REVIEW ARTICLE

Drug Safety 2008; 31 (12): 1097-1114
0114-5916/08/0012-1097/$48.00/0

Assessment of Neuropsychiatric Adverse Events in Influenza Patients Treated with Oseltamivir

A Comprehensive Review

Stephen Toovey,[1] *Craig Rayner*,[1] *Eric Prinssen*,[1] *Tom Chu*,[2] *Barbara Donner*,[1] *Bharat Thakrar*,[1] *Regina Dutkowski*,[3] *Gerhard Hoffmann*,[1] *Alexander Breidenbach*,[1] *Lothar Lindemann*,[1] *Ellen Carey*,[3] *Lauren Boak*,[4] *Ronald Gieschke*,[1] *Susan Sacks*,[3] *Jonathan Solsky*,[3] *Ian Small*[4] and *David Reddy*[1]

1 F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Roche Palo Alto LLC, Palo Alto, California, USA
3 Hoffmann-La Roche Inc., Nutley, New Jersey, USA
4 Roche Products Ltd, Welwyn Garden City, UK

Contents

Abstract

After reports from Japan of neuropsychiatric adverse events (NPAEs) in children taking oseltamivir phosphate (hereafter referred to as oseltamivir [Tamiflu®; F. Hoffmann-La Roche Ltd, Basel, Switzerland]) during and after the 2004–5 influenza season, Roche explored possible reasons for the increase in reporting rate and presented regular updates to the US FDA and other regulatory authorities. This review summarizes the results of a comprehensive assessment of the company's own preclinical and clinical studies, post-marketing spontaneous adverse event reporting, epidemiological investigations utilizing health claims and medical records databases and an extensive review of the literature, with the aim of answering the following questions: (i) what the types and rates of neuropsychiatric abnormalities reported in patients with influenza are, and whether these differ in patients who have received oseltamivir compared with those who have not; (ii) what levels of oseltamivir and its active metabolite, oseltamivir carboxylate are achieved in the CNS; (iii) whether oseltamivir and oseltamivir carboxylate have pharmacological activity in the CNS; and (iv) whether there are genetic differences between Japanese and Caucasian patients that result in different levels of oseltamivir and/or oseltamivir carboxylate in the CNS, differences in their metabolism or differences in their pharmacological activity in the CNS.

In total, 3051 spontaneous reports of NPAEs were received by Roche, involving 2466 patients who received oseltamivir between 1999 and 15 September 2007; 2772 (90.9%) events originated from Japan, 190 (6.2%) from the US and 89 (2.9%) from other countries. During this period, oseltamivir was prescribed to around 48 million people worldwide. Crude NPAE reporting rates (per 1 000 000 prescriptions) in children (aged ≤16 years) and adults, respectively, were 99 and 28 events in Japan and 19 and 8 in the US. NPAEs were more commonly reported in children (2218 events in 1808 children aged ≤16 years vs 833 in 658 adults) and generally occurred within 48 hours of the onset of influenza illness and initiation of treatment. After categorizing the reported events according to *International Classification of Diseases* (9th edition) codes, abnormal behaviour (1160 events, 38.0%) and delusions/perceptual disturbances (661 events, 21.7%) were the largest categories of events, and delirium or delirium-like events (as defined by the American Psychiatric Association) were very common in most categories.

No difference in NPAE reporting rates between oseltamivir and placebo was found in phase III treatment studies (0.5% vs 0.6%). Analyses of US healthcare claims databases showed the risk of NPAEs in oseltamivir-treated patients (n = 159 386) was no higher than those not receiving antivirals (n = 159 386). Analysis of medical records in the UK General Practice Research Database showed that the adjusted relative risk of NPAEs in influenza patients was significantly higher (1.75-fold) than in the general population. Based on literature reports, NPAEs in Japanese and Taiwanese children with influenza have occurred before the initiation of oseltamivir treatment; events were also similar to those occurring after the initiation of oseltamivir therapy.

No clinically relevant differences in plasma pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate were noted between Japanese and Caucasian adults or children. Penetration into the CNS of both oseltamivir and oseltamivir carboxylate was low in Japanese and Caucasian adults (cerebrospinal fluid/plasma maximum concentration and area under the plasma concentra-

tion-time curve ratios of approximately 0.03), and the capacity for converting oseltamivir to oseltamivir carboxylate in rat and human brains was low. In animal autoradiography and pharmacokinetic studies, brain : plasma radioactivity ratios were generally 20% or lower. Animal studies showed no specific CNS/behavioural effects after administration of doses corresponding to ≥100 times the clinical dose. Oseltamivir or oseltamivir carboxylate did not interact with human neuraminidases or with 155 known molecular targets in radioligand binding and functional assays. A review of the information published to date on functional variations of genes relevant to oseltamivir pharmacokinetics and pharmacodynamics and simulated gene knock-out scenarios did not identify any plausible genetic explanations for the observed NPAEs.

