

3.10. *Delayed reactions and inhibition of human sialidase (neuraminidase) by OCB*

Li et al. [59] reported that they identified a nonsynonymous SNP (single nucleotide polymorphism) in dbSNP database, R41Q, near the enzymatic active site of human cytosolic sialidase HsNEU2, a homologue of the virus neuraminidase that is the target of OCB. This SNP could increase the unintended binding affinity of human sialidase to OCB, thus reducing sialidase activity. Theoretically administration of oseltamivir to people with this SNP (present in 9.29% of Asian populations but absent in European and African American subjects) might further reduce their sialidase activity and these authors suggest that this Asian-enriched sialidase variation caused by the SNP, probably in homozygous form, may be associated with certain severe adverse reactions to oseltamivir [59].

In the CA1 region of hippocampal sections, OCB facilitated neuronal firing, without involving GABAergic disinhibition, and OCB produced further facilitation following administration of ethanol [46]. From these findings, the authors indicated that oseltamivir has an effect on the central nervous system, especially when combined with other agents such as ethanol.

Neither of the two papers cited above [46,59] refers to sudden deaths during sleep as a major component of the adverse reaction profile of Tamiflu to which the central inhibitory effect of unchanged oseltamivir probably contributes. However, reduction of human cytosolic sialidase activity by OCB might be a possible mechanism involved in delayed type adverse reactions to Tamiflu including not only neuropsychiatric reactions but also hyperglycemia, pneumonia, exacerbation of infection, renal and hepatic disorders, GI tract hemorrhage and others [63,64].

In mammalian cells, four types of sialidase have been identified. They are classified according to their major intracellular localization as intralysosomal sialidase (NEU1), cytosolic sialidase (NEU2), and plasma membrane-associated sialidases (NEU3) and mitochondrial sialidase (NEU4) [96,97].

Hepatic NEU3 may be associated with sensitivity to insulin and to glucose tolerance through modification of ganglioside composition and peroxisome proliferator-activated receptor gamma signaling [101].

Introducing a review on sialidase and cancer [66], the authors make the following general point:

Sialic acids are generally found in the terminal position of the carbohydrate groups of glycolipids and glycoproteins. They have been proposed to play important roles in various biological processes by influencing conformation of glycoproteins, recognizing and masking biological sites of the molecules and cells. The removal of the sialic acids catalyzed by sialidase is an initial step in the degradation of glycoproteins and gangliosides. Sialidases of mammalian origin, therefore, have been implicated not only in lysosomal catabolism but also in regulation of functional molecules involved in many biological phenomena [62,73] through modulating sialoglycoconjugates. In fact, the lines of evidence for their involvement in cellular events including cell differentiation, cell growth, and apoptosis have been accumulated. Alterations in sialylation during malignant transformation have been observed to be closely associated with malignant phenotype in terms of metastatic potential and invasiveness, although no definite conclusion between sialic acid contents and malignant properties could be drawn because of some controversial experimental results.

Sialidase is also involved in a wide variety of other physiological processes, including immune functions [82,89,92] such as helper T cell, neutrophil, cytokines and so on [92]. It might be involved in the late onset pneumonia, and in the aggravation of infection leading to sepsis with multiorgan failure including precipitation of a disseminated intravascular coagulation syndrome (DIC).

Long term impairment of Immune function may increase the susceptibility to cancer development. The pharmaceutical company concerned has reported on two long term carcinogenesis studies, cited in

the new drug approval package (NAP) of oseltamivir capsules for preventative use [15]: they comprise two-year studies in mice and in rats.

In the two-year mouse carcinogenesis study, the proportion of deaths and of liver cell tumours, both seen in male mice, significantly increased in a dose-dependent manner, although the pharmaceutical company denied that there was a causal relationship. The “safe” level was 125 mg/kg, which is only 6 times higher than the human therapeutic dose level (calculated on the basis of the AUC of OCB) and this may explain the chronic toxicity observed in the animals.

