her temperature thereafter fell until January 19th after which it rose again to 37.9°C (100.2 F). Her mother took her to a clinic. Rapid testing for influenza A and B was negative and the doctor prescribed *d-chlorpheniramine maleate, tulobuterol, carbocysteine, tipepidine hibenzoate, pranoprofen and paracetamol* suppositories. Her mother gave her all these drugs except pranoprofen and paracetamol only on the first day (January 20th) since her body temperature fell promptly. On January 22nd however her body temperature rose again and her mother returned with her to the clinic; her temperature was now 38.6°C (101.5 F) and a doctor diagnosed influenza though without specific testing; he prescribed Tamiflu 18 mg b.i.d. She was given an initial dose at 15:30. The mother, who was carrying the girl on her back, noticed something abnormal at 16:20. The mother tried to let her sit at this time but she could not sit unsupported. She fell down with flaccid extremities and lost consciousness with cyanotic lips and froth. The mother took her to the clinic again at 16:45, and when the doctor saw her she exhibited clonic seizures and was unconscious. She was treated with a 4 mg suppository of diazepam, and the seizures ceased within some 10 minutes. Her consciousness apparently recovered after one hour and three quarters (18:30) and the doctor recorded no abnormal findings when she left the clinic. The mother recalled that her body temperature was less than 38.6°C (101.5 F). She did not take another Tamiflu.

Her temperature fell and other common cold-like symptoms disappeared except on 25th when her body temperature was 38.9°C (102.0 F) without taking any medicines.

On January 26th, her mother noticed that she did not crawl as she used to do before the events on 22nd. The movement of her upper extremities was not much affected but she crawled dragging her both legs. She could no longer stand supported; she did not put down her legs and did not try to stand. Her normal mental and physical condition which was acutely impaired at the time of the event has since that time ceased to develop satisfactorily. When she was two years and two months old, she became able to stand by grasping something. At the age of two and a half she could walk one or two steps. By the age of two years and eleven months she could stand up unsupported and could walk about 10 m, and she could walk by herself at around three years of age.

Following the acute events of January 22nd the child became very passive and ceased to speak. She spoke a little for a short period before her second years birthday, but thereafter she essentially lost the ability to speak until she was three and half years old. She can now say "papa" "bye bye" and "puapua" (this means mama. She cannot pronounce mama).

After the acute event she stopped trying to grasp a spoon and to eat by herself. It was not until she was 3 years and 5 months old that she could eat by herself again.

She is now 5 years old but she cannot put on clothes by herself, cannot excrete independently, cannot eat nor go up and down the steps alone. She is almost entirely dependent on others for her daily activity at home and in the society.

Magnetic resonance imaging (MRI), performed in April 2006, showed very slight atrophy in the right hippocampus, and poor development in the bilateral sylvian fissure was suspected. No seizure-spike was observed but basal waves were not completely normal by the EEG taken in April 2006.

2.5. *A late onset case with neuropsychiatric symptoms lasting for two weeks*

Case 8. A 15-year-old junior high school boy with a body temperature of 39.2°C was diagnosed as influenza B by a rapid testing by his family physician. Tamiflu 75 mg b.i.d. was commenced on the evening on February 8th together with paracetamol 400 mg b.i.d. and various other drugs to relieve the symptoms of flu. His body temperature fell to about 38.0°C next day and about 37.0°C on 10th, but he

could not go to school. On 12th his body temperature was within the normal range but he was lethargic throughout the day.

After he took the last dose of Tamiflu on 13th (6th day since commencement of Tamiflu), he went to school where he sat erect with his legs folded under him (Japanese sitting style) on the desk and began to sing loudly during a lesson. He could not communicate with his classmates or look them in the eyes. He seemed to be delirious. His parents took him back home where again he was lethargic, though no other abnormality of behaviour was apparent, and he was unwilling to return to school. After four days his parents took him to the physician who referred him to a general municipal hospital. There he was thought to be suffering from abnormal behaviour induced by Tamiflu and was admitted.

Routine examinations including urinalysis, complete blood count and blood chemistry, head CT, brain MRI, EEG etc. were normal. Serum ammonium level was also normal. During the physical examination before admission, he commented "There are insects on my mask" which led the staff to suspect that he was experiencing visual hallucinations.