The available data do not suggest that the incidence of NPAEs in influenza patients receiving oseltamivir is higher than in those who do not, and no mechanism by which oseltamivir or oseltamivir carboxylate could cause or worsen such events could be identified.

Reports from Japan on the safety of oseltamivir phosphate (hereafter referred to as oseltamivir [Tamiflu®; F. Hoffmann-La Roche Ltd, Basel, Switzerland])[1] in children during the 2004–5 influenza season showed that some children had experienced neuropsychiatric adverse events (NPAEs). In the following seasons, ongoing pharmacovigilance by Roche found that the number of NPAEs in Japan had increased. In November 2006, the US FDA provided an update to its Pediatric Advisory Committee, notifying it of 129 NPAEs reported in association with oseltamivir use in children and adults worldwide between 29 August 2005 and 6 July 2006, including three deaths, compared with 126 events in total in the 6 years between approval in October 1999 and 29 August 2005.[1] Most of the events were in Japan. At the time, the FDA concluded that the relative contribution of oseltamivir to these events was unknown, and indicated this in an update to the product label.[2]

In assessing these events, Roche explored possible reasons for the increase in the reporting rate and has presented regular updates and analyses to the FDA and other regulatory authorities, most recently a full update to the Pediatric Advisory Committee in November 2007.[3] Over the influenza seasons in Japan from 2004–5 to 2006–7, disease incidence did not increase, the characteristics of the circulating virus did not change and no changes took place in drug manufacturing, formulation, dosage or administration of oseltamivir. Notably, the number of prescriptions issued to Japanese children aged ≤16 years fell by 33% over the period in question (table I). In 2006, the Japanese Ministry of Health, Labour and Welfare (MHLW) reported survey data showing that the frequency of NPAEs in Japanese influenza patients receiving oseltamivir during the 2005–6 influenza season was the same as in those not receiving the product.[4] In March 2007, however, the Japanese MHLW warned doctors against prescribing oseltamivir to those aged 10–19 years, after two reports of abnormal behaviour in young patients who had taken the drug resulted in injury and death. Changes were made to the product labelling in Japan to alert prescribers to these events.

Of the 80 countries in which oseltamivir is approved, Japan is the country with the highest usage (see table I), possibly because, unlike most other countries, rapid diagnostic testing for influenza at the point of care is standard medical practice. Rapid test kits are fully reimbursed in Japan, as is antiviral treatment. Antivirals were prescribed to an estimated 60% of clinically diagnosed Japanese influenza patients in 2004–5, compared with about 30% in the

1 The use of trade names is for product identification purposes only.

Table I. Seasonal usage of oseltamivir worldwide (millions of prescriptions)

Influenza season	All patients				Patients aged ≤16 y			
	Japan	USA	RoW	total	Japan	USA	RoW	total
1999–2000	0.00	0.70	0.00	**0.70**	0.00	0.01	0.00	**0.01**
2000–1	0.00	0.74	0.00	**0.74**	0.00	0.11	0.00	**0.11**
2001–2	2.11	0.66	0.00	**2.77**	0.62	0.06	0.00	**0.68**
2002–3	7.21	0.59	0.20	**8.00**	4.49	0.14	0.03	**4.66**
2003–4	5.76	1.54	0.16	**7.45**	2.62	0.35	0.03	**2.99**
2004–5	9.03	1.72	0.41	**11.16**	3.81	0.45	0.06	**4.32**
2005–6	7.18	2.40	0.29	**9.87**	3.52	0.79	0.03	**4.34**
2006–7	5.11	1.96	0.24	**7.31**	2.53	0.95	0.07	**3.56**
Total	**36.40**	**10.30**	**1.30**	**48.00**	**17.58**	**2.85**	**0.22**	**20.66**
% by region	75.8	21.5	2.7	100.0	85.1	13.8	1.1	100.0

RoW = rest of world.

US and ≤1% in France and the UK.[5] Since the first launch of oseltamivir, 76% of all prescriptions dispensed worldwide were in Japan (see table I), and in patients aged ≤16 years, 85% of cumulative usage was in Japan.

The steps taken by Roche to gain a better understanding of influenza-associated NPAEs and possible mechanisms for them have included a review of the company's own preclinical and clinical studies, analysis of post-marketing spontaneous adverse event reporting, epidemiological investigations utilizing health claims and medical records databases and an extensive review of the literature. This review summarizes the results of this comprehensive assessment, whose aim was to answer the following questions:

1. What are the types and rates of neuropsychiatric abnormalities reported in patients with influenza, and do these differ in patients who have received oseltamivir compared with those who have not?

