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Citation	Journal of hospital infection, 94(2), 150-153 https://doi.org/10.1016/j.jhin.2016.05.012
Issue Date	2016-10
Doc URL	http://hdl.handle.net/2115/67230
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Type	article (author version)
File Information	JHI-D-15-00648_R1.pdf

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Three-day regimen of oseltamivir for post-exposure prophylaxis of influenza in wards

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Keywords: Influenza, Post-exposure prophylaxis, Oseltamivir

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25 Summary

26 Inpatients who had close contact with influenza patients were given oseltamivir (75 mg
27 capsule once daily for adults or 2 mg/kg (maximum of 75 mg) once daily for children) for
28 3 days as post-exposure prophylaxis (PEP). The index influenza patients were
29 prescribed a neuraminidase inhibitor and were immediately discharged or transferred
30 to isolation rooms. Protective efficacy of oseltamivir for 3 days was 93% for all
31 influenza patients (95% CI, 53%-99%; P=0.023) and it was 94% for patients with
32 influenza A (95% CI, 61%-99%; P=0.017), which are comparable to those of oseltamivir
33 for 7 to 10 days as PEP. (98 words)

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Introduction

Influenza is a common respiratory disease that results in death of about 30,000 to 49,000 people in the United States every year ¹. A number of nosocomial influenza outbreaks in hospitals have been reported ². Therefore, prevention of nosocomial transmission of influenza is important. Post-exposure prophylaxis (PEP) using oseltamivir was shown to be effective for reducing secondary spread of influenza in families ^{3, 4} and in pediatric wards ⁵. Oseltamivir as a 75 mg capsule once daily for adults and at a dose of 2 mg/kg (maximum of 75 mg) once daily for children for 7 to 10 days has generally been used for PEP ³⁻⁵.

In this study, index cases in which influenza developed during hospitalization were immediately discharged or transferred to isolation rooms, and persons who were in close contact with the index influenza patients were administered oseltamivir for 3 days as PEP. The purpose of this study was to analyze the effectiveness of a 3-day regimen of oseltamivir for PEP.

Methods

Hokkaido University Hospital is a 936-bed tertiary care hospital in Sapporo, Japan. Patients hospitalized in Hokkaido University Hospital between December 2005 and March 2015 were included in this study. Index patients were defined as patients who developed flu-like symptoms (e.g., fever, cough, and fatigue) with a positive immunochromatographic test (ICT) during hospitalization. ICTs used to diagnose influenza were BD Flu Examen (Nippon Becton, Dickinson and Company,

Tokyo, Japan) from December 2005 to January 2007, Espline influenza A&B-N (Fujirebio Inc., Tokyo, Japan) from February 2007 to February 2013 and BD Veritor System Flu A + B (Becton, Dickinson and Company, Sparks, MD, USA) from March 2013. The index patients who developed influenza during hospitalization were prescribed a neuraminidase inhibitor and were immediately discharged or transferred to isolation rooms. All inpatients with a positive immunochromatographic test were reported to the infection control team. Patients hospitalized for treatment of influenza were excluded from this study.

Persons in close contact with the index patients were defined as persons sharing a room within 48 hours of illness onset of index cases. Persons in close contact were immediately listed and recommended PEP using oseltamivir: a 75 mg capsule once daily for adults or 2 mg/kg (maximum of 75mg) once daily for children for 3 days. For patients with creatinine clearance of 10 to 30ml/min, the same dose of oseltamivir was prescribed on the first and third days. The costs of PEP were paid by the hospital for preventing further nosocomial infection. Written informed consent was obtained for the administration of oseltamivir. Close contacts who refused PEP were separated into isolation rooms. Those persons, regardless of whether they accepted or refused PEP, were monitored for influenza-like symptoms for 7 days after identification. Close contacts who received PEP were incorporated into the PEP group and those who refused PEP were incorporated into the non-PEP group.

Statistical analysis was performed using JMP software version 12.1.0 (SAS Institute, Cary, NC, USA). For demographic variables, continuous variables were analyzed using Student's *t* test. Frequency analysis was performed by the chi-square test. The difference in prevalence between the PEP and non-PEP groups was tested by

Fisher's exact test at the level of significance of 5%. Protective efficacy and its 95% confidence interval (CI) were also computed by calculating relative risk and its 95% CI first and then subtracting each of them from 1. Ethical approval for this study was obtained from the Institutional Review Board of Hokkaido University Hospital for Clinical Research.

