Original Article

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Association between anaphylaxis and anti-influenza drug use: An analysis of the Japanese Adverse Drug Event Report database

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SUMMARY We aimed to investigate the association between anaphylaxis and anti-influenza drug use using the Japanese Adverse Drug Event Report (JADER) database, a national spontaneous reporting database in Japan. We surveyed registered cases from the JADER database between April 2004 and November 2019. The target drugs were five anti-influenza drugs, namely oseltamivir, zanamivir, peramivir, laninamivir, and baloxavir. Adverse events associated with anaphylaxis, "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," and "anaphylactoid shock," were evaluated. The association between anaphylaxis and anti-influenza drug use was assessed by calculating the reporting odds ratio (ROR) and information component (IC) as a measure of disproportionality. Signals were considered positive if the lower limit of the 95% confidence interval (CI) of ROR was > 1, and that of IC was > 0. The number of anaphylaxis cases associated with anti-influenza drug use was 199 (0.9%). Signals were detected for inhaled laninamivir (ROR: 4.24 [95% CI: 3.06-5.88], IC: 1.83 [1.35-2.30]), intravenous peramivir (ROR: 2.97 [2.11-4.17], IC: 1.40 [0.90-1.89]), and oral baloxavir (ROR: 3.05 [2.22-4.18], IC: 1.44 [0.98-1.90]). Conversely, signals were not detected for oral oseltamivir or inhaled zanamivir. Although zanamivir and laninamivir were used as dry powder inhalers containing lactose as an additive, they differed in terms of signal detection. Our analysis indicated that the signal of anaphylaxis may varies based on the main component or dosage form of each anti-influenza drug. Appropriate use of these drugs is essential to prevent anaphylaxis and improve health status.

Keywords Anti-influenza drug, anaphylaxis, Japanese Adverse Drug Event Report database, laninamivir, peramivir, baloxavir

1. Introduction

Influenza is one of the most common viral respiratory infections, associated with high morbidity and mortality. According to the United States Centers for Disease Control and Prevention, the annual number of influenza-related deaths ranges from 291,000 to 646,000 worldwide (*1*). Neuraminidase and cap-dependent endonuclease inhibitors are commonly used to treat and prevent influenza. Japan is one of the largest consumers of anti-influenza drugs worldwide (*2*). Currently, five anti-influenza drugs are mainly used in Japan, and their route of administration and dosage form vary based on the main component (oral formulation: oseltamivir capsule/dry syrup, baloxavir tablet/granules; inhaled formulation: zanamivir and laninamivir dry powder inhalants; intravenous formulation: peramivir intravenous) (Table 1). The supply of anti-influenza drugs to healthcare facilities in Japan between 2018 and 2019 accounted for 13.72 million individuals, consisting of oseltamivir, 4.64 million; zanamivir, 590,000; laninamivir, 2.89 million; peramivir, 320,000; and baloxavir, 5.28 million (*3*).

Drug-induced anaphylaxis is a well-known life-threatening adverse effect associated with several drug classes (antimicrobials (especially beta-lactams), nonsteroidal anti-inflammatory drugs, opiates, and local anesthetics) (*4,5*). Recently, a study using data from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database identified the top 50 drugs associated with reports of drug-induced anaphylaxis and drugs with more than 20 reported deaths following anaphylaxis (*6*). Although anti-influenza drugs were not included in this list, anti-influenza drug-induced anaphylaxis has been reported in clinical trials and post-marketing settings and the corresponding warning has been issued in package inserts. Nevertheless, to date, there is limited literature on anaphylaxis associated with neuraminidase inhibitors, and hence the relevant information is lacking. Another study using data from the FAERS database reported that signals associated

