were observed in this animal. The $AUC_{0-\infty}$ of 100 mg/kg of OCB administered intravenously was 53.9 μg·h/ml, which is only 12 times higher than the average human AUC_{0-24} (4.6 μg·h/ml) on day 7 in individuals treated with 75 mg oseltamivir b.i.d. The $AUC_{0-\infty}$ of safe level i.v. doses (20 mg/kg) in rats was 8.55 μg·h/ml, i.e. less than twice the usual human AUC.

Lung oedema with congestion was observed in one female dead rat among ten treated with 2000 mg/kg of OP for three days in an oral toxicity test for two weeks.

Leukocytosis, an increased glucose level, histological change in renal tubules, increased relative weight of liver and kidney were also observed in various doses and various animals treated for various periods.

In the marmoset monkey 7-day oral toxicity tests, one of four animals treated with 2000 mg/kg of OP was sacrificed on day two, because of dying after severe vomiting, sleep, slow movement and collapse. Other three animals were all sacrificed on day four and the test for this dose group was discontinued. In all of the animals killed, reddening of the stomach mucosa macroscopically and mucosal bleeding with erosions, ulcers and atrophy was observed in the stomach histologically. In the animal killed on day two, these findings in duodenum and jejunum were also observed with macroscopically swollen small intestine. In stead of 2000 mg/kg, new dose group was started at the level of 1000 mg/kg of OP. In this dose group, reddening macroscopically and atrophy histologically of the stomach mucosa were observed. Vomiting was observed in the 500 mg/kg OP group, but this level was considered as non-observed adverse effects level (NOAEL) by the manufacturer, though the lowest level (100 mg/kg) should be the real NOAEL.

The safety index (animal AUC_{0-24} with no toxicity by human average AUC_{0-24} when taking 75 mg capsule b.i.d.) is only 3 for the four-week toxicity studies in rats and the six month oral toxicity studies in rats, 8 for the two week oral toxicity study in rats and 10 for the marmoset monkey 7-day oral toxicity study.

(6) Interaction with alcohol (acting as a partial agonist and antagonist).

Recently, in 28 weeks old rat experiment, oseltamivir (50 mg/kg ip) administered two hours prior to injection of ethanol (3.3 g/kg ip) shortened the duration of the loss of righting reflex (LORR) induced by ethanol, while the rectal temperature measured one hour after ethanol injection was significantly lower in rats treated with oseltamivir than in those not receiving oseltamivir treatment [46]. In the CA1 region of hippocampal slices, oseltamivir (100 μM) induced paired-pulse facilitation in population spikes without changes in excitatory postsynaptic potentials. Similarly, 3 μM OCB facilitated neuronal firing, though the facilitation did not involve GABAergic disinhibition [42]. These results apparently mean that oseltamivir may act as an agonist while OCB acts as an antagonist to ethanol.

However, none of eight human cases presented here was reported to have taken alcohol. Only two cases among hundreds of serious neuropsychiatric adverse reactions to Tamiflu (including instances of sudden death) were reported to have been taking alcohol.

The quantity of ethyl alcohol released when 75 mg of oseltamivir is fully metabolized to OCB is only 11 mg. This may be too small to affect one's neuropsychiatric state including respiration compared with the levels resulting from ethanol injection in animals (3.3 g/kg ip as above) or human consumption of alcohol (about 20–25 g in a bottle of beer or two glasses of wine).

3.3. Similarity of symptoms and findings in animals and in human

Table 3 shows that oseltamivir has almost exactly the same effects in humans and in animals except for the psychiatric symptoms which are difficult to demonstrate in animal toxicity studies. The spectrum

Table 3

Similarity of symptoms and histological findings in animals and human subjects after treatment with oseltamivir-p

