薬害C型肝炎被害救済に関する立法措置に際して、2008年1月、福田康夫総理が「薬害再発防止に最善かつ最大の努力を行う」、舛添要一厚生労働大臣が「二度と薬害を起こさない行政の舵取りをしっかり行いたい」と述べられ、「薬害肝炎事件の検証及び再発防止のための医薬品行政のあり方検討委員会」が行われています。

「二度と薬害を起こさない行政」は、だれもが望むところですが、タミフルによる被害について因果関係を認識して被害を救済するかどうかは、「二度と薬害を起こさない行政の舵取り」の試金石であると考えます。

いくら行政の形を変え、人員を整えても、タミフルによる害の因果関係を認め早期救済ができなければ、今後も薬害は続発することでしょう。

「二度と薬害を起こさない行政」は、タミフルと突然死、異常行動との因果関係を認めるところから始まると存じます。何卒、ご賢察のほど、よろしくお願い申し上げます。

なお、以下についても、考慮くださるようお願いいたします。

1. 厚労省の研究班、因果関係見直しのため提出された資料、製薬企業（中外製薬、ロシュ社）による資料についても、NPO法人医薬ビジランスセンター（薬のチェック）では、そのつど、その意味を考察し問題点を指摘し、タミフルによる突然死や異常行動後事故死との因果関係をむしろ積極的に示唆するものばかりであることを指摘してまいりました。

2. たとえば、本件を検討された最終の安全対策調査会において公表された1万人規模の疫学調査では、異常行動の発症はタミフル非処方群に比してタミフル処方群に有意に高率（10歳未満も全年齢でも）に認められたにもかかわらず、一次予備解析結果では逆転した結果（タミフル群が非タミフル群より有意に異常行動が少ない）となっていました。これは重大な誤分類のためであることも指摘し、再解析を要望したところです。

3. また、7日齢の幼若ラットを用いた毒性試験で多数のラットが死亡したことがうかがえるにもかかわらず、何匹に用いて何匹が死亡したのか、つまり、分母も分子も不明のデータを用いて安全対策調査会では「問題なし」との結論を出しておられます。

4. ところが、その後疫学調査については一次予備解析以降、何ら新たな解析が公表されていませんし、毒性試験のデータ開示を求めても、開示が実現していません。問題のないデータならどうして開示を拒否するのでしょうか。

   追加分析や、新たな毒性試験データなしでも因果関係の指摘は十分可能ですが、適切な追加分析と新たな毒性試験データが開示されたら、因果関係はより確実なものになる、と確信いたします。

   ぜひ速やかに、適切な追加分析と新たな毒性試験データの開示を求めます。

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Fatal neuropsychiatric adverse reactions to oseltamivir: Case series and overview of causal relationships

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Abstract. *Background*: Infection-associated encephalopathies such as Reye's syndrome have been one of the major public health problems in many countries. The not dissimilar neuropsychiatric adverse reactions, including deaths, observed with Tamiflu (oseltamivir phosphate: OP) have been another current problem especially in Japan.

Methods: Among the cases with neuropsychiatric adverse reactions to Tamiflu on which I was consulted, those cases in which medical charts, autopsy records and/or prescription certificates were available were analyzed and described. In order to obtain a complete view of the spectrum of neuropsychiatric adverse reactions attributed to Tamiflu and of existing knowledge of the causal relationship, adverse reaction case reports and accounts of personal experiences were collected using PubMed, Japonica Centra Revuo Medicina, the websites of MHLW, PMDA and FDA and other Internet sources. Information on animal toxicity and clinical trial findings was derived from the texts of the officially approved data sheet for Tamiflu.