Table 1. Dosage form and administration route of anti-influenza drugs

Generic name	Dosage form	Administration route
Oseltamivir	Capsule, dry syrup	Oral
Zanamivir	Dry powder inhalant	Inhaled
Peramivir	Intravenous	Intravenous
Laninamivir	Dry powder inhalant	Inhaled
Baloxavir	Tablet, granules	Oral

with anaphylaxis were detected for baloxavir (*7*). Although most drug-induced anaphylaxis episodes are caused by the main drug components, additives have also been reported to cause anaphylaxis. A case of anaphylaxis attributable to a miniscule amount of milk protein contained in lactose used as an additive has been reported (*8*). In addition, a case of anaphylactic shock caused by benzyl alcohol in an intravenous formulation, after a change in the route of administration from oral formulation, has also been reported (*9*). Intravenous administration is associated with an increased rate of anaphylactic shock (*10*). Therefore, as anti-influenza drugs contain various ingredients and vary in dosage forms and administration routes, it is important to consider these differences when evaluating their association with anaphylaxis. In addition, anti-influenza drugs are often used in outpatient settings, except for peramivir, which is an intravenous formulation, and the dosage form is often selected based on the patient's age and respiratory function. Therefore, clarifying the association between anaphylaxis and the use of each anti-influenza drug will help in improved drug selection.

In recent years, studies have utilized data from the Japanese Adverse Drug Event Report (JADER) database, a national spontaneous reporting database in Japan (*11-13*), to investigate the association between adverse events and drugs. Therefore, in this study, data from the JADER database were used to analyze the association between anaphylaxis and anti-influenza drug use.

2. Materials and Methods

2.1. Data source

Data recorded in the JADER database between April 2004 and November 2019 were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website (*http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp*). The data structure consists of four sets, namely, patient demographic information (demo), drug information (drug), adverse event (reac), and medical history (hist). The adverse events in reac are based on the medical terminology as preferred terms (PT) in the Medical Dictionary for Regulatory Activities/ Japanese version (MedDRA/J).

The target drugs were four neuraminidase inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir) and a cap-dependent endonuclease inhibitor (baloxavir). Adverse events were associated with anaphylaxis, "anaphylactic reaction (PT code: 10002198)," "anaphylactic shock (PT code: 10002199)," "anaphylactoid reaction (PT code: 10002216)," and "anaphylactoid shock (PT code: 10063119)" in MedDRA/J version 21.0. Cases with both target drugs and adverse events were extracted from all cases recorded in the JADER database, and sex, age, drug involvement, and clinical outcome were surveyed. In the JADER database, patient age is rounded to every 10 years (*e.g.*, 10's, 20's, and 30's). In some cases, age is registered as a particular category ("newborn," "infant," "child," "adolescent," "adult," or "elderly"). In this study, age was categorized into four groups (< 20 years, 20-59 years, ≥ 60 years, and unknown/other) for tabulation; cases belonging to the categories of "newborn," "infant," "child," and "adolescent" were categorized as < 20 years, "adult" as 20-59 years, and "elderly" as ≥ 60 years. Drug involvement in the JADER database is classified into three categories, namely "suspected drugs," "drug interactions," and "concomitant drugs." Cases in which anti-influenza drugs were reported as "suspected drugs" were included in the analysis. The clinical outcomes of anaphylaxis cases were categorized into either "poor outcomes," that included "unrecovered," "death," or "sequelae," or "good outcomes," that included "recovery" or "remission." The missing data were categorized as "unknown."

2.2. Disproportionality analysis

The reporting odds ratio (ROR) (*14*), as a frequency-based method, and information component (IC) (*15*), as a Bayesian method, were used to evaluate the association between drugs and adverse events based on the case/non-case method. We compiled a cross-tabulation table based on the presence or absence of adverse events associated with anaphylaxis and anti-influenza drugs, and calculated the ROR and IC. We defined the signals as positive when the lower limit of the 95% confidence interval (CI) of ROR was > 1, and that of IC was > 0.