Symptoms and findings		*Humans*	*Animals: rats and marmosets**
General symptoms	Temperature	Low temperature	Lowering of temperature
	Movement/ behaviour	Could not move, could not speak even when attempting to do so (suppressed behaviour), abnormal behaviour (excitatory behaviour)	Decreased spontaneous movement (suppressed behaviour)*
	Sleep	Somnolent	Prone to sleep*
	Respiration	Suppressed respiration, abnormal respiration, shallow and weak respiration, irregular and mixed patterns (deeper and lighter respiration) respiratory arrest	Slow and weak respiration, irregular respiration
	Face appearance	Pale, cyanosis, blackish hue	Cyanotic before death
	collapse	Collapse, cardiopulmonary arrest	Collapse*
	Death	Death	Death
Psycho-sensory symptoms	Abnormal behaviour Hallucination/ delirium	Abnormal behaviour, Hallucination/delirium	These symptoms may be difficult to detect in animal experiments and have never been investigated in animal toxicity studies of oseltamivir-p.
	Loss of consciousness	Decreased level or loss of consciousness, anterograde amnesia	
	Visual abnormality	Besides visual hallucinations, misleading visual impressions of real objects (size, patterns).	
	Auditory abnormality	Normal sounds appear very loud or non-existent sounds are experienced. Patient may cover both ears to protect from supposedly loud noises.	
Pathological/ histological findings	Lung, heart and brain	Marked pulmonary oedema is often observed in the sudden and autopsied death cases (8 of 11 including our cases). Temporary pulmonary oedema may be observed in the resuscitated cases. Brain oedema and/or bleeding may also be observed in sudden death cases.	Lung oedema was observed in nine of 18 dead rats. No macroscopic or histological abnormalities were reported for the brain. But it does not mean the possibility. GI bleeding is frequently observed in the high dose group of marmoset monkey.

of effects in humans and in animals including lung oedema is exactly the same as that of central nervous suppressants such as benzodiazepines and barbiturates.

3.4. Neuropsychiatric symptoms and disinhibition due to CNS suppressants

Respiratory suppression and abnormal behaviour are different effect profiles of central nervous system suppressants.

It is well established that benzodiazepines and barbiturates that induce respiratory suppression may cause bizarre uninhibited behaviour including anxiety, irritability, hallucinations, and hypomanic behaviour or even hostility and rage as a result of disinhibition or dyscontrol reactions [7]. Paranoia, depression and even suicidal behaviour may also occasionally accompany the use of benzodiazepines and barbiturates [7].

Table 3
(Continued)

Symptoms and findings		Humans	Animals: rats and marmosets*
Significant differences between fatal and surviving cases	Very slight differences seem to determine death or survival	Even life-threatening cases recovered without sequels except in two instances, but there are many fatalities. There seem to be very slight differences between fatalities and surviving cases. Most of the surviving cases recovered within a few days, though delirium and psychiatric symptoms occasionally continued for more than a few months.	None of the surviving animals cases had pathological changes. No deaths were observed in the 500 mg/kg group while few died in the 700 mg/kg group and most died in the 1000 mg/kg group. No abnormal findings were observed except vacuolization in liver cells of all dead rats and lung oedema in 9 of 18 dead rats
	Timing of onset of reaction	Symptoms appear at the first dose or on the first day of administration in most cases. Symptoms usually subside even on continuation, as transport of OP to the brain decreases in parallel with the improvement in the influenza. Symptoms occurred on day 2 to day 3 in some cases.	In rats before weaning, most deaths occur following the first dose. As animals grow older, BBB function develops and oseltamivir is prevented to enter into the brain by increased efflux transporter function of BBB. In some mature marmoset cases, symptoms appeared on day 2 to day 4.

* *Two male and two female marmosets which weighed around 400 g were treated with 2000 mg/kg of oseltamivir-p. Of these* four, one exhibited suppressed behaviour, fell asleep, collapsed and died on day 2. The remaining three were sacrificed on day 4 (therefore, all were reported as "dead"). All animals hemorrhaged in the GI tract (erosions, ulcers, hemorrhage and atrophy). No toxico-kinetic data including Cmax and AUC were available for this experiment.

These forms of disinhibition or "dyscontrol" may all be viewed as different expressions of a broad spectrum of effects exerted by central nervous system suppressants such as benzodiazepines and barbiturates.

3.5. *Differences from infection-associated encephalopathy including Reye's syndrome and/or influenza-associated encephalopathy*

Following restrictions on the use of NSAIDs as antipyretics for children in Japan in 2000 [37], the proportion of NSAIDs users among cases of Reye's syndrome and/or influenza-associated encephalopathy decreased from about 30% to below 10% and the proportion of case fatalities resulting from influenza-associated encephalopathy decreased from about 30% to about 10%. Two years (i.e. two winter seasons) elapsed during which the proportion of case fatality of influenza-associated encephalopathy decreased, before the marketing of Tamiflu dry syrup for children in Japan commenced in September 2002.