On admission, signs and symptoms characteristic of delirium were observed: he tried to pull out his venous lines out or attempted to go home shouting "This is not a hospital this is a nursing home for elderly people". His doctor decided that he should be away from the hospital for several days (February 17th to 23rd), since he could not be maintained there.

On February 19th, his parents took him back to the hospital to be tested (SPECT), but he did not want to go inside the building. Finally he underwent a test but could not complete it because of his agitation during the procedure. On 20th he was referred to another hospital for a second opinion, but he could not await until his turn; rushing out of the hospital into the street he narrowly avoided being run over by a car.

After February 22nd he tried to attend school with his parents during his hospital leave and did so without any apparent trouble. He was formally discharged from hospital care on 23rd February. On 26th (Monday) and on 27th (Tuesday), he went to school and noticed that he had engaged in strange behaviours only after reading text messages from his classmates on his mobile phone. He was very much ashamed with this, but could not himself recall what he had done. After this he became fully normal and controlled. The entire episode had lasted for 18 days after commencement of Tamiflu, 16 days since the initial fever fell to normal, 14 days after the onset of lethargy, and 13 days after beginning of abnormal behaviour.

He was reluctant to attend the school's graduation ceremony on March 13th although he had been able to take an entrance examination for high school on March 7th. Once he realized that he had passed the examination, he gradually regained his usual cheerfulness.

There was no sign of alcohol consumption during the course of these events.

3. *Discussion*

Oseltamivir phosphate is easily dissociated in the GI tract to form oseltamivir which is absorbed from the gut and is extensively hydrolysed to OCB (Ro64-0802) and ethanol by liver microsomal carboxyesterase (hCE-1); apart from this, up to one fourth of oseltamivir is distributed via circulation and enters the brain tissue through the blood-brain barrier [13–15]. OCB is a potent selective inhibitor of influenza A and B virus neuraminidase [13–15], while oseltamivir phosphate and oseltamivir lack antiviral activity. The absolute bioavailability of OCB is 79.0% (SD 11.6%) [13–15].

3.1. Profile of adverse reactions to Tamiflu in human subjects

(1) Low body temperature.

One of the most prominent adverse reactions (AR) to oseltamivir observed in humans is low body temperature. According to the Chugai Pharm Co. (Chugai), 136 cases of reduced body temperature cases were reported to the company by June 2005. It is pointed out in the literature that low body temperature may be related to oseltamivir and the complication is not limited to children; that adult cases with low body temperature were also observed [85]. Chugai agrees that the reduction in body temperature is one of the adverse reactions to oseltamivir which may inhibit the body temperature regulating center in the brain [16].

Reduction in body temperature by inhibition of this regulating center undoubtedly means that oseltamivir readily passes the blood–brain barrier (BBB) and enters the brain not only of babies younger than one year old but also of older children and even adults who have not consumed alcohol when they are infected with influenza or other acute infectious diseases.

(2) Sudden onset psychiatric disorders including abnormal behaviour, delirium and hallucination.

Cases 1 and 2 are the typical cases showing a sudden onset of abnormal behaviour and occurrence of accidents. MHLW reported the case of a teenage girl with abnormal behaviour as a result of hallucination [62]: as soon as her body temperature fell, she ran to the window but her mother stopped her from jumping from the window, thus preventing an accident. MHLW warned of the possibility of abnormal behaviour by publishing this case in June 2004 [62]. Chugai had received 69 reports of hallucinations by June 2005 [16], though only 10 cases of hallucination and 8 of abnormal behaviour had been reported as adverse reactions to Tamiflu on the Japanese PMDA website up to March 2005 [77]. After my presentation of this issue at a scientific meeting in November 2005, 35 further incidents of abnormal behaviour were reported in three months between January and March 2006 [77].

The Japanese MHLW has announced that since 2001, when marketing of oseltamivir started in Japan and up to May 31st 2007 it had received 1377 reports of adverse reactions [63,64]. Of these, 567 were serious neuropsychiatric cases, including at least 211 showing abnormal behaviour [63,64]. Of 71 deaths reported by MHLW, accidental deaths from abnormal behaviour were noted in eight (five in teenagers, three in individuals aged 20 or over) [63,64].

