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Original Article

Association of severe abnormal behavior and acetaminophen with/without neuraminidase inhibitors☆

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ABSTRACT

Background: Even though abnormal behavior related with influenza and neuraminidase inhibitors (NI) has been discussed, the risks of acetaminophen and co-administration of NI and acetaminophen have not been examined. This study assesses those risks.

Materials and methods: All cases of patients with influenza who present with severe abnormal behavior are reported by physicians of all clinics and hospitals throughout Japan. The numbers of people diagnosed as having influenza, whether prescribed NI and acetaminophen or not, were extracted from the National Database of Electronic Medical Claims (NDBEMC). The study period was from September 2009 to March 2016.

Results: We found two consistent results among four combinations of age class and severity. The one was that patients who did not use NI or acetaminophen showed significantly higher incidence of abnormal behavior than zanamivir with acetaminophen, another one was that patients with oseltamivir only has higher incidence than zanamivir with acetaminophen. Concerning about acetaminophen, the use of it significantly decrease risk for severe and the most severe instances in 5–9-year-old patients with laninamivir and the severe instances in 10–19-year-old patients with zanamivir.

Discussion: We also demonstrated that acetaminophen alone or co-administered with NI does not seem to raise the risk of abnormal behavior in influenza patients.

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-years-olds, has been public health concern in Japan and throughout the world [1–10].

Our earlier study [10] used 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 in May 2015 [11–14]. Results showed that patients not administered any neuraminidase inhibitors (NI) or those administered peramivir sometimes showed higher risk of abnormal behavior than those administered oseltamivir, zanamivir, or laninamivir.

However, that study did not consider risks associated with acetaminophen, which is suspected to have some association with behavioral problems [15–17]. Of course, it also ignored co-administration of NI and acetaminophen. Therefore, the present study examines the risk of acetaminophen with and without NI for abnormal behavior of influenza patients using NDBEMC, covering a longer period than that addressed in earlier research.

2. Materials and methods

2.1. Data

All cases of patients with influenza who presented with severe abnormal behavior were reported by physicians of all clinics and

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hospitals throughout Japan to us. Section managers of the Tuberculosis and Infectious Diseases Control Division, and managers of the Safety Division of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), Japan requested all physicians corporate in reporting by fax or using the internet every year since 2007. However, a reporting system functioning via the internet was closed in 2016. Thereafter, only fax has been available currently. In Japan, almost all influenza-like illness cases were assessed using rapid test, with results confirmed as positive for influenza virus infection.

We defined severe abnormal behavior as active motion that can be life-threatening given no intervention, including behaviors such as sudden running away, jumping from a high place, or rampaging involving self-injury. We defined only the most severe abnormal behaviors as sudden running away and jumping from a high place because they can be expected to engender death with higher probability than other severe abnormal behaviors.

The influenza season is defined as the period from the 36th epidemiological week to the 35th week of the following year. We have continued to survey abnormal behaviors from the 2006/2007 seasons up to the present day.

After approval for NDBEMC was obtained from MHLW, the numbers of patients diagnosed as having influenza, excluding suspected cases, either prescribed or not-prescribed NI or acetaminophen, were extracted and counted. We were permitted to use the NDBEMC information obtained from seasons 2009/2010 through 2016/2017 [14].

2.2. Study period and subjects

The NDBEMC information is available for a shorter period than information related to abnormal behavior. Therefore, the study period had to be limited to September 2009 through March 2016. However, the approval and availability of drugs differed among drug types. The study period for peramivir was limited to September 2010 and thereafter. Similarly, for laninamivir, it was limited to September 2012 and thereafter. Subjects were grouped into two age groups: 5–9 and 10–19 years old.

2.3. Analysis

We evaluated differences in incidence rates among patients administered types of NI with/without acetaminophen and those who were not administered any NI or acetaminophen (hereinafter, un-administered) using a Fisher's exact test. We adopted 5% as the significance level.

2.4. Ethics

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. Permission to use NDBEMC data was obtained from the Health Insurance Department, MHLW, Japan, on September 8, 2017.

3. Results

Table 1 presents the number of influenza patients of the 5–9 and 10–19 year old, in NDBEMC by the administered drug: un-administered (U), oseltamivir only (O), zanamivir only (Z), peramivir only (P), laninamivir only (L), acetaminophen only (A), oseltamivir and acetaminophen (OA), zanamivir and acetaminophen (ZA), peramivir and acetaminophen (PA), and laninamivir and acetaminophen (LA). It also shows the number of abnormal behavior cases and the incidence per million patients by age group by the administered drug. Table 2 presents the relative risks and *p*-values of the exact test for the only combinations with significant difference. The relative risk is defined as the incidence in the first column over the incidence in the second column. All results including insignificant results are presented in Supplemental Table.

We found two consistent results among four combinations of age class and severity. One was that U showed significantly higher incidence of abnormal behavior than ZA did. Moreover, O has higher incidence than ZA.

Regarding acetaminophen, the risk of A was not significantly higher than the risk of U. Moreover, the acetaminophen use significantly decrease risk of L in the most severe instances in 5–9-year-old patients and Z in the severe instances in 10–19-year-old patients.

