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Oseltamivir and early deterioration leading to death: A proportional mortality study for 2009A/H1N1 influenza

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Abstract. *Objective*: To examine the epidemiological association between sudden deterioration leading to death and Tamiflu use.

Design: Proportional mortality study.

Setting: Japan.

Participants: 162 deaths without deterioration before the first consultation among all 198 deaths of mostly confirmed 2009A/H1N1 influenza.

Population at risk: Age-specific population of influenza patients prescribed Tamiflu and Relenza.

Main outcome measure: Age-stratified pooled odds ratio (OR) for early (within 12 hours) deterioration and overall death of Tamiflu prescribed to Relenza prescribed patients.

Results: Of 119 deaths after Tamiflu was prescribed, 38 deteriorated within 12 hours (28 within 6 hours), while of 15 deaths after Relenza, none deteriorated within 12 hours. Pooled OR for early deterioration and overall death were 5.88 (95% CI: 1.30 to 26.6, $p = 0.014$) and 1.91 ($p = 0.031$) respectively. Baseline characteristics including risk factors did not contribute to early deterioration after Tamiflu use.

Conclusions: These data suggest Tamiflu use could induce sudden deterioration leading to death especially within 12 hours of prescription. These findings are consistent with sudden deaths observed in a series of animal toxicity studies, several reported case series and the results of prospective cohort studies. From "the precautionary principle" the potential harm of Tamiflu should be taken into account and further detailed studies should be conducted.

Keywords: Oseltamivir, sudden death, adverse effect, proportional mortality study, 2009A/H1N1 influenza

1. Introduction

Influenza is generally self-limiting but prevalent worldwide, primarily in the winter season every year, and has caused pandemics occasionally in the past.

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Drugs are sometimes associated with increased death among patients with influenza [1–7]. Case fatality among patients with encephalopathy has decreased sharply since non-steroidal anti-inflammatory drugs (NSAIDs) were restricted for use in influenza as antipyretics in Japan in 2000 [5].

Oseltamivir phosphate, a product form of Tamiflu (Gilead Sciences, Roche and Chugai) is a prodrug of oseltamivir carboxylate, a neuraminidase inhibitor. Japan consumed more than 70% of world sales of Tamiflu before 2007 [8]. A case series of accidental deaths from abnormal behaviours and sudden deaths shortly after Tamiflu use has been reported [5].

Since the outbreak of 2009A/H1N1 influenza, antivirals, including Tamiflu, were recommended by the World Health Organisation (WHO) and by US Centers for Disease Control (CDC) [9, 10] and their use has become popular worldwide.

After the pandemic, antivirals are continuing to be recommended as effective and safe drugs [11, 12] despite insufficient evidence on reduction of complications [13] and no evidence that Tamiflu could reduce mortality in a systematic review of observational studies of 2009A/H1N1 influenza [14]. Tamiflu [15] or antiviral [16] could not prevent or treat cytokine storm, because inhibition of viral neuraminidase does not induce or inhibit cytokine storm [17].

Causal associations between Tamiflu and sudden death or abnormal behavior have been denied by regulators as well as by the Japanese Ministry of Health Labor and Welfare (MHLW) and WHO [12].

However evidence indicating association with these events are accumulating [18, 19]. One prospective cohort study reported five to seven-fold increased risks of delirium and unconsciousness during the early phase of influenza infection by Tamiflu use [20]. These results are consistent with the findings from case series and preclinical findings [5]. However, there has been no epidemiological study that has examined the causality of increased mortality and Tamiflu use.

After the outbreak of novel influenza, MHLW amended enforcement regulations of "The National Epidemiological Surveillance of Infectious Diseases (NESID) regulated by the new Infectious Diseases Control Law" [21, 22]. According to the regulation, MHLW demanded physicians to report all cases of patients with influenza-like illness who required hospitalization using a form that included patients age, sex, baseline diseases, results of rapid testing (influenza A or B), date of PCR testing for novel influenza, symptoms, date and reason of hospitalization, whether admitted to intensive care unit, whether artificially ventilated and outcome including death (with date of discharge) [21, 23]. In the interest of public health [21], MHLW had disclosed narrative reports of all death cases which included almost all the information outlined above from the municipal health authorities on its website as press releases, including the first death case reported on August 15th 2009 and the last death case reported on March 13th 2010 [24].