2. What levels of oseltamivir and its active metabolite, oseltamivir carboxylate are achieved in the CNS?

3. Do oseltamivir and oseltamivir carboxylate have pharmacological activity in the CNS?

4. Are there genetic differences between Japanese and Caucasian patients that result in different levels of oseltamivir and/or oseltamivir carboxylate in the CNS, differences in their metabolism or differences in their pharmacological activity in the CNS?

1. Clinical Safety Assessment

1.1 Post-Marketing Reports of Neuropsychiatric Adverse Events (NPAEs) in the Roche Global Safety Database

Between 1999 and 15 September 2007, oseltamivir was prescribed to around 48 million people worldwide (table I). To estimate the reporting rate of NPAEs in patients given oseltamivir (for treatment or prophylaxis) in Japan, the US and other countries, an analysis was conducted of post-marketing spontaneously reported adverse events (AEs) in the Roche global safety database. All serious AEs (SAEs) from clinical trials, irrespective of the reporter's causality assessment, and all spontaneous reports of AEs from countries where oseltamivir is marketed are coded into the database. This includes all events reported to Chugai Pharmaceuticals, Roche's marketing partner in Japan. Expedited and cumulative single-case reporting to health authorities is then undertaken.

A broad case definition of NPAEs was prospectively defined, encompassing 51 *Medical Dictionary for Regulatory Activities* (MedDRA) high-level terms in three system organ classes (SOCs) [nervous system disorders, psychiatric disorders and accidents/injuries]. A search for these high-level terms from the date of the launch of oseltamivir in each country to 15 September 2007 resulted in the identification of 98 associated preferred terms (MedDRA terminology), each of which were grouped into one

Table II. Summary of post-marketing neuropsychiatric events in children (aged ≤16 y) and adults receiving oseltamivir for influenza treatment or prophylaxis[a]

Category	All adverse events			Serious adverse events		
	all	>16 y	≤16 y	all	>16 y	≤16 y
Abnormal behaviour	1160	123	1037	179	28	151
Accident/injury	33	20	13	23	11	12
Cognition disturbance	113	68	45	32	23	9
Convulsions	138	53	85	126	48	78
Delirium	176	35	141	62	18	44
Delusions/perceptual disturbance	661	212	449	111	44	67
Depressed level of consciousness	183	72	111	69	29	40
Encephalitis	11	6	5	11	6	5
Loss of consciousness	108	82	26	48	36	12
Miscellaneous psychiatric	368	117	251	47	18	29
Panic attack	12	6	6	5	3	2
Parasomnia	72	25	47	5	1	4
Suicidal events	16	14	2	14	12	2
Total no. of events	**3051**	**833**	**2218**	**732**	**277**	**455**
Total no. of patients	**2466**	**658**	**1808**	**562**	**212**	**350**

a *Medical Dictionary for Regulatory Activities* terms and associated preferred terms in three classes (nervous system disorders, psychiatric disorders and accidents/injuries) grouped into 13 categories. Includes all reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

of 13 clinically meaningful categories according to *International Classification of Diseases* (ICD) [9th edition] descriptions (see table II for full information). Detailed case review was done for all serious NPAEs.

A total of 3051 NPAEs were spontaneously reported in 2466 patients, of which 2218 (72.7%) were in children ≤16 years (table II). The great majority of NPAEs were in Japanese patients (90.9%), with 6.2% in the US and 2.9% from other countries. In the context of the number of oseltamivir prescriptions dispensed (see table I), NPAEs are generally rare events and are reported more often in Japan than in the US (table III); the numbers in this analysis translated to crude reporting rates (in events per 1 000 000 patients) of 99 in Japan and 19 in the US in children aged ≤16 years, and 28 events in Japan and 8 in the US in adults.

Table III. Crude reporting rate of post-marketing neuropsychiatric events (events per million oseltamivir prescriptions)[a]

Country	Children (aged ≤16 y)	Adults (aged >16 y)
USA	19	8
Japan	99	28
Rest of world	36	56

a Reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

More male patients (1745) reported events than female patients (1144). Most events (2368 [77.6%]) occurred within the first 2 days of oseltamivir treatment. Most NPAEs (84.9%) improved or resolved; 732 events were classified as SAEs, and although these were most common in Japan (613/2772; 22%), they were relatively more frequent in the US (76/190; 40%). Nineteen NPAEs were associated with fatal outcomes.

