

Association of moderately abnormal behavior and administered neuraminidase inhibitors

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SUMMARY Our earlier study investigated the incidence of severe abnormal behavior associated with neuraminidase inhibitors (NIs), but some studies have specifically examined the association of oseltamivir use and moderately abnormal behavior. Therefore, this study was undertaken to assess associations between moderately abnormal behavior and administered drugs. All cases of patients with influenza who exhibited moderately abnormal behavior were reported to us by physicians of all sentinel clinics and hospitals for influenza throughout Japan. Open Data of the National Database of Electronic Medical Claims include the numbers of patients diagnosed as having influenza who were prescribed NI. Incidence by NI was tested using Fisher's exact test. We received 518 moderately abnormal cases in 5-9-year-olds and 207 moderately abnormal behavior cases in 10-19-year-olds. The incidence among NI ranged from 193 per one million influenza patients in laninamivir among 10-19-year-olds to 1021 for peramivir among 5-9-year-olds. Estimation results revealed the order of risk among NIs as peramivir, oseltamivir, zanamivir and laninamivir in moderate abnormal behavior. Because of data limitations, risk among patients with and without NI cannot be compared.

Keywords Moderately abnormal behavior, neuraminidase inhibitors, influenza, relative risk, incidence

1. Introduction

Since February 2007, when two influenza-infected Japanese junior high students jumped from a great height and died, abnormal behavior in influenza patients, especially in 10-19-year-olds, has been a public health concern in Japan and throughout the world (1-9). Although the Ministry of Health, Labour and Welfare abolished the Yellow Letter restricting the issuance of oseltamivir prescriptions to 10-19-year-old influenza patients on August 21, 2018 (10), abnormal behavior has persisted as an important public health concern.

Our earlier study (8) to assess the incidence of severely abnormal behavior, which was defined as active motion that can be life-threatening if given no intervention, including behaviors such as sudden running away, jumping from a high place, or rampaging involving self-injury. Results showed that no significant difference in the incidence rates of abnormal behavior by the type of neuraminidase inhibitor (NI).

By contrast, some studies have specifically examined the association of oseltamivir use with abnormal behavior and with adverse neuropsychiatric events (11). Nevertheless, because they used comparison of a small sample with nationwide data, these studies might specifically examine moderately abnormal behavior that might not be life-threatening even if given no intervention (12,13). We also collect information about moderately abnormal behavior along with that of severely abnormal behavior. However, the incidence of moderately abnormal behavior has not been evaluated in the earlier investigations, yet (8).

The National Database of Electronic Medical Claims (NDBEMC), which includes all electronic medical claims, accounting for about 98.4% of all medical claims throughout Japan as of May 2015. However, use of the data takes more than one year because an application must be filed to obtain permission to use data for analyses. Therefore, analysis using NDBEMC might be unrealistic. Instead, the NDBEMC open data are data of NDBEMC that are available for general

use. The data include the amounts of prescribed drugs, but do not include information related to diagnosis. Because the earlier study specifically addressed only the severe abnormal behavior, the object of the present study specifically examines association between moderate abnormal behavior and administered NI.

2. Materials and Methods

2.1. Data

All cases of patients with influenza who presented moderately abnormal behavior were reported to us by physicians of all sentinel clinics and hospitals for influenza throughout Japan. Of the 5,000 sentinels for influenza, 3,000 were pediatric medical facilities; 2,000 were of internal medicine. These accounted for almost 10% of pediatric and internal medicine facilities nationwide. In Japan, almost all influenza-like illness cases are assessed using rapid tests, reporting results confirmed as positive for influenza virus infection. We defined the moderately abnormal behaviors as non-life-threatening abnormal behaviors, even if no intervention was given. We have continued to survey abnormal behaviors since the 2006/2007 season.

The influenza season is defined as the period from the 36th epidemiological week to the 35th week of the following year. We extracted data from NDBEMC open data for the amounts with NI by age class and transformed the data to the number of patients using standard formulation by age or body weight evaluated at average weight in an age class.

2.2. Study period and subjects

The study period was limited to September 2014 through March 2018. Subjects were grouped into two age groups: 5-9 and 10-19-year-olds.

2.3. Analysis

We evaluated differences in incidence rates among patients administered types of NI as relative risks using Fisher's exact test. Incidence was defined as the number of influenza patients of moderately abnormal behavior multiplied by 10 and dividing the estimated number of patients with each NI. We adopted 5% as the significance level.

2.4. Ethical consideration

This study was approved by the Committee for Ethical Consideration, National Institution of Infectious Diseases, Japan: approval numbers were 261, 312, 375, and 462. Approval by the Kawasaki City Institution for Health and Safety, Committee for Ethical Consideration was 27-5.

3. Results and Discussion

Table 1 presents the number of influenza patients of the 5-9 and 10-19-year-olds with moderate abnormal behavior according to the administered drug: oseltamivir, zanamivir, peramivir, or laninamivir. It also shows the incidence per million patients by age group according to the administered drug. Moderately abnormal behavior was reported from the sentinels of influenza, as described above.

Results show that, for 5-9-year-olds, 518 moderately abnormal cases were reported. For 10-19-year-olds, 207 moderately abnormal behavior cases were reported. The highest incidence among NI was 1,021 per one million influenza patients for peramivir among 5-9-year-olds. The lowest was 193 in laninamivir among 10-19-year-olds.