Results and discussion: This paper reports eight cases in total: five of these died and three survived. Two died as a result of accidents resulting from abnormal behaviour. Three others died suddenly during sleep (two infants and one adult). One of the infants and the adult were found at autopsy to have severe lung oedema. A 14-year-old boy experienced agitation, cyanosis, loss of consciousness and seizures but recovered completely, while a 10-month-old girl showed retarded development and mental retardation after initially appearing to recover from the acute event involving loss of consciousness and seizure. A 15-year-old boy had a delayed onset of complications but developed prolonged neuropsychiatric adverse reactions after taking an almost complete course of Tamiflu; in this case the symptoms lasted for two weeks.

Following our review of known clinical cases of this type, which included 80 fatalities (among them 50 instances of sudden death and 8 cases of accidental death consequential upon abnormal behaviour, and in the light of our study of animal experiments and the latest laboratory findings, we propose to classify adverse reactions to Tamiflu as follows:

(1) *Sudden onset adverse reactions* typically occurring after taking one or two doses of Tamiflu; these result from the central nervous system suppressant action of oseltamivir, a pro-drug of oseltamivir carboxylate (OCB: an active metabolite). The group includes cases of sudden death during sleep or associated with respiratory suppression, sudden onset of abnormal behaviour and occurrence of other neuropsychiatric disorders having an acute onset but a short duration.

(2) *Delayed onset adverse reactions* occurring after taking several doses or a full course of Tamiflu, probably caused by OCB. Examples include delayed onset neuropsychiatric reactions with prolonged duration, pneumonia, sepsis, bleeding and *hyperglycemia.*

(3) *Allergic and miscellaneous* reactions involving various organs.

The mechanisms underlying the adverse reactions to oseltamivir and the causal relationships may be summarized as follows:

(1) Oseltamivir has a depressant effect on the central nervous system (CNS); the signs, symptoms and pathological findings are similar to those induced by hypnotics and sedatives (decreased body temperature, decreased spontaneous movements, slow/irregular breathing, cyanosis and pulmonary oedema). Severe sequels may reflect delayed neuronal damage resulting from temporary cardiopulmonary arrest.

(2) Abnormal behaviour, delirium, hallucinations and even suicide could be the consequences of disinhibition or loss of control induced by the CNS depressant effect.

(3) Delayed onset reactions to Tamiflu may be related to its inhibitory action on sialidase (neuraminidase), a key enzyme for antiviral activity and involved in a wide variety of mammalian physiological processes including immune functions, cell

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apoptosis and glucose metabolism reflecting its ability to influence the conformation of glycoproteins and gangliosides that are important components of cell structure and function.

Conclusion: Three sudden deaths during sleep and two near deaths with or without sequels, as well as two deaths from accidents resulting from abnormal behaviour in older children and adolescents shortly after taking Tamiflu are probably related to the central depressant action of oseltamivir. Late onset neuropsychiatric symptoms after taking a full dose of Tamiflu, which we observed in one case, may be related to the inhibition of human neuraminidase by OCB, an active metabolite of Tamiflu.

Keywords: Tamiflu, oseltamivir, adverse drug reaction, sudden death, influenza, animal toxicity, fever, delirium, organ damage, encephalopathy

Abbreviations

OCB: Oseltamivir carboxylate,
NAP: New drug approval package,
MHLW: Ministry of Health Labour and Welfare,
PMDA: Pharmaceuticals and Medical Devices Agency.

1. Introduction

Acute encephalopathy following viral infection, such as Reye's syndrome and/or influenza-associated encephalopathy, has been one of the major public health problems experienced not only in Japan but also in the US [8,69] and elsewhere. After the publication of warnings against and restrictions on the use of salicylates in young children, Reye's syndrome disappeared in the US [9]. Similarly, restrictions on the use of non-steroidal anti-inflammatory drugs (NSAIDs) as antipyretics in Japan in 2000 led to a dramatic decrease in case mortality of Reye's syndrome and/or of encephalitis/encephalopathy after viral infection [37].

However, further cases of sudden death associated with influenza in previously healthy children were reported both in the United States [8] and in Japan [84] during the winter of 2002/03.

