J Infect Chemother 20 (2014) 789–793

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

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

Original article

Abnormal behavior during influenza in Japan during the last seven seasons: 2006–2007 to 2012–2013

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ARTICLE INFO

Article history:
Received 21 May 2014
Received in revised form
13 August 2014
Accepted 16 August 2014
Available online 3 October 2014

Keywords:
Abnormal behavior
Influenza
Oseltamivir
Antiviral drug

ABSTRACT

A few mortalities and cases of severe abnormal behavior have been reported after oseltamivir administration for influenza, thus increasing medical and public concerns regarding the drug's safety. We investigated the association between oseltamivir and abnormal behavior for seven years. All outpatient clinics and hospitals all over the country were requested to report severe abnormal behavior that could have resulted in a fatality if nobody intervened, such as abrupt running outside the home or intention of jumping off a building. The survey was performed prospectively between the 2007–2008 and 2012–2013 seasons, and retrospectively for the 2006–2007 season. As the result of the investigation, eight-hundred fifty-eight cases were reported and among of them 95.7% were positive by the influenza rapid diagnosis test. The epidemic curve of severe abnormal behavior showed a pattern similar to influenza-like illness. The same pattern was observed regardless of age group, gender, or timing of the incidents after waking. Consequently, specific association between the types of medications used or the types of antiviral and abnormal behavior was not observed clearly. The reported abnormal behaviors include fatal cases that would have died if nobody had stopped. This suggested that patients with influenza should be observed with caution for possible abnormal behavior whether taking oseltamivir or other neuraminidase inhibitor anti-influenza drugs.

1. Introduction

On November 12, 2005 at the Japanese Society for Pediatric Infectious Diseases [1], it was presented an association between oseltamivir administration and the deaths of two teenagers who were behaving abnormally, and this report became a matter of medical and public concern. On February 28, 2007, after being administered oseltamivir, a boy jumped off a building and died. Although a link between oseltamivir and such abnormal behavior was not established, the Ministry of Health, Labour and Welfare (MHLW) recommended on March 20, 2007 that doctors are required to abstain to prescribe oseltamivir (and other antiviral) for patients aged 10–19 years. They also added a recommendation that family members of patients with influenza should watch them carefully. These two recommendations have been followed since then. The relationship between oseltamivir administration and abnormal behavior has been examined in various studies, however, specific association between them has not been shown [2–9]. At the same time, MHLW established the research group to investigate about abnormal behavior among patients with influenza-like illness (ILI). Hence, we studied the reported cases retrospectively in the 2006–2007 season and conducted prospective studies in the last six seasons (2007–2008 to 2012–2013). This study summarizes the results obtained during the past seven years.

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http://dx.doi.org/10.1016/j.jiac.2014.08.016
1341-321X/

2. Materials and methods

All outpatient clinics and hospitals all over the country were requested to voluntarily report patients with ILI who presented with severe abnormal behavior. All reports were made either online or via Fax to the Infectious Diseases Surveillance Center, National Institute of Infectious Diseases (NIID).

2.1. Reporting criteria

Abnormal behavior in patients with influenza was defined as that in patients with ILI, and included behavior that deviated from normal behavior often observed among influenza patients. ILI was defined as shown all the following symptoms: acute onset, high fever >38 °C, upper respiratory symptoms, systemic symptoms including fatigue, or positive results from an influenza rapid diagnosis kit. Although abnormal behaviors vary from hallucination without motion to delirium with sudden running away, in this study, severe abnormal behavior was defined as active motion behavior which can be life-threatening if no one intervened, including sudden running away, intention to jumping off from a high altitude, rampage with self-injury, and so on.

2.2. Analysis

First, we compared the number of patients of severe case of abnormal behavior with the number of ILI patients per sentinel from official sentinel surveillance based on the Infectious Diseases Control Law by week. The number of patients of severe case of abnormal behavior was summed up to week based on fever onset date. Official sentinel surveillance has been reporting the number of ILI patients per sentinel medical institution from about 3000 pediatric and 2000 internal medicine medical facilities (5000 of 65,000 facilities in nationwide).

Moreover, the patients of severe abnormal behavior were analyzed about age, highest body temperatures, timing of abnormal behavior and kind of taking drug. About age of patients, we used ANOVA (analysis of variance) to compare age distribution in each season. ANOVA analysis is used for comparison of multiple independent populations [10]. In this study, we employed 5% as significant level. About drug use, cases are classified into not taking any drug, acetaminophen only, zanamivair only, zanamivir and acetaminophen, oseltamivir only, oseltamivir and acetaminophen, laninamivir, multiple combinations of antivirals with/without acetaminophen. In this classification, if the administration could not identified at least one drug of antivirals and acetaminophen, then the kind of status was defined “Unknown”. Analyses initially included all cases with severe abnormal behavior and included only cases with abrupt running or intention of jumping off buildings.

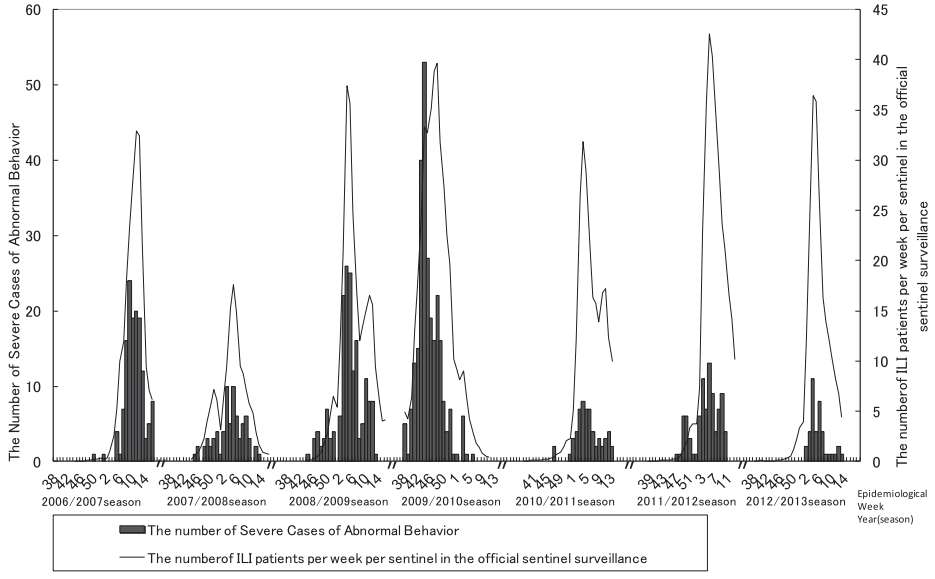
2.3. Ethics

The study was approved by the NIID committee for ethical consideration, and approval numbers 129, 216, 261, 312, 375, and 462 were obtained for each year.

3. Results

A total of 859 cases with severe abnormal behavior were reported from 2006–2007 season to 2012–2013 season, The maximum number of cases in each season was 272 (in 2009–2010 season), and the minimum number was 43 (in 2012–2013 season). Of all cases, 95.7% were positive by the influenza rapid diagnosis test.

Fig. 1 shows the time of fever onset for the patients who presented with severe abnormal behavior (bar chart) along with the same details regarding official sentinel surveillance (line), which consisted of 3000 pediatric and 2000 internal medicine medical



Note: The bar chart indicates the number of severe cases of abnormal behavior (left axis), and the line chart indicates the number of ILI patients per week per sentinel in the official sentinel surveillance (right axis).

Fig. 1. Fever onset date in patients who displayed severe abnormal behavior and patients with influenza-like illness (ILI) in the official sentinel surveillance.