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Original Article

Severe abnormal behavior incidence after administration of neuraminidase inhibitors using the national database of medical claims

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ABSTRACT

An earlier study using the number of abnormal behaviors reported to the study group as the numerator and the number of influenza patient prescribed each neuraminidase inhibitor (NI) estimated by respective pharmaceutical companies found no significant difference among incidence rates of the most severe abnormal behaviors by type of NI throughout Japan. However, the dataset for the denominator used in that earlier study was the estimated number of prescriptions. In the present study, to compare the incidence rates of abnormal behavior more precisely among influenza patients administered several sorts of NI or administered no NI, we used data obtained from the National Database of Electronic Medical Claims (NDBEMC) as the denominator to reach a definitive conclusion. Results show that patients not administered any NI (hereinafter un-administered) or those administered peramivir sometimes showed higher risk of abnormal behavior than those administered oseltamivir, zanamivir, or laninamivir. However, the un-administered or peramivir patients were fewer than those taking other NI. Therefore, accumulation of data through continued research is expected to be necessary to reach a definitive conclusion about the relation between abnormal behavior and NI in influenza patients. Since severe abnormal behaviors with all types of NI or of un-administered patients have been reported, there are some risks in the administration of NI or even in un-administered cases. Therefore, we infer that the policy mandating package inserts in all types of NI.

1. Introduction

Since two influenza-infected Japanese junior high students jumped from a great height and died in February 2007, abnormal behavior in influenza patients, especially teenagers, has been an international public health concern. However, although many investigations have examined abnormal behavior in Japan as well as other countries, especially such behavior related to administered drugs, no report of a relation has been forthcoming [1–14].

Our first study of Japan, which used the number of abnormal behaviors reported to the study group as a numerator and the number of influenza patients prescribed each neuraminidase inhibitor (NI) provided by the pharmaceutical companies as the denominator, found no significant difference among incidence rates of the most severe abnormal behaviors by type of NI [15]. Results indicated a negative perspective to the putative relation between abnormal behavior and prescribed NI. That report was the first of an examination for relative risk among types of NI. However, the study had several limitations, the most important of which was that the

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numbers of influenza patients prescribed each NI were estimated and reported by pharmaceutical companies. The data were estimated from three databases: one database covered only 0.9% of all pharmacies in Japan; the other two databases respectively included medical claims for approximately 0.8% and 0.4% of the total population. Moreover, these three databases had been evaluated for their precision by only a single study [16].

A second shortcoming was that these three databases identified only NI-prescribed influenza patients. The databases cannot show the number of influenza patients who had *not* been prescribed NI. However, the research group investigating abnormal behavior of influenza patients found that a substantial fraction of abnormal behavior cases had occurred with influenza patients who had not been administered NI. Therefore, our previous study [15] was able to evaluate relative risks among types of NI, but it was unable to evaluate the absolute risk of NI compared with that of non-prescribed patients.

To overcome these two shortcomings, other data covering the entire population and including some information about non-prescribed influenza patients are needed. Fortunately, such a useful database can be accessed: the National Database of Electronic Medical Claims (NDBEMC) includes all electronic medical claims, accounting for about 96.2% of all medical claims throughout Japan. Moreover, all physicians are obligated to record a diagnosis on medical claims [17–19]. As described herein, we examine those data using the number of patients with or without NI from NDBEMC as the denominator to compare the most reliable incidence rate of abnormal behavior available at the moment and thereby to reach a conclusive answer for this important question.

2. Materials and methods

2.1. Data

Definitions of abnormal behavior in patients with influenza and the methods for investigation were described in a report of a previous study [11]. In brief, all cases of patients with influenza who presented with severe abnormal behavior were reported by physicians of all clinics and hospitals throughout Japan, based on a request from the section managers of the Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare (MHLW), and of the Safety Division of Pharmaceutical and Food Safety Bureau, MHLW. All reports were made either online or via fax.

For this study, influenza-like illness was defined as showing any of the following symptoms: (A) acute onset, high fever >38 °C, upper respiratory symptoms, and systemic symptoms including fatigue, or (B) positive results from an influenza rapid diagnosis kit [11]. We defined severe abnormal behavior as active motion behavior 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. Additionally, we defined the most severe abnormal behaviors as only sudden running away and jumping from a high place because they can be expected to lead to death with higher probability than other severe abnormal behaviors.

In Japan, the influenza season is defined as the period from the 36th epidemiological week to the 35th week of the following year. We applied the survey of abnormal behaviors to the 2006/2007 to 2014/2015 season.

After approval was obtained from MHLW, the numbers of patients diagnosed as influenza, either prescribed or not-prescribed NI, excluding suspected cases, were extracted and counted using the National Database of Electronic Medical Claims (NDBEMC). This national database for electronic medical claims accounts for 96.2% of all medical claims in Japan as of September 2013. The count made by NDBEMC is regarded as the true number of influenza patients. We were permitted to use the NDBEMC information obtained from seasons 2010/2011 through 2013/2014 [20].

2.2. Study period and subjects

The information of NDBEMC is available for a shorter period than information related to abnormal behavior. Therefore, the study period was limited to the 2010/2011 to 2013/2014 seasons. Subjects were grouped into two age groups: 5–9 and 10–19, years old.

2.3. Analysis

We evaluated differences in incidence rates among types of NI and not administered any NI (hereafter, un-administered) groups of patients using a Fisher's exact test. We adopted 5% as the significance level.

2.4. Ethics

For the investigation of abnormal behavior patient records and information were anonymized and de-identified before analysis: we collected no personally identifiable information such as names, addresses, or dates of birth. Moreover, we counted only patients with a certain condition from the collected information. Ethical guidelines for epidemiological research in Japan require no receipt of informed consent from patients in this case. The studies of abnormal behavior were approved by the NIID Committee for Ethical Consideration: approval numbers were 261, 312, 375, and 462. Use of NDBEMC data was approved on May 12, 2015 by the Health Insurance Department, MHLW, Japan.

3. Results

Table 1 presents the number of influenza patients of two age groups, 5–9, and 10–19-year-old patients, including both prescribed NI and non-prescribed patients, in each season from NDBEMC. The total estimated number of patients, irrespective of whether NI had been prescribed or not, was 1.2–2.3 million for ages 5–9. For ages 10–19, the total estimated number of patients was 1.5–2.1 million. The respective maximum and minimum numbers of NI were 0.18 and 0.10 million for oseltamivir, 0.74 and 0.50 million for zanamivir, 0.85 and 0.45 million for laninamivir, and 0.03 and 0.00 million for peramivir.

Table 2 presents the number of abnormal behavior cases and incidence per million patients by age group for patients administered NI and un-administered patients. The largest number of cases of abnormal behavior was observed for ages 5–9 with oseltamivir in both most severe (12 cases) and all severe abnormal behavior (22 cases). However, the largest number of incidences was shown for ages 5–9 with peramivir: 46.6 in all severe abnormal behaviors.

The relative risk and resultant *p*-values of the exact test are presented in Table 3 for the most severe cases. Results of the exact test show that the incidence of the most severe abnormal behavior with zanamivir was significantly lower than un-administered for ages 5–9 (the relative risk was 0.09). For ages 10–19, the incidence of un-administered was higher than with zanamivir (4.76) or laninamivir (4.55). Table 4 presents the relative risk and *p*-values of the exact test for all severe cases. Results of all severe abnormal behavior mostly include the results for the most severe case, which are zanamivir and un-administered for ages 5–9 (0.05), and laninamivir and un-administered for ages 10–19 (0.30). Moreover, for all cases of severe abnormal behavior, the incidence of un-

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