

## Incomplete Inhalation of Laninamivir Octanoate in Children with Influenza

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### Abstract

**Background:** Laninamivir octanoate (LO), an inhaled neuraminidase inhibitor, has been used against influenza in Japan. However, children who cannot inhale well might not receive the full dose. We examined the relation between the residual amounts of LO in the device after its use and the time to fever resolution in children with influenza.

**Methods:** The subjects of the study were 161 children (4-15 years) who had been diagnosed as having influenza from 2011-2014 and who had demonstrated an ability to properly use an inhalation training device. After its use, the LO device was returned to the authors and the residual amount of LO was measured. After flu symptoms had resolved, the patients' parents reported the time to fever resolution in a questionnaire.

**Results:** The percentage of the residual LO was not significantly correlated with the time to fever resolution or with patient age. The percentage of residual LO tended to be higher and the time to fever resolution tended to be longer in 4-6 year-olds than in older children. In the 4-6 year group, seven patients were inhaling steroids. These patients tended to inhale more of the LO dose and tended to have a shorter time to fever resolution than the other patients.

**Conclusions:** Physicians need to be aware that some 4-6 year-old influenza patients will not be able to inhale the full dose of LO. Influenza patients, even young ones, who are also inhaling steroids for other conditions are better able to inhale LO.

**Keywords:** Laninamivir; Influenza; Inhalation; Asthma; Child

### Introduction

In Japan, four neuraminidase inhibitors (NAIs) are available for treating influenza depending on the patient's condition. These include Peramivir, which is given by intravenous injection, oseltamivir (OT), which is taken orally as a capsule or a powder, and two NAIs that are inhaled orally: zanamivir (ZN) and laninamivir octanoate (LO).

LO is a single-dose NAI that has been used for treating patients with influenza since 2010 in Japan. A single inhalation of LO was estimated to be as effective as repeated doses of OT [1]. LO was also found to be as effective as ZN, although younger children had some difficulty with inhaling [2]. However, children with asthma who inhale steroids everyday had little difficulty with inhaling LO. A single inhalation of LO could be simpler than the administrations of OT and ZN, which require 2 doses per day for 5 days. However, with only a single LO use per day, the amount of LO that reaches the trachea and lungs might not be sufficient in patients who do not inhale well. There is no article on correlation between inhalation rates of LO, patient's age and the time to fever resolution although some previous papers written in Japanese have been examined inhalation rates of LO in children [3-6]. In this study, we measured the amount of residual LO after inhalation in children with influenza and determined whether it had any relation with the time to fever resolution as reported by the parents.

### Methods

#### Study design and criteria for enrollment

The study was conducted between December 2011 and April 2014 at our hospital. The institutional review board of our hospital approved the study protocol. Eligible patients were children from 4 to 15 years of age (15 years is the maximum age that our pediatric department accepts), who had an axillary temperature of 38.0°C or higher, who presented at the onset of respiratory symptoms (cough and/or sore throat) and who or whose parents wanted inhalation of LO for the treatment. Influenza virus infection was diagnosed based on the results obtained with a

rapid diagnostic kit (Poctem Influenza A/B [Sysmex, Kobe, Japan]). Patients were excluded from this study if they (1) were diagnosed as having influenza without the diagnostic kit, (2) had any underlying disease except asthma, (3) had a fever for more than 48 hours from the time of fever onset (defined as the time when axillary temperature was first measured as 38.0°C or more), when they were diagnosed as having influenza, or (4) could not pass an inhalation test. The inhalation test was conducted with a device freely provided by Daiichi Sankyo (Tokyo, Japan) that makes a whistling sound if the patient inhales hard enough.

#### Drug administration

On the day of diagnosis, the patient inhaled from the inhalation device as instructed by a pharmacist at either the hospital pharmacy or at one of four pharmacies near the hospital. Each container requires four or eight separate inhalations. The dose of LO was 20 mg for patients less than 10 years of age and 40 mg for patients 10-15 years of age [7]. Only 20% (w/w) of a dose was LO and the other 80% was lactose. We asked the parents of the patients to evaluate the time to fever resolution without the use of acetaminophen during the recovery period.

