fatal anaphylaxis[†]
	Overall	<20 years	≤20 years	Overall	<20 years	≤20 years	
	16,916	1784	15,132	418	9	409	2.5%
Classification							
1. Diagnostic agents (except extracorporeal diagnostic medicines)	3428 (20.3%)	67 (3.8%)	3361 (22.2%)	120 (28.7%)	2 (22.2%)	118 (28.9%)	3.5%
X-ray contrast agents	2994	44	2950	112	2	110	
Other diagnostic agents (except extracorporeal diagnostic medicines)	404	20	384	7	0	7	
Reagents for various function tests	30	3	27	1	0	1	
2. Biological preparations	3405 (20.1%)	742 (41.6%)	2663 (17.6%)	36 (8.6%)	2 (22.2%)	34 (8.3%)	1.1%
Human blood preparations	2660	279	2381	31	0	31	
Vaccines	559	385	174	3	1	2	
Other biological preparations	120	25	95	1	0	1	
Mixed biological preparations	53	51	2	1	1	0	
Antitoxins and anti-leptospiral sera	7	1	6	0	0	0	
Toxins and toxoids	6	1	5	0	0	0	
3. Antineoplastic agents	2147 (12.7%)	80 (4.5%)	2067 (13.7%)	50 (12.0%)	0 (0%)	50 (12.2%)	2.3%
Other antitumor agents	1486	74	1412	25	0	25	
Antineoplastic preparations extracted from plants	543	4	539	22	0	22	
Antitumor antibiotics and preparations	55	1	54	1	0	1	
Antimetabolic agents	37	0	37	2	0	2	
Alkylating agents	26	1	25	0	0	0	
4. Antibiotic preparations	2103 (12.4%)	265 (14.9%)	1838 (12.1%)	100 (23.9%)	2 (22.2%)	98 (24.0%)	4.8%
β-Lactams (cephems)	1416	181	1235	68	0	68	
β-Lactams (penicillins)	294	28	266	20	1	19	
β-Lactams (carbapenems)	67	4	63	6	0	6	
Macrolides	60	10	50	1	0	1	
Glycopeptides	51	5	46	2	1	1	
Antifungal agents	49	7	42	0	0	0	
β-Lactams (oxacephems)	42	9	33	0	0	0	
Lincomycines	14	3	11	0	0	0	
Lipopeptides	11	2	9	1	0	1	
Other antibiotic preparations	99	16	83	2	0	2	
5. Other agents affecting metabolism	1241 (7.3%)	77 (4.3%)	1164 (7.7%)	29 (6.9%)	0 (0%)	29 (7.1%)	2.3%
Agents affecting metabolism (NEC)	854	10	844	28	0	28	
Antidotes	317	40	277	1	0	1	
Enzyme preparations	54	27	27	0	0	0	
Antidiabetic agents	8	0	8	0	0	0	
Agents for treatment of gout	4	0	4	0	0	0	
Agents for habitual intoxication	3	0	3	0	0	0	
Agents for liver disease	1	0	1	0	0	0	
6. Chemotherapeutics	849 (5.0%)	130 (7.3%)	719 (4.8%)	11 (2.6%)	1 (11.1%)	10 (2.4%)	1.3%
Synthetic antibacterial agents	697	80	617	8	1	7	
Antiviral agents	116	45	71	3	0	3	
Other chemotherapeutics	30	5	25	0	0	0	
Anti-tuberculosis agents	5	0	5	0	0	0	
Sulfonamide preparations	1	0	1	0	0	0	
7. Agents affecting central nervous system	834 (4.9%)	99 (5.5%)	735 (4.9%)	20 (4.8%)	0 (0%)	20 (4.9%)	2.4%
8. Agents affecting peripheral nervous system	526 (3.1%)	53 (3.0%)	473 (3.1%)	17 (4.1%)	0 (0%)	17 (4.2%)	3.2%
9. Agents affecting digestive organs	392 (2.3%)	38 (2.1%)	354 (2.3%)	3 (0.7%)	2 (22.2%)	1 (0.2%)	0.8%
10. Hormone preparations (including antihormone preparations)	305 (1.8%)	53 (3.0%)	252 (1.7%)	5 (1.2%)	0 (0%)	5 (1.2%)	1.6%
11. Agents relating to blood and body fluids	262 (1.5%)	19 (1.1%)	243 (1.6%)	5 (1.2%)	0 (0%)	5 (1.2%)	1.9%
12. Agents affecting sensory organs	240 (1.4%)	16 (0.9%)	224 (1.5%)	2 (0.5%)	0 (0%)	2 (0.5%)	0.8%
13. Antiallergic agents	208 (1.2%)	41 (2.3%)	167 (1.1%)	2 (0.5%)	0 (0%)	2 (0.5%)	1.0%
14. Agents affecting respiratory organs	189 (1.1%)	47 (2.6%)	142 (0.9%)	0 (0%)	0 (0%)	0 (0%)	N.A.
15. Other	787 (4.7%)	57 (3.2%)	730 (4.8%)	18 (2.0%)	0 (0%)	18 (4.4%)	2.3%