I have collected nine papers reporting on 15 animal experiments designed to investigate the effects of NSAIDs on mortality in infected animals [19,23,45,46,49,52,71,72,83]. One experiment was excluded because proportions of death of both groups were 0; reports on 14 experiments were therefore examined. Various NSAIDs were tested including ibuprofen, flurubiprofen, mefenamic acid, indomethacin, salicylates and so on. Various microorganisms including viruses, bacteria and protozoas were used. Proportions of death from these experiments were meta-analyzed. Peto odds ratio for NSAIDs use on proportion of death in infected animals was 7.54 with 95% confidence interval (CI): 4.50–12.66 ($p < 0.0001$) and I^2 (inconsistency) = 9% (95% CI: 0–52.1%) [36]. Other evidence suggesting NSAIDs as a major cause of fatal influenza-associated encephalopathy is to be found in a case-control study reported in the Japanese Task Force's paper "A case control study on factors related to onset and severity of influenza-associated encephalopathy" [81]. Three children among four fatal cases from influenza-associated encephalopathy took NSAIDs, while among 84 controls (flu without encephalopathy) only five (6.0%) had taken

NSAIDs. A strong association between NSAID use and fatal influenza-associated encephalopathy was thus observed: the crude odds ratio was 47.4 (95% CI; 3.29–1458, $p = 0.0019$) [36], though the task force reported that the study could not demonstrate any definite relation of NSAIDs to the occurrence of influenza-associated encephalopathy. The odds ratio for paracetamol was not significant (OR 2.25; 95% CI; 0.19–58.6) [74].

The clinical course of sudden death and accidental death from abnormal behaviour after taking Tamiflu is very different from that seen in Reye's syndrome or influenza-associated encephalopathy. It is reported that the latter usually continue for less than two or three days until proving fatal [85], but they run for at least a half day or one day even in the most severe cases. However, in the Tamiflu cases, an infant may stay well for the first few hours after taking a single dose of the drug, but soon later he or she may deteriorate suddenly and stop breathing within ten minutes. This is one of the most important differences between the previously so-called "influenza-associated encephalopathy" or "infection-related encephalopathy" and this newer complication.

This new type of encephalopathy among infants was first found in the winter of 2002/2003 just after the marketing of Tamiflu dry syrup for children had started. However a similar adult case of sudden death had been already reported in March 2001 [MHLWB01-529], just after the Tamiflu capsule was marketed in February 2nd 2001 in Japan. A man in his sixties who had usually been healthy developed a 39°C fever; he was suspected of having flu and was treated with Tamiflu 75 mg b.i.d. Several hours after taking the second dose of Tamiflu he got worse and consulted another hospital. Although his condition was not deemed so serious as to merit urgent treatment, he suddenly went into arrest immediately after arriving at a further hospital and died about two hours later from multi-organ failure.

In Case 5, the patient was treated with NSAIDs (dipyrone and naproxen). These might have influenced the development of myocardiopathy by enhancing the induction of cytokines in viral infection [57]. The fatal course may however be too short for acute left ventricular failure to be established without the contribution of lung oedema caused by Tamiflu.

Times of onset of most sudden deaths and of neuropsychiatric symptoms [25] are very similar. These facts also suggest that the majority of sudden deaths and neuropsychiatric symptoms after taking Tamiflu are different from the pattern observed with infection-associated encephalopathy including Reye's syndrome and/or influenza-associated encephalopathy

3.6. Non-Tamiflu-related sudden death and seizure-inducing drugs

It has been claimed that sudden death could occur due to influenza itself. However, in spite of a thorough search, I have never seen any report of sudden death caused by influenza. Sudden deaths that are believed to be caused by influenza are actually induced by the drugs used to treat it. Six child cases of sudden death were observed during the 2002/03 winter season [84]. All of these cases were found dead during sleep; three died during daytime naps and the other three at night. Although four of them took only a single dose of Tamiflu and an 8-year-old boy took amantadine, one boy aged a year and seven months had according to the original reported taken no drug [84]. This "non-drug" case is sometimes referred as an example of sudden death caused by influenza. However, it was found later that the boy had in fact been given theophylline [99]. The cause of the sudden death of this infant was thus probably either cardiac arrhythmia and/or hypoxia due to a seizure caused by theophylline.

Seizure is a well documented dose-related toxic reaction to some drugs including both amantadine and theophylline [7,24]. In experiments with a pentylenetetrazol convulsion model, it has been found that amantadine in a dose of 25 mg/kg and particularly in a dose of 100 mg/kg potentiates convulsive seizures

[58]. In an electroshock test, amantadine decreased the convulsive threshold [52]. As to theophylline: interferon reduces the drug's clearance and increases its elimination half-life in human subjects [95]. The concentration of theophylline thus increases when one has influenza especially with high fever.