A preliminary proportional mortality study [25] of 74 death cases, showed a crude (no adjustment for age) significant relative risk of Tamiflu to Relenza use of 6.46 for sudden-type death. Therefore, we have investigated all 198 cases to examine the hypothesis that Tamiflu use is associated with sudden death shortly after its use. The primary objective of this study is to assess the epidemiological association between Tamiflu use and early deterioration leading to death compared with another antiviral (Relenza).

2. Subjects and methods

2.1. Study design

The research design is a proportional mortality study [26]. We obtained data on death cases and of populations at risk by the type of antivirals prescribed using the following procedures.

2.2. Death cases and their information

The subjects are all 198 death cases from confirmed 2009 A/H1N1 influenza (including 19 probable cases) that MHLW had posted on its website [24].

The following information on death cases were collected from the documents in the press releases of 198 cases: sex, age, risk factors, "time from fever to the first consultation", "mild or not mild/not deteriorated or deteriorated before or at the first consultation or arrested/dead before the first consultation", "positivity of rapid testing at the first consultation", "use of Tamiflu, Relenza or no antivirals at the first consultation or at the second consultation or later", "mild or not at the consultation when antivirals were prescribed", "time from fever (onset) to the consultation when antivirals were prescribed", "time from the first consultation to deterioration", "time from the consultation when antivirals were prescribed to deterioration", "use of antipyretics" (cold remedies, corticosteroids or other immune suppressants such as cytotoxic anticancer agents were included and collectively referred to as "antipyretics").

"Mild" was defined as "healthy other than mild influenza infection". Hence patients who had any other symptoms or complications such as dyspnea or pneumonia of any severity or who had been in a hospital with other diseases and not deteriorated were classified as "not mild/not deteriorated". "Deteriorated/Deterioration" was defined as "becoming as serious as those requiring a ventilator due to loss of consciousness or serious unconsciousness, shock, cardiopulmonary arrest, multiple organ failure including acute respiratory distress syndrome or death or other similar states. Those patients who had only "severe influenza" or only "influenza-associated encephalopathy" were excluded from "Deteriorated/Deterioration" and classified in "not mild/not deteriorated".

2.3. Classification according to the disease course of the patients

We classified the patients into two groups: ordinarily consulted patients (group A) and the patients who had already deteriorated before or during the first consultation (group B). Patients classified into group A were used for the proportional mortality analysis. However baseline characteristics were compared between group A and group B. Group A was divided into group AX for mild and AY for "not mild (but not deteriorated)" at the first consultation, and group AA for mild and group AB for "not mild" at the consultation when antivirals were prescribed. The numbers of people classified in each category and the number of people according to their antiviral use are shown in Fig. 1.

2.4. Outcomes

The primary outcome was early (within 12 hours) deterioration from the moment the antiviral was prescribed. Secondary outcomes were overall proportion of death and early deterioration from the first consultation.

We categorized the time from when antiviral was prescribed and from the first consultation to deterioration in three groups (early: 0–12 hours, intermediate: 13–48 hours and late: >48 hours). Classification was performed unblinded by two author groups (three Japanese authors in each group) with disagreements resolved by discussion. If antiviral was not prescribed, the time from last consultation to deterioration was used for comparison with time from antiviral prescription to deterioration for antiviral users.

When both Tamiflu and Relenza were used for one patient, we classified the time to deterioration from each prescription.