Classifications that account for 5.0% or more are shown in detail; classifications that account for 1.0% or less are defined as “other”; N.A., not applicable; NEC, not elsewhere classified.

[†] % of fatal anaphylaxis: percentage of fatal anaphylaxis cases in all anaphylaxis cases, by drug classification.

antineoplastic agents, 2.3% (50/2147 cases); and other agents affecting metabolism, 2.3% (29/1241 cases).

Number of AN incidences by drug name

The number of AN incidences by drug classification is shown in Table 2. In the case of diagnostic agents including X-ray contrast agents, iopamidol was associated with 1275 cases (37.2%), iohexol with 866 cases (25.3%), iomeprol with 543 cases (15.8%), and ioversol with 137 cases (4.0%); altogether, iodine-based nonionic contrast agents accounted for 82.3% of this drug classification. Of the AN cases caused by biological preparations including human blood preparations, platelet concentrate was associated with 1136 cases (33.4%), washed red cells with 670 cases (19.7%), and fresh frozen human plasma with 604 cases (17.7%). Thus, blood preparations for transfusion were responsible for 70.8% of this drug classification. Among the antineoplastic agents, the platinum agent oxaliplatin was associated with 778 cases (36.2%), followed by the taxane drug paclitaxel with 311 cases (14.5%). With regard to antibiotic preparations, ceftriaxone sodium hydrate was associated with 430 cases (20.4%), followed by cefoperazone sodium/sulbactam sodium with 256 cases (12.2%) and cefazolin sodium with 237 cases (11.3%); altogether, the three most common cephem antibiotics accounted for 43.9% of this drug classification.

With regard to the other drug classifications, the agent affecting metabolism nafamostat mesylate was associated with 660 cases (53.2%), followed by the chemotherapeutic levofloxacin hydrate with 349 cases (41.4%), general cold medicines (acting as central nervous system drugs) with 109 cases (13.1%), the agent affecting the peripheral nervous system rocuronium bromide with 279 cases (53.0%), and, as an agent affecting sensory organs, the ophthalmological agent moxifloxacin hydrochloride with 143 cases (59.6%).

Table 3 shows the frequency of fatal AN cases by drug name. The most frequent drug name for each drug classification was the diagnostic agent iopamidol associated with 56 cases (46.7%), the antibiotic preparation cefoperazone sodium/sulbactam sodium with 27 cases (27.0%), the antineoplastic agent paclitaxel with 17 cases (34.0%), the biological preparation platelet concentrate with 9 cases (25.0%), the agent affecting metabolism nafamostat mesylate with 23 cases (79.3%), the agent affecting the central nervous system diclofenac sodium with 7 cases (35.0%), and the agent affecting the peripheral nervous system scopolamine butylbromide with 8 cases (47.1%).

Route of administration

Table 4 shows the number of AN incidences with respect to the route of administration. In 11,426 cases, drugs were administered intravenously, representing 67.5% of all cases. Drugs were administered orally in 2884 cases (17.0%). Similarly, among fatal cases, intravenous administration was most common, with 310 cases (74.2%), followed by oral administration, with 24 cases (5.7%).

The ratio of fatal to non-fatal cases of AN was highest for intracoronary drug administration (9.3%), followed by rectal (8.0%) and intraarterial (7.1%) administration. The ratio of fatal to non-fatal cases of AN was 2.7% in the intravenous administration group,

Table 2
Frequency of anaphylaxis by drug name.