3. Results

The total number of cases recorded in the JADER database between April 2004 and November 2019 was 622,289, and the number of cases with anaphylaxis was 23,016. Among the cases with anaphylaxis, 199 (0.9%) cases that included anti-influenza drugs as suspected drugs were identified – oseltamivir in 57 cases, zanamivir in 23 cases, peramivir in 37 cases, laninamivir in 42 cases, and baloxavir in 43 cases (Table 2). In three of these cases, two drugs, peramivir and laninamivir, were together reported as suspected drugs (based on the individual number of cases specified for each drug, the total number of cases summed up to 202 (57 + 23 + 37 +

Table 2. Background data (sex and age) of cases with anti-influenza drug as the suspected drug among all the anaphylaxis cases (*n* = 23,016)

	No. of cases (%)					
	Oseltamivir *n* = 57	Zanamivir *n* = 23	Peramivir *n* = 37[a]	Laninamivir *n* = 42[a]	Baloxavir *n* = 43	Total *n* = 199
Sex						
Male	15 (26.3)	10 (43.5)	19 (51.4)	23 (54.8)	15 (34.9)	79 (39.7)
Female	40 (70.2)	13 (56.5)	17 (45.9)	19 (45.2)	26 (60.5)	115 (57.8)
Unknown	2 (3.5)	0 (0.0)	1 (2.7)	0 (0)	2 (4.7)	5 (2.5)
Age						
< 20 years	14 (24.6)	10 (43.5)	13 (35.1)	23 (54.8)	9 (20.9)	66 (33.2)
20-59 years	36 (63.2)	9 (39.1)	11 (29.7)	13 (31.0)	30 (69.8)	99 (49.7)
≥ 60 years	7 (12.3)	1 (4.3)	12 (32.4)	6 (14.3)	4 (9.3)	30 (15.1)
Unknown/Others	0 (0.0)	3 (13.0)	1 (2.7)	0 (0.0)	0 (0.0)	4 (2.0)

[a]As there were three cases in which both peramivir and laninamivir were considered suspected drugs, the total number of cases listed in the column for all individual suspected drugs did not add up to 199.

Table 3. List of drugs reported as suspected drug along with anti-influenza drugs

Suspected drug	No. of cases
Acetaminophen	21
Levofloxacin	6
Cefcapene pivoxil hydrochloride, loxoprofen sodium	5 per drug
Lysozyme hydrochloride, maoto (herbal medicine), moxifloxacin hydrochloride, piperacillin sodium	2 per drug
Ambroxol hydrochloride, ampicillin sodium, aspirin-dihydroxyaluminum aminoacetate-magnesium carbonate combination, azithromycin, benproperine phosphate, cefazolin sodium, cefditoren pivoxil, ceftriaxone sodium, clofedanol hydrochloride, codeine phosphate, dimemorfan phosphate, garenoxacin mesylate, L-carbocysteine, meropenem, methylprednisolone sodium succinate, nafamostat mesylate, pranoprofen, prednisolone sodium succinate, tipepidine hibenzate, tosufloxacin tosylate	1 per drug

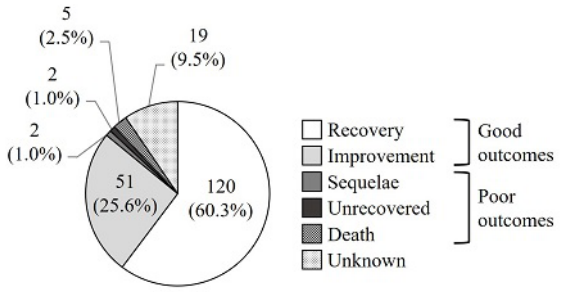

Figure 1. Clinical outcomes of anaphylaxis associated with the use of anti-influenza drugs. The clinical outcomes of anaphylaxis cases were categorized into either "poor outcomes," that included "unrecovered," "death," or "sequelae," or "good outcomes," that included "recovery" or "remission." Nine patients (4.5%) had a poor clinical outcome, of which five (2.5%) died.

42 + 43 = 202)).