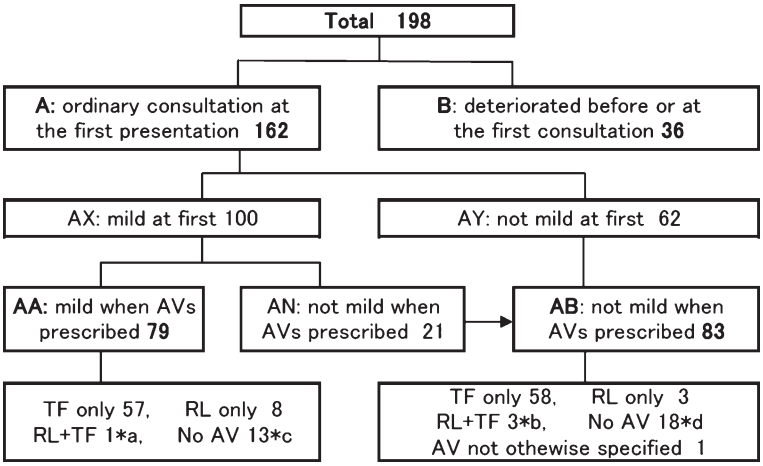

Fig. 1. Classification flow of death cases by course of illness. *a: Encephalopathy developed after RL use, ventilated after taking TF. *b: (1) First TF, later RL followed by two courses TF and one course RL (2) First RL and later TF, (3) TF and RL were used for the treatment of pneumonia simultaneously. *c, d: Those not prescribed antiviral before deterioration. *d: Of the 18, nine were prescribed Tamiflu only after ventilated. CPA: cardiopulmonary arrest, TF: Tamiflu, RL: Relenza, AV: antiviral.

Table 1
Estimated number of patients presented with influenza and those prescribed antivirals by age

Age (year)	% presented by age*a	Number presented	% prescribed AVs*c	Number prescribed AV	% share of AV*d		With antiviral		NAV (no antiviral)
					TF%	RL%	TF	RL	
0–9	36.4	7,520,200	85	6,392,200	77.9	22.1	4,979,500	1,412,700	1,128,000
10–19	36.8	7,602,900	85	6,462,400	21.2	78.8	1,370,000	5,092,400	1,140,400
20–59	25.3	5,227,000	85	4,442,900	86.1	13.9	3,825,400	617,600	784,000
≥60	1.5	309,900	85	263,400	82.7	17.3	217,800	45,600	46,500
Total	100	20,660,000*b	85	17,561,000	58.2	41.8	10,392,800	7,168,200	3,099,000

*a: data from [28].
*b: data from [27, 28].
*c: from percent of the season when Tamiflu was most prescribed [29].
*d: data from [29]. Cut off age for elderly people is 65 years but the share was similar between <60 and ≥60. Hence we calculated stratified odds ratio without adjusting for this difference.
AV: antiviral TF: Tamiflu (oseltamivir), RL: Relenza (zanamivir), NAV: no antiviral.

2.5. *The age-specific population at risk*

Estimated numbers of patients prescribed Tamiflu, Relenza and those not prescribed antivirals by age categories are summarized in Table 1. Age-specific populations at risk were estimated using the following data: (1) Age-specific estimated numbers of influenza patients who visited medical facilities in Japan, (2) Estimated proportion of patients who were prescribed antivirals and (3) Age-specific share of type of antiviral prescribed.

(1) Age-specific numbers of patients

The estimated total number of patients who visited medical facilities in Japan including non-sentinel facilities from week 28 of 2009 to week 10 of 2010 was 20,660,000 [27, 28]. Age specific numbers of influenza patients who visited medical facilities were calculated by allocating proportionally to the % of each age group based on the data officially estimated from the sentinel report from the 28th week in 2009 to the 10th week in 2010 [28] (Table 1).

(2) Estimated proportion of patients who were prescribed antivirals

The proportion of patients who were prescribed antivirals was estimated to be 85%. This was based on the maximum reported yearly proportion between the 2005 and 2008/9 seasons in the document submitted to the advisory panel of Pharmaceutical Affairs Council on the safety of antivirals by Chugai Pharmaceutical Co Ltd [29]. Sensitivity analyses were performed assuming proportions of patients prescribed antivirals of 60%, 70%, 80% and 90%. These proportions were chosen based on the reported proportions in the other influenza seasons and, in addition, it was reported during May to June 2009, that 90% of the 217 confirmed cases with known clinical symptoms were prescribed antivirals [30].

(3) Age-specific share of antiviral prescribed patients.

The age-specific shares of antivirals prescribed to patients are listed in Table 1. These are the data from May, 2009 to October 2009 submitted to the advisory panel above by GlaxoSmithKline Co. Ltd [29].