#### Questionnaire

We received verbal consent from the parents to fill out a questionnaire. The parents were given a questionnaire to be filled out at

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home. The questionnaire asked about symptoms before and after drug administration, including the time to fever resolution and asthmatic symptoms. We defined the time until the beginning of the first 12-hour period in which the temperature returned to less than 37.5°C without recent acetaminophen as time to fever resolution and coughing and wheezing as asthmatic symptoms, same as in previous study [2]. Parents were instructed to mail the completed questionnaire to our hospital «after the patient was completely cured».

### Residual LO

Hospital staff picked up the used LO device at the pharmacies. To measure the residual LO, a technician held the open container upside down, and tapped on it. The amount that fell out of the container was weighed to the nearest mg.

### Statistical analysis

Statistical differences between the groups were evaluated by Mann-Whitney U test or multiple regression analysis. The relation between the estimated residual rates and the patient's age or the time to fever resolutions was analyzed by a Pearson's correlation coefficient test.  $P < 0.05$  was considered to indicate a statistically significant difference. All analyses were performed using Excel 2003 (Microsoft, USA) with the add-in software Statcel 2 (OMS Press, Saitama, Japan).

## Results

### Patient disposition and characteristics

Of 1006 patients who were diagnosed as having influenza, 597 were excluded according to the above 4 criteria. The remaining 409 patients were prescribed LO (Figure 1). Of the 409 questionnaires, 231 were returned. Thirty-eight patients of the remaining 231 patients were excluded for incomplete answers on the questionnaire and another 32 patients were excluded for lack of inhalation data. The remaining 161 patients were placed in four age groups. The age, sex, and disease characteristics of these groups are given in Table 1. None of the patients was administered steroid intravenously or orally. The four groups did not significantly differ with respect to the year of the flu season, sex, vaccination state, or influenza type. The proportion of patients with a history of asthmatic symptoms and with current use of inhaled steroid in the 4-6 year-old group was larger than in the other groups.

### Clinical outcome

The mean percent of residual LO for the 161 patients was  $15.7 \pm 13.7$  % and varied from 0 % to 58 %. No significant correlation was found between estimated residual rate of LO and time to fever resolution after treatment in all the patients (Figure 2A,  $p=0.81$ ). Moreover, no significant correlation was found between the rate and the patient's age (Figure 2B,  $p=0.22$ ). But in the 4-6 year-old group, the residual rate tended to be higher (mean  $\pm$  SD:  $20.8 \pm 17.0$ ) and the time to fever resolution tended to be longer (mean  $\pm$  SD:  $47.5 \pm 39.0$ ) than in the other groups, although the difference was not significant (Table 2).

Seven of the patients in the 4-6 year-old group were inhaling steroids for asthma. For each of these patients, the estimated residual rate less than 20 %, meaning they could inhale LO better than the other 4-6 year-old patients could (Figure 3A,  $p=0.056$ ), although the difference did not reach the level of significance. The time to fever resolution in the 7 patients also tended to be shorter (Figure 3B,  $p=0.14$ ).

### Discussion

When the data for all patients is combined, the residual rate of LO was not correlated with either the time to fever resolution (Figure 2A) or patient age (Figure 2B). In addition, no correlation was found between the time to fever resolution and the estimated inhalation dose in mg/kg body weight (Supplementary Figure 1,  $p=0.77$ ). The sample size might be too small to show a significant correlation. However if this result is true, we need to examine whether LO doses in children with influenza are overdose or not. The times to fever resolution for influenza A and B groups were significantly different (Supplementary Figure 2,  $p < 0.05$ ) and differences between with or without influenza vaccination were not observed (Supplementary Figure 3,  $p=0.81$ ). Several studies (written in Japanese) have examined inhalation rates of LO. To properly inhale LO, children should have a vital capacity of 1-4 L and an ability to create a pressure difference of 1.2-4 kPa [3]. Most children meet these criteria [3]. In a study of 55 children, the rate of residual LO was found to be inversely correlated with patient age, and the body temperature at 24 hours after the treatment was significantly higher in 32 patients whose residual volumes were above 20 %, although the difference was not significant [4]. Patients under 10 years of age inhaled significantly less LO than patients over 10 years of age [5]. Inhalation of LO was found