In anaphylaxis cases associated with anti-influenza drug use, females and patients aged 20-59 years accounted for a large proportion in each category (57.8% and 49.7%, respectively). In cases in which oral oseltamivir or baloxavir was the suspected drug, the proportion of females and patients aged 20-59 years exceeded 60% in each category. In cases in which inhaled zanamivir or laninamivir was the suspected drug, patients aged < 20 years accounted for a large proportion (43.5% and 54.8%, respectively). In cases in which intravenous peramivir was the suspected drug, minor differences were found in the proportion of reports among the age groups (Table 2). Acetaminophen was the most common drug reported as a suspected drug along with anti-influenza drugs in 21 cases, followed by levofloxacin in 6 cases, cefcapene pivoxil hydrochloride in 5 cases, and loxoprofen sodium in 5 cases (Table 3). Nine patients (4.5%) had a poor clinical outcome, of which five (2.5%) died (Figure 1).

The results of the disproportionality analysis are shown in Table 4. A signal for anaphylaxis was detected for all five anti-influenza drugs combined (ROR: 1.26 [95% CI: 1.09-1.45], IC: 0.31 [0.10-0.52]), whereas no signal was detected for the four neuraminidase inhibitors combined (ROR: 1.08 [0.92-1.27], IC: 0.11 [-0.13 to 0.34]), and a signal was detected for the inhaled neuraminidase inhibitors (ROR: 1.50 [1.17-1.93], IC: 0.54 [0.18-0.91]). In the analysis of each neuraminidase inhibitor, signals were detected for laninamivir (ROR: 4.24 [3.06-5.88], IC: 1.83 [1.35-2.30]) and peramivir (ROR: 2.97 [2.11-4.17], IC: 1.40 [0.90-1.89]). Further, a signal was detected for baloxavir (ROR: 3.05 [2.22-4.18], IC: 1.44 [0.98-1.90]). For the three drugs, laninamivir, peramivir, and baloxavir, wherein anaphylaxis signals were detected, further analysis based on different age groups was conducted, and the results are shown in Table 5. For laninamivir and peramivir, signals were detected in all age groups, with the highest ROR and IC in patients aged < 20 years for laninamivir and patients

Table 4. Signal index of each anti-influenza drug

Suspected drug	Cases	Non-case	ROR [95% CI]	IC [95% CI]
All	199	4123	1.26 [1.09-1.45]	0.31 [0.10-0.52]
Neuraminidase inhibitors	156	3760	1.08 [0.92-1.27]	0.11 [-0.13 to 0.34]
<Oral>				
Oseltamivir	57	2318	0.64 [0.49-0.83]	-0.62 [-1.00 to -0.23]
<Inhaled>	65	1130	1.50 [1.17-1.93]	0.54 [0.18-0.91]
Zanamivir	23	873	0.69 [0.45-1.04]	-0.51 [-1.11 to 0.09]
Laninamivir	42	258	4.24 [3.06-5.88]	1.83 [1.35-2.30]
<Intravenous>				
Peramivir	37	325	2.97 [2.11-4.17]	1.40 [0.90-1.89]
Cap-dependent endonuclease inhibitor				
Baloxavir	43	368	3.05 [2.22-4.18]	1.44 [0.98-1.90]

ROR: reporting odds ratio; IC: information component; 95% CI: 95% confidence interval

Table 5. Signal index by age for the three anti-influenza drugs, peramivir, laninamivir, and baloxavir, for which signals were detected in Table 4