After I warned of the possible involvement of Tamiflu (oseltamivir phosphate), an ethylester prodrug of oseltamivir carboxylate (OCB) as the cause of sudden death [33,34], eight families consulted me for an expert opinion on the cause of their children's deaths or the serious adverse events which they had experienced when using this drug, making their medical records available for my perusal. I presented three of these fatal cases at a scientific meeting in November 2005 [35].

The present paper will describe five deaths and three life-threatening cases of neuropsychiatric adverse reactions involving Tamiflu. The mechanism of such adverse reactions to Tamiflu and the causal relationship will be discussed.

2. Materials and methods

After the presentation of the above material at the scientific meeting in 2005 [35], and during the period up to the end of August 2007, the families of five additional cases made their medical charts, autopsy records and/or prescription certificates available to me for investigation.

I analyzed eight cases in all in which the necessary documents were available for study. Histories were again taken from the families.

In order to examine the full spectrum of neuropsychiatric adverse events associated with Tamiflu and to discuss the causal relationship, case reports and data on adverse events or reactions as well as accounts of personal experiences were collected from a wide range of sources. Information was derived variously from direct phone calls and e-mails to our center, by searches using PubMed, "Japonica Centra Revuo Medicina" (a Database of Japanese medical journals), the websites of the Japanese Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) as well as the US Food and Drug Administration (FDA) and various other internet sources.

Data on animal toxicity and clinical trial findings were based on the studies cited in the "New drug approval package" (NAP) issued for Tamiflu capsules (used both for treatment and for prevention), and for Tamiflu dry syrup (in Japanese) [13–15].

The mechanism of adverse reactions to Tamiflu and the causal relationship will be discussed, focusing on the following points:

(1) the profile of adverse reactions to Tamiflu in human subjects,
(2) the drug's toxicity profile in animals,
(3) the similarity of the symptoms and findings in animals and in humans,
(4) the neuropsychiatric symptoms and forms of dyscontrol experienced with other CNS suppressants,
(5) differences between Reye's syndrome and influenza-associated encephalopathy,
(6) cases of non-Tamiflu related sudden death and seizure-inducing drugs,
(7) fever delirium and Tamiflu delirium,
(8) brain/lung oedema and hypoxia,
(9) sequels and appearance of delayed neuronal cell damage following cardiac arrest,
(10) delayed adverse reactions and inhibition of human sialidase (neuraminidase) by OCB,
(11) limitations of postmortem measurements of oseltamivir and OCB levels,
(12) methods of assessment for adverse reactions,
(13) what this paper adds to earlier reports,
(14) possible further study required to confirm causality and for other reasons.

For the statistical analysis EpiInfo (version 3-3-2) was used for case controlled study or cross sectional studies. The latest version of StatDirect was used for meta-analysis of the death rate during toxicity testing of non-steroidal anti-inflammatory drugs (NSAIDs) using infected animals.

2.1. Case reports

Eight cases are summarized in Table 1. Seven were sudden onset cases in which the events occurred soon after the first or second dose of Tamiflu, while one was a delayed onset neuropsychiatric case in which the adverse events occurred after the end of a full course of Tamiflu and continued for some two weeks.

Of the seven sudden onset cases, two were accidental deaths, probably after non-suicidal abnormal behaviour, three cases were sudden deaths during sleep, and the other two were life-threatening cases: one without any sequels after occurrence of abnormal behaviour, cyanosis, and seizure, and another with sequels after cyanosis and seizure.

