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Review

Influenza and the use of oseltamivir in children

Ergin Çiftçi[1], Adem Karbuz[1], Tanıl Kendirli[2]

[1]Department of Pediatrics, Division of Pediatric Infectious Diseases, Ankara University School of Medicine, Ankara, Turkey
[2]Division of Pediatric Intensive Care, Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey

Abstract

Influenza is an infectious disease which causes significant morbidity and mortality. In the USA, approximately 200 000 hospital admissions and 36 000 deaths occur annualy due to severe influenza infections. Although influenza often causes a simple respiratory infection, it sometimes causes disorders affecting several organs including the lung, heart, brain, liver and muscles or serious life-threatening primary viral or secondary bacterial pneumonia. Currently, oseltamivir is the most important and effective drug for severe influenza infections. Severe influenza infections can be controlled and related deaths may be prevented with initiation of this drug especially within first 2 days. Oseltamivir is usually well tolerated and its most commonly reported side effect is related with the gastrointestinal system. In conclusion, the course of influenza changes in a positive direction and the rates of complications and mortality significantly reduce in patients in whom oseltamivir treatment is initiated as soon as possible.

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Keywords: Critically ill child, influenza, oseltamivir, pediatric intensive care

Introduction

Influenza is an infectious disease which causes significant morbidity and mortality. In the USA, it is responsible of approximately 200 000 hospital admissions and 36 000 deaths annualy (1). Influenza is a disease caused by influenza viruses which has a sudden onset, causes respiratory tract infection with fever and generally limits itself. However, it may also lead to acute respiratory distress syndrome (ARDS), meningitis, encephalitis and similar life-threatening severe clinical conditions. Currently, the most important and efficient drug for severe influenza infections is oseltamivir. With initiation of this drug especially in the first two days, severe influenza infections can be brought under control and prevention of related deaths may be achieved (1-3).

General information about influenza

Influenza viruses are included in the Orthomyxoviridae family. They are classified in three different types including influenza A, influenza B ande influenza C according to major antigenic properties. The types which most commonly cause to morbidity in humans are influenza A and B.

Influenza A is divided into different subtypes with completely different antigenic properties as a result of different associations of the hemagglutinin and neuraminidase structures which are surface glycoproteins. At least 16 different hemagglutinins and 9 different neuraminidases are found in influenza A (2). A single hemagglutinin and a single neuraminidase are present in influenza B. While hemagglutinin is responsible of binding of the virus to sialic acid receptors found on the respiratory tract epithelial cells of the host, neuraminidase is responsible of release of virions from the infected cells and development and progression of the disease (3). All types of hemagglutinins and neuraminidases are found in poultry, whereas hemaglutinin type 1, 2, 3 and 5, 7 and 9 (in recent years), neuraminidase type 1 and 2 have been found in humans in seasonal influenza, epidemics and pandemics (2).

Address for Correspondence: Adem Karbuz, E-mail: karbuzadem@hotmail.com
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Antigenic drift and shift which occur as a result of minor and major changes in hemagglutinin and neuraminidase glycoproteins are the precursors of epidemias and pandemias, respectively. Antigenic shift occurs only in influenza A virus and a new virus different from the old virus emerges (1, 2).

Standard denomination of influenza viruses by the World Health Organization (WHO) is made by influenza-specific type, host (for strains of animal origin), place of first isolation, number of the strains and year of isolation, respectively. In addition, associations of hemagglutinin and neuraminidase are written in parenthesis in influenza A. For example, the influenza A epidemic which started in 1977 in Russia was defined as follows: A/USSR/90/77 (H1N1), Influenza B/Hong Kong/20/2003 (1, 2, 4).

Influenza and its effects

Although influenza causes a simple respiratory tract disease with fever, it may sometimes lead to disorders which involve many organs including the lung, heart, brain, liver and muscle and even severe life-threatening viral or bacterial pneumonia (3). Influenza which causes both seasonal disease and epidemics and pandemics has a severe course in extreme age groups (<6 months or >65 years) and in individuals with accompanying comorbidity and necessitates hospitalization and even intensive care support. Especially the individuals who suffer from chronic cardiovascular and lung disease, who receive regular medical care because of chronic metabolic disease, who have immune deficiency, who can not remove respiratory secretions, who have neurological disease predisposing to microaspirations, elderly people and children carry a high risk (2, 5).