FDA [27] holds reports on 103 neuropsychiatric cases (95 cases of these including 3 death cases are from Japan). 75 patients (73%) experienced neuropsychiatric symptoms after one or two doses of Tamiflu. The times of onset of symptoms from the administration of oseltamivir ($n = 58$) are as follows: 0.5 h = 12 (21%), 1–1.5 h = 12 (21%), 2–2.5 h = 8 (14%). 38 patients (66%) experienced symptoms within less than four hours, and 54 patients (93%) experienced them within some 6 hours after the last dose of Tamiflu. On the other hand, a few patients experienced adverse reactions after a full course of treatment dose and after 12 hours or more. It should be noted that the time elapsing from the commencement of Tamiflu until the onset of symptoms is very short in most of the cases.

The MHLW task force reported on October 26th 2006 the results of a survey analyzing 2846 children with flu in the winter of 2005/06, performing in order to the investigate causal relationship between oseltamivir and abnormal behaviour [63]. It calculated the frequency of abnormal behaviour in patients treated with Tamiflu and patients not yet treated for each period by dividing a day in three parts (morning, afternoon and night) for seven days and examining the cumulative frequency for the whole study period. It concluded that there was no significant difference between these two groups (11.9% vs. 10.6%: hazard ratio 1.16, 95% CI 0.90–1.49). There are however many limitations in this study. For instance, it is neither

a randomized controlled study nor a case-control study. It is merely a comparison of the situation before and after taking Tamiflu. It is not known which occurred earlier, the ingestion of Tamiflu or the event within each period of first Tamiflu intake for whole study period.

However, based on this study data, proportions of patients with abnormal behaviour in the afternoon (from noon to 6 p.m.) on the first day of fever can be calculated for patients known to have been treated with Tamiflu cases (treated) and those definitely not treated with the drug (pre-treatment and non-treatment cases: pre/non-treatment).

Proportions of children with abnormal behaviour, according to the information provided by physicians, were 0.45% in pre/non-treated cases and 1.82% in treated cases. According to the information provided by families, the proportions of children experiencing "Terror or fear" was 0.38% vs. 2.00%. The figures for "Hallucination" were 0.055% vs. 0.66%, for "Sudden screaming/delirious speech" was 0.60% vs. 2.35% and for "Anger" 0.55% vs. 2.03%. Thus relative risks (and the relevant 95% confidence intervals) were 4.02 (1.52–10.53), 5.22 (1.85–14.68), 11.99 (1.57–91.30), 3.89 (1.56–9.62) and 3.69 (1.40–9.67) respectively. However, these high relative risks were only clearly observed in the afternoon on the first day of fever and were not observed from the second day to the seventh day. This tendency coincides with FDA's analysis based on cases reported from Japan [26] and the high frequency of vomiting occurring only on the first day of the treatment [14].

The MHLW task force reported on December 25th 2007 the first preliminary results of a survey analyzing 10,316 children with flu in the winter of 2006/07 [98]. In this report there are many serious misclassifications of cases: for example, a part of cases with events were deleted from Tamiflu-prescribed group and added to non-prescribed group. This miscalculation yielded very low odds ratio (0.382: 95% CI 0.338–0.432, $p < 0.0001$). However, correct odds ratio is estimated at least 1.37 (95% CI 1.18–1.58) and up to 2.56 (1.83–3.61, $p < 0.0000001$) [39].

(3) Sudden death, hypoxia, respiratory depression and lung oedema.

Of 71 deaths reported by MHLW [64], the number of instances of "sudden death" according to its classification is 13. However, according to my analysis, in which cases of death following sudden cardiopulmonary arrests are included, the number of instances of "sudden death" was in fact 41. These 41 cases include one instance which was classified by MHLW as an "anaphylactic shock" "possibly related to Tamiflu" by MHLW but should be classified as sudden death by my classification. In this case a woman in her eighties was diagnosed as having suffered anaphylactic shock although no typical signs and symptoms of anaphylaxis such as urticaria, wheezing or evidence of laryngeal oedema were recorded on the case card. In addition, her family told the doctor that her level of consciousness suddenly declined just after taking Tamiflu, paracetamol and cefcapene pivoxil, leading to her death. However, neither the doctor nor the MHLW pointed to the presence of any typical signs and symptoms of anaphylaxis, and diagnosed her as anaphylactic shock simply because she suddenly died after taking the medicines.

In addition to the 71 deaths reported by MHLW, there were nine other sudden deaths which the ministry did not recognize as adverse reactions [38]. Of these nine cases four had already been recorded by the MHLW as adverse *events* but were not included as adverse *reactions*. Nor were my present Case 3, a literature case report by Fujii [29], an Internet report or two cases reported only by phone included in the cases that MHLW has disclosed to date.