In the two-year carcinogenesis study of Tamiflu in rats (75 males and 75 females for each dose level: 0 mg/kg, 0 mg/kg, 50 mg/kg, 150 mg/kg, 500 mg/kg), the proportion of animals developing lymphoma (male: numbers are 0, 1, 1, 1, 3 respectively), epithelial tumor of the thymus (female: 0, 1, 1, 2, 3), angioma (male: 2, 1, 1, 3, 5) was significantly increased in a dose dependent manner, although the pharmaceutical company denied that there was causality. A completely safe dose derived from the rat carcinogenesis study may be 50 mg/kg which is only 1.6 times higher than the clinical dose level for treatment based on the AUC of OCB. The intermediate level is about 5.8 times higher.

There is only one reported case of acute hemorrhagic colitis induced by Tamiflu but in that instance an allergic mechanism was involved [100]. However, among the 80 fatal cases now known, bleeding episodes were described in eight, including one case without severe infection, sepsis or multiorgan failure (see Section 2.5).

Plasminogen binds neuraminidase and is activated to form plasmin. Neuraminidase is therefore a plasminogen receptor and its plasminogen-binding activity determines the pathogenicity of the WSN virus (a mouse-adapted human isolate A/WSN/33 (WSN), a neurovirulent influenza virus strain that causes systemic infection when inoculated intranasally into mice) [30].

One certainly cannot exclude the possibility that activation of normal human plasminogen by human neuraminidase (sialidase) might be inhibited by OCB, in which case normal fibrinolysis might be affected, resulting in abnormal coagulopathy including DIC.

3.11. Limitations of postmortem measurement of oseltamivir and OCB level

One problem encountered in current work is the limited sensitivity of the methods most commonly used to detect the relevant substances in the system. On July 3rd 2006, for example a 14-year-old boy died from an accident resulting from abnormal behaviour after taking Tamiflu; the case was reported by the media on July 4th 2006. In the course of the autopsy required by law the concentration of oseltamivir and OCB in the brain and in the plasma was measured by an HPLC-UV method which can measure 100 ng/g or more of oseltamivir and OCB as reported by Fuke et al. [30]. The concentration of OCB in the femoral blood was 400 ng/ml. The highest concentration in all specimens was in the liver at 18300 ng/g. In all the brain samples taken, however, the concentrations did not attain the minimum detection level of the method. It may be noted in this connection that the average C_{max} after administering one capsule of Tamiflu (75 mg) to a healthy volunteer is 60 ng/ml which is well below the level detectable with the method used by Fuke (100 ng/g). Moreover, oseltamivir is rapidly hydrolyzed in the circulation. In plasma samples taken from rats and mice the half life of oseltamivir was found to be only 20–60 min. In human postmortem blood, the half life may be longer than in that of rats or mice, but oseltamivir may be almost completely changed into OCB in human postmortem blood and tissues within 24 h. Therefore, Fuke et al. would hardly detect unchanged oseltamivir in the postmortem tissues and plasma, even if they used more sensitive methods as HPLC/MS/MS (quantification limit is about 1 ng/g). Causality in a case such as the above cannot readily be excluded unless the latter methods are available.

3.12. *Methods of assessment for adverse reactions*

Where a causal relationship between a drug and an adverse event cannot be excluded, the latter should, according to the definition adopted by the International Conference on Harmonization, be referred to as an "adverse reaction" [43].

Only a short period has so far elapsed since oseltamivir (Tamiflu) was first marketed in Japan and elsewhere. Initially, sudden death and death resulting from abnormal behaviour were not recognized as occurring specifically in those treated with Tamiflu. Today, no-one can realistically deny that there is a causal relationship. These "events" should therefore now be classified as "adverse reactions" even if the causal relationship still requires further elucidation. It may be noted that the classifications of possible adverse reactions as "rather negative" or "unlikely", that the MHLW employs in Japan are not equivalent to "completely excluded"; they leave open the possibility that there may be a causal relationship, even though MHLW uses them to throw doubt on causality.