The two most common categories for NPAEs were abnormal behaviour (1160) and delusions and perceptual disturbances (661). Although delirium as a category accounted for 176 events, delirium and delirium-like events were associated with many events in other categories; the majority of single or combined events found were consistent with delirium as defined by the American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV]). Whereas infection and fever are known to be common causes of delirium in children, particularly those aged 6–12 years, febrile delirium is most common in those aged 1–4 years.[6]

1.1.1 Delirium and Delirium-Like Symptoms

Delirium or delirium-like symptoms were associated with NPAEs in 8 of the 13 categories (see table IV and table V for full information), based on DSM-IV definitions; these events and their association with fever, increased motor activity and injury were analysed separately. In all, 2726 such events were found: 2083 in children (94% of all reported NPAEs in children) and 643 in adults (77% of all reported NPAEs in adults). In children, 345 (17%) occurrences of this type of event were classified as SAEs (table IV), the majority (67%) of which started within the first 2 days of the illness; 44% were reported to be associated with fever, although in the vast majority of the remaining cases body temperature was not reported. Increased motor activity was reported in 114 (34%) of the SAEs, most commonly in the categories of abnormal behaviour, delusions and perceptual disturbances and delirium; 26 of the SAEs (8%) were associated with injuries.

In adults, 161 (25%) delirium and delirium-like events were SAEs (table V). Increased motor activity and injuries were reported in association with 28 (17%) and 8 (5%) SAEs, respectively. As the analysis is based on spontaneously reported events for which information is frequently incomplete, information on associated fever was limited. Early onset of delirium and delirium-like SAEs was seen in many adult cases (46% within 2 days of influenza diagnosis and 11.2% within 2 hours of starting oseltamivir treatment); although less prevalent than in children (67% of delirium and delirium-like SAEs within 2 days of influenza diagnosis and 29.8% within 2 hours of starting oseltamivir treatment), this finding suggests a temporal association with the early onset of influenza, which goes in parallel with the start of oseltamivir.

1.1.2 Accidents and Injuries

In all, 33 accidents and injuries were reported as AEs in influenza patients taking oseltamivir, the most frequent cause of which was falls (16 events). Of the 33 events, 23 (70%) were classified as SAEs, 12 of which were falls (see also section 1.1.3). The NPAE most frequently associated with these SAEs was abnormal behaviour; other associated NPAEs

Table IV. Analysis of delirium and delirium-like events in influenza patients aged ≤16 y who received oseltamivir[a]

Category	No. of events[b]	No. of SAEs/no. of patients with SAEs	No. of patients (%) with SAEs occurring within 2 d of diagnosis	Fever at SAE onset	Increased motor activity associated with SAEs	Injury associated with SAEs	Abnormal motor activity associated with SAEs but restrained by others, e.g. parents
Delirium	140	43/43	29 (67)	15	16	2	3
Delusions and perceptual disturbances	449	67/60	38 (63)	29	17	1	3
Cognition disturbances	45	9/7	4 (57)	1	1	0	1
Parasomnia	47	4/3	2 (66)	0	0	0	0
Abnormal behaviour	1036	151/150	104 (69)	77	62	18	29
Depressed level of consciousness	111	40/40	28 (70)	14	10	4	3
Panic attacks	6	2/2	1 (50)	0	1	0	0
Miscellaneous psychiatric	249	29/27	18 (67)	9	7	1	2
Total	**2083**	**345/332**	**224 (67)**	**145**	**114**	**26**	**41**

a Reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

b Serious and non-serious.

SAE = serious adverse event.

Table V. Analysis of delirium and delirium-like events in adult influenza patients who received oseltamivir

Category	No. of events[a]	No. of SAEs/no. of patients with SAEs/no. of patients with SAEs aged ≥65 y	No. of patients (%) with SAEs occurring within 2 d of diagnosis	Fever at SAE onset	Increased motor activity associated with SAEs	Injury associated with SAEs	Abnormal motor activity associated with SAEs but restrained by others, e.g. carers
Delirium	35	18/18/10	7 (39)	1	5	0	0
Delusions and perceptual disturbances	208	43/35/17	13 (48)	2	2	1	0
Cognition disturbances	66	23/23/10	1 (4)	0	1	0	0
Parasomnia	23	1/1/0	1 (100)	0	0	0	0
Abnormal behaviour	120	27/27/4	22 (81)	6	12	5	5
Depressed level of consciousness	72	29/29/6	16 (55)	5	1	2	0
Panic attacks	6	3/3/0	1 (33)	1	1	0	0
Miscellaneous psychiatric	113	17/16/3	9 (56)	1	6	0	1
Total	**643**	**161/152/50**	**70 (46)**	**16**	**28**	**8**	**6**

a Serious and non-serious.