Pandemics caused by influenza viruses

Three important influenza pandemics occurred in the past 20th century: (H1N1, Spanish Flu) in 1918, (H2N2, Asian Flu) in 1957 and (H3N2, Hong Kong Flu) in 1968. The most dramatic impact among these occurred with 1918 Spanish H1N1 pandemic which is thought to have caused to death of approximately 50-100 million people worldwide (6). The last influenza pandemic occurred in 2009 with H1N1. It was named swine flu because it originated from swines. Many studies addressing hospitalizations related with pandemic H1N1, intensive care requirements in hospitalized patients, mortality results and clinical properties of the patients in detail were published from different parts of the world (7-10). According to the data of the Centers for Disease Control and Prevention, it was estimated that about 61 million people were affected from pandemic H1N1 between April 2009 and April 2010, 274 000 hospitalizations were required and 12 470 patients died (7). The World Health Organization reported more than 17 798 cases of laboratory confirmed "Pandemic Influenza (H1N1) 2009" including mortality from more than 214 countries and regions worldwide by the date of April the 11st, 2010 (8).

In the studies published, it was reported that hospitalization occurred in 1-10% of the pandemic H1N1 cases and intensive care was required in 10-25% of the patients who were hospitalized (9). In a multi-center study conducted in Turkey, requirement for intensive care was found in 15.6% of the children who were hospitalized because of confirmed H1N1 and 30.1% of these patients were lost (9). In a study conducted in Argentina, requirement for intensive care was found in 19% of the patients who were hospitalized and 5% of these patients were lost (10).

The most commonly observed clinical finding in patients who require intensive care is respiratory failure (9, 11). The mortality rate was found to be 0-47% in patients who were being followed up in intensive care unit and found to have pandemic H1N1 (12, 13). The main reason of mortality related with H1N1 infections is respiratory failure and ARDS. In addition, multiple organ failure related with severe hypoxia and cardiovascular failure and secondary bacterial infections leading to pneumonia or sepsis also contribute to the mortality rate (9).

Antiviral treatment in influenza disease

In cases of severe influenza, antiviral treatment initiated as soon as possible in addition to supportive treatment is lifesaving. Among the antiviral drugs which act by inhibiting influenza virus replication; amantadin, rimantadin, zanamivir and oseltamivir are available on the market. The first two of these are M2 inhibitors and act only on influenza A. Zanamivir and oseltamivir are neuraminidase inhibitors and act on both influenza A and influenza B. In recent years, use of M2 inhibitors have not been recommended because of widespread development of resistance and treatment failures (3). Currently, oral oseltamivir and zanamivir administered by inhalation are the main drugs which are used and recommended for treatment and prevention of influenza (14). Peramivir is the only neuraminidase inhibitor drug administered by the intravenous route as a single dose which was licensed in 2010 in Japan and Republic of Korea and was approved by the FDA (Food and Drug Administration) in USA for treatment of uncomplicated acute influenza in Decem-

ber 2014 in individuals aged older than 18 years. There are limited data related with use of peramivir in treatment of severe influenza with complications. An adult patient with myocarditis who presented with heart failure and showed a fatal prognosis related with influenza A reported in Korea was treated successfully with a single dose IV administration of peramivir (15).

Influenza viruses hold on to the host cells by way of viral hemagglutinins and infect the cells. As viral replication progresses in the infected cell, neuraminidase is synthesized. The synthesized neuraminidase separates sialic acid in the glycoproteins which act as receptors for adherence of the virus found on the surface of the host cell. In this way, the severity of infection increases by release of viral particles from the infected cells and spread of the virus from cell to cell. With inhibition of this enzyme, the virus is kept bound to the host cell and other virions. As a result, spread of the virus from cell to cell and infection of cells are prevented (2, 16).

Oseltamivir

Oseltamivir was approved by the FDA in 1999 for the first time for children aged older than 13 years and for adults for treatment and prophylaxis of influenza. In 2000, the age limit in treatment of influenza was reduced to one year and use of prophylaxis in this age group was also approved in 2005. In 2009 pandemic influenza period, use of oseltamivir was authorized transiently in babies aged younger than 1 year old between April the 28th, 2009 and October the 23th, 2010 (16, 17). Oseltamivir was approved in more than 100 countries by February 2011 and it has been used in more than 83 million patients since it was put on the market (18). Oseltamivir dose recommendations for treatment and prophylaxis of influenza are shown in Table 1 (14). The World Health Organization recommends oseltamivir treatment for all patients in severe and progressive influenza and even recommends a higher dose and longer treatment depending on the clinical reponse for patients with immunosupression.