Characteristics	Total (n=161)	4-6 years old (n=30)	7-9 years old (n=40)	10-12 years old (n=55)	13-15 years old (n=36)
<b>Season</b>					
No. (%) in 2011-2012	89 (55.3)	18 (60.0)	20 (50.0)	30 (54.6)	21 (58.3)
No. (%) in 2012-2013	29 (18.0)	5 (16.7)	8 (20.0)	7 (12.7)	9 (25.0)
No. (%) in 2013-2014	43 (26.7)	7 (23.3)	12 (30.0)	18 (32.7)	6 (16.7)
<b>Age (year)</b>					
Mean $\pm$ SD	10.2 $\pm$ 2.83	5.9 $\pm$ 0.73	8.6 $\pm$ 0.95	11.3 $\pm$ 0.87	13.8 $\pm$ 0.61
No. (%) male	98 (60.5)	20 (66.7)	27 (67.5)	32 (58.2)	18 (50.0)
No. (%) vaccinated against influenza virus	73 (45.1)	14 (46.7)	21 (52.5)	25 (45.5)	12 (33.3)
No. (%) influenza A positive	104 (64.2)	22 (73.3)	22 (55.0)	35 (63.6)	25 (69.4)
No. (%) of patients with history of asthmatic symptoms	42 (25.9)	15 (50.0)	9 (22.5)	11 (20.0)	6 (16.7)
No. of patients with current use of inhaled steroid	12	7	2	3	0

Table 1: Age, sex and disease characteristics.

Group	n	Estimated residual rate of LO (%)		Time to fever resolution after treatment (hour)	
		Mean $\pm$ SD	Median	Mean $\pm$ SD	Median
4-6 years old	30	20.8 $\pm$ 17.0	16.5	47.5 $\pm$ 39.0	36.5
7-9 years old	40	14.4 $\pm$ 11.1	13.0	35.8 $\pm$ 34.4	22.0
10-12 years old	55	13.7 $\pm$ 12.5	10.0	34.8 $\pm$ 22.2	33.0
13-15 years old	36	15.9 $\pm$ 14.3	12.3	37.2 $\pm$ 25.3	28.5

Table 2: Clinical outcome.