2.6. Comparison

The primary comparison was between Tamiflu users and Relenza users. A secondary comparison was between Tamiflu users and those not prescribed antivirals. We included patients who took "antipyretics" in the primary analysis because of no difference between groups. However, for the comparison with patients not prescribed antivirals, those who took "antipyretics" were significantly greater in the no antiviral group. Hence these patients were excluded from both groups because these medications may confound the comparison.

2.7. Statistical methods and analysis

The epidemiological design we used was a proportional mortality study [26]. Simply this means the proportion of patients exposed to Tamiflu who died was compared to the proportion of patients exposed to Relenza who died. The analysis was stratified by age-group to adjust for different risks of death from influenza and different distributions of type of antiviral prescribed (Table 1).

The primary outcome was pre-specified based on previous data showing adverse reaction to Tamiflu soon after taking the first dose in case series [5, 31, 32], preliminary analysis of press-released cases [25], epidemiological studies [20, 5] and animal toxicity studies [5]. Initially we used finer groupings (0–6, 7–12, 13–24, 25–48, 49–72, >72 hours) but collapsed into three groups to obtain sufficient numbers in each group for analysis. The categorisation of antiviral prescription to deterioration (3 categories) was repeated by two of the Japanese authors four months after the initial categorisation. Agreement of the categorisations over time was excellent (weighted kappa = 0.95). There were seven cases where the categorisation of antiviral prescription to deterioration was discordant over time and these were resolved by discussion.

We estimated age stratified pooled odds ratio by fixed effects model (Mantel-Haenszel, Robins-Breslow-Greenland) using Stats-Direct version 2.6.5 software. Pooled odd ratios were also calculated by Exact Fisher (conditional maximum likelihood) method as a sensitivity analysis because there were no patients who deteriorated within 12 hours of Relenza prescription. Hence an exact method is appropriate. Because the proportion of exposed patients who died is very small, odds ratios are equivalent to relative risks. We used a p value of 0.05 as the level of significance and did not adjust for the multiplicity of testing, because this is not a hypothesis confirming study.

3. Results

Of the 198 death cases 162 were classified in group A and 36 were classified in group B. Among 162 of group A, 79 were classified in group AA and 83 were classified in group AB (Fig. 1). Numbers of deceased patients prescribed or not prescribed antivirals in each group are shown in Fig. 1.

3.1. Baseline characteristics

We summarized and compared the baseline characteristics of 198 subjects as shown in Table 2. Compared with patients in group A, patients in group B were younger, consulted later, had less risk factors, used more antipyretics/cold remedies, died earlier and were more likely to have confirmed 2009A/H1N1 influenza (Table 2-a). Among the patients in group B none received antiviral before deterioration and more than half received no antiviral even after deterioration (Table 2-a). Antiviral prescription patterns (Tamiflu vs Relenza) were not significantly different between before (119 vs 15) and after deterioration (24 vs 1).

Compared with patients in group AA, patients in group AB were older, had more risk factors, were less likely to have rapid test positivity, were prescribed antivirals later and died later (Table 2-b). Proportions of Tamiflu users were nearly identical in group AA (73.4%) and group AB (74.5%) before deterioration.

Tamiflu was prescribed in 119 cases and Relenza was prescribed in 15 cases before deterioration. Baseline characteristics for patients prescribed Tamiflu, those prescribed Relenza and those prescribed no antivirals are compared in Table 2-c. Other than age distribution (where more Relenza was prescribed for teens), no statistical differences were observed between antiviral groups. However, those not prescribed antivirals were less likely to have positive rapid test results and more likely to be prescribed antipyretics.

3.2. Comparison of deterioration leading to death

Numbers and proportions of deterioration leading to death (/million) by antivirals, age and by the time from consultation (when antivirals were prescribed) to deterioration are shown in Table 3.

Of 119 patients who died after Tamiflu was prescribed, 38 deteriorated within 12 hours, while of 15 who died after Relenza was prescribed, none deteriorated within 12 hours, and of 31 who died without prescription of antiviral before deterioration, four deteriorated within 12 hours (three of these four were prescribed antipyretics). Most of the 38 patients prescribed Tamiflu (28 or 74%) had deteriorated within 6 hours and this was consistent for all age groups.