When many similar reports of supposed adverse events are collected, the causality of these events should not only be individually assessed; there should also be a collective analysis. Individual reports should be compared with others, and their similarities and differences should be discussed. In addition, the spectrum of clinical events should be compared with the spectrum of symptoms observed in animal toxicity studies. To date, however, MHLW and its scientific advisory panel have analyzed such events only individually and have practically denied that there are causal relationships. Nor have FDA, MHLW and their advisory panels discussed the similarity of symptoms in human and in animals both dead and surviving, despite the very close similarity between the symptoms observed in humans and in animals, as discussed in this paper. However, in view of the criticism advanced by the victims and the mass media after the occurrence of a series of fatal accidents, MHLW has decided that causality will now be reassessed.

One must stress that sudden deaths, occurring within 10 min in a hitherto normal child, have never been reported in cases of influenza-associated encephalopathy or Reye's syndrome except following the use of seizure-inducing drugs. In most persons with abnormal behaviour, the body temperatures during the delirious phase were much lower in those with fever delirium.

The causal relationship between Tamiflu and death (sudden death during sleep and accidental death after abnormal behaviour) thus seems to be very strong. Delayed types of adverse events such as delayed onset or prolonged neuropsychiatric symptoms which begin even after full dose of Tamiflu and last for a week or more even for months, pneumonia after the end of taking Tamiflu, bleeding disorders, hyperglycemia, renal disorders and so on may be related to Tamiflu and more especially to OCB.

If one takes these facts into account it would seem that, even if in cases of sudden death and/or abnormal behaviour or delayed reactions there are confounding factors such as complications, treatment with other medicines and high fever, the causal relationship with Tamiflu should not be seriously doubted so long as the patient is known to have taken Tamiflu before the onset of the symptoms.

3.13. *What this paper adds to earlier reports*

This paper is built primarily around a case series of eight patients, based on their medical records and history taking from bereaved families. However, in most of the cases of sudden or accidental death, the doctors concerned arrived at their diagnoses only by taking the history from the families.

The strength of the present paper lies in the inclusion of cases manifesting a variety of clinical courses and a variety of causes: three are sudden deaths, two are deaths after abnormal behaviour, two are near

fatal cases with or without sequels and one a case of a late onset neuropsychiatric disorder that lasted two weeks. The evidence relating to these cases is augmented by the disclosure by MHLW of the relevant adverse reaction reports that the pharmaceutical company in question had submitted to the authorities (i.e. MHLW). In addition, brief results of animal toxicity tests conducted by Roche were made available (in Japanese: TK data were corrected very recently by the manufacturer at the meeting of the MHLW's scientific panel [17]).

This paper adds the following three major points to earlier reports: this is the first original paper presenting a case series of fatal or near fatal adverse reactions to Tamiflu; it is also the first paper overviewing the full spectrum of adverse reactions to Tamiflu, and the first paper discussing the causality and underlying mechanisms of the full spectrum of reactions to Tamiflu. It is true that some evidence of these matters has been published earlier: Shiomi briefly described four such cases but presented them only as "adverse events", not recognized as adverse reactions to Tamiflu [84]; two fatal cases of abnormal behaviour and one of sudden death were reported earlier by myself at a scientific meeting [35]; 71 other cases have been listed on the Internet [63,64], and several fatal cases have been personally collected. However, this is the first original paper dealing comprehensively with these matters and examining data both from animals and from man.