Oseltamivir is a prodrug with good bioavailability when used by the oral route in contrast to zanamivirin. Seventy five to eighty percent of the dose given orally is easily absorbed in the gastrointestinal system. In hepatic cells, more than 90% is transfromed to oseltamivir carboxylate which is an active metabolite. Intake of oseltamivir with food does not affect the plasma concentration, but the time to reach the highest concentration may be prolonged. Oseltamivir carboxylate is distributed well in the regions in the upper and lower respiratory tract which are affected by viral infection. Both the prodrug oseltamivir phosphate and ist active metabolite oseltamivir carboxylate are eliminated in urine without changing by way of tubular secretion. In individuals with renal failure with a creatinine clearance lower than 30 mg/mL, the dose should be adjusted. There is insufficient information about the issue if the dose should also be adjusted in patients with hepatic failure. The plasma half life of oseltamivir carboxylate is between 6 and 10 hours. This allows twice a day dosing (2, 16-18).

Table 1. Oseltamivir doses recommended for prophylaxis and treatment of influenza (obtained from CDC, FDA and Tamiflu® product information)

Drug Influenza type	Age (years)	Treatment dose (5-day)	Prophylaxis dose (10-day)
	0-1 year[a]		
	<14 days[b]	3 mg/kg/dose, once a day	Not applied
	<3 months	3 mg/kg/dose, twice a day	Not applied
	3-11 months	3 mg/kg/dose, twice a day	3 mg/kg/dose, once a day
Oseltamivir, Influenza type A and B	1-12 years		
	<15 kg	30 mg, twice a day	30 mg, once a day
	15-23 kg	45 mg, twice a day	45 mg, once a day
	24-40 kg	60 mg, twice a day	60 mg, once a day
	>40 kg	75 mg, twice a day	75 mg, once a day
	13-17 years and adults	75 mg, twice a day	75 mg, once a day

[a]Oseltamivir has been approved by FDA for use in children aged below one year. On April the 28th, 2009, approval was given by FDA for use in emergency. This was terminated on June the 23th, 2010. However, children aged below one year were also included for use of oseltamivir by FDA on December the 21st, 2012.

(see. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333205.htm) .

[b] The WHO later recommended use of oseltasmivir at a dose of 3 mg/kg/dose once a day for treatment of patients who are found to have suspicious or confirmed influenza for children aged below 14 days.

(see. http://www.cdc.gov/flu/professionals/antivirals/antiviral-dosage.htm).

Oseltamivir usually has few side effects and the most commonly reported side effect is related with the gastrointestinal system. Vomiting is observed in approximately 15% of the children who use this drug. The other side effects include diarrhea, abdominal pain, nausea, insomnia, dizziness, headache and ear disorders. In addition, a very important side effect which was found in the post-marketing period and which was mostly reported in Japan is neuropsychiatric symptoms which may even lead to death (19, 20). In Japan, a 15-year old girl who was given oseltamivir for treatment of influenza developed delirium like symtomps including insomnia, visual hallucinations and long-term memory loss. These findings disappeared following discontinuance of the drug and initiation of benzodiazepin treatment. In this patient who had no previous neurological disease and whose neurological examination was performed in detail, it was found that abnormal decceleration on EEG which is characteristic for influenza-related encephalopathy was not observed, the active metabolite of oseltamivir was eliminated later than expected, CSF glutamate receptor antibodies increased and dysfunction was present in the limbic gamma aminobutiric acidergic nerves (21). However, the issue if the neuropsychiatric effects are directly related with the drug or with influenza itself has not been elucidated (5, 22). Nevertheless, WHO emphasizes that use of this drug in young adolescents with sleep disorder should be closely monitored. Intake of oseltamivir with food causes a considerable decrease in gastrointestinal side effects. A clinically significant drug interaction related with oseltamivir has not been reported up to today (2).

Oseltamivir treatment, time of initiation of treatment and its effects on the disease

There are many publications related with the efficiency of oseltamivir treatment especially in the direction of the experiences obtained from 2009 H1N1 pandemic (9-13). The efficiency of use of oseltamivir on the disease was found to be positive both in previous seasonal influenzas and in the epidemics and the final pandemic. No severe advers effect related with the drug was observed.