Age-specific ORs and age stratified ORs by fixed effects model for those prescribed Tamiflu to those prescribed Relenza are shown in Table 3. Stratified OR (95% CI, p value) for 12 hours or less, 13–48 hours, more than 48 hours and any time were 5.88 (95% CI: 1.30 to 26.60, $p = 0.014$), 2.32 (0.81 to 6.62, $p = 0.17$), 0.87 (0.44 to 1.74, $p = 0.83$) and 1.91 (1.08 to 3.39, $p = 0.031$) respectively. The lower limit of the 95% CI and p value by exact Fisher method for 12 hours or less were 2.68 and $p = 0.0003$ respectively

Table 2a
Comparison of baseline data (1): A vs B

Baseline characteristics		A ($n=162$)%	B ($n=36$)%	A vs B P value Chi-square (linear trend)
Age	0–9	15.4	22.2	0.0872
	10–19	3.1	8.3	
	20–59	42.0	50.0	(0.0409)
	≥60*a	39.5	19.4	
Sex	Male	58.0	69.4	ns
	Not known	0.6	0.0	
Risk factor	Present	66.7	50.0	0.0601
	Not known	4.3	8.3	
Fever to presentation	≤12 hr	67.9	30.6	<0.0001
	13–48 hr	24.1	27.8	ns
	>48 hr	8.0	19.4	ns
	Not known	0.0	22.2	<0.0001
Confirmation by PCR		88.3	100.0	0.0274
TF before deterioration		73.5	0.0	<0.0001
RL before deterioration		9.3	0.0	
No AV before deterioration		19.1	100.0	
any "antipyretics etc" before presentation*b		1.9	11.1	0.0217
Fever to death (median, days)		5.82	2.96	0.0008*c

*a: $P=0.0334$.
*b: All three (1.9%) in group A and one (11.1) in group B were immunosuppressants, definition of "antipyretics": see text.
*c: by Mann-Whitney U test.

(Table 3). Evidence of heterogeneity by age was not found for any time period ($p>0.43$) and all I^2 were 0%.

The breakdown of numbers of patients who deteriorated within 12 hours of antiviral prescription by various baseline characteristics comparing with all 162 deaths is summarized in Table 4. Baseline characteristics were similar for patients who deteriorated within 12 hours of Tamiflu prescription compared to the overall distribution for all characteristics except risk factors: odds ratio 2.2 (95% CI: 1.04 to 4.64, $p=0.049$).

The results of sensitivity analyses of stratified ORs if the proportion of patients who were prescribed antivirals was assumed to be 60%, 70%, 80% or 90%, were consistent with the results using a proportion of 85% (data not shown).

Those prescribed "antipyretics" before or at the first consultation and before antiviral prescription were seven in the Tamiflu group, one in the Relenza group and six in "no antiviral" group (Table 2-c). Excluding these from both groups the numbers compared were 112, 14 and 25 respectively and the numbers of those deteriorated within 12 hours were 37, 0 and 1 respectively. With regards to deterioration within 12 hours, no difference was found between Relenza users and the "no antiviral" group.

Stratified ORs (95% CI, p value) for deterioration leading to death after Tamiflu use versus after Relenza use was 5.78 (95% CI = 1.28 to 26.1, $p=0.015$) by fixed effects model or $p=0.0003$ by Exact Fisher and

