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REVIEW ARTICLE

# Widespread use of neuraminidase inhibitors in Japan

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**Abstract** Almost all patients with an influenza-like illness in Japan are now tested with rapid diagnostic tests, and when positive, they are treated with a neuraminidase inhibitor (NAI). Japan may have had the lowest case fatality rate for symptomatic illness (<0.001%, 198/20.7 million) in the H1N1/09 pandemic because of the universal implementation of early treatment with NAI. A study of 1,000 children hospitalized because of a H1N1/09 infection revealed that NAIs, primarily oseltamivir, had been used to treat 984 (98.4%) of the 1,000 patients. In 88.9% of the patients, treatment with NAIs was initiated within 48 h after the onset of illness. In addition to oseltamivir and zanamivir, the newly approved inhalant drug, laninamivir, and the newly approved intravenous drug, peramivir, were used in Japan during the 2010–2011 season. Neuropsychiatric disorders that were suspected of being adverse reactions to oseltamivir became a cause of concern in 2007. The Health, Labour and Welfare Ministry issued an emergency instruction to suspend the use of oseltamivir to treat patients between the ages of 10 and 19 years. However, according to the Vital Statistics data, the widespread use of oseltamivir has not caused an increase in deaths as a result of accidental falls or intentional jumps from buildings. Although oseltamivir is widely used in Japan, no outbreaks have been caused by oseltamivir-resistant viruses, and no serious illness caused by oseltamivir-resistant viruses has ever been reported.

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## Introduction

Since the approval of zanamivir for use in influenza virus infection in Japan in 1999, and of oseltamivir in 2000, rapid diagnostic tests have been routinely performed by clinicians in patients who have an influenza-like illness, and patients with positive test results, including otherwise healthy adults and children without any underlying illness, have usually been treated with neuraminidase inhibitors (NAIs) [1, 2].

It is also characteristic of Japan to use rapid diagnostic tests for influenza routinely, together with treatment with an NAI. Using the rapid tests [3] allows Japanese clinicians to diagnose influenza accurately and prescribe an NAI with confidence. The cost of rapid diagnostic tests and NAI treatment are largely covered by the public health insurance systems in Japan.

This article reviews several problems associated with the widespread use of NAIs in Japan, a situation not seen in any other country.

## Low influenza mortality rate and high rate of treatment with neuraminidase inhibitors in Japan

Even though 20.7 million cases of pandemic influenza A (H1N1) 2009 (abbreviated H1N1/09) infection were reported in Japan during the 2009–2010 season, only 198 deaths were reported nationwide [4]. Moreover, not only were there no reports of deaths of pregnant women, who

are considered at particularly high risk [5], but there were no severe cases that required mechanical ventilation among pregnant women. Japan may have had the lowest incidence of severe cases in the H1N1/09 pandemic and the lowest case fatality rate for symptomatic illness (<0.001%, 198/20.7 million) among the countries where a widespread epidemic was reported.

Although the number of influenza patients during the 2009–2010 season has been estimated to be 16% of the total Japanese population (20.7 million/128 million), 59% of the patients were children 15 years of age or younger (12.2 million/20.7 million) [6]. As in other countries, Japan had a large number of pediatric patients, but the number of pediatric deaths was very low: only 38 among children aged 14 years or younger and 41 among those aged 19 years old or younger. Average annual pediatric influenza mortality over the 5-year period from 2004 to 2008 in Japan was 31 deaths per year among the group aged 14 years old or younger and 34 deaths per year among the group aged 19 years old or younger. Thus, pediatric influenza deaths did not increase during the H1N1/09 epidemic in Japan.

By contrast, the numbers of pediatric deaths during the H1N1/09 pandemic increased in other countries. For example, the number of deaths among children increased markedly in the United States, where the estimated median number of deaths was 1,280. That number was at least several times higher than in the seasonal influenza epidemic [6].