Results

A total of 86 index patients were identified among the hospitalized patients. Forty-six (53.5%) of the 86 index patients developed flu-like symptoms within 3 days of admission, suggesting that they had been infected with influenza virus outside the hospital. After diagnosis of each index case, a total of 227 close contacts were identified. Of the 227 close contacts, 212 received oseltamivir as PEP and 15 did not because of concerns about side effects of oseltamivir. The mean ages $\pm$ standard deviations were 48.4 $\pm$ 22.9 years for the PEP group and 31.1 $\pm$ 29.0 years for the non-PEP group ($P=0.006$ for the t -test). The male-to-female ratios were 125: 87 for the PEP group and 9: 6 for the non-PEP group ($P=0.937$ for the chi-square test). The mean duration between onset of flu-like symptoms of the index cases and oral administration of oseltamivir for the close contacts in the PEP group was 1.0 $\pm$ 1.2 days, whereas the mean duration between onset of flu-like symptoms of the index cases and separation of the index cases for the non-PEP group was 0.8 $\pm$ 0.7 days ($P=0.3827$ for the t -test).

Seventy-nine index patients were diagnosed as having influenza A, and the incidence of influenza in the PEP group (2 of 200, 1.0%) was lower than that in the non-PEP group (2 of 12, 16.7%) (protective efficiency, 94%; 95% CI, 61%-99%; $P=0.017$)

(Table 1). Two patients for whom PEP failed to prevent influenza A infection had impaired renal function (creatinine clearance of 10 to 30 ml/min): one patient took oseltamivir only on the first day and developed influenza on the following day, and the other patient took oseltamivir on the first and third days and developed influenza on the fifth day. Seven index patients were diagnosed as having influenza B, and none of the close contacts, both those who received PEP and those who did not, became infected (Table 1). The overall protective efficacy of the 3-day regimen of oseltamivir for PEP was 93% (95% CI, 53%-99%; $P=0.023$) (Table 1).

Discussion

Several studies have been conducted on the effectiveness of PEP with oseltamivir using 7 to 10-day regimens³⁻⁶. In our hospital, patients who developed influenza during hospitalization have been separated into a private room immediately after diagnosis for preventing influenza transmission. This led us to the idea that the period for administration of PEP with oseltamivir could be shortened to less than 7-10 days. In the 2004/05 influenza season, we started PEP with oseltamivir using a 5-day regimen. Fifty-two inpatients who were in close contact with influenza patients received PEP with oseltamivir for 5 days and none of them had flu-like symptoms. This encouraged us to start a 3-day regimen from the 2005/06 influenza season. The results have been evaluated annually and we became convinced that a 3-day regimen of oseltamivir as PEP was effective. The subtypes of influenza A viruses detected in Japan from 2005-2006 to 2014-2015 seasons and the numbers of contacts with or without PEP in our hospital are summarized in Table 2⁷. The data shown in Table 2

suggest that oseltamivir was effective in preventing onset of influenza A after exposure to three subtypes of influenza A viruses.

In previous studies, protective efficacy of oseltamivir was shown to be 89%⁴ and 68%³ in households and 89%⁵ in pediatric wards. Protective efficacy of oseltamivir in this study was 93% for all of the influenza patients and 94% for the patients with influenza A, indicating the effectiveness of the 3-day regimen of oseltamivir for PEP.

PEP with oseltamivir for two patients in this study who had impaired renal function failed to prevent influenza infection. Although an every-other-day schedule of oseltamivir has been recommended for patients with impaired renal function⁸, prescription of oseltamivir on the first and third days might not be sufficient for the 3-day regimen of oseltamivir for PEP. Additionally, because virus shedding occurs at 1-2 days before onset of influenza⁹, it is difficult to calculate the true interval between exposure to influenza virus and oral administration of oseltamivir for the close contacts. This makes it difficult to determine the causes of failure to prevent influenza by PEP.

Further studies are necessary.

There are limitations in this study. Our study was not a randomized placebo-controlled study, because we could expect effectiveness of PEP from previous studies^{3,4}. It is known that younger people are more frequently affected than elderly people by influenza¹⁰. Therefore, the effectiveness of PEP might be potentially overestimated because the persons in the non-PEP group were younger than those in the PEP-group. Because there was a more than 10-fold difference in the numbers of patients in the PEP and non-PEP groups, there might be potential biases including vaccine status, which was not investigated in this study.

In conclusion, protective efficacy of the 3-day regimen of oseltamivir for PEP in preventing nosocomial transmission of influenza is comparable to that of 7 to 10-day regimens, provided that index cases are immediately separated from contacts. The 3-day regimen of oseltamivir has an advantage over 7 to 10-day regimens in terms of economics of health care.

Acknowledgements

We thank Stewart Chisholm for proofreading the manuscript and Yoshihiro Sakoda for helpful advice.

References

1. Centers for Disease C, Prevention Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep* 2010; **59**: 1057-62.
2. Voirin N, Barret B, Metzger MH, Vanhems P Hospital-acquired influenza: a synthesis using the Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION) statement. *J Hosp Infect* 2009; **71**: 1-14.
3. Hayden FG, Belshe R, Villanueva C *et al.* Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004; **189**: 440-9.
4. Welliver R, Monto AS, Carewicz O *et al.* Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial.