3.14. Possible further studies to confirm causality and provide further elucidation

The number of patients suffering adverse reactions to Tamiflu may be substantial; the fact that 5 fatal cases were observed in Osaka alone in one season could mean that some 50–60 fatalities per year might occur nationally in Japan. These adverse reactions are important and serious, and the association between such grave but rare reactions and the drug should be investigated epidemiologically, e.g. using a case-control study. In the past, no such case-control study could be carried out; it was very difficult to select matched controls, because most people in Japan who consulted physicians for flu or flu-like symptoms were immediately treated with Tamiflu. However, Tamiflu is not necessary for the treatment of seasonal flu; this view is accepted in Europe, but not in Japan. However, in March 2007 the Japanese authorities advised against prescribing Tamiflu to adolescents aged 10–19 years. If therefore oseltamivir is indeed to be used for seasonal flu during a coming winter in Japan, a case-control study could be carried out since a substantial number of people might not use Tamiflu knowing its harmful effects, while others would still use it. This may be one of the best methods to assess the association further, though serious reporting bias would be confounded because of the legal threats.

Another piece of evidence that could confirm the causal relationship between sudden death and the use of Tamiflu could well be obtained by performing animal infection-toxicity studies. In those studies, the proportion of oseltamivir concentrations in the brain to plasma would be very high in the animals infected with an influenza virus or similar agent or treated with lipopolysaccharide. Also, if a toxicity study using infected animals is conducted, the ratio of concentration in the brain of an infected animal to that of a non-infected animal would be very high, comparable to the differences in concentration observed in infant rats before weaning as compared with mature rats.

4. Conclusion

1. It can be concluded that oseltamivir has central nervous system suppressive action resembling that of hypnotics, sedatives and anesthetics. Signs and symptoms and histo-pathological findings in animal studies with doses 10–20 times higher than those used clinically (calculated on an AUC

basis) are similar to those observed in human cases, including pulmonary oedema, decreased body temperature, decreased movements and slow/irregular breathing.

2. In addition, delirium, abnormal behaviour, hallucinations and even suicide could be included in those symptoms, as resulting from the disinhibitory effects of central nervous system depressants, including oseltamivir, leading to loss of control.
3. One can therefore conclude that sudden onset type of reactions such as sudden death and death from accidents due to abnormal behaviour in older children and adolescents, especially when observed shortly after taking the first dose of Tamiflu, are probably related to its use.
4. Dyspnoea with cyanosis followed by seizure and cardiopulmonary arrest after taking Tamiflu with or without sequels may be related to the drug. Severe sequels may be a consequence of delayed neuronal cell damage after cardiopulmonary arrest due to the acute toxicity of oseltamivir.
5. Delayed/prolonged type of adverse reactions, which usually begin after an almost complete course of Tamiflu, are probably related to the inhibition of human sialidase (neuraminidase) by OCB. They include neuropsychiatric symptoms of delayed onset (which often last a week or more and may be exacerbated in the absence of any evident secondary trigger), pneumonia, exacerbation of infection (frequently leading to sepsis with multi-organ failure and death), bleeding disorders, hyperglycaemia and renal disorders.
6. Even where in cases of sudden death and/or abnormal behaviour there are confounding factors such as treatment with other medicines or high fever, it would be unwise to exclude a causal relationship with Tamiflu where this is known to have been taken before the onset of the symptoms.

Cases 1–3 in this paper were presented at a session of the Japanese Society for Pediatric Infectious Diseases in Tsu, Mie Prefecture, November 12th 2005.

After the submission of this paper, the families of two additional cases made their medical charts, autopsy records available to me for investigation by the end of 2007: A 44-year-old man died during sleep with severe pulmonary oedema at autopsy and a 29-year-old woman died with low body temperature (34°C) with severe cyanosis and collapse followed by seizure with pulmonary oedema at autopsy [40]. MHLW also added two adult death cases: both from exacerbation of infection [65]. After the submission of this paper, three investigators [18,68,74] found equivocally that P-glycoprotein is the efflux transporter of oseltamivir at the BBB.

Conflict of interest

Rokuro Hama provided scientific opinions for 8 cases where applications were made for adverse reaction relief. He has received no funding from the pharmaceutical industry or the Japanese government.

Written consent was obtained from the patients involved or their relatives for publication of his study.

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