The very low mortality rate caused by the H1N1/09 epidemic in Japan was probably attributable to the universal implementation of early treatment with NAIs since the year 2000. Early treatment with NAIs was more widely and more thoroughly implemented during the H1N1/09 epidemic than ever before. For example, a study of 1,000 hospitalized children because of a H1N1/09 infection revealed that NAIs, primarily oseltamivir, had been used to treat 984 (98.4%) of the 1,000 patients [6]. In 88.9% (593/667) of the patients for whom accurate data were available, treatment with NAIs was initiated within 48 h after the onset of illness, and in 69.9% (466/667), it was started within 24 h after the onset of illness. The result was that only 12 (1.2%) of the 1,000 patients required mechanical ventilation, and only1 patient died of H1N1/09 infection [6].

Treatment with NAIs may have been responsible for the markedly lower number of patients who developed serious viral pneumonitis, which typically starts on day 4–5 after the onset, than has been reported in other countries [7]. Surprisingly only a few autopsy cases showing the diffuse alveolar damage that is consistently associated with fatal cases of H1N1/09, were reported in Japan.

After the pandemic caused by H1N1/09, effectiveness of early treatment with NAIs in reducing serious cases and deaths was reported in several countries [5, 8–10]. Delayed use of antivirals was reported in England, where only 10% of the pediatric fatal cases had been treated with antiviral therapy within 48 h of symptom onset [11].

## Antiviral use in Japan

In addition to oseltamivir and zanamivir, the newly approved inhaled drug, laninamivir [12, 13] and the newly approved intravenous drug, peramivir [14], were used in Japan during the 2010–2011 season, bringing to four the total number of NAIs currently being used in hospitals and clinics nationwide. In addition to the NAIs, the polymerase inhibitor, T-705 (favipiravir), will be approved for use in Japan in the near future [15, 16].

Figure 1 shows the percentages of prescriptions for NAIs in five hospitals in Tokyo during the first wave of the H1N1/09 pandemic (September 2009–January 2010) and the second wave of the H1N1/09 pandemic (December 2010–February 2011). The total number of prescriptions, including the prescriptions for both adults and children, was 2,799 in the first wave and 1,835 in the second wave.

Oseltamivir accounted for more than 90% of the prescriptions for NAIs in Japan before the pandemic occurred, but because many teenagers contracted H1N1/09 influenza in the first wave of the pandemic, the percentage of prescriptions for zanamivir increased to 28% of the total in the first wave (Fig. 1). Oseltamivir cannot be prescribed for teenagers in Japan because of fear of the abnormal behavior that had been reported to be caused by oseltamivir. Laninamivir and peramivir began to be used in Japan in the second wave of the H1N1/09 pandemic. The percentage of prescriptions for oseltamivir has not changed, but the use of zanamivir has decreased in comparison with in the first wave.

The Japanese Association for Infectious Diseases recommends that influenza patients who have been hospitalized, especially patients with pneumonia, be treated with oseltamivir or peramivir, and that outpatients without

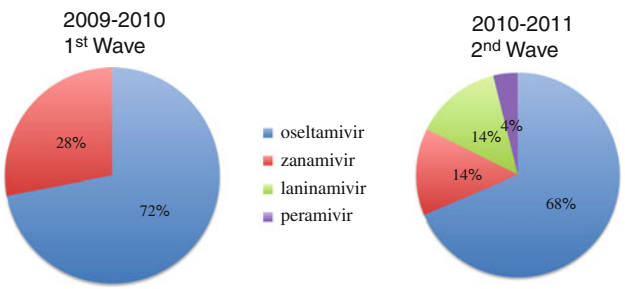


**Fig. 1** Percentage of patients who received prescriptions for neuraminidase inhibitors in Japan: *left*, during the first wave; *right*, during the second wave

**Table 1** Cost of treatment with neuraminidase inhibitors approved for use in Japan

| | |
|---|---|
| Oseltamivir (Tamiflu) | |
| Two capsules per day for 5 days | 3,090 yen (36 US$) |
| Zanamivir (Relenza) | |
| Two inhalations per day for 5 days | 3,370 yen (40 US$) |
| Laninamivir octanoate (Inavir) | |
| For children under 10 years | 2,080 yen (24 US$) |
| For adults | 4,160 yen (49 US$) |
| Peramivir (Rapiacta) | |
| For adults and children | 5,630 yen (66 US$) |

complications be treated with oseltamivir, zanamivir, or laninamivir. Peramivir can be used to treat outpatients who cannot be treated with oseltamivir or are unable to inhale zanamivir or laninamivir, especially young children and elderly persons.