- 1
2
3 180 *JAMA* 2001; **285**: 748-54.
- 4
5 181 5. Shinjoh M, Takano Y, Takahashi T, Hasegawa N, Iwata S, Sugaya N
6
7 182 Postexposure prophylaxis for influenza in pediatric wards oseltamivir or
8
9 183 zanamivir after rapid antigen detection. *Pediatr Infect Dis J* 2012; **31**: 1119-23.
- 10
11
12 184 6. Chang YM, Li WC, Huang CT *et al*. Use of oseltamivir during an outbreak of
13
14 185 influenza A in a long-term care facility in Taiwan. *J Hosp Infect* 2008; **68**: 83-7.
- 15
16
17 186 7. National Institute of Infectious Diseases, Infectious Agents Surveillance Report,
18
19 187 [http://www.nih.go.jp/niid/en/iasr/510-surveillance/iasr/graphs/2414-iasrgvak1e.h](http://www.nih.go.jp/niid/en/iasr/510-surveillance/iasr/graphs/2414-iasrgvak1e.html)
20
21 [tml](http://www.nih.go.jp/niid/en/iasr/510-surveillance/iasr/graphs/2414-iasrgvak1e.html), Nov. 22, 2015 present.
- 22
23
24 189 8. Fiore AE, Fry A, Shay D *et al*. Antiviral agents for the treatment and
25
26 190 chemoprophylaxis of influenza --- recommendations of the Advisory Committee
27
28 191 on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; **60**: 1-24.
- 29
30
31 192 9. Lau LL, Cowling BJ, Fang VJ *et al*. Viral shedding and clinical illness in
32
33 193 naturally acquired influenza virus infections. *J Infect Dis* 2010; **201**: 1509-16.
- 34
35
36 194 10. Gu Y, Shimada T, Yasui Y, Tada Y, Kaku M, Okabe N National surveillance of
37
38 195 influenza-associated encephalopathy in Japan over six years, before and during
39
40 196 the 2009-2010 influenza pandemic. *PLoS One* 2013; **8**: e54786.
- 41
42
43 197

Table 1. Results of post-exposure-prophylaxis using oseltamivir for persons in close contact with influenza patients

	Index cases (n)	Close contacts (n)	PEP*	Disease/Contacts	Protective Efficacy (95% CI)	<i>p</i> **
Influenza A+B	86	227	yes	2/212 (0.9%)	93% (53%-99%)	0.023
			no	2/15 (13.3%)		
Influenza A	79	212	yes	2/200 (1.0%)	94% (61%-99%)	0.017
			no	2/12 (16.7%)		
Influenza B	7	15	yes	0/12 (0.0%)	-	-
			no	0/3 (0.0%)		

*PEP: post-exposure-prophylaxis, **Fisher’s exact test.

Table 2

Table 2. Subtypes of influenza A viruses detected in Japan from 2005-2006 to 2014-2015 seasons and numbers of contacts with or without PEP in our hospital

Series	Influenza A virus subtype				Contacts with PEP (disease)		Contacts without PEP (disease)		Total
	AH1pdm	A(H1)	A(H3)	Total					
2005/2006	0 (0.0%)	1375 (28.7%)	3424 (71.3%)	4799 (100.0%)	17	(0)	2	(0)	19
2006/2007	0 (0.0%)	633 (20.9%)	2396 (79.1%)	3029 (100.0%)	2	(0)	0	(0)	2
2007/2008	0 (0.0%)	3819 (87.5%)	544 (12.5%)	4363 (100.0%)	6	(0)	3	(0)	9
2008/2009	9732 (60.8%)	3607 (22.6%)	2661 (16.6%)	16000 (100.0%)	16	(0)	1	(0)	17
2009/2010	22264 (99.3%)	0 (0.0%)	168 (0.7%)	22432 (100.0%)	20	(0)	0	(0)	20
2010/2011	6250 (61.9%)	0 (0.0%)	3849 (38.1%)	10099 (100.0%)	19	(2)	1	(0)	20
2011/2012	15 (0.3%)	0 (0.0%)	5145 (99.7%)	5160 (100.0%)	36	(0)	0	(0)	36
2012/2013	163 (3.1%)	0 (0.0%)	5044 (96.9%)	5207 (100.0%)	33	(0)	0	(0)	33
2013/2014	3494 (66.8%)	0 (0.0%)	1736 (33.2%)	5230 (100.0%)	7	(0)	2	(2)	9
2014/2015	12 (1.0%)	0 (0.0%)	1150 (99.0%)	1162 (100.0%)	44	(0)	3	(0)	47