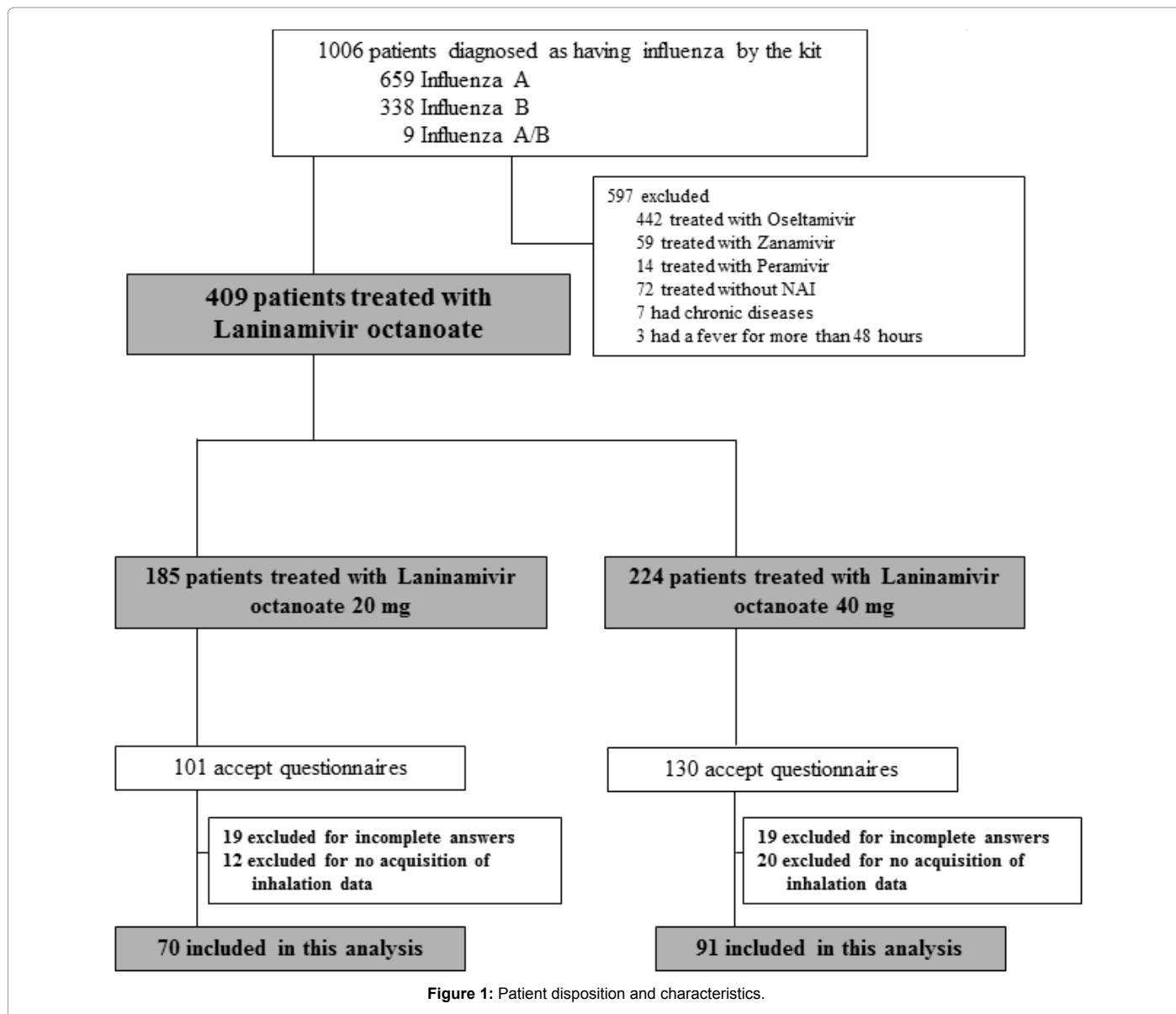


Figure 1: Patient disposition and characteristics.

to be unsatisfactory in a large percentage of patients under the age of 6 years [6]. Patients with influenza should inhale as much of the LO dose as possible and patients less than 10 years old who inhale only 20 mg of LO need to be taught how to inhale it just before the inhalation [8]. These reports and the present report show that younger children need to be taught how to inhale LO by using the training device just before the treatment. However, some children under 7 years of age who passed the training test could not inhale LO well. This may be because inhaling LO powder is different from inhaling on the training device without powder, which may cause the children to reduce the volume inhaled. The proportion of patients in the present study who had a history of asthma and who were inhaling steroids on a daily basis was higher in the group of 4-6 years of age than in the other groups. Unsurprisingly, this group had better inhalation success than the other age groups. We suggest that younger children generally hesitate to inhale LO powder even if they pass the training test, but having previous experience with inhalers may reduce this hesitation.