4. Discussion

We used data from patients of two age classes: 5–9 years old and 10–19 years old. The two fatality cases were 10–19 years old. Moreover, in response to these events, the Dear Healthcare Professional Letters of Emergent Safety Communications (the Yellow Letter) published in March 2007 [18] ordered physicians to refrain from prescribing oseltamivir to 10–19-year-old influenza patients. Therefore, we specifically examined this age class. However, in this age class, the prescription of oseltamivir is expected be much less frequent, as recommended by the Yellow Letter. Therefore, we also investigated patients younger than 10 years old. Nevertheless, 0–4-year-old patients must be ignored because, even if behaving abnormally, they cannot move quickly to the degree that caregivers cannot hold or control them. Therefore, the risk posed to such younger children should not be considered in the same manner as that to children older than five years of age.

Results demonstrated that U exhibited higher incidence than ZA. To interpret this result, one must bear in mind that we used the number of patients that had not been prescribed in NDBEMC as the denominator of the incidence of U. The numerator includes influenza patients who were prescribed some NI or acetaminophen, but who showed abnormal behavior before taking those drugs. Therefore, a mismatch was found between the definitions of the numerator and the denominator for the incidence of U patients. To resolve this mismatch, more detailed information is needed about the prescription of NI and acetaminophen for un-administered patients who nonetheless exhibited abnormal behavior. Results of that investigation suggest a subject for our future research.

In contrast, additional effects of acetaminophen on U patients were found to be not significant. At least, A patients had never shown significantly higher incidence than U or patients with NI alone. Therefore, acetaminophen might not be riskier than either U or NI. However, as with U, the prescription of acetaminophen does not definitely indicate its administration. Acetaminophen is a medication intended to be taken as needed. Its different prescription and administration might be more widespread than those of NI. Therefore, more information related to administration of acetaminophen as well as its prescription must be collected for more precise evaluation of risks related to acetaminophen.

Moreover, we found consistently that O is significantly higher than ZA. This result implies the risk of O was higher than that posed by ZA. However, O was significantly safer than L in 5–9-year-old patients. Conversely, no significant differences were found between O and U or any other NI, except for L. It is noteworthy that oseltamivir did not pose a higher risk than the non-use of oseltamivir. To investigate that point, some more detail information of ZA might be necessary for the evaluation of risk of oseltamivir as suggested by the additional effect of acetaminophen described above.

Table 1
Administered Drugs for Influenza Patients by Age Class in the National Database of Electronic Medical Claims, Number of Abnormal Behavior Cases and their Incidence per One Million Patients.

Age: 5–9		Severe		Most Severe Cases	
Severity	Number of influenza patients	Number of abnormal behavior cases	Incidence per one million patients	Number of abnormal behavior cases	Incidence per one million patients
un-administered (U)	2,579,838	30	11.6	16	6.2
oseltamivir only (O)	2,132,136	36	16.9	22	10.3
zanamivir only (Z)	740,128	7	9.5	3	4.1
peramivir only (P)	47,648	1	21.0	1	21.0
laninamivir only (L)	72,655	7	96.3	4	55.1
acetaminophen only (A)	611,077	9	14.7	6	9.8
oseltamivir and acetaminophen (OA)	4,294,658	39	9.1	22	5.1
zanamivir and acetaminophen (ZA)	1,522,938	5	3.3	1	0.7
peramivir and acetaminophen (PA)	12,297	1	81.3	0	0.0
laninamivir and acetaminophen (LA)	1,661,996	19	11.4	8	4.8
Age: 10–19					
un-administered (U)	2,127,086	38	17.9	28	13.2
oseltamivir only (O)	487,005	11	22.6	8	16.4
zanamivir only (Z)	1,662,907	35	21.0	13	7.8
peramivir only (P)	87,464	4	45.7	2	22.9
laninamivir only (L)	1,330,413	13	9.8	8	6.0
acetaminophen only (A)	682,258	7	10.3	7	10.3
oseltamivir and acetaminophen (OA)	890,035	9	10.1	4	4.5
zanamivir and acetaminophen (ZA)	3,977,858	43	10.8	20	5.0
peramivir and acetaminophen (PA)	22,219	0	0.0	0	0.0
laninamivir and acetaminophen (LA)	3,590,311	17	4.7	12	3.3

Note: The upper panel shows the situation for 5–9 years old patients. The lower panel shows the situation for 10–19 years old patients. Data for the number of influenza patients by prescribed drug were from the National Database of Electronic Medical Claims for the study period of September 2009–March 2016. For peramivir, it was after September 2010. For laninamivir, it was after September 2012. Non-prescribed (U) shows patients for whom neither NI nor acetaminophen was prescribed. For acetaminophen, the number includes both continuous use and taken as needed. We cannot divide the data related to their respective uses. The incidence rate is defined as the corresponding number of abnormal behavior cases divided by the number of influenza patients multiplied by one million.