SAE = serious adverse event.

were depressed level of consciousness, delusions and perceptual disturbance and hallucinations. The majority of serious accidents and injuries occurred during the first 2 days of illness, many of which were associated with fever.

1.1.3 Suicidal Events

As described earlier, warnings issued by the Japanese MHLW about oseltamivir use in children were prompted by two deaths in 14-year-old children in February 2007, and speculation in the lay press that these were suicides. In fact, of 16 suicidal events reported to be associated with oseltamivir use, only three completed suicides were reported, all in adult men (Japan, 2; Singapore, 1) and all with significant confounding factors. Four deaths in Japanese children, including the two in 14-year-old children mentioned, were related to falls, with no suggestion of suicidal intent, and so categorized under accidents and injuries. The fact that three of the children fell from higher floors of multi-storey buildings probably led to them being reported as suicides. Abnormal behaviour and depressed consciousness (one each) were reported in association with two of these cases; detailed information on the other two cases is not available.

Given that cumulatively, 36.4 million oseltamivir prescriptions have been dispensed in Japan, corresponding to nearly 500 000 patient-years of exposure, and that annual suicide rates in the general population in Japan (per 100 000 people) in 2004 were 35.6 in males and 12.8 in females,[7] three cases of completed suicide is lower than the expected figure.

1.1.4 NPAEs in Patients Receiving Oseltamivir Prophylaxis

NPAEs were reported in 19 patients who were taking oseltamivir for influenza prophylaxis. Single-case review revealed that 16 of the 19 cases were highly confounded by: underlying medical conditions (6 cases); concomitant medication (2 cases); temporal coincidence of treatment initiation with neuropsychiatric symptoms (2 cases); disqualification as prophylaxis cases with evidence of influenza (1 case) or influenza-like illness (3 cases); for 2

cases there was insufficient information to make a determination.

2. NPAEs in Prospective Clinical Trials of Oseltamivir

To supplement data from post-marketing surveillance, data from prospective phase III clinical studies in the Roche database were analysed, using the same event terms and categories. In all, data from 8000 patients of all ages receiving oseltamivir were analysed, 5384 as treatment and 2616 as prophylaxis. Of these, 3535 and 1662, respectively, took part in randomized, blinded studies.[5]

'On-treatment' neuropsychiatric events (onset during drug administration or within 2 days of the last dose) were recorded in 26 of 5384 (0.5%) patients of all ages receiving oseltamivir as treatment; these were mainly "miscellaneous psychiatric" and loss of consciousness. In randomized, controlled treatment studies,[5] the reporting rate was very similar to placebo (0.5% and 0.6%, respectively). In 1080 children aged ≤16 years receiving oseltamivir as treatment, only three NPAEs were recorded (irritability[2] and anxiety), the same rate (0.3%) as in 738 placebo recipients.[5]

Reporting rates in the prophylaxis studies were also low (13 patients, 0.5%); in randomized controlled studies, significantly fewer oseltamivir patients (12/1662; 0.7%) reported NPAEs than placebo recipients (20/1128; 1.8%; $p < 0.05$).[5]

2.1 Supratherapeutic Doses

No NPAEs were reported in volunteers who received single oseltamivir doses of up to 1000 mg (n = 6), which is more than ten times the normal therapeutic dose of 75 mg twice daily, or twice-daily doses of 500 mg (n = 8) for 7 days.[5] In an ECG study of the effects of oseltamivir, 97 and 99 volunteers, respectively, received doses of 225 and 450 mg twice daily for 5 days. One volunteer at each dose level reported anxiety during the first 2 days of dose administration, which resolved within 1 day.[5]

3. NPAEs in Retrospective Observational Studies

Three retrospective observational studies were recently conducted to investigate the safety and effectiveness of oseltamivir. These utilized health claims data from recognized US databases, UnitedHealthCare (known as the Ingenix Research Data Mart [RDM]) and Thomson Healthcare MarketScan® Commercial Claims and Encounters Database and Medicare Supplemental and Coordination of Benefits Database (known as MedStat).

In the first study, patients in the Ingenix RDM aged >1 year and with a diagnosis of influenza in an outpatient setting between 1 November 1999 and 30 April 2005 were divided into two cohorts: patients dispensed oseltamivir in the 30 days after the diagnosis (60 834) and patients who had no antiviral dispensed (183 786). Propensity-score matching was used to achieve close similarity of the two cohorts.[8] NPAEs were analysed in three hierarchical categories: all events, major NPAEs (excluding chronic disorders, conditions with stated aetiology, congenital or hereditary disorders and spinal cord disorders) and NPAEs specific to CNS stimulation. The NPAE reporting rate in the 30-day post-diagnosis period related to a medical or similar claim was 3.84% (oseltamivir) and 4.26% (no antiviral), and for major NPAEs, 3.35% and 3.70%, respectively. The reporting rate for CNS stimulation events in the two cohorts was also very similar (both combined and individually). Exposure-adjusted odds ratios (ORs) for NPAE risk in the oseltamivir cohort relative to the no-antiviral cohorts were: 0.89 (95% CI 0.85, 0.94) for all NPAEs, 0.89 (95% CI 0.85, 0.94) for major NPAEs and 0.88 (95% CI 0.83, 0.94) for CNS stimulation events. The use of oseltamivir did not appear to be associated with a higher risk of NPAEs in any of the categories studied.