The time to fever resolution tended to be longer in the 4-6 year-old

group, but the sample size was too small to show a significant difference. If the difference is real, what are the possible explanations for it? (1) Is fever of younger children with influenza naturally longer? In patients with influenza, the frequency of pneumonia is known to be higher in younger patients, especially in those less than 2 years old, than in older patients [9]. A relative longer duration of fever appears common in younger children with influenza. (2) Is the clinical effect of influenza vaccination weaker in younger children? Vaccination against influenza reduces the severity of clinical symptoms [10]. Although the percent of the children that was vaccinated was not significantly different among the age groups, vaccination might be less effective in the 4-6 year-old children than in the older groups. (3) Could the younger patients have a different subtype of influenza? We diagnosed the patients as having influenza A or B by using the diagnostic kit, but did not investigate the subtype or gene mutations of their viruses. For example, the H275Y mutation that is found in most influenza A/H1N1 cases and in a few percent of influenza A/H1N1pdm cases induces resistance to OT and Peramivir [11,12]. Because there was no report that more cases infected

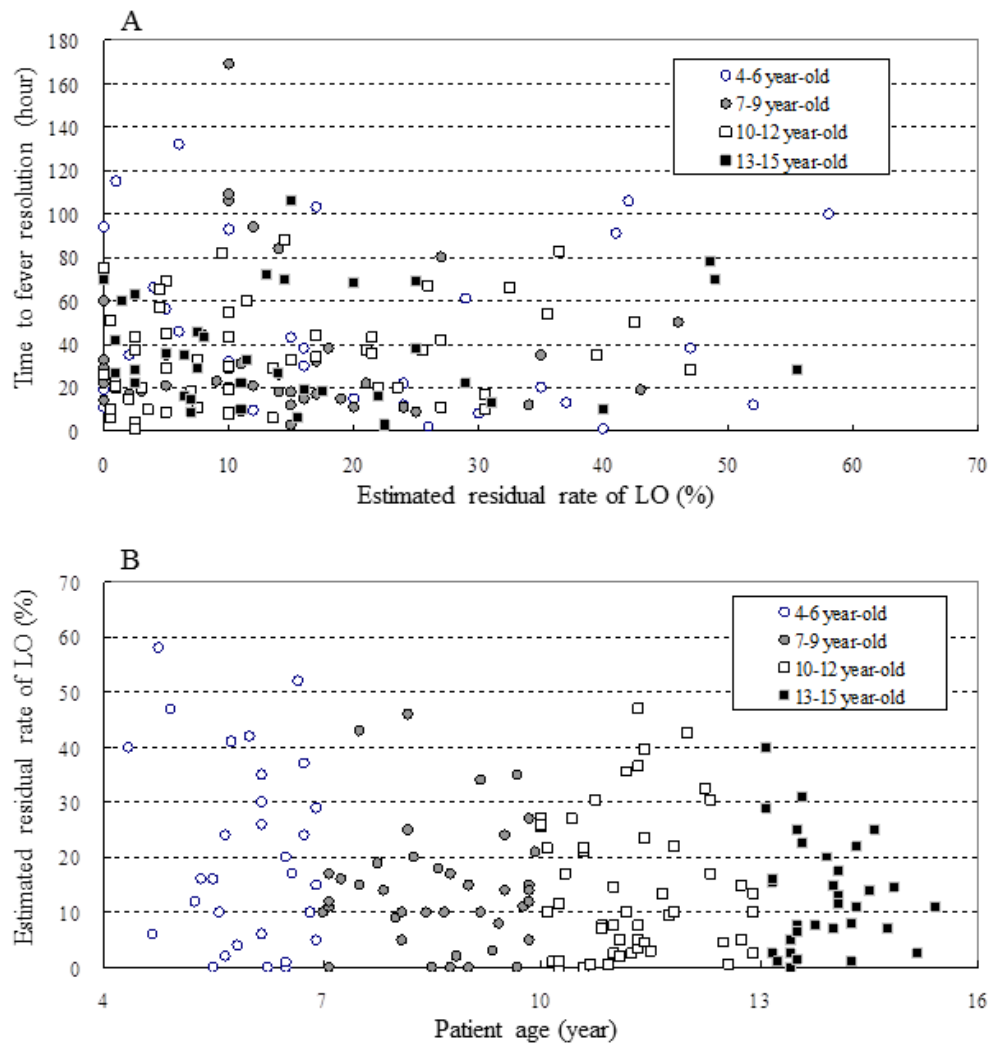


Figure 2: Relation between estimated residual rate of LO and time. Relation between rate and the patient's age.