Actually, U and A patients were not be administered NI. Therefore, those patients might show milder symptoms than those shown by patients with NI. However, Table 2 presents the implication that U is risker than OA, ZA, and LA, and that A is risker than ZA or LA, even though insignificant difference were found for some combinations of age and severity. Therefore, U or A patients do not show mild symptoms, at least in abnormal behavior.

The incidence rate of P and PA in Table 1 seem quite higher than others. Peramivir, unlike other NI, is an injected drug that is regarded as useful for hospitalized patients with severe complication or patients who are unable to take drugs orally or through inhalation [19,20]. Therefore, the number of prescriptions and administration are expected to be much smaller than those of other NI. Therefore, its incidence is expected to be higher. This

Table 2
Results of Relative Risks and their *p*-values (Significant Results Only).

Age		5–9		10–19	
Numerator	Denominator	Severe	Most Severe	Severe	Most Severe
un-administered (U)	laninamivir only (L)	0.1 (0.000)	0.1 (0.002)		
un-administered (U)	oseltamivir and acetaminophen (OA)				2.9 (0.033)
un-administered (U)	zanamivir and acetaminophen (ZA)	3.5 (0.005)	9.4 (0.005)	1.7 (0.026)	2.6 (0.001)
un-administered (U)	laninamivir and acetaminophen (LA)			3.8 (0.000)	3.9 (0.000)
oseltamivir only (O)	laninamivir only (L)	0.2 (0.000)	0.2 (0.010)		2.7 (0.047)
oseltamivir only (O)	oseltamivir and acetaminophen (OA)	1.9 (0.009)	2.0 (0.024)		3.7 (0.033)
oseltamivir only (O)	zanamivir and acetaminophen (ZA)	5.1 (0.000)	15.7 (0.000)	2.1 (0.044)	3.3 (0.008)
oseltamivir only (O)	laninamivir and acetaminophen (LA)			4.8 (0.000)	4.9 (0.001)
zanamivir only (Z)	laninamivir only (L)	0.1 (0.000)	0.1 (0.002)	2.2 (0.019)	
zanamivir only (Z)	zanamivir and acetaminophen (ZA)			1.9 (0.004)	
zanamivir only (Z)	laninamivir and acetaminophen (LA)			4.4 (0.000)	2.3 (0.050)
peramivir only (P)	laninamivir only (L)			4.7 (0.018)	
peramivir only (P)	acetaminophen only (A)			4.5 (0.028)	
peramivir only (P)	oseltamivir and acetaminophen (OA)			4.5 (0.024)	
peramivir only (P)	zanamivir and acetaminophen (ZA)			4.2 (0.018)	
peramivir only (P)	laninamivir and acetaminophen (LA)			9.7 (0.001)	6.8 (0.043)
laninamivir only (L)	acetaminophen only (A)	6.5 (0.001)	5.6 (0.016)		
laninamivir only (L)	oseltamivir and acetaminophen (OA)	10.6 (0.000)	10.7 (0.001)		
laninamivir only (L)	zanamivir and acetaminophen (ZA)	29.3 (0.000)	83.8 (0.000)		
laninamivir only (L)	laninamivir and acetaminophen (LA)	8.4 (0.000	11.4 (0.001)		
acetaminophen only (A)	zanamivir and acetaminophen (ZA)	4.5 (0.000)	15.0 (0.003)		
acetaminophen only (A)	laninamivir and acetaminophen (LA)				3.1 (0.023)
oseltamivir and acetaminophen (OA)	zanamivir and acetaminophen (ZA)	2.8 (0.025)	7.8 (0.015)		
zanamivir and acetaminophen (ZA)	peramivir and acetaminophen (PA)	0.0 (0.047)			
zanamivir and acetaminophen (ZA)	laninamivir and acetaminophen (LA)	0.3 (0.008)	0.1 (0.041)	2.3 (0.003)	

Note: Only significant results are shown. Numbers without parenthesis denote the relative risk, which is the incidence of the first column divided by the incidence of the second column. Numbers within parentheses are *p*-values for relative risk in the same cell. A null cells or not shown combinations represent insignificant results.

limitation may be resolved by accumulation of data for abnormal behavior.

Another limitation is that the amount and duration of administration of oseltamivir, zanamivir, or acetaminophen were not analyzed. Conversely, laninamivir or peramivir were administered at once. The amount and duration of the administration of those drugs might be important information if abnormal behavior reflects a doze response. To solve this issue, we must change the questionnaire format for reporting. That remains as a challenge for additional research.

5. Conclusion

We demonstrated that acetaminophen alone or co-administered with NI does not raise the risk of abnormal behavior in influenza patients. On 21 August 2018, MHLW abolished the Yellow Letter restricting the issuance of prescription of oseltamivir to 10–19-year-old influenza patients [21]. We hope our studies contributed to that decision. However, because novel drug other than NI or generic NI drugs were launched in 2018, we must monitor the association of abnormal behavior of influenza patients and administered drugs continuously.

Conflicts of interest

No author has any conflict of interest, financial or otherwise, to declare in relation to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.01.008.

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