In the case of a one-year-and-seven-month-old boy, when an ambulance doctor arrived and saw him within a few hours after death, the doctor found rigor mortis already in his body [99]. It is also well documented that if one has experienced a seizure and/or high fever just before death, rigor mortis tends to appear earlier than usual. Evidence suggesting that this boy may well have experienced a seizure prior to death is the fact that his twin brother, who also had influenza during theophylline treatment for his asthma, experienced a seizure one hour after the mother noticed his brother's death [99].

I believe that sudden death during sleep occurs only in those patients treated with oseltamivir, other central nervous suppressants, seizure-inducing drugs including theophylline and hypoglycemic drugs and/or proarrhythmic drugs.

3.7. Fever delirium and Tamiflu delirium

Delirium or psychosis is not a rare complication of infection [72] and it has been claimed by some specialists in pediatrics that delirium after Tamiflu treatment may in fact be fever delirium [86]. There are however many reported cases in which delirium or hallucination after taking Tamiflu occurred at low body temperatures: for example, as low as 34–35°C.

In order to analyze the relationship between body temperature and abnormal behaviour, I analyzed two groups of suspected delirium cases, namely cases with no drug history and Tamiflu-treated cases collected from phone-calls/e-mails and from the Internet. 67 delirious cases were collected in total, 15 non-drug cases and 52 Tamiflu-treated cases including 35 phone-calls/e-mail cases. Information about body temperature was available for 12 non-drug cases and 35 oseltamivir cases. The differences between fever delirium and abnormal behaviour after Tamiflu treatment are summarized in the Table 4(A). 80% of instances of delirium or abnormal behaviour occurred in the absence of fever or after the temperature had started to fall after taking Tamiflu, while only one among 12 non-drug cases occurred in the absence of fever (Odds ratio = 44.0; 95% CI: 4.37–1081.12, $p = 0.000018$).

To perform another comparison, I searched PubMed and "Japonica Centra Revuo Medicina" (a database of Japanese medical journals) using the key words "fever" and "delirium" and found four papers [48,72,73,88] in which the temperature of patients with delirium was described. All papers were

Table 4

Comparison of temperature during delirium (with Tamiflu, untreated or published cases of apparent fever delirium in the literatures)

	Treated with Tamiflu	(A) No drug treatment	(B) Published cases of fever delirium
Delirium in absence of fever	28 (80%)	1[a] (8%)	81 (37.0%)
Delirium with high fever	7 (20%)	11 (92%)	138 (63.0%)
Odds ratio of delirium occurring without fever on Tamiflu treatment as compared with controls (95% confidence interval[b] and p value[c])		44.0 (4.37–1081) $p = 0.000018$	6.81.(2.68–18.02) $p = 0.0000018$

[a] One case with only nasal symptoms before fever developed. [b] Cornfield 95% confidence limits for OR using EpiInfo Version 3-3-2. [c] Fisher's exact test 2-tailed p-value using EpiInfo Version 3-3-2.

from Japan and reported a total of 226 fever delirium cases among which temperatures were known in 219 cases. Although authors did not state whether NSAIDs antipyretics and antihistamines were used or not, there is no doubt that many of these patients were treated with them. However, the proportion of patients with a body temperature lower than 39.0°C during fever delirium was only 37.0% (81/219) which is far less than the 80% (28/35) in patients with delirium treated with Tamiflu. Odds ratio was 6.81 (95% CI: 2.68–18.02, $p = 0.0000018$ Table 4(B)). Only 10.9% of fever delirium patients reported in papers (24/219) had temperatures below 38.0°C.

3.8. *Brain/lung oedema and hypoxia*

(1) *The drug in the brain and its elimination by efflux transporters in the blood–brain barrier.*

Drugs acting on the central nervous system (CNS) have to cross the blood–brain barrier (BBB) or the blood-cerebrospinal fluid barrier. Recent studies have shown that this is not only a static anatomical barrier but also a dynamic one in which efflux transporters play a role [4,7,87] on the apical cell membrane of brain capillary endothelial cells adjacent to the blood lumen.

The fact that oseltamivir levels with a Cmax 64 times higher are found in the brain of 7-day-old rats compared with 42-day-old rats [15] indicates that the drug might not be easily eliminated from the endothelial cells by the immature efflux transporters.