	Cases	Non-case	ROR [95% CI]	IC [95% CI]
Peramivir				
< 20 years	13	81	2.61 [1.45-4.70]	1.10 [0.27-1.93]
20-59 years	11	66	3.19 [1.69-6.05]	1.30 [0.40-2.20]
≥ 60 years	12	174	2.16 [1.20-3.87]	0.93 [0.11-1.76]
Laninamivir				
< 20 years	23	102	3.68 [2.34-5.80]	1.53 [0.88-2.17]
20-59 years	13	97	2.57 [1.44-4.58]	1.10 [0.29-1.92]
≥ 60 years	6	58	3.35 [1.45-7.77]	1.25 [0.10-2.40]
Baloxavir				
< 20 years	9	88	1.66 [0.84-3.30]	0.58 [-0.38 to 1.54]
20-59 years	30	123	4.68 [3.14-6.98]	1.84 [1.27-2.41]
≥ 60 years	4	154	0.84 [0.31-2.27]	-0.20 [-1.51 to 1.11]

ROR: reporting odds ratio; IC: information component; 95% CI: 95% confidence interval

aged 20-59 years for peramivir. A signal for baloxavir was detected only in patients aged 20-59 years.

4. Discussion

In this study, we evaluated the association between anaphylaxis and anti-influenza drug use by analyzing data available from the JADER database. Our results suggest that inhaled laninamivir, intravenous peramivir, and oral baloxavir are associated with anaphylaxis.

There have been several case reports of anaphylaxis associated with neuraminidase inhibitor use (*8,16,17*), but to date, the status in the real world and the relevance have not been clarified. Recently, an analysis of the adverse effects associated with neuraminidase inhibitors using data from the FAERS database was conducted (*18*); however, anaphylaxis was not the focus of that study. Meanwhile, another analysis using data from the FAERS database detected a signal associated with anaphylaxis following baloxavir use, a cap-dependent endonuclease selective inhibitor (*7*). Anti-influenza drugs are often used in outpatient settings, except for peramivir, which is an intravenous formulation, and the dosage form is often selected based on the patient's age and respiratory function. Therefore, clarifying the association between anaphylaxis and the use of each anti-influenza drug will help in drug selection.

Among all anaphylaxis cases registered in the JADER database, anti-influenza drugs were reported as suspected drugs in 199 (0.9%) cases. Generally, drug-induced anaphylaxis occurs more frequently in females/women than in males/men (4,19), and a similar trend was observed for anti-influenza drugs. Furthermore, for individual drugs, the percentage of females was higher for oral oseltamivir and baloxavir than for other drugs, whereas for inhaled zanamivir, laninamivir, and intravenous peramivir, minor difference in sex was observed. Anaphylaxis associated with anti-influenza drug use was reported more frequently in patients aged 20-59 years, accounting for approximately half of all cases. For oral oseltamivir and baloxavir, most cases were patients aged 20-59 years (63.2% and 69.8%, respectively), whereas the percentage of patients aged < 20 years was relatively higher for inhaled zanamivir and laninamivir (43.5% and 54.8%, respectively). For intravenous peramivir, a minor difference was observed in the percentage of patients by age, whereas elderly patients accounted for a higher percentage than that observed with other drugs (dosage forms). The percentage of anaphylaxis cases by dosage form differed

by age, and this may be attributed to the differences in dosage forms selected based on age.

A signal for anaphylaxis was detected for five anti-influenza drugs combined, but disappeared when the patients were limited to neuraminidase inhibitors. A signal was also detected for baloxavir; hence, the effect of baloxavir on the association between anaphylaxis and anti-influenza drug use was large. Further analysis by age showed that the baloxavir signal was detected only in patients aged 20-59 years. Therefore, careful observation is necessary for this age group.

Morikawa *et al.* reported a case of anaphylaxis caused by laninamivir dry powder inhaler, and attributed the anaphylaxis to β-lactoglobulin and its sugar adducts contained in the lactose used as an additive (*8*). Lactose is widely used as an excipient in pharmaceutical products, and its allergenicity has not yet been characterized. However, it has been confirmed that a trace amount of milk protein is present as a contaminant, even in high-purity lactose (*20*). The lungs can better absorb macromolecular compounds, such as proteins, than gastrointestinal tract (*21*); therefore, pulmonary administration may increase the absorption of allergens (*8*). The dosage forms of zanamivir and laninamivir are dry powder inhalants, both of which contain lactose as an additive; thus, the package insert of these drugs cautions against their use in patients with milk allergy. In this study, a signal associated with anaphylaxis was detected in case of inhaled neuraminidase inhibitors (zanamivir and laninamivir) combined. However, when analyzed by individual drugs, a signal was detected only for laninamivir, but not for zanamivir. This difference is attributed to the purity of lactose used as an excipient, the amount of lactose inhaled at one time, and the allergenicity of the main ingredients.