Overall it would seem that, of the total 80 deaths on record, 50 were sudden deaths or deaths from sudden cardiopulmonary arrest (18 in those below 10 years old, 32 in those aged 20 or over). Of these,

21 were sudden deaths during sleep, 13 were sudden death with respiratory disturbance, and 17 were sudden cardiopulmonary arrests.

Of the eight cases presented here, three (Cases 3–5) died during sleep and two (Cases 6 and 7) were very nearly fatal, with severe cyanosis and seizure probably due to hypoxia from respiratory suppression.

A 3-year-old boy described in the literature [29] died within an hour while his parents were taking him to a hospital by their car after they noticed his abnormal respiration.

After the news release of my presentation in November 2005, I received phone calls and e-mails from a total of more than 50 people who had experienced (either personally or in their families) adverse reactions to Tamiflu. Among these, there were two fatalities. One was a 53-year-old male with dyspnea, cyanosis and subsequent cardiopulmonary arrest while still in the ambulance. The other was a 60-year-old male with dyspnea and cyanosis, who died in hospital after cardiopulmonary resuscitation.

Of the eight cases of my report, two (Cases 4 and 5) were autopsied and both showed marked lung oedema, changes that are frequently observed among dead rats after treatment with Tamiflu (occurring in one experiment in 9 of 18 animals treated), pointing to sudden deaths from hypoxia due to central suppression of respiration.

The following two cases whose case reports were disclosed on the MHLW website [63] are also important in considering the continuity of the spectrum covering respiratory suppression and sudden deaths due to Tamiflu.

A two years old boy (MHLW-B04026215) with hydrocephalus and an Arnold–Chiary malformation and a VP-shunt took oseltamivir phosphate 18 mg as Tamiflu dry syrup five times in four days. He became unusually lethargic on day 4 and stopped taking the drug. Late on day 4 his temperature fell to some 35°C and he suddenly suffered cardiac arrest with facial pallor. After about twenty minutes he was resuscitated in an ambulance. At a hospital his body temperature was 34°C and lung oedema was observed on chest X-ray without pneumonia; the latter recovered easily after adequate oxygenation. Brain oedema was however also observed and after repeated incidents of cardiac arrest and resuscitation, he died 85 days after the commencement of Tamiflu, probably due to hypoxic multi-organ failure.

Another previously healthy boy (MHLW-B05005388) took Tamiflu syrup for two days. His age appears to have been about ten months old, in view of the dose level of Tamiflu (16.5 mg) and the fact that he could toddle by grasping fixed objects. On day 3, he became flaccid just after waking. During medical examination he developed pulmonary arrest; he was therefore intubated and given artificial respiration manually. After three further incidences of cardiopulmonary arrest and resuscitation with the aid of a ventilator, lung oedema was observed by chest X-ray; this was relieved by the next day following adequate oxygenation. He could be weaned from the artificial ventilator on day 5 after the principal event, but he had sequels which rendered him bedridden although he could drink and eat something.

The mechanism of lung oedema is discussed below.

The spectrum and continuity of symptoms due to respiratory suppression after taking oseltamivir (i.e. sudden deaths with or without lung oedema, sudden arrests with sequels and complete recovery) are summarized in Table 2.

(4) Cases with multiple neuropsychiatric symptoms.

There are several cases exhibiting a variety of combinations of multiple neuropsychiatric symptoms occurring after taking Tamiflu; manifestations include low body temperature, hallucinations, abnormal behaviour, suppressed activity, suppressed respiration, cyanosis, dyspnea and subsequent seizure.

Among the cases reported by telephone or e-mail is that of a woman in her thirties who noted that as her body temperature fell to 34.1°C, she tried to call her family for help but could not, and subse-

Table 2

Spectrum and continuity of symptoms due to respiratory suppression – sudden death, sequels or complete recovery after taking oseltamivir

1. Sudden death without pulmonary oedema (the hypoxic period prior to death may have been too short to allow for development of lung oedema).
2. Sudden death mainly during sleep with pulmonary oedema (Cases 4, 5).
3. Sudden cardiopulmonary arrest for a substantial period; resuscitated but transient lung oedema ensued and patient died after several weeks or months due to hypoxic multiorgan failure (MHLW-B04026215).
4. Sudden cardiopulmonary arrest for a substantial period; resuscitation followed by transient lung oedema with sequels rendering patient bedridden (MHLW-B05005388).
5. Probably sudden cardiopulmonary arrest for a period with seizure; apparent recovery followed by sequels (retrograde development with subsequent retardation and gradual development).
6. At least one episode of loss of consciousness and possible hypoxic seizure; complete recovery without sequels (Case 6 and many similar cases in MHLW's reports).
7. Asthenia, dyspnea and/or cyanosis without seizure followed by complete recovery (many cases in MHLW's reports).

quently lost consciousness. After regaining consciousness, she could not move and experienced visual and auditory hallucinations.