Three hundred twenty seven patients who were treated in hospital because of severe seasonal influenza were examined retrospectively and 760 patients hospitalized because of influenza were examined prospectively. A significant reduction in the mortality rate was found in both groups (23, 24). In the study of Lee et al. (25), use of oseltamivir in the first four days was shown to be related with increased survival in multivariate logistic regression analysis.

H5N1 avian influenza (bird flu) has a more severe course compared to seasonal influenza. Progressive pneumonia which requires mechanical ventilation and leads to respiratory failure is found in a significant portion of the patients (26). By August the 10th, 2012, 359 of 608 confirmed avian H1N1 subjects reported to WHO since November 2003 have lost their lives (27). In a case series reported from Indonesia, it was noted that the mortality rate significantly decreased with oseltamivir initiated in the first 2 days (28). In addition, higer survival rates were obtained with use of oseltamivir in the four days after the onset of symptoms when the data of 91 patients whose disease onset times and oseltamivir initiation times could be reached were examined (case fatality rate 8/46 [17%] vs 31/45 [69%]; OR, 10; 95% CI, 3.9-28.2) (29).

In one study, a correlation was found between delayed elimination of pharyneal influenza viral RNA load and increased disease severity for 2009 pandemic H1N1 influenza (30). Presence of longer viral spread was found to be a significant and independent risk factor for prolonged hospitalization (31, 32). In a study reported from Vietnam, 292 patients who were found to be PCR-positive for pandemic H1N1 were hospitalized. All patients received oseltamivir treatment. In the first days of treatment, a rapid reduction was obtained in viral spread. On the fifth day of treatment, 86% of the patients became PCR-negative for H1N1. Fever subsided after the first 24 hours in 78% of the patients and a mild course was observed in all patients (33). The time of viral spread was shortened with early initiation of oseltamivir both in seasonal influenza and pandemic H1N1 (25, 31, 32, 34-36).

In most studies, the following point has been emphasized: the earlier oseltamivir treatment is initiated, the better the clinical outcome (37). The fact that no mortality was observed in a multi-center study reported from Korea and a mortality rate of only 0.1% was reported in a study conducted in Japan was associated with early diagnosis and early initiation of antiviral treatment (98.6%oseltamivir treatment) (38, 39). In the study of Jain et al. (40), the mean time of initiation of treatment was three days in the patients who were hospitalized because of severe pH1N1 (oseltamivir treatment was given to the majority), six days in the patients who required intensive care and eight days in the patients who died (treatment was not initiated in 48 hours in any of the patients) (40). In a study conducted by Lee et al. (25, 31), it was shown

that the hospitalization time was averagely shortened two days with use of oseltamivir in the first 48 hours of the disease in 356 patients who were hospitalized with laboratory confirmed influenza (25, 31).

In the study conducted by Coffin et al. (43), 1 257 children admitted to the pediatric intensive care were addressed. No difference was found in terms of time of stay in the intensive care unit, hospital mortality rate and presentation in seven days following discharge. However, the total hospital stay was found to be shorter in intensive care patients who were treated with oseltamivir compared to the patients who did not receive oseltamivir treatment. The patients who received treatment in the first 24 hours stayed in the hospital for an approximately 18% shorter time.

The results of a few studies in which the effects of oseltamivir treatment initiated for influenza were reported are summarized in Table 2 (33, 36, 38, 40, 43-46).

Oseltamivir and its use in intensive care unit

Intensive care unit patients are problematic in terms of many aspects. They may have multiple organ failure or shock. In these patients, problems in absorption may be observed in the gastrointestinal system depending on disrupted intestinal perfusion, intestinal wall edema and the disease severity. A few studies related with absorption and efficiency of oseltamivir in the intestines in such patients have been reported. In one study, the plasma concentration of oseltamivir carboxylate which is the active metabolite with administration of oseltamivir in intensive care patients was found to be 2 000-4 000-fold higher than 50% of the highest inhibitory level reported by Gubareva et al. (47) for pandemic influenza virus isolates. In this study, no correlation was found between high concentration and clinical outcomes. Assuming that the drug reaches to the infected lung tissue well, it has been reported that standard doses are sufficient, no higher doses are needed and dose adjustment is necessary in patients with renal dysfunction requiring dialysis (47, 48).