As mentioned earlier, anaphylaxis associated with inhaled neuraminidase inhibitor use occurred mostly in patients aged < 20 years. Furthermore, for laninamivir, a signal associated with anaphylaxis was detected in all age groups, with the highest ROR and IC in patients aged < 20 years. Previous studies have shown that the cause of anaphylaxis varies by age, with food being the most common cause in children, and drugs in adolescents and adults (*4,22,23*). In this study, we could not determine whether the main component or the additive was the cause of anaphylaxis associated with inhaled neuraminidase inhibitor use. The possibility that the additive lactose may be the cause of anaphylaxis can explain the high proportion of reports in children. Several patients with anaphylaxis caused by inhaled neuraminidase inhibitor use had a history of food allergy (data not shown). On September 4, 2019, laninamivir in inhalation suspension as a new formulation was listed in the National Health Insurance, and is currently available for clinical use. This formulation does not contain lactose as an additive, and can be administered by spontaneous breathing in patients with difficulty using the existing dry powder inhalers. In the future, it may be possible to compare the incidence of anaphylaxis between two commercially available inhaled laninamivir formulations, and clarify the effect of lactose, as an additive, on anaphylaxis development.

For intravenous peramivir also, a signal associated with anaphylaxis was detected. As intravenous administration delivers the drug directly into the blood stream, it has a relatively high potential to induce anaphylaxis. In an analysis using data from the Italian pharmacovigilance database, intravenous formulations were reported to have a high rate of anaphylactic shock (*10*), which is in line with our results. Furthermore, for peramivir, as signals were detected in all age groups with minor differences in the percentage of reports, caution must be exercised in patients of all ages.

In this study, we focused on the use of anti-influenza drugs, and ignored the effects of co-administered drugs. When we surveyed the suspected drugs besides anti-influenza drugs in each case, acetaminophen was the most common co-administered drug (21 cases), followed by levofloxacin (6 cases), cefcapene pivoxil hydrochloride (5 cases), and loxoprofen sodium (5 cases). Of these drugs, acetaminophen and levofloxacin were among the top 50 drugs associated with anaphylaxis in a survey using data from the FAERS database (6). Therefore, analysis considering the presence or absence of these drugs may be necessary in the future.

Drugs, as anaphylaxis inducers, are associated with the severity level, including fatal, of anaphylaxis (*19,24*). It has also been reported that drugs are the most common cause of fatal anaphylaxis, accounting for 58.8% of anaphylaxis-related deaths (*24*). In this study, 4.5% of anaphylaxis cases associated with anti-influenza drug use presented poor clinical outcomes, whereas 2.5% of patients died. It may be possible to reduce anaphylaxis-associated fatality by effectively selecting drugs based on individual patient characteristics.

This study had some limitations. As this study was a disproportionality analysis using data from a spontaneous report database, the ratio of adverse event onset to each target drug user was not calculated. Additionally, differences in the drugs prescribed based on patients' background, such as age and presence or absence of predisposition to allergy were not considered. Therefore, caution should be exercised when interpreting these results.

In conclusion, a signal associated with anaphylaxis was detected for inhaled laninamivir. As dry powder-type inhalants often contain lactose as an additive, caution must be exercised when administering them to patients with milk allergy. Signals were also detected with intravenous peramivir and oral baloxavir. Proper use of these drugs is necessary to prevent anaphylaxis and improve health status. Further extensive studied are needed to validate these results.

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