2.2. Two cases with abnormal/strange behaviour and accidental death

Case 1. A 14-year-old boy had a body temperature 38.0°C (100.4 F) on the evening on February 4th 2005. It rose to 39.0°C (102.2 F), accompanied by other flu symptoms and was diagnosed as influenza

Table 1
Characteristics of the patients

Case no.	Age (Y/M)	Sex	Influenza type	Oseltamivir dose	Signs and symptoms (leading to death)	Outcome	Autopsy: findings	Body temperature** (°C)
1	14	M	A	75 mg × 1	Accidental death after abnormal behaviour	Death	Not done	37.5
2	17	M	A	75 mg × 1	Accidental death after abnormal behaviour	Death	Not done	39.2
3	2/9	M	A	2 mg/kg × 1	Sudden cardiopulmonary arrest during nap (10 min)	Death	Not done	34.0
4	3/3	M	A	2 mg/kg × 1	Death during nap	Death	Brain oedema and marked lung oedema without inflammation	?
5	39	M	B	150 mg × 1	Death during sleep	Death	Dilated heart and lung oedema without sign of inflammation and fibrosis	?
6	14	M	A	75 mg × 1	Abnormal behaviour, dyspnoea, cyanosis, seizure and weak breathing	Recovered without sequels		37.5
7	0/10	F	? *	2 mg/kg × 1	Flaccid extremities, loss of consciousness, cyanosis and seizure	Marked mental and physical retardation followed by gradual development		? (not high)
8	15	M	B	75 mg 1 day, 75 mg × b.i.d. 4 days, and 75 mg 1 day,	Lethargy at d 5, abnormal behaviour/delirium on day 6, hallucination on the third day and neuropsychiatric symptoms for some two weeks after the end of the Tamiflu course.	Recovered without sequels		Normal

* Influenza or adverse effect of influenza vaccine (Occurring 6 days after inoculation). ** Body temperature around the time of the event (degrees centigrade).

A by rapid testing at a clinic. After he had returned home and slept for two hours, his body temperature fell to 37.5°C (99.5 F). After he took a first dose of Tamiflu (one 75 mg capsule containing 75 mg of oseltamivir; equivalent to 98.5 mg of OP), he watched a video on TV for about 1.5 hours with his elder sister, and went to bed in his room. However, about 30 minutes later, his mother could not find him there. Noticing that the entrance door was open, she looked out into the stairway and heard a shout "a boy has fallen". His residence was on the ninth floor of a condominium. She went down to the ground level and found that the boy was her son.

His fingerprints were found on the bannister rail of the staircase leading down from the condominium. They showed that he had first climbed over the bannister and grasped it, from which it was concluded that he had first hung from the bannister and had then fallen the nine stories to the ground. His body was severely damaged, except for his head and he died from massive bleeding. There was no sign of his having consumed alcohol.

Case 2. A 17-year-old high school boy with high fever (39.0°C or 102.2 F) consulted his family doctor on February 4th 2004. He was initially treated with amantadine (50 mg b.i.d.), though rapid flu testing was negative. The next morning he had 39.7°C (103.5 F) and again consulted the doctor, at which time he tested positive for influenza A. He took a Tamiflu 75 mg capsule at home around noon. One and a half hours later, he complained of nausea. By about 2 p.m. his body temperature was 39.2°C (102.6 F), after which his father left home, leaving him alone. While all the family members were away from home, he suddenly went outside and jumped over the fence around his house. He ran on the several centimeters thick snow, then jumped over a concrete fence, crossed a railway line and jumped over a guardrail along a highway: passers-by noted that he was smiling. On the road he was run over by an oncoming truck and killed. These events occurred some three hours and forty-five minutes after taking Tamiflu and about nine hours after taking the last dose of amantadine (50 mg). There was no sign of his having consumed alcohol.

2.3. Three cases of sudden death during sleep

Case 3. A boy aged two years and nine months and weighing 13 kg, who had previously been in good health developed a temperature of 38.3°C (100.8 F) and was taken to the family doctor on February 5th 2005. He was influenza A positive as determined by rapid testing.

After having been alert and relatively well in the morning, he was given one dose of Tamiflu dry syrup (25.5 mg) together with one dose of other drugs, including cyproheptadine, carbocysteine and tipepidine hibenzoate. His temperature at this time was 39.2°C (102.6 F). He did not complain of vomiting or headache and he fell asleep ten minutes after taking the medicines. One and a half hours after taking the medicines, he woke up crying and complained of headache. He did not stop crying even when his mother took him in her arms to console him. It took forty to fifty minutes before he stopped crying and fell asleep again, some two hours and 20 minutes after taking the medicines. Two hours and 45 minutes after the treatment his mother noticed that he turned over in his sleep. Just ten minutes later she touched him and found him flaccid and not breathing. She called an ambulance and he arrived at the hospital some thirty minutes later. His body temperature at this time was 34°C (93.2 F). He was successfully resuscitated and his heartbeat resumed but he died next day (28 hours after admission to the hospital). His AST/ALT/LDH/CK levels were slightly elevated at admission and extremely high just before his death which was found to be due to hypoxic organ failure resulting from cardiopulmonary arrest. There was no sign of his having taken alcohol.

Case 4. A boy aged 3 years and 3 months and weighing 13.5 kg had generally been in good health though he suffered from atopic dermatitis without asthma. When he developed a body temperature of 38.5°C (101.3 F) that has persisted for several hours he was taken to the family doctor on December 27th 2002. At the clinic his temperature was found to be 39.6°C (103.3 F) and rapid testing led to a diagnosis of influenza A. He was treated with aminophyllin (50 mg) in 200 ml electrolyte solution and inhalation of procaterol with sodium cromoglycate for a mild wheezing bronchitis. Tamiflu 55 mg (4.1 mg/kg/day) and other drugs (including antihistamines and mucolytics) were prescribed for him. After coming back home at around 14:00, he took only one dose of Tamiflu (27.5 mg) of the various drugs prescribed and fell asleep shortly afterwards. He woke up after one hour and then slept again while watching a video on TV. At this time his mother remained in the room, checking him on occasion; after some time, believing he was asleep since he was lying on his left side, she switched off the video. At around 16:00 his mother found that he was lying face down; he now had rhinorrhea and was apparently not breathing.

He was taken by ambulance to a hospital emergency unit where he arrived at 16:34. He was intubated and treated with cardiac massage immediately on arrival, and was treated with three intravenous doses of 0.1 mg adrenaline and eleven intravenous doses of 1 mg adrenaline. Resuscitated nevertheless failed and he was pronounced dead at 17:15.

According to the autopsy report required by law, the major macroscopic findings comprised moderate lung congestion with marked pulmonary oedema, mild congestion of the spleen and of the renal pelvis. The brain was markedly congested and swollen (wt. 1331 g) especially in the pons and medulla, but no brain herniation was observed.

Histological examination showed that the lung tissue was slightly congested with some macrophagic infiltration, while the bronchial mucosa was slightly swollen and infiltrated with lymphocytes and neutrophils. There were no signs of pneumonia and the histological findings were compatible with bronchitis due to typical influenza virus infection and lung congestion after sudden cardiac arrest. A pulmonary lesion was not the cause of his death. No particular findings were observed in the heart and other organs except in the brain. Brain oedema was slight; no evidence of meningitis or encephalitis was found and no brain herniation appeared to be present. Diffuse microgliosis was observed in the brain and pons. Most of the astroglial fibers were segmented on GFAP staining, a typical but non-specific signs of disorganization of the blood–brain-barrier of unknown cause.

His glucose level was 196 mg/dl (10.9 mmol/l) at 16:41 and 466 mg/dl (25.9 mmol/l) at 16:52 though he had no diabetes mellitus. Rapid increase in the glucose level may be induced by very high doses of adrenaline (11.3 mg in total) such as were used for resuscitation. There was no sign of alcohol consumption.