In the final H1N1 pandemic, it was shown that obesity was a risk factor for increased disease, but was not correlated with mortality in intensive care patients. It has been emphasized that obesity is a significant risk especially in patients admitted to intensive care unit (11). In a study related with the pharmacokinetics of oseltamivir used in obese patients, it was concluded that dose adjustment was not necessary (48).

During the severe 2009 H1N1 pandemic, some guidelines recommended administration of oseltamivir by the nasogastric route in adults. However, there is no guideline recommending this route for pediatric intensive care patients. In a study conducted in France, oseltamivir was given by the nasogastric route to 11 pediatric intensive care patients aged between 1 month and 16 years during the 2009 pandemic and the plasma concentrations were measured. Treatment was decided according to the clinical picture, presence of underlying severe comorbidity including lung and heart disease and immunosupression. Oseltamivir was given at a dose of 1.5-6.8 mg/kg/dose twice a day. No serious advers effect related with oseltamivir was observed even with the highest dose. Mild diarrhea developed in three children. The levels of both oseltamivir and its active metabolite oseltamivir carboxylate were found to be considerably higher above the lowest inhibitory (MIC) value for influenza and serious adverse effect related with the drug was not observed. This study showed that nasogastric administration could allow high-efficient therapeutical oseltamivir carboxylate in this age group. In addition, it was confirmed that oseltamivir had a wide safety range (49).

It has been previously emphasized that the most common reason of need for intensive care in the course of influenza is development of ARDS. Recently, extracorporal membrane oxygenation (ECMO) support has been used in many developed centers for acute respiratory distress syndrome. In a study in which the effect of ECMO support on oseltamivir treatment was examined, three patients were evaluated. Oseltamivir treatment was given to these patients at a two-fold higher dose. In two of the patients, a sufficient plasma oseltamivir carboxylate concentration was obtained. In one patient, a low plasma oseltamivir carboxylate concentration was found. It was thought that gastric hemorrhage and reduction in gastric movements caused this low concentration in this patient. As a result of this study, it was reported that the standard dose was sufficient to reach adequate plasma concentrations in patients who received ECMO support and this was safe, but more multi-center studies should be conducted (50).

Infection control precautions should be applied to prevent infection in the other patients who are hospitalized in the intensive care unit during follow-up of the patients with influenza which is transmitted by dropled spread. The main precautions include monitorization of patients in isolated rooms and paying attention to contact and droplet isolation precautions. In cases where patients can not be isolated, prophylaxis with oseltamivir in patients who

Table 2. Results of the studies which reported the effects of oseltamivir treatment initiated for influenza

Study	Influenza type	Study group	Oseltamivir treatment	Results and/or interpretations
Hien TT. et al. (33)	Pandemic H1N1	292 hospitalized patients Mean age 26.4 years (1-69 years)	All patients received standard oseltamivir treatment	Treatment days/patient RT-PCR On the 3rd day, 3.62% negative On the 5th day, 5.86% negative After 24 hours, 228/292 patients were afebrile Mild disease in all patients
Yu H et al. (36)	Pandemic H1N1	1291 patients Mean age 20 years (12-26 years) No need for intensive care	983 (76%) patients were treated with oseltamivir on the third day (mean) of the symptoms	Decrease in development of radiographically confirmed pneumonia with treatment, shorter lasting fever and decreased viral RNA scattering, no mortality
Ko JH. et al. (38)	Pandemic H1N1	804 patients Mean age 5 years (0-18 years) 95 intensive care patients	98.8% patients were treated with antiviral medication. Oseltamivir was given to 776 (98.6%) of 787 patients. Use of antiviral medication in the first two days of disease onset: 73%	No mortality was found possibly in relation with early diagnosis and early initiation of antiviral drugs
Jain S. et al. (40)	Pandemic H1N1	Data of 268 patients related with use of antiviral medication are present Mean age 21 years (21 days-86 years) 122 patients <18 years 67 intensive care patients	200 patients received antiviral treatment. 188 patients received oseltamivir treatment. The time of initiation of antiviral treatment was the third day (mean)	Use of antiviral drugs was found to be beneficial especially when initiated in the early period. When the patients who were admitted to intensive care or who died were examined, the rate of use of antiviral drugs in the first 48 hours following onset od symptoms was observed to be lower. 19 patients (7%) mortality: 90% received antiviral treatment. The mean time between disease onset and initiation of antiviral treatment : 8 days None of the patients received antiviral treatment in the first 48 hours following onset of symptoms
Coffin SE. et al. (43)	Seasonal influenza	1 257 pediatric intensive care patients Mean age 1.7 years	264 children were given oseltamivir in the first 24 hours after hospital admission	Initiation of oseltamivir in the first 24 hours after hospitaliation was found to be related with shorter hospital stay. However, no difference was found in terms of duration of stay in pediatric intensive care unit, hospital mortality rate and representation rate.
Louie JK. et al. (44)	Pandemic H1N1	1 950 intensive care patients 1859 hospitalized patients (95%) Data related with antiviral treatment are present Mean age 37 years (1 week-93 years) Survival in 1260 patients	1 676 (90%) patients were treated with neurominidase inhibitors. 183 patients (10%) did not receive treatment. 1 671 patients (99.76%) received oseltamivir.	A correlation was found between use of neurominidase inhibitors in treatment and survival: 107 (58%) of 183 patients who were untreated, 75% of 1676 patients who were treated (p≤.0001). As early as treatment is initiated, as higher the survival rate (p<.0001). Treatment initiated in 5 days following onset of symptoms increased the survivial rate compared to the patients who were given no treatment (p<.05). The mortality rate was 26% in all hospitsalized patients who received antiviral treatment and 42% in the ones who did not receive treatment.