Table 2b
Comparison of baseline data (2): AA vs AB

Baseline characteristics		AA ($n=79$)%	AB ($n=83$)%	P value Chi square (linear trend)
Age	0–9	21.5	9.6	0.0019
	10–19	5.1	1.2	
	20–59	48.1	36.1	(0.0006)
	≥60	25.3	53.0	
Sex	Male	62.0	54.2	ns
	Not known	1.3	0.0	
Risk factor	Present	54.4	78.3	0.0013
	Not known	6.3	2.4	
Fever to presentation	≤12 hr	63.3	72.3	NS
	13–48 hr	27.8	20.5	
	>48 hr	8.9	7.2	
Fever to AV before deterioration	≤12 hr	35.4	26.5	0.0035
	13–48 hr	43.0	28.9	(0.016)
	>48 hr	5.1	21.7	
	No antiviral	16.5	22.9	ns
Rapid testing	(+) at first	59.5	44.6	0.0575
	(−) at first	10.1	13.3	ns
	Others	30.4	42.2	ns
Confirmation by PCR		92.4	84.3	ns
TF before deterioration		73.4	73.5	ns
RL before deterioration		11.4	7.2	ns
No AV before deterioration		16.5	21.7	ns
Any “antipyretics” before presentation		2.5	1.2	ns
Fever to death(median, days)		3.93	6.98	0.0078*a

*a: by Mann-Whitney U test.

Tamiflu use versus no antiviral use (where time was from the last consultation) was 3.75 (95% CI = 1.02 to 13.78, $P=0.05$) by Fixed effects model or 8.48 (95% CI = 1.42 to 345, $P=0.009$) by Exact Fisher.

Similar results were obtained for “early deterioration from the first consultation”

Odds of early death (within two days from when antivirals were prescribed to death) was significantly higher in Tamiflu users than Relenza users (pooled odds ratio = 3.45, 95% CI: 1.11 to 14.82, $P=0.0295$ by Exact Fisher).

4. Discussion

This is the first epidemiological study that has shown an association between sudden deterioration leading to death and Tamiflu use. Results show that Tamiflu is associated with a six-fold increase in

Table 2c
Comparison of baseline data by antivirals

Baseline characteristics		TF ($n=119\%$)	RL ($n=15\%$)	NAV ($n=31\%$)	*P* value Chi square or Fisher	
					TF vs RL	TF vs NAV
Age	0–9	16.0	6.7	16.1	ns	0.0821
	10–19	0.8	20.0	6.5	0.0043	
	20–59	39.5	40.0	51.6	ns	
	≥60	43.7	33.3	25.8	ns	
Sex	Male	58.0	66.7	58.1	ns	ns
	Not known	0.0	0.0	3.2		
Risk factor	Present	70.6	73.3	54.8	ns	ns
	Not known	5.0	0.0	4.5		
Fever to presentation	≤12 hr	64.7	80.0	74.2	ns	ns
	13–48 hr	27.7	20.0	12.9		
	>48 hr	7.6	0.0	12.9		
Fever to AV prescribed	≤12 hr	36.1	46.7		ns	
	13–48 hr	45.4	26.7			
	>48 hr	18.5	26.7			
When AV prescribed*a	mild	48.7	60.0	41.9	ns	ns
Rapid testing	(+) at first	60.5	60.0	16.1	ns	<0.0001
	(−) at first	14.3	26.7	48.4		<0.0001
	others	25.2	13.3	35.5	ns	
Confirmation by PCR		89.1	86.7	83.9	ns	ns
"Antipyretics"*b	Before presentation	2.5*c	0.0	0.0	ns	ns
	At first consultation	3.4*d	7.1*e	19.4	ns	0.0057
Fever to death*f		6.0	5.4	6.7	ns	ns
First consultation to death*f		5.0	5.4	6.2	ns	ns
Antiviral prescription to death*f		4.0	3.6		ns	

*a: TF (Tamiflu), RL (Relenza) and NAV (No antiviral) are all prescribed before deterioration.
*b: definition of "antipyretics": see text.
*c: all are immunosuppressants/anti-cancer drugs.
*d: all were antipyretics at the first consultation before Tamiflu prescribed.
*e: antipyretics at the 1st consultation with Relenza.
*f: median, days (by Mann-Whitney U test).

sudden deterioration leading to death compared to Relenza, about a four-fold increase compared to no antivirals and no antipyretics.