1. Diagnostic agents (except extracorporeal diagnostic medicines)	
Total	3428
Iopamidol	1275 (37.2%)
Iohexol	866 (25.3%)
Iomeprol	543 (15.8%)
Ioversol	137 (4.0%)
Gadoteridol	132 (3.9%)
2. Biological preparations	
Total	3405
Platelet concentrate	1136 (33.4%)
Washed red cells	670 (19.7%)
Fresh-frozen human plasma	604 (17.7%)
Influenza HA vaccine	202 (5.9%)
3. Antineoplastic agents	
Total	2147
Oxaliplatin	778 (36.2%)
Paclitaxel	311 (14.5%)
Carboplatin	196 (9.1%)
Docetaxel hydrate	171 (8.0%)
Cisplatin	162 (7.5%)
4. Antibiotic preparations	
Total	2103
Ceftriaxone sodium hydrate	430 (20.4%)
Cefoperazone sodium and sulbactam sodium	256 (12.2%)
Cefazolin sodium	237 (11.3%)
Piperacillin sodium	105 (5.0%)
Cefaclor	100 (4.8%)
5. Other agents affecting metabolism	
Total	1241
Nafamostat mesylate	660 (53.2%)
Sugammadex sodium	288 (23.2%)
6. Chemotherapeutics	
Total	849
Levofloxacin hydrate	349 (41.1%)
Garenoxacin mesylate hydrate	200 (23.6%)
7. Agents affecting central nervous system	
Total	834
General cold remedies (non-prescription medicine)	109 (13.1%)
Loxoprofen sodium hydrate	104 (12.5%)
8. Agents affecting peripheral nervous system	
Total	526
Rocuronium bromide	279 (53.0%)
9. Agents affecting sensory organs	
Total	240
Moxifloxacin hydrochloride	143 (59.6%)

Drugs that accounted for more than 100 cases are shown.

Table 3
Frequency of fatal anaphylaxis by drug name.

1. Diagnostic agents (except extracorporeal diagnostic medicines)	
Total	120
Iopamidol	56 (46.7%)
Iohexol	31 (25.8%)
Iomeprol	14 (11.7%)
2. Antibiotic preparations	
Total	100
Cefoperazone sodium and sulbactam sodium	27 (27.0%)
Ceftriaxone sodium hydrate	21 (21.0%)
Ampicillin sodium and sulbactam sodium	8 (8.0%)
Piperacillin sodium	7 (7.0%)
Piperacillin sodium and tazobactam sodium	5 (5.0%)
3. Antineoplastic agents	
Total	50
Paclitaxel	17 (34.0%)
Oxaliplatin	8 (16.0%)
Cisplatin	6 (12.0%)
4. Biological preparations	
Total	36
Platelet concentrate	9 (25.0%)
5. Other agents affecting metabolism	
Total	29
Nafamostat mesylate	23 (79.3%)
6. Agents affecting central nervous system	
Total	20
Diclofenac sodium	7 (35.0%)
7. Agents affecting peripheral nervous system	
Total	17
Scopolamine butylbromide	8 (47.1%)
8. Chemotherapeutics	
Total	13

Drugs that accounted for more than 5 cases are shown.

Table 4
Frequency of fatal anaphylaxis by drug administration route.

Administration route	All anaphylaxes n = 16,916	Fatal anaphylaxis n = 418	% of fatal anaphylaxes[†]
Intravenous	11,426 (67.5%)	310 (74.2%)	2.7%
Oral	2884 (17.0%)	24 (5.7%)	0.8%
Skin, local, dermal	862 (5.1%)	9 (2.2%)	1.0%
Hemodialysis	507 (3.0%)	18 (4.3%)	3.6%
Intra-arterial	282 (1.7%)	20 (4.8%)	7.1%
Intramuscular	179 (1.1%)	11 (2.6%)	6.1%
Inhalation	105 (0.6%)	1 (0.2%)	1.0%
Rectal	75 (0.4%)	6 (1.4%)	8.0%
Ocular, intraocular, subconjunctival	70 (0.4%)	0 (0.0%)	0.0%
Intracoronary	54 (0.3%)	5 (1.2%)	9.3%
Unknown, other	472 (2.8%)	14 (1.6%)	3.0%

[†] % of fatal anaphylaxes: percentage of fatal anaphylaxis cases to anaphylaxis cases (by administration route).

which had the highest number of fatal cases, and 0.8% in the oral administration group, which had the second-highest number of fatal cases.

Discussion

This is the first study in which drug-induced AN cases were analyzed using data from the JADER database. We found that the incidence rates of both drug-induced AN cases and fatal cases of AN generally remained unchanged between 2005 and 2017. Among drug classifications, antineoplastic agents were most frequently associated with AN, whereas antibiotic preparations were most frequently associated with fatal AN. Intravenous drug administration was the most common route of administration in AN cases.