(2) *Increase of intra-cranial pressure.*

There are several reasons to conclude that Tamiflu increases intra-cranial pressure. For example, a 5-month-old male infant who was treated with Tamiflu for prevention of influenza vomited one and a half hours after receiving the drug and his mother noticed his fontanelle was bulging [26]. After the second dose of Tamiflu in the next evening, he did not vomit but his fontanelle bulged again. His mother described how "the large fontanelle bulged one or two hours after administration of oseltamivir in the evening and returned to the usual size by the next morning". She said that this phenomenon was repeatedly observed throughout the treatment period of eight days [26]. This is one of the firm pointers to an increase in intra-cranial pressure induced by oseltamivir itself, since the infant did not have influenza and at this age the BBB might not yet have matured.

In a randomized controlled trial of Tamiflu for the prevention of adult influenza, headache, nausea and vomiting were complained of significantly more often in the Tamiflu group than in the placebo group [15]. The Number Needed to Harm (NNH) for inducing headache, nausea and vomiting was 25, 24 and 55 respectively. This again suggests that Tamiflu increases intra-cranial pressure.

In a randomized controlled trial of Tamiflu for treatment of influenza in children, vomiting only on day 1 was observed significantly more often in the Tamiflu group than the placebo group (odds ratio 3.4: 95% CI 1.9–6.1) [14]. NNH for inducing vomiting on day 1 was 15, while the odds ratio for vomiting on day 2 or later was 0.8 (95% CI: 0.47–1.4). This once more suggests that Tamiflu increases intra-cranial pressure only on day 1 when used to treat influenza.

(3) *Brain oedema and aquaporins.*

Recent studies have shown that aquaporins (AQPs) play an important role in the induction and resolution of oedema in various organs and tissues [5,45,51,54,60,75] including brain [54,45,75] and lungs [5,54,75]. AQP4 is upregulated in response to cerebral oedema induced by various agents or factors [54,75]. AQP4-mediated transcellular water movement is crucial not only for the development of brain oedema after intoxication and ischaemic stroke, but also for fluid clearance in vasogenic brain oedema [54].

(4) *Lung oedema and aquaporins.*

Epithelial Na^+ channel (ENaC), Na^+/K^+-ATPase pumps, and several aquaporin water channels are the best described molecular transporters in the lung when pathological conditions lead to the development of pulmonary oedema. Lung oedema results from the impairment of alveolar cells and/or capillary endothelial cells, both of which actively transport fluids from the alveolar space to the blood vessels. In acute lung injury (ALI), especially in severe sepsis (systemic inflammatory response by infection), an inflammatory process damages the capillary endothelium rather than the alveolar epithelium, resulting in high permeability of the lung capillaries to fluid, which leads to clinical pulmonary oedema. In contrast to the endothelium, the alveolar epithelium is often spared in ALI, and the rate of alveolar fluid clearance (AFC) in ALI can therefore be maintained and perhaps even increased [102].

(5) *Lung oedema, brain oedema and hypoxia.*

Although the role of Tamiflu in the development of lung oedema in two of the autopsied cases is not completely clarified, it is at least possible that severe hypoxia induced by the respiratory suppressive action of oseltamivir might have contributed to the induction of lung oedema just prior to respiratory arrest in both cases. The difference between dead and surviving humans and animals is very impressive, although intermediate cases also occur [63,64]: fatal cases exhibited severe and frequent lung oedema both in animals and human subjects, while complete recovery was observed in surviving animals and most of the human cases. In the present clinical series for example, fatal Cases 4 and 5 had severe lung oedema, while Case 6 and case #5769078 reported by the FDA completely recovered without sequels [26]. There are many such cases in the published data [63,64] (Table 2).

There are some intermediate cases in one of which a boy died after serious hypoxic brain damage with transient lung oedema just after he had been resuscitated. Another boy had very severe sequels following the occurrence of temporary lung oedema just after he had been resuscitated.

Lung oedema following severe hypoxia is frequently observed in various diseases such as acute asphyxia [6], sleep apnoea syndrome [11,12,10,28,98], and high-altitude disease [2,41,42,94], but also immediately after extubation [47], and under the influence of drugs including sedatives [64,76] and others [19,83]. When severe hypoxia results from high-altitude disease, brain oedema is observed in addition to lung oedema [41], and has often resulted in death [41]. High-altitude pulmonary oedema (HAPE) is the most common cause of death from exposure to high altitudes [1,41].

Hypoxia downregulates the synthesis and activity of both ENaC and Na^+/K^+-ATPase time- and concentration-dependently in cultured alveolar epithelial cells [20,76]. Interestingly, this effect is completely reversed after reoxygenation [20,76].