These results are consistent within all age groups and various baseline characteristics including the patients' risk factors. In addition, the severity at the time when antivirals were prescribed did not appear to contribute to the rapid deterioration because all patients who were positive by rapid testing, including mild cases, were recommended for treatment with antivirals (Tamiflu or Relenza) in Japan [34] and the

Table 3
Number, proportion and odds ratio of deterioration leading to death by the time from antiviral prescribed to deterioration: Tamiflu vs Relenza

Time to deterioration	Age	Number of death		Proportion (million cases)		Odds ratios or pooled odds ratios				% Weights
						OR	95% CI		*P* value	
		TF	RL	TF	RL	*a,*b	LL	UL		(fixed)
≤12 hr	0–9	12	0	2.4	0.0	7.09	0.79	–	0.081	29.1
	10–19	1	0	0.7	0.0	11.15	0.10	–	0.2120	7.9
	20–59	16	0	4.2	0.0	5.33	0.62	–	0.1514	32.1
	≥60	9	0	41.3	0.0	3.97	0.41	–	0.3743	30.9
	Total	38	0	Pooled OR*a		5.88	1.30	26.60	0.014	
				Pooled OR*b		–	2.68	–	0.0003	
13–48 hr	Total	41	5	Pooled OR*a		2.32	0.81	6.62	0.173	
>48 hr	Total	40	10	Pooled OR*a		0.87	0.44	1.74	0.83	
Any time	0–9	19	1	3.8	0.7	5.39	0.86	224.0	0.100	7.3
	10–19	1	3	0.7	0.6	1.24	0.02	15.43	>0.9999	5.9
	20–59	47	6	12.3	9.7	1.26	0.54	2.96	0.695	48.2
	≥60	52	5	238.7	109.7	2.18	0.87	6.98	0.113	38.6
	Total	119	15	Pooled OR*a		1.91	1.08	3.39	0.031	

TF: Tamiflu RL: Relenza.
*a: pooled odds ratio: by Fixed effects (Mantel-Haenszel, Robins-Breslow-Greenland), odds ratio for stratum was calculated by adding 0.5 to each cell if one of the cells is "zero".
*b: pooled odds ratio by Exact Fisher (conditional maximum likelihood).
– : not estimable due to zero events in the Relenza arm.

distribution of proportion of cases prescribed each antiviral or no antiviral before deterioration was similar in the mild and not mild groups in this study.

According to vital statistics, the number of death cases from influenza during July 2009 to March 2010 was 303, of which 198 (65.3%) were included in this study. All 198 cases were diagnosed with influenza A by rapid testing and/or by PCR. About ninety percent of the analysed patients were diagnosed as novel influenza by PCR. Therefore the subjects of our study have low risk of reporting bias for confirmed death cases from 2009A/H1N1 influenza in Japan.

Although the information for each patient is based on the press release by MHLW, it may be reliable enough for epidemiological analysis because it is based on the initial report by the physicians using a standardized reporting form and the follow-up collection of information by the corresponding health centers.

Reliable data for age specific proportion of patients who were prescribed Tamiflu and those prescribed Relenza were available. The total share of Tamiflu based on the information of Chugai Pharmaceutical was only a few percent lower than that of GSK: for example, share of Tamiflu by Chugai's data and by GSK's data were 73.9% and 79.8% for the 07/08 season and 59.7 and 63.0 for the 08/09 season respectively. Therefore, the estimated odds ratios using the data by GSK are not likely to be an over-estimate.

Results from a prospective cohort study suggested that the incidence of unconsciousness increased significantly after Tamiflu use with a hazard ratio of 1.79 ($p = 0.038$), and unconsciousness was found to

Table 4
Breakdown number of patients who deteriorated within 12 hours of antiviral prescription by various baseline characteristics (comparison of all cases)

		ALL deaths	Deteriorated within 12 hours	
			TF	RL
Risk factors *a (complications)	+	108	20	0
	(−)/unknown	54	18	0
Sex	Male	94	20	0
	Female	67	18	0
Disease state when AV was prescribed	Mild	79	17	0
	Not mild	83	21	0
Disease state at the first consultation	Mild	100	23	0
	Not mild	62	15	0
Onset of fever to the first presentation	≤12 hr	110	28	0
	13–24 hrs	30	7	0
	>24 hrs	22	3	0
Onset of fever to AV prescribe	≤24 hr	86	27	0
	>24 hrs	44	11	0

*a: odds of having no/unknown risk factors was higher for patients with deterioration within 12 hours: odds ratio = 2.22 (95% CI: 1.04 to 4.64, $p = 0.049$).

occur a short time after Tamiflu use. During the early phase of influenza, risk ratio of unconsciousness of Tamiflu use to non-use was about five to six with 2.0 the lower limit of 95% confidence interval [20]. This figure is consistent with the stratified odds ratios in comparison to Relenza in this study: 1.91 ($p = 0.031$) and 5.88 ($p = 0.014$) for any time and for 12 hours or less after prescription of antivirals respectively.