Changes in AN and fatal AN cases over time

The number of cases of drug-induced AN tended to increase from 2005 to 2011 but showed a decreasing trend from 2016 and did not change much over the 13 years of the study period. In contrast, in the US, the frequency of drug-induced AN cases requiring emergency room treatment increased two-to three-fold over a 10-year period.[13,14] In Australia, Spain, and England, the numbers of patients hospitalized with drug-induced AN tended to increase from the late 1990s to the early 2010s,[15–17] similar to the trend we observed between 2005 and 2011. As the JADER data used for this study included reports to the PMDA from the year following the AN incidence, there may be AN cases that occurred up to 1 year before June 2018 (when the study data were obtained) that had not yet been reported. Therefore, unreported cases may have affected the decline in the number of cases since 2012.

Regional differences have been noted in drug-induced AN fatal cases. A substantial increase in drug-related AN fatal cases has been reported in Australia; whereas UK data did not reveal similar increases.[17,18] In the present study, we observed a temporary increase in the frequency of drug-induced AN fatal cases in 2013, but there was no major change in the AN fatality rate (per 100,000 people), which ranged from 0.02 to 0.03 cases/year between 2005 and 2017. In the Vital Statistics published by the Ministry of Health, Labour and Welfare, which consists of aggregated data from death reports submitted to public agencies, 352 cases of fatal cases from drug- or serum-induced anaphylactic shock (clinically determined) were documented between 2005 and 2017. The annual number of AN fatalities reported in the Vital Statistics varies between 21 and 37; however, as in the present study, there was no increase in the number of reported fatal cases over time. From the JADER data over the same period, there were 418 cases of AN-related fatal cases, which differs slightly from the total in the Vital Statistics. However, JADER data comprise reports on cases with suspected side effects of drugs as submitted by drug manufacturers, medical institutions, and patients, and they include cases for which the causal relationship remains unclear, which might explain the observed differences in case numbers.

AN incidence by sex and age

Although the results of this study did not indicate any sex bias among AN cases, the ratio of male to female cases being 1.03:1, there were significantly more AN fatal cases among men. According to the report by Worm *et al.*, male sex is a risk factor for severe AN.[19] In contrast, drug-induced AN is more frequent among women,[20] and female sex is reportedly a risk factor for AN from X-ray contrast agents.[21] Although the reason for the more frequent AN fatal cases among men in this study remains unclear, differences between men and women in terms of comorbidities, such as hypertension and cardiovascular disease, use of concomitant medications, and frequency of the use of AN-triggering drugs, may have affected the results.

By age group, the ratio of fatal cases to AN cases was lowest in the group <10 years, at 0.2%, and gradually increased until reaching 6.5% in the age group 80–89 years. Elderly people have a high risk of severe AN.[19] In a South Korean study, it was reported that patients aged 70 years or older are at risk for drug-induced AN shock.[20] According to a US report, drug-induced AN was least common among children, and its prevalence tended to gradually increase from the age group 20–39 years to the age group 60–79 years.[3] Individuals aged 60 years or older are often affected by multiple diseases, and it is not uncommon for them to use antibiotic preparations, antineoplastic agents, or diagnostic agents. When administering such drugs to elderly patients, it is important to have intramuscular adrenalin medication and be prepared to give injections upon AN onset and monitor the status of the patient.

Numbers of AN incidences by drug classification

AN cases, in descending order, were more frequently associated with antineoplastic agents, biological preparations (including human blood preparations), other agents affecting metabolism, diagnostic agents (including X-ray contrast agents), and antibiotic preparations. Approximately half of adult AN cases were triggered by diagnostic agents and biological preparations, whereas approximately half of pediatric cases were triggered by biological preparations, antibiotic preparations, and chemotherapeutics. Antibiotic preparations and non-steroidal anti-inflammatory drugs (NSAIDs) are common triggers of drug-induced AN.[9] However, age differences have been noted, with AN being more frequently associated with antibiotic preparation use in children,[22–24] unlike in adults, in whom antineoplastic agents, diagnostic agents, including X-ray contrast agents, antibiotic preparations, and NSAIDs, are reportedly the major triggers of AN.[25,26] According to a report on drug-induced AN events that occurred in South Korean medical institutions, cases in descending order of prevalence were associated with antineoplastic agents, diagnostic agents (including X-ray contrast agents), and antibiotic preparations[20]; the finding of high prevalence associated with the use of antineoplastic agents was similar to the result in our study.