In the second study, using the MedStat combined databases, patient selection (during influenza seasons 2000–6) was done in a similar way to the Ingenix RDM study, except that the oseltamivir and no-antiviral cohorts (n = 36 751 in each) were propensity matched separately by payer type and influenza season.[9] Oseltamivir users had a significantly

lower risk of a NPAE or CNS event both in the 14- and 30-day periods after diagnosis (OR of 0.76 [95% CI 0.68, 0.84] and 0.80 [0.74, 0.87], respectively).

Roche performed a third study to re-analyse data from both Ingenix RDM and MedStat databases, but grouped NPAEs into the same categories used to analyse the post-marketing surveillance data (except accident and injury), allowing results to be compared more directly.[5] Like the other two studies, the study population was individuals diagnosed with influenza in an outpatient setting, but the period studied was from October 2001 to September 2006, and the outcome was claims for NPAEs occurring in the 14 days after diagnosis; in addition, a more detailed propensity-score matching method was used (using 25 strata instead of five). This resulted in 83 307 cases in each cohort from the Ingenix RDM database and 76 079 cases in each from the MedStat databases.

In both databases, logistic regression analysis of all NPAEs showed a significantly lower risk of an event in the oseltamivir cohort: the estimated ORs were 0.65 (95% CI 0.58, 0.72) and 0.74 (0.61, 0.90). Analysis by category showed that in most categories in each database, CIs were wide and the difference in risk was not statistically significant; in the other categories, the difference was significantly lower in the oseltamivir cohort. Separate analysis of the two databases for patients aged ≤16 years (n ≈26 000–31 000 per cohort) did not show any significant difference in NPAE risk between cohorts. In addition, the absolute reporting rate for all NPAEs in influenza patients of all ages receiving oseltamivir during the seasons in question was very low (Ingenix RDM, 542 events [0.65%]; MedStat, 173 events [0.23%]) and compared favourably with the rate in the no-antiviral cohort (Ingenix RDM, 835 events [1.00%]; MedStat, 233 events [0.31%]).[5]

The findings of these three retrospective studies suggest that the risk of NPAEs in oseltamivir-treated patients is no greater than in patients not receiving antivirals.

4. Epidemiology Analysis in General Practice

To gain more insight into the incidence of NPAEs in influenza patients *per se*, an analysis of patients in the UK General Practice Research Database (GPRD) was performed. Using the Read[10] classification of clinical terms and the corresponding MedDRA translation provided by the GPRD, grouping NPAEs as was performed as described in section 1.1, but using 10 rather than 13 categories. For 68 771 patients with a diagnosis of influenza or influenza-like illness between 1 October 2001 and 31 March 2006, the rate of events in the 30 days after diagnosis was compared with the rate in the general database population of 3 012 203 patients. Overall, there was a 75% increased risk for NPAEs in the influenza patients compared with the general GPRD population (relative risk: 1.75 [95% CI 1.54, 1.98]). For individual categories, there was a statistically significant increased risk for delusions, panic attack, depressed level of consciousness, loss of consciousness and cognition disturbances in the influenza patients compared with the general GPRD population. For these events, there was an approximately 1.8- to 2.5-fold increased risk in the influenza patients. Small numbers of children with influenza available in GPRD, coupled with the rarity of NPAEs, do not allow any meaningful comparisons of individual events between the two paediatric groups. However, overall, there was a suggestion of an increased risk in children with influenza. With a relative risk of 1.40 (95% CI 0.79, 2.49) in children, the results were not inconsistent with those for all ages where the estimated overall relative risk of NPAEs comparing influenza patients with the general population was 1.75 (95% CI 1.54, 1.98). As described previously, oseltamivir is used much less frequently in the UK than in Japan and the US. Only 56 of all influenza patients analysed received the drug (seven of those aged ≤16 years), none of whom experienced a NPAE.