Sugaya reported a case with low body temperature and cyanosis [86]. Among the series of cases reported in the present paper, Case 5 experienced delirium, severe dyspnea, cyanosis, suppressed respiration and subsequent seizure. His body temperature was 37.4°C. He experienced a second episode with delirium, agitation, dyspnea and subsequent seizure 6 hours after the first episode. In this case the body fell to 36.7°C about 100 min after taking paracetamol.

A Japanese case (case #5769078) reported by the FDA [26] involved a 15-year-old male patient treated with oseltamivir 75 mg b.i.d. for influenza. He experienced delirium, involuntary movement, seizure and subsequent loss of consciousness and collapse. His temperature was 38.1°C on arrival at hospital. After admission, his temperature went down to 37.6°C with stable vital signs. He experienced a second episode of delirium with abnormal behaviour at midnight but he did not remember this incident. The first EEG showed no abnormality but a second EEG showed a spine-like spike.

This case was reported as one of seizure. As noted above however, various other symptoms were also present, notably two episodes of delirium (one with decreased temperature and antegrade amnesia, loss of consciousness and collapse), with improvement over the next two days.

(5) Reactions with delayed onset and/or a prolonged course.

Case 8 is one of the typical cases with delayed onset and prolonged course. There are substantial numbers of cases in which neuropsychiatric reactions appear only after several days of treatment with Tamiflu. However, in some cases neuropsychiatric symptoms appeared after taking a few doses and they continued for more than a week or even for as long as several months. For example, a 9-year-old boy was treated with two doses of Tamiflu for his flu A [44]. Even after his body temperature had decreased to normal, he had not fully recovered and he experienced reduced consciousness with amnesia for a week. These symptoms recurred about a month later without any triggering factor and on this occasion lasted about a week.

There are in total 22 known deaths which are neither sudden deaths nor accidental deaths resulting from abnormal behaviour [59,60]. Of those, four are deaths from sepsis following exacerbation of pneumonia after possible respiratory suppression. Nine cases are possibly related to exacerbation of mainly

pneumonia. Gastroinestinal (GI) bleeding occurring six days after one dose of Tamiflu 75 mg was the main cause of death in a case treated with dialysis due to renal failure.

GI bleeding was observed in eight patients in all including three cases classified as instances of sudden death (two boys under 10-year-old and a man in his thirties) [63,64]. Bleeding was one of the complications in four adult cases classified under the headings severe infection or sepsis [63,64].

Beside these disorders recorded as causes of death, hyperglycemia is one of the typical delayed reactions to Tamiflu. This conclusion is based on the analysis of several randomized controlled trials and the adverse reaction is described in the New Drug Approval Package (NAP) of oseltmivir (in Japanese): Tamiflu capsule for treatment [13].

(6) Reactions of allergic origin and other possible complications.

A further five deaths were associated with disorders of an allergic nature: two involved fulminant hepatitis with hepatic failure (one with a positive and one with negative drug-induced lymphocyte stimulation test: DLST), and the three others involved toxic epidermal necrolysis, pancytopenia and agranulocytosis respectively [63,64].

Acute hemorrhagic colitis induced by oseltamivir with positive DLST for oseltamivir was reported [100].

The clinical course of death could in three cases not be classified, as the available information was insufficient.

(7) Summary of profile of adverse reactions to Tamiflu.

In view of the above, the serious adverse reactions to oseltamivir reported so far may be roughly classified into three groups:

(1) Sudden onset adverse reactions related to the central nervous system suppressant action of oseltamivir:

   (a) *Sudden death, mainly during sleep, after complaints of dyspnea or abnormal respiration, or death with sudden pulmonary or cardiopulmonary arrest.* Somnolence, sleep, vomiting, headache and/or hypothermia may be frequently observed as initial prodromal symptoms. Dyspnea, cyanosis, agitation, or loss of consciousness with grand mal seizures may be often observed just before the sudden death. However, sudden death might also occur during apparent sleep.