Table 2. Results of the studies which reported the effects of oseltamivir treatment initiated for influenza

Study	Influenza type	Study group	Oseltamivir treatment	Results and/or interpretations
Morgan CI. et al. (45)	Seasonal influenza: Influenza A 67.6% Influenza B 30.2% H1N1 season: 94.3% confirmed H1N1, 4.8% untyped	312 patients hospitalized in relation with H1N1 Seasonal influenza in 222 children who needed intensive care Mean age for H1N1 influenza 107 months (56-154 months) Mean age for seasonal influenza 68 months (15-128 months)	For H1N1: oseltamivir treatment in the first 48 hours following presentation: 96% For seasonal influenza: oseltamivir treatment in the first 48 hours following presentation: 15%	Significantly lower morbidity and mortality in critically ill children who were found to have H1N1. This was related with the fact that children who had H1N1 were treated with oseltamivir with a higher rate compared to the ones who had seasonal influenza. Mortality rate for seasonal influenza: 11% Mortality rate for H1N1: 0%
Farias JA et al. (46)	Pandemic H1N1	437 patients with acute respiratory tract infection in pediatric intensive care unit 147 (34%) critically ill patients İnfluenza A H1N1 Mean age 10 months	28-day survival following pediatric intensive care unit admission: 92% with oseltamivir treatment 86% with oseltamivir treatment in 24 hours 28-day mortality following pediatric intensive care unit admission: 91% with oseltamivir treatment 68% with oseltamivir treatment in the first 24 hours	Use of oseltamivir in the first 24 hours following presentation at hospital has prophylactic effect OR 0.2 (CI 95% 0.07-0.54) 28-day mortality rate: 39% (n:57)

have had contact is used in most clinics. Oseltamivir given with the aim of prophylaxis following contact decreases, but does not completely eliminate the risk of infection. It should even be kept in mind that infection with oseltamivir-resistant influenza may develop afterwards (14). Oseltamivir prophylaxis should be used in risky patient groups considering the pros and cons. Again, no study related with this issue has been found in the literature.

Oseltamivir resistance

Oseltamivir resistance has been found with a rate of 0.9% in influenza A (H1N1) pdm 09 viruses tested by the Centers for Disease Control since October the 1st, 2015 and no resistance has been found in influenza A (H3N2) and influenza B viruses (51). In addition, the prevalence of influenza A (H1N1) pdm 09 virus which showed osletamivir resistance throughout 2013-2014 influenza season was found to be low (approximately 1%) in USA (52). Clinicians should follow up local surveillance data including influenza types and subtypes observed in communities and their resistance states. These data can be obtained from the CDC or national refence laboratories.

In conclusion, prognosis changes favourably in patients in whom oseltamivir treatment is initiated as soon as possible and both complications and mortality rates decrease with a significant rate. In cases where influenza is suspected stongly, initiation of oseltamivir treatment should be considered before the laboratory result is reported. Although studies have shown that use of oseltamivir is generally efficient and drug-related serious side effects are not observed in pediatric intensive care patients in whom the oral route can not be used, IV form of oseltamivir is necessary. It is clear that this gap will be closed in a short time

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