Based on our analysis of the JADER dataset, fatal cases were associated with antibiotic preparations, antineoplastic agents, and diagnostic agents, in descending order of association. According to a survey conducted in the United States, approximately 40% of fatal AN cases were triggered by antibiotic preparations, followed by X-

ray contrast agents, and antineoplastic agents, similar to the results of the present study.[3]

AN associated with X-ray contrast agents reportedly occurs at a rate of one case per several thousand.[27] Recent years have seen the frequent use of low-osmolar nonionic contrast agents. Such agents have fewer side effects; according to a large-scale survey in Japan, the rate of severe and serious side effects in patients exposed to low-osmolar nonionic contrast agents were 0.04% and 0.004%, respectively.[28] In the present study, the biological preparations were primarily blood preparations and did not include antibody drugs, such as omalizumab. Severe allergic reactions (AN and anaphylactic shock) to blood preparations are relatively common, with 1 out of 6000 cases with platelet preparations, 1 out of 8800 cases with plasma preparations, and 1 out of 51,000 cases with red blood cell preparations.[29] The present study did not perform the analysis of underlying diseases and complications. The clinical background of individual cases may explain why AN was more commonly associated with the use of diagnostic agents and antineoplastic agents. However, the need to pay attention to a potential AN onset when using these drugs is abundantly clear.

Numbers of AN incidences by drug name

With regard to diagnostic agents, biological preparations, antineoplastic agents, and other agents affecting metabolism, two or three drug classifications accounted for more than half of the cases associated with these drug categories. Low-osmolar nonionic contrast agents were common diagnostic agents in AN cases whereas platinum agents were common antineoplastic agents; these findings were similar to results reported in a South Korean study.[20] As sales volumes differ among drugs, and the method/frequency of drug use, concomitant drugs use, underlying diseases, and complications vary from case to case, simple comparisons of report counts would not suffice, and it is not possible to state unconditionally that drugs with a large number of AN reports are high-risk drugs. With regard to biological preparations, data on blood transfusions published by the Japanese Red Cross Society indicate that platelet preparations are more frequently associated with side effects than other drugs. The results of the present study also suggest that platelet preparations account for a high proportion of AN cases in the therapeutic category; thus, the risk of platelet preparation-induced AN can be considered high.

Route of administration

Intravenous administration was associated with 70% of AN cases possibly because drugs that are administered intravenously, such as antineoplastic agents, biological preparations, diagnostic agents, and antibiotic preparations, are the major triggers for AN. However, the relative frequency of AN-related fatal cases according to the route of administration was, at 9.3%, highest for intracoronary drug administration, but we surmised that this type of drug administration was related to the treatment of cardiovascular diseases such as myocardial infarction, and these fatal cases were associated with the high mortality risk of the underlying cardiovascular disease.

Limitations

This study had some limitations. First, there was a gap between AN occurrence and its reporting to the PMDA, which means that for data around June 2018, when the dataset was downloaded, the AN incidence rate may be lower than the actual figure. AN incidence reports to the PMDA are continuous, and the data may need to be analyzed regularly in the same way as done in this study. Second, we were not able to examine in detail the treatment of cases with AN and those leading to death. Therefore, we have not been able to evaluate treatment conditions such as the rate of adrenalin use. To reduce the number of fatal cases from AN, a more comprehensive study of the treatment details is required. Third, we did not analyze clinical data such as the underlying disease for each case. Thus, we have not been able to study the possibility of the underlying disease itself being a potentiating factor for AN, nor the impact that the disease would have on the risk of death. Despite these limitations, we have provided the results of a large-scale data analysis using JADER, and we believe our findings to be valuable data.

In conclusion, this study showed that in Japan, the average frequencies of drug-induced AN and fatal AN are 1.03 cases/year and 0.03 cases/year per population of 100,000 people, respectively. These figures have not substantially changed over the course of more than 10 years. Diagnostic agents, biological preparations, antineoplastic agents, and antibiotic preparations were common therapeutic categories of drugs associated with AN induction, similar to what has been reported in countries other than Japan. Diagnostic agents and antibiotic preparations were associated with around 50% of fatal AN; therefore, these drugs should be used in circumstances facilitating prompt responses to any AN that may occur. We anticipate that the results of this study will provide beneficial information for healthcare professionals and that they will be widely circulated along with AN guidelines.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest

ME and SS received lecture fees from Viatris. ME received consulting fees from Novartis Pharma, Sanofi, and ARS Pharmaceuticals.The rest of the authors have no conflict of interest.

Authors' contributions

ME and CS designed this study. CS performed data analysis. CS and SS wrote the manuscript. NY and ME contributed to data interpretation and critically revised the manuscript for important intellectual content. CS and SS contributed to the study management and critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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