Table 2 presents the relative risks and *p*-values of the exact test. The relative risk is defined as the incidence in the first column over the incidence in the second column. Almost all results were found to be statistically significant except for relative risk among zanamivir and laninamivir, which were not significant among 10-19-year-olds. In both of age classes, peramivir was found to have the highest incidence, followed by oseltamivir and zanamivir. The lowest incidence was that of laninamivir.

The cases of moderately abnormal behavior were 2-10 times greater than cases of severely abnormal behavior (8). Moderately abnormal behaviors were reported only from the influenza sentinels. Therefore, the implied incidence of moderately abnormal behavior was 20-100 times higher than the reported incidence of severely abnormal behavior. Even though almost all relative risks were significant because of the large number of cases, the characteristics of the results were similar to those obtained for severely abnormal behavior.

Another study conducted in Japan (7) found 28 cases of A-type abnormal behavior among the 10,000 cohort. That is the most severely abnormal behavior in their definition: "Abnormal behavior potentially leading to an accident or harm to another person." Consequently, their inferred incidence was 2,800 per million patients. Our obtained results were 193-1,021 per million patients in the two age classes. Therefore, incidence found in the earlier study was approximately 2-14 times higher than our estimate.

The incidence with oseltamivir was at least 777 for 5-9-year-olds and 414 for 10-19-year-olds. An earlier study (7) found 24 cases of A-type abnormal behavior, implying incidence of 2,400 per million patients. That figure is 3-6 times greater than our estimates. The A-type abnormal behavior found in that earlier study (7) apparently occurs more often than the moderately abnormal behavior found in the present study. One must bear in mind that data used for the earlier study

Table 1. Number of moderately abnormal behavior cases and incidence per million patients by age group and administered drug

Administered drug/ Age class	No. of moderately abnormal behavior cases reported		Incidence per million patients	
	5-9	10-19	5-9	10-19
Oseltamivir	240	20	777.1	414.7
Zanamivir	55	57	502.8	277.9
Peramivir	8	4	1021	328.9
Laninamivir	88	97	445	193.0
None	127	43		

Notes: "Incidence per million patients" is defined as the "Number of moderately abnormal behavior cases reported" multiplied by 10 and divided by the estimated number of patients with each neuraminidase inhibitor (NI). "None" in the administered drug column denotes patients who were not administered any NI.

Table 2. Relative risk and *p*-values

Age class		5-9		10-19	
Numerator	Denominator	relative risk	<i>p</i> -value	relative risk	<i>p</i> -value
Zanamivir	Zanamivir	1.545	0.000	1.492	0.000
Oseltamivir	Peramivir	0.070	0.000	0.052	0.000
Oseltamivir	Laninamivir	19.181	0.000	52.084	0.000
Zanamivir	Peramivir	0.492	0.000	0.845	0.303
Zanamivir	Laninamivir	1.129	0.025	1.440	0.000
Peramivir	Laninamivir	2.294	0.000	1.704	0.001

Notes: Relative risk is the incidence of the first column divided by the incidence of the second column.

were collected in 2007. Our data period was after 2007, when public health concern had emerged and abnormal behavior had continued. This difference of data might account for the greater size gap. Therefore, we conclude that A-type abnormal behavior reported from the earlier study (7) might be comparable to less severely abnormal behavior than the moderate behavior examined in the present study.

Comparison of our results with those of an earlier study (8) indicated no significant difference in the incidence rates of severe abnormal behavior by the type of NI. We found that almost all relative risks among NI were significant. This difference might derive from the definition of abnormal behavior. We specifically examined moderate abnormal behavior, but the earlier study was limited to severe behavior, which was defined as life-threatening if given no intervention. Therefore, the numbers of cases of the two definitions were much different. These differences might clarify the present result among NI. However, it is notable that the risk order among NI, which was peramivir, oseltamivir, zanamivir, and laninamivir in moderate abnormal behavior, might not hold in severe abnormal behavior even though data of severe abnormal behavior will be accumulated comparably to the moderate abnormal behavior found in the present study.

The present study is constrained by some limitations. The most potentially important limitation is that related to the sampling fraction of sentinels for influenza able to report moderately abnormal behavior. We assumed that sampling fraction to be 10% for both age classes. However, as described above, some differences might

arise in the fraction rates for pediatric and internal medicine facilities. The fraction rate might actually be higher for pediatric facilities than for internal medicine facilities. Some 15-19-year-old influenza patients might visit internal medicine rather than pediatric facilities. Therefore, the sampling fraction for 15-19-year-olds might be smaller than others. That point has not been well investigated. Therefore, we do not consider that point for adjustment. It remains as a challenge for future research.

Secondly, because we used NDBEMC open data as the number of patients with NI, we cannot analyze patients without NI. The NDBEMC open data which we used did not include information about diagnosis, although NDBEMC data include it. It takes a long time, actually several years, as described above, to use NDBEMC itself to analyze abnormal behavior without NI.

4. Conclusion

Results show that the order of risk among NI was peramivir, oseltamivir, zanamivir, and laninamivir in moderate abnormal behavior with an exception. Comparison with moderate abnormal behavior without NI persists as the next challenge for research on this subject.

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