## Prices of treatment with neuraminidase inhibitors

Table 1 compares the prices of the four NAIs currently approved for use in Japan. The lowest drug cost is for treatment of children under 10 years old with laninamivir, and the highest price is for intravenous treatment with peramivir. The price of laninamivir for children under 10 years old is 24 US dollars, whereas two inhalers are required to treat each adult, and the price is almost double, 49 US dollars. Because the cost of NAIs is covered by the public health insurance systems in Japan, patients pay only 10–50% of the cost shown in Table 1. Peramivir is not expensive in Japan, because peramivir is a long-acting NAI and is infused only once, on the first day of treatment.

## The long-acting neuraminidase inhibitors peramivir and laninamivir

### Peramivir

In 2010, intravenous peramivir was approved in Japan for the treatment of influenza A and B virus infection. Peramivir exhibits strong neuraminidase inhibitory activity against influenza A and B viruses [17], including pandemic H1N1 2009 and highly pathogenic viruses, such as the H5N1 subtype [18, 19]. The most important characteristics of peramivir are the certainty of drug delivery because it is administered intravenously and its long-lasting antiviral activity.

Peramivir is administered to adults as a single 300-mg intravenous dose infused over 15 min [20]. In Japan, peramivir is used as a long-lasting NAI because of its strong affinity for influenza virus neuraminidase [21], although the mechanism of the long-lasting activity of peramivir is different from laninamivir. The single 300-g intravenous dose of peramivir on the first day of treatment described above is sufficient for otherwise healthy adult patients (Fig. 2). For high-risk patients, including elderly patients and severely ill patients who require hospital admission, a 600-mg dose of peramivir is infused on the first day of treatment, and multiple daily doses are an option, depending on the condition of the patient. A 10 mg/kg dose of peramivir is administered to children on the first day of treatment and multiple daily doses are a treatment option, depending on the condition of the patient. Thus, peramivir can be used to treat patients ranging from high risk [14] to otherwise healthy.

**Fig. 2** *Left*, peramivir 150 mg vial; *right*, 300-mg bag for intravenous drip infusion

Peramivir exerts long-lasting anti-influenza activity following a single infusion. Peramivir strongly binds to the neuraminidase of influenza viruses and inhibits activation of neuraminidase much longer than oseltamivir or zanamivir [21]. Moreover, after a single intravenous infusion the serum concentration of peramivir is much higher than that of oseltamivir [20]. The median plasma concentration of peramivir has been reported to be nearly two orders of magnitude higher than after standard doses of oral oseltamivir, which is another factor that contributes to the long-lasting activity of peramivir. On the other hand, peramivir is rapidly excreted by the kidneys, and because almost none can be detected in the blood 24 h after an infusion [20], peramivir cannot be used prophylactically.

Peramivir should be administered within 48 h of the onset of illness. Early treatment with peramivir is essential, as with other NAIs. Some physicians think that peramivir should be used only in severe cases in which the patient's condition deteriorates after treatment with oseltamivir or zanamivir. However, the efficacy of treatment with peramivir 48 h after the onset of illness has not been

demonstrated. In view of the certainty of drug delivery because of being administered intravenously, peramivir should be administered as a first-line therapy, especially to the patients who have high-risk factors or cannot take drugs orally or inhale drugs.

Peramivir has cross-resistance with oseltamivir [22]. Repeated 600-mg doses of peramivir appear to be effective in patients infected with an oseltamivir-resistant virus [14]. Clinical tests of peramivir performed in children with influenza caused by pandemic H1N1/09 during the 2009–2010 season revealed a resistant virus with a H275Y mutation in about 6% of the children treated with peramivir. However, no extension of infection by the resistant virus to people in the vicinity or serious cases caused by the resistant virus have been reported.

### Laninamivir

Inhaled laninamivir was approved for use in Japan in 2010. Laninamivir octanoate, an octanoyl ester prodrug of laninamivir, has been shown to have neuraminidase inhibitory activity against various influenza A and B viruses, including oseltamivir-resistant viruses [23]. Laninamivir has also been shown to be effective against H5N1 virus in vitro [24]. The chemical structure of the active drug, laninamivir, is similar to that of zanamivir. The most important characteristic of laninamivir octanoate is its long-lasting antiviral activity, and because of this, laninamivir is administered in the form of a single inhalation on the first day of treatment.

The device for inhalation of laninamivir is shown in Fig. 3. Because the prodrug, laninamivir octanoate, has already been placed in the device, there is no need for the patient to insert any powder or capsules into the device. The doses indicated are 20 mg for children under 10 years old and 40 mg for children over 10 years old and adults.


**Fig. 3** Device for inhalation of laninamivir

The prodrug, laninamivir octanoate, is inhaled into the respiratory tract of the influenza patient, where it is absorbed by the epithelial cells lining the respiratory tract, possibly in the peripheral bronchioles. After entering the cells, laninamivir octanoate is rapidly hydrolyzed to the active substance, laninamivir. Laninamivir in the cells is slowly released into the respiratory tract, resulting in long-lasting anti-influenza virus activity. Thus, the mechanism of the long-lasting activity of laninamivir is basically different from that of peramivir.

Laninamivir octanoate rapidly appears in the plasma after inhalation and disappears with a half life of 2 h. The active substance, laninamivir, on the other hand, is slowly eliminated from the body, and remains in the plasma for as long as 144 h after administration, in other words, 6 days after inhalation [25].

A double-blind, randomized controlled trial revealed that a single inhalation of laninamivir was highly effective in children infected with the oseltamivir-resistant seasonal influenza A H1N1 virus with the H274Y mutation [12]. On the other hand, the efficacy of inhalation of laninamivir octanoate in adults has been reported not to be inferior to that of multiple oral doses of oseltamivir [13], although most of the viruses isolated in that study were oseltamivir-resistant seasonal H1N1 viruses with the H274Y mutation, the same as in the pediatric study. Otherwise healthy adults might have recovered rapidly from influenza regardless of whether they were treated with neuraminidase inhibitors because the influenza illness caused by the A H1N1 virus was mild in adults. No viruses resistant to laninamivir have ever been reported [12, 13].

## Abnormal behavior and neuraminidase inhibitors

Although NAI treatment has become routine therapy for seasonal influenza in Japan [26], neuropsychiatric disorders that were suspected of being adverse reactions to oseltamivir became a cause of concern in 2007. In March 2007, the Ministry of Health, Labour and Welfare issued an emergency instruction to suspend the use of oseltamivir to treat patients between the ages of 10 and 19 years because it was difficult for parents to prevent abnormal behavior by children who were treated with the drug. Because oseltamivir still cannot be prescribed for teenagers in Japan, teenagers with influenza virus infection are being treated with zanamivir, laninamivir, or peramivir.

It is unknown whether jumps or falls from buildings are a rare symptom of influenza or an adverse reaction to oseltamivir. In a case that was typical of those reported, a

**Table 2** Number of deaths in falls from buildings in the 10- to 19-year-old population from 1995 to 2005 based on Vital Statistics data [29]

| Year | Age 10–14 years | | Age 15–19 years | |
|---|---|---|---|---|
| | W13 | X80 | W13 | X80 |
| 1995 | 8 | 11 | 33 | 109 |
| 1996 | 8 | 9 | 24 | 113 |
| 1997 | 9 | 10 | 19 | 94 |
| 1998 | 12 | 23 | 38 | 138 |
| 1999 | 11 | 14 | 24 | 109 |
| 2000 | 9 | 16 | 27 | 130 |
| 2001 | 6 | 12 | 26 | 126 |
| 2002 | 7 | 12 | 21 | 79 |
| 2003 | 7 | 21 | 20 | 123 |
| 2004 | 5 | 11 | 15 | 98 |
| 2005 | 9 | 8 | 17 | 100 |

Oseltamivir has been used in Japan since 2001

W13 (ICD-10), fall from, out of, or through a building or structure; X80 (ICD-10), intentional self-harm by jumping from a high place

12-year-old boy who had taken oseltamivir in the afternoon and in the evening one day woke up suddenly at midnight and ran up the staircase. He jumped from the second floor of his house, fracturing his leg. He was diagnosed with influenza B virus infection in the emergency department of the hospital, and he later explained that he was being chased by a stranger in a dream and was afraid.

Delirious behavior and hallucinations have been reported in children with influenza [27, 28]. The abnormal behaviors of children after taking oseltamivir that have been reported in Japan may be an extension of delirium or hallucinations caused by influenza. To determine whether the number of deaths as a result of falls has increased in Japan since the introduction of oseltamivir, the number of deaths in falls from buildings in the 10- to 19-year-old population from 1995 to 2005 was investigated based on Vital Statistics data [29] (Table 2). The number of deaths as a result of intentional self-harm by jumping was also investigated. As shown in Table 2, there were no increases in deaths by accidents or by suicide after the introduction of oseltamivir in 2001; instead, the number of deaths actually decreased.

According to the Vital Statistics data [29], the widespread use of oseltamivir has not caused an increase in deaths as a result of accidental falls or intentional jumps from buildings. The number of deaths in both categories peaked in 1998, the year when influenza A/Sidney/5/97 caused the largest epidemic in children in the previous 10 years, suggesting that influenza virus infection may cause falls.

On the other hand, a subsequent investigation showed that serious accidents, such as falls from buildings, occurred with influenza patients not only treated with oseltamivir, but also those treated with zanamivir or even without treatment. Mild abnormal behavior has also reported to be associated with treatment with laninamivir [12]. Moreover, an autopsy of a teenage boy who was treated with oseltamivir and died as a result of fall from a building failed to detect oseltamivir in the brain [30].

In Japan, it is generally thought that abnormal behavior is caused by influenza virus infection and that, in most cases, it occurs in the early stage of illness, such as within 48 h after the onset of illness. Therefore, it is stressed that children with influenza virus infection should be observed by their guardians until 48 h after the onset of influenza illness, regardless of whether the children are treated with NAIs.

## Lower effectiveness of oseltamivir against influenza B

A large mixed epidemic caused by influenza A (H3N2) and B, an A/Wyoming (H3N2)-like strain and B/Shanghai-like strain, occurred in Japan during the 2004–2005 season [26]. It was the first large influenza B epidemic after the introduction of oseltamivir in Japan. During the epidemic, many Japanese pediatricians claimed that children with influenza B often had a persistent high fever, even though they had been treated with oseltamivir within 48 h of the onset of illness. Some physicians suspected that the epidemic was caused by oseltamivir-resistant influenza B strains.

The effectiveness of oseltamivir against influenza A (H3N2) and influenza B was compared on the basis of the duration of the febrile period during that season, and the mean duration of fever after the start of oseltamivir was found to be significantly longer in the influenza B group than in the influenza A (H3N2) group (2.18 vs. 1.31 days, $P < 0.001$). The difference was marked in young children, 1–5 years old (2.37 vs. 1.42 days), but was not significant in older children, 11–15 years old. The $IC_{50}$ of oseltamivir against influenza A (H3N2) virus and B virus was $0.5 \pm 0.2$ and $76.8 \pm 42.5$ nM, respectively. Oseltamivir is much less effective against influenza B virus infection in young children, probably because of the low sensitivity of influenza B viruses to oseltamivir [26].

A recent randomized controlled study conducted in young children showed that oseltamivir was not effective against influenza B virus infection [31]. Because of the low sensitivity of influenza B viruses to oseltamivir, the clinical effectiveness of oseltamivir in children should be assessed separately against influenza A and against influenza B. However, clinical trials have often come to conclusions without distinguishing between patients infected with influenza A and B [32, 33]. Perhaps the effectiveness of oseltamivir was underestimated in children.

## Conclusion

Almost all patients with an influenza-like illness in Japan are now tested with rapid diagnostic tests, and when positive, they are treated with a NAI; this has become standard practice in clinics nationwide. Although oseltamivir is widely used in Japan, no outbreaks have been caused by oseltamivir-resistant viruses, and no serious illness caused by oseltamivir-resistant viruses has ever been reported. According to the recent report by the National Institute of Health of Japan, there has been no increase in oseltamivir-resistant viruses in Japan, i.e., they still account for less than 1–2% of all isolated viruses in the country [34].

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