4.1. Strengths and limitations of this review

For this proportional mortality study we could analyse mortality data and the number of population at risk with low bias from the documents that MHLW and the national institute released. We could confirm that the association of Tamiflu use and sudden deterioration leading to death is strong especially within 12 hours of prescription and that this is not associated either with the patients risk factors or the severity of influenza at the time when antivirals were prescribed or other baseline characteristics.

A limitation of this study may be that the mortality information is base on documents press released by MHLW. However, selection bias and information bias could be reduced because the data are based on what MHLW demanded from physicians and regional health centers during the entire period of 2009A/H1N1 influenza season. Excluding those patients in whom antipyretics were known to be used, the association of rapid deterioration and Tamiflu was similar in comparisons with Relenza and no antiviral.

Accurate proportions of patients prescribed antivirals by age group were not available, hence reliability of stratified odds ratio for Tamiflu use compared to no-antiviral is somewhat limited. However, 85% may be a reasonable estimate because it is the highest proportion among several seasons in recent years. In

addition sensitivity analysis assuming a wide range of plausible proportions of patients getting antivirals (60–90%) showed a consistent result associated with Tamiflu exposure compared to Relenza.

4.2. What is already known on this subject

Antivirals (especially Tamiflu) are widely recommended and used to treat influenza especially since April 2009 based on insufficient evidence for efficacy, effectiveness and safety. A case series of sudden deaths shortly after Tamiflu use and a series of animal toxicity tests indicate the causal association for sudden death but the causality is not accepted by the regulatory authorities.

4.3. What this study adds

An epidemiological study indicates that Tamiflu use could induce sudden deterioration leading to death especially within 12 hours that is consistent with sudden deaths observed in a case series of clinical reports, in a series of animal toxicity studies, and results of neuropsychiatric events including unconsciousness reported in some prospective cohort studies.

5. Conclusion

The results of this study suggest that Tamiflu could induce sudden deterioration leading to death especially within 12 hours of prescription including those patients who were not mild (or severe) at the time when antiviral was prescribed.

Although this is not a hypothesis confirming study, causality between Tamiflu and sudden deterioration leading to death shortly after its use may also be epidemiologically suggested. Considering the evidence from this study in addition to a series of animal toxicity studies, case series of sudden death and the results from prospective cohort studies, it is strongly suggested that Tamiflu could cause sudden deaths especially within 12 hours.

Last but not least, from the view point of "the precautionary principle" the potential harm we have shown should be taken into account for prescribing and further detailed studies conducted using all data including clinical, laboratory and image data currently available.

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Contributors

Rokuro Hama developed the original idea for the study, drafted the protocol, made the data extracting form, extracted and analysed the data and drafted the full English manuscript;

Mark Jones advised the analysis methods (proportional mortality study and statistical analysis) to make protocol, checked the analysed results and provided critical input to the manuscript as a biostatistician.

Hiroki Okushima, Masahiro Kitao, Narumi Noda are the co-workers who drafted the protocol, made the data extracting form, classified, extracted the data and drafted the first preliminary manuscript written in Japanese.

Keiji Hayashi as a pediatrician and **Keiko Sakaguchi** as a lay person contributed to draft the protocol, extracted, checked and corrected the data with other four Japanese authors.

Guarantor

Rokuro Hama will act as guarantor for the study.

Ethics approval

Was not required.

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None.

Conflict of interest

Rokuro Hama reports that he receives royalties from two books published in 2008 titled "Tamiflu: harmful as was afraid" and "In order to escape from drug-induced encephalopathy". He also has salary support from a grant awarded in 2010 from NIHR (UK) for work on a Cochrane review of neuraminidase inhibitors. None reported by others.

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