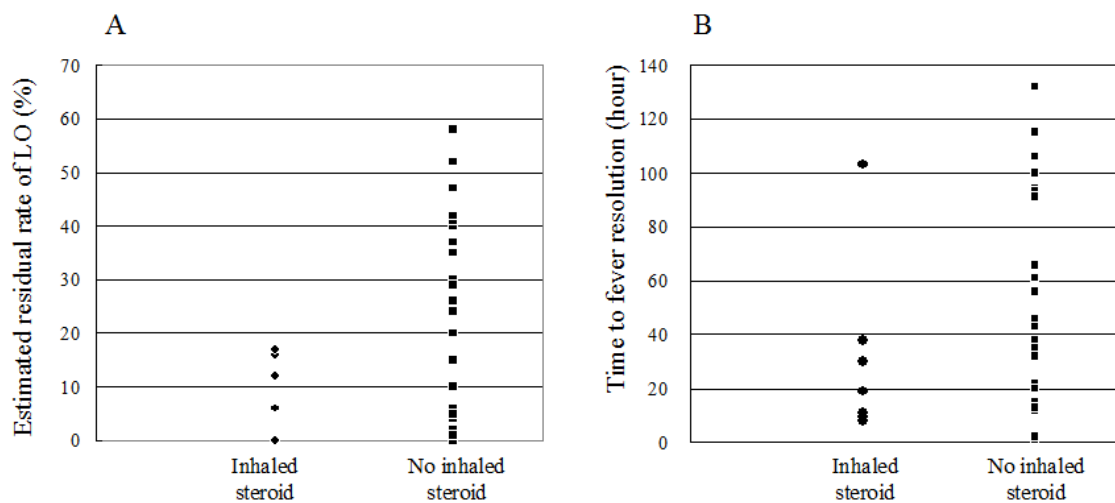


Figure 3: Estimated residual rate. Time to fever resolution.

resistant type influenza were in young patients like in 4-6 year of the age, it seems very unlikely that the difference in fever resolution was due to the subtype of influenza virus. (4) Is the clinical effect of LO naturally weaker in younger children? NAIs might be more effective in children than in control patients because children have less developed immune systems than adults [1]. However, there is no evidence that NAIs are more effective in younger patients than in older patients. It does not seem that this is the only reason because as mentioned above insufficient inhalation of LO results in elongation of the time to fever resolution in the 4-6 year-old patients and may be considered as a major cause.

The patients and their parents in the 4-6 years group had probably experienced any inhales and used to inhale it. This is why larger population, half of the patients, in the 4-6 years group had a history of asthmatic symptoms in this study. Although younger children with experience with asthma inhalers appeared to inhale LO better in this study, it has been recently reported that inhalation of LO may present some risks to patients with a history of asthma or chronic obstructive pulmonary disease because NAI inhalers might induce bronchial spasms in these patients and such patients may need to inhale a bronchodilator before inhaling LO [8]. Among the seven patients in the 4-6 years group who inhaled steroids, one patient experienced an asthmatic attack after the LO treatment. This patient did not use a bronchodilator before LO treatment. None of the other six patients in this group (including two who used a bronchodilator before LO treatment) experienced an attack. However, our results were not sufficient to conclude that the LO was responsible for the asthmatic attack.

A limitation of this study is that the weight of the residual LO may not accurately indicate the amount of LO inhaled, as some LO may have remained in the patients' mouth. Another limitation is that the time to fever resolution was determined by the parents, which could introduce bias.

Our results suggest that 4-6 year-old influenza patients do not inhale LO well and that their time to fever resolution may be longer, but patients who inhale steroids on a daily basis may be more successful at inhaling LO.

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