5. Onset of NPAEs in Influenza Patients and Relationship with Oseltamivir or Other Antiviral Treatment

A literature search was performed to identify reports of NPAEs in patients with influenza and their relationship with oseltamivir or other antiviral treatment. MEDLINE and EMBASE databases were searched on 15 July 2007 for all publications up to this date in English containing the term 'influenza' (and similar constructions such as 'flu') and at least one of roughly 30 terms relating to CNS disorders and symptoms, such as 'encephalitis', 'loss of consciousness' or 'depressed level of consciousness', 'delirium', 'convulsion', 'hallucination' and 'abnormal behaviour'. This identified 338 publications, abstracts of which were screened by two experts to exclude those not relevant to oseltamivir and influenza-associated neurological disorder. The five publications remaining after screening are summarized below.

Two of the five reports were from Japan. In 6121 patients aged <15 years who had received oseltamivir for influenza between January 2004 and March 2006, delirious behaviour was noted in five children before oseltamivir treatment started and in four after treatment had begun.[11] The delirious behaviour, which was observed ~1 day after the onset of fever, manifested as meaningless speech, disorientation, fearfulness and running around the room. No patient had neurological sequelae and the authors of the report concluded that oseltamivir was not responsible for the delirious behaviour. The same conclusion was reached by the authors of another report on 50 Japanese children aged from 5 months to 15 years old who were hospitalized with influenza during the 2005–6 season.[12] Abnormal behaviour, manifesting as fright, hallucinations, excitation and unintelligible speech, was reported in 14 cases, 13 of whom had received oseltamivir (two also received zanamivir). The abnormal behaviour preceded initiation of antiviral therapy in six children, and no differences were seen between the behaviours occurring before and after initiation of antiviral therapy.

The remaining three reports were from the Chang Gung Children's Hospital in Taiwan. CNS dysfunction was reported in 26 of 84 children (aged ≤18 years) admitted to the hospital with influenza.[13] The symptoms were more common in older children (aged ≥6 years), and included 18 with confusion, nine with visual hallucination and four with seizures. No information was presented on what antiviral therapy, if any, was given, but all but one of the 26 recovered fully by the time of discharge. In a second report, 11 of 92 children admitted to the hospital for influenza (aged 1–11 years) were found to have neurological symptoms that occurred mostly within 3 days of illness onset.[14] Six children presented with either visual or olfactory hallucinations or personality changes such as an unwillingness to speak, and five had seizures. Antiviral therapy was given to only 5 of 92 hospitalized children (two received oseltamivir) but the specific therapy for the 11 with NPAEs is not reported. The third Taiwanese study reported five children with influenza aged 3–5 years who had visual hallucinations and abnormal behaviour such as restlessness and incoherent speech within 3 days of the onset of febrile illness.[15] All had EEG abnormalities, but were discharged in a stable condition within 8 days. None of the children received any antiviral treatment.

Two additional sources of information on the occurrence of NPAEs in influenza patients receiving antivirals other than oseltamivir were identified. The first was the Japanese MHLW website (http://www.mhlw.go.jp/), on which emerging case reports of NPAEs in influenza patients with and without exposure to antivirals were posted. These reports were reviewed to identify patients treated with antivirals other than oseltamivir or no antiviral and then categorized using the same approach employed in the analysis of spontaneously reported NPAEs with oseltamivir. As of 16 June 2007, there were five case reports of NPAEs involving Japanese patients taking amantadine, 12 reports with zanamivir and 25 cases involving no antiviral therapy (table VI). The type and severity of NPAEs reported with non-oseltamivir antivirals or no antiviral were similar to those seen in the oseltamivir post-marketing

Table VI. Neuropsychiatric adverse events (NPAEs) reported to the Japanese Ministry of Health, Labour and Welfare involving influenza patients receiving amantadine, zanamivir or no antiviral (as of 16 June 2007)

NPAE event category	Amantadine (n = 5)	Zanamivir (n = 12)	No antiviral (n = 25)
Abnormal behaviour	1	10	16
Accidental injury	0	0	5
Cognition disturbance	4	1	0
Delirium	0	1	4
Delusions/perceptual disturbance	1	2	2
Decreased level of consciousness	1	0	1
Suicidal events	1	1	0
Miscellaneous psychiatric	3	2	1
Parasomnia	0	0	1
Death	1	0	1

surveillance cases, including delirium with a prominent behavioural abnormality, and death. More cases were reported in males than in females (2 : 1 ratio) and in children than adults.