Case 5. A 39-year-old previously healthy man developed flu-like symptoms on the evening of February 25th 2005. His body temperature was 37.4°C when he consulted his family physician at a hospital at 7:30 p.m. He was diagnosed as having influenza B and was treated with 0.5 g of intramuscular dipyrone and infused with 500 ml of maltose-lactated Ringer's solution containing 1 g of cefpirome sulfate over a couple of hours. He was then prescribed Tamiflu (two 75 mg capsules b.i.d.), cefcapene pivoxil hydrochloride (100 mg t.i.d.), naproxene (100 mg t.i.d.), ambroxol hydrochloride and throat lozenges. Returning home, he took one dose of each medication. 10 minutes later, at around 10:00 p.m., he went to bed. Next morning his mother found he was lying face upwards with open mouth and open eyes but leaning a little to his left, and apparently not breathing. His mother called an ambulance, but when it arrived the crew informed his mother that he was dead and took the body to the hospital where death was confirmed.

Autopsy was confirmed by a specialist in forensic medicine at the university medical school. Major findings of the autopsy and histology were as follows: dilated and heavy heart (448 g) without inflammation or fibrosis, pulmonary oedema without pneumonia, massive amounts of sputum in the bronchi and of a pinkish or brownish mucous in the trachea and larynx and a liquefied adrenal medulla. Viral testing revealed influenza B. Examination of the urine with triage testing proved negative for amphetamines, hypnotics, marijuana and antidepressants. Troponin testing in the urine also proved negative. The time of death was estimated at around 1:00 a.m., i.e. about three hours after taking the medicines. The cause of death was diagnosed as acute left heart failure due to dilated cardiomyopathy.

It is notable that this man had been entirely healthy before developing influenza. He had no trouble during or after the infusion of cefpirome in 500 ml of fluid over a couple of hours and he had shown no signs or symptoms of heart failure before taking one dose of each medication just before falling asleep. It can therefore be assumed that his heart failure and lung oedema set in after he had taken the medicines. There was no sign of his having consumed alcohol.

2.4. Two life-threatening cases with or without sequels

Case 6. A 14-year-old boy with a body temperature of 39.0°C (102.2 F) and other flu symptoms was diagnosed as suffering from influenza A by rapid testing at a clinic near the ski resort which he and his family had visited on 31st December 2005. He vomited about one hour after taking the first dose of Tamiflu (one 75 mg capsule) at 11:00 a.m. His father then took him back to the family home, which involved some 8 hours of driving, arriving at about 20:00. As soon as the boy arrived home, he took a second Tamiflu capsule. One hour after the second dose, he developed a headache and looked agitated saying "can't breathe", "Wau Wau" and something else that made no sense.

His father held him tight to calm him but his face became cyanotic and then he suddenly turned pale, his eyes turned upwards, his extremities became flaccid and he lost consciousness. By the time an ambulance arrived he had begun to breathe again but very weakly, and his father was very anxious that the breathing might fail again. In the ambulance the body temperature was 37.5°C (99.5 F) but after admission to hospital it rose again to 38.8°C (101.8 F), falling once more to 36.7°C (98.1 F) after taking paracetamol. Seven hours after he had taken the second dose of Tamiflu he again became agitated, shouting and with evident dyspnea and his eyes were again turned upwards. He recovered completely 15 hours after taking the second dose of Tamiflu. His electro-encephalogram (EEG) showed no evidence of encephalitis/encephalopathy. He now had no fever, there was no recurrence of neuropsychiatric and respiratory disorders and he was discharged on the third day of admission. There was no sign of alcohol consumption at any time.

Case 7. A 10-month-old girl who was born on March 12th 2002 weighed 3324 g at birth; there were no birthing complications. She grew steadily, could sit unsupported by the 6th to 7th month and began crawling backward for the first time in the 9th month and also began crawling forward a little later. She could stand supported and was making early attempts to walk and talk ("ma-ma-ma" and "ba-ba-ba"). She could hold a spoon and eat with it when her mother put some food on it. She also played with her toy telephone. At a routine check-up on December 26th 2002 her height was 71.2 cm and body weight was 9.0 kg. All these facts suggest that her physical, cognitive and emotional development was initially normal.

On 16th January 2003, she was inoculated with influenza HI vaccine 0.1 ml. In the evening on that day, her body temperature rose to 38.6°C (101.5 F), she had a running nose and productive cough;