AQP-independent water transport, involving either alternative transcellular water channels or paracellular pathways, plays a major role in Alveolar Fluid Clearance [91].

3.9. Sequels and delayed neuronal cell damage following cardiac arrest

Case 7 and MHLW's two cases (B04026215 and B05005388) had sequels or hypoxic multi-organ failure after cardiopulmonary arrest and resuscitation. Though it is not known whether oseltamivir causes this type of sequels, I believe that the clinical courses of these three cases are compatible with that of the neurological sequels following global ischemia [3,22,55]. However various other disorders such as acute disseminated encephalomyelitis (ADEM) [23,31], Rett syndrome [71,93] and various causes of apparent life threatening events (ALTE) in infants [61] should be differentiated as a cause.

A wide spectrum of neurological sequels may follow global ischemia, ranging from brain death, vegetative states, and impairment of higher intellectual function to syndromes characterized by amnesia and

cortical blindness, post-anoxic myoclonus, delayed leukoencephalopathy, and spinal stroke [3] including paraplegia [22] or lower-limb paralysis [55].

129 patients underwent surgical repair of thoracoabdominal aneurysms, with an overall 30-day mortality rate of 35% [22]. Spinal cord ischemia occurred in 25 cases (21%) of 116 who survived operation. Partial ischaemia occurred in six cases (25%), and complete paraplegia occurred in the remainder [22].

Animals experiencing 12 minutes of hemorrhagic shock followed by 5 minutes of cardiac arrest showed severe neuronal damage in the *Cornu Ammonis* field CA1 region of the hippocampus, severe hind-limb paralysis and neuronal damage in the lumbar spinal cord 6 hours to 7 days after resuscitation [55]. In view of the results of this experiment, it was suggested that hind-limb paralysis after global ischemia might result from spinal cord damage.

Loss of intellectual ability including speech and behaviour, minimal atrophic change in the right hippocampus and minimal development in the sylvian fissure, suspected in the light of MRI findings in the present Case 7 are compatible with damage in the hippocampal area. The account of this patient's crawling movement ("dragging her legs") some days after the event is compatible with paraplegia or hind-limb palsy after global ischemia. Thus it is reasonable to suppose that this girl may have suffered delayed neuronal cell damage in the central nervous system, especially in the hippocampal area and in the lumbar spinal cord, due to global ischemia after cardiopulmonary arrest caused by the oseltamivir-induced inhibition of respiratory function. The very slight worsening observed after the mother first noticed her behavioural and mental abnormalities may well rule out the possibility of acute disseminated encephalomyelitis (ADEM) since in that condition a monophasic peak of symptom worsening is more usually observed [23,31]. The very slight changes found on the MRI similarly seem incompatible with that condition.

More recently, this girl has shown some gradual development, which means that her development retardation is not progressive. Absence of stereotypic hand movements also argues against the presence of Rett syndrome [93]. In the present case, the abnormality occurred abruptly after the event. Retardation of an infant with Rett syndrome starts after apparently normal development for more than 6 months, but not so abruptly [71] as in her case. Her breathing disturbance appeared shortly after she took Tamiflu. She has never shown breathing disturbances while awake except during the acute event. These are other reasons why a diagnosis of Rett syndrome seems inappropriate in her case.

Seizure, gastro-oesophageal reflux disease (GORD), respiratory syncytial virus (RSV) infection, pertussis or other lower and upper respiratory tract infections (LRTI and URTI), aspiration pneumonia, asthma and other causes including ear, nose and throat problems, cardiac problems including cardiac arrhythmia or QT prolongation, inborn metabolic disorders were listed as causes of hypoxia in a review by McGovern [61]. Ingestion of drugs or toxins was reported in eleven patients (1.5% of all diagnoses in that paper).

Seizure may not have been a primary cause of the hypoxia seen in Case Nr. 7 but could have been secondary to hypoxia due to respiratory suppression. She had no gastro-oesophageal reflux and was not so severely infected as one would expect with RSV infection or pertussis. Patients whose causes of life-threatening events are suspected to be LRTI, URTI or other forms of infection may be treated with various medicines. In such cases, the possibility that these medicines themselves have induced the life-threatening event cannot be ruled out. Patient Nr. 7 did not aspirate and had no asthma. Her QT interval was 0.397 s and she has never had syncope suggesting Adams-stokes syndrome either before or after the event. She has never been suspected to have any inborn metabolic disorder.