   (b) *Abnormal behaviours and other acute onset neuropsychiatric disorders.* Low body temperature, hallucinations, agitation and/or difficulty of movement may be observed before abnormal behaviour is noted. Visual, auditory or pain hallucination may occur and even suicidal ideation or suicidal attempts have been reported.

(2) Delayed onset serious adverse reactions such as delayed onset neuropsychiatric reactions with prolonged course, pneumonia, sepsis, bleeding and hyperglycemia. Reactions of this type usually occur after taking several doses or a full course of Tamiflu. This type of complication could however occur even after taking a single dose in cases of severe renal failure because of a prolonged high plasma concentration of OCB.

(3) Reactions of allergic origin such as fulminant hepatitis, toxic epidermal necrolysis, agranulocytosis, pancytopenia and others.

3.2. *The toxicity profile of Tamiflu in animals*

(1) Deaths.

Sudden deaths were observed in at least three animal toxicity studies submitted to the MHLW [14,15]:

(a) In a dose finding toxicity study on 7-day-old rats, 18 of 24 treated with 1000 mg/kg of oseltamivir phosphate (OP) (i.e. 761 mg/kg of oseltamivir (OT)), died within seven hours after the treatment. Vacuolization of liver cells was observed in all dead rats and lung oedema was also observed in nine of the 18 dead rats on histological examination. No death was observed in 500 mg/kg (381 mg/kg of OT) or lower dose groups including the vehicle group.

(b) In a series of 7-day-old rat toxicity studies, it was noted that two to three hours after the first dose of OP had been administered, 2 of 14 rats died in the 700 mg/kg (533 mg/kg of OT) group and 3 of 14 rats died in 1000 mg/kg group. Symptoms such as decreased body temperature, decreased spontaneous movements and slow and/or irregular breathing were observed in 6 of 14 rats in the 700 mg/kg group and 12 of 14 rats in 1000 mg/kg group. Tremor was observed in one rat and collapse was observed in another rat among 14 rats of 1000 mg/kg group.

(c) In a series of toxico-kinetic tests, young rats were treated with a single OP dose of 1000 mg/kg. Seven of 56 seven-day-old rats died between 10 minutes and 4 hours after a single dose of OP. Symptoms such as decreased body temperature, paleness and decreased spontaneous movements were observed in 8 of 56 rats. One of twenty eight 14-day-old rats died 10 minutes after the treatment. No particular abnormality was however in the surviving or dead animals. No drug-related deaths were observed among twenty eight 24-day-old rats or twenty eight 42-day-old rats.

(2) Symptoms suggesting central nervous system suppression.

Symptoms such as decreased body temperature, decreased spontaneous movements and slow/irregular breathing before death and frequent findings of lung oedema at autopsy suggest that the major cause of death is probably respiratory suppression due to central nervous system suppression.

(3) 64 times higher concentration in the immature brain.

The ratio of maximum concentration (Cmax) of OT in the brain of 7-day-old rats to that of mature (42-day-old) rats was about 64 and the ratio of Cmax of OT in 7-day-old rats' brain to plasma was about 0.81. A ratio of Cmax of active metabolite (OCB) in the brain of 7-day-old rats to that of mature (42-day-old) rats was only 3.1. The ratio of Cmax of the active metabolite in 7-day-old rats' brain to that in plasma was 0.72 [15].

(4) The non-fatal rat dose was 10–20 times higher than clinical dose.

Non-fatal dose in rats (500 mg/kg of OP) is about 100 times the recommended human dose in children (5.3 mg/kg/day as OP or 4 mg/kg/day as OT) calculated on a mg/kg basis for OP, but it is only 10–20 times the recommended dose in terms of $AUC_{0-24\ h}$ of OCB. No data are available for comparison between concentrations of oseltamivir in the brain and plasma of 7-day-old rats and those measured in human infants less than one year of age.

(5) Other toxicities: pneumonia, GI bleeding and renal toxicities [13].

Three of six rats treated with 100 mg/kg (equivalent to free form) of OCB intravenously for two weeks developed acute alveolitis. Of the three, one exhibited wheezing on day 14 and was sacrificed the next day. Diffuse hemorrhagic alveolitis (pneumonia) and pulmonary microvascular thromboembolism