The second information source was a presentation given to the FDA Pediatric Advisory Committee on 27 November 2007 on the CNS tolerability of zanamivir by representatives of GlaxoSmithKline (GSK), the manufacturer of zanamivir.[3] This presentation included a review of information from the GSK global safety database identifying spontaneous and post-marketing surveillance reports involving influenza patients with NPAEs who were taking zanamivir during the 2006–7 influenza season. Unblinded SAEs from clinical trials were also included. The review identified 145 cases with one or more events within the 'nervous system disorders' or 'psychiatric disorders' MedDRA SOCs, all of which were spontaneous reports from Japan that occurred after January 2007. As with the MHLW reports, approximately double the number of cases involved males compared with females, and the vast majority (99%) involved children (aged 6–14 years). GSK also reviewed the database for cases before 30 September 2006, and identified 119 reports with one or more events within the MedDRA SOCs of interest. Although the ratio of male : females was similar to that seen in the 2006–7 reports, these earlier cases differed substantially in other respects. The majority came from the US (41%), and only 12% involved children and adolescents. In both the earlier and later case series, no causal association between the observed NPAEs and zanamivir treatment could be demonstrated.

These findings indicate that NPAEs occurring in influenza patients are similar whether they are exposed to antivirals or not, and that they may occur before treatment initiation.

6. Pharmacokinetic Profile in CNS

6.1 Comparative Systemic Clinical Pharmacokinetics

Oseltamivir, the ingredient in pharmaceutical preparations of Tamiflu®, is an ethyl ester pro-drug that is delivered orally as a phosphate salt; it is hydrolysed in the body by human high-capacity carboxylesterases (HCEs) to the active metabolite oseltamivir carboxylate.[16,17]

Dose-concentration relationships in healthy adult Japanese and Caucasian volunteers (n = 14 each) were compared in a randomized, placebo-controlled study in which oseltamivir (75 or 150 mg) was administered twice daily for 6 days, plus a single dose on day 7. Individual and mean pharmacokinetics (PK) and exposures to oseltamivir and oseltamivir carboxylate were similar in the two groups (figure 1), with no evidence of ethnic differences in the individual area under the plasma concentration-time curve $(AUC)_{12}$ values at steady-state.[18] Although a prospective comparison has not been done in children, data from four separate studies have been pooled to compare oseltamivir with oseltamivir carboxylate plasma concentrations in 141

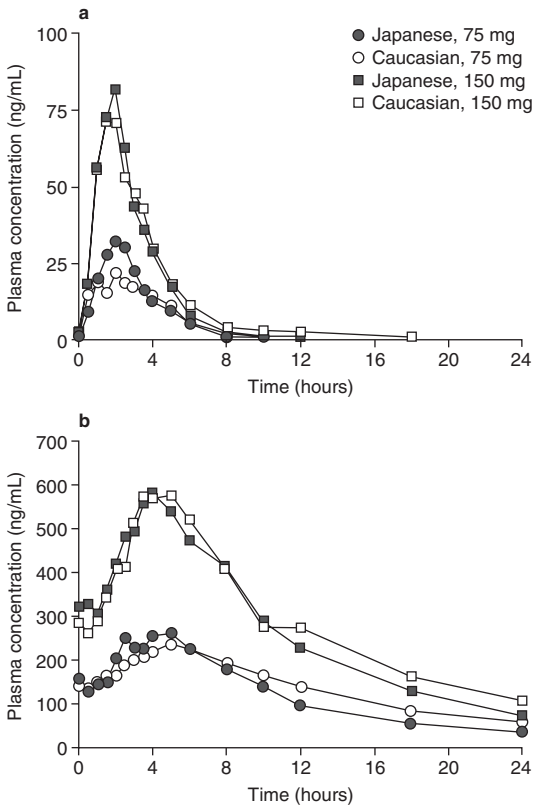

Fig. 1. Plasma concentration-time curves for (**a**) oseltamivir and (**b**) oseltamivir carboxylate in Caucasian and Japanese volunteers after doses of 75 and 150 mg twice daily (reprinted from Schentag et al.[18] by permission of SAGE Publications, Inc.).

Caucasian and 18 Japanese children. After normalization to a 2-mg/kg dose, interquartile ranges for oseltamivir concentration were 3.63–26.75 ng/mL (Caucasian) and 3.95–22.05 ng/mL (Japanese); results for oseltamivir carboxylate were very similar.[19] The sparse sampling data from this analysis are shown in figure 2.

The results of these studies do not suggest any clinically relevant difference between Japanese and Caucasians in the exposure to oseltamivir and oseltamivir carboxylate after standard doses of oseltamivir – indeed, the data in adult volunteers supports registration of the same oseltamivir dose in Japanese patients as in Caucasians. While no signal for defined PK subpopulations (including across ethnic groups) was observed in the clinical programme, it is possible that differences in the systemic PK of oseltamivir and oseltamivir carboxylate between individuals could result at least in part from gene polymorphisms. This possibility is described in section 8 of this article.

6.2 Extent of Oseltamivir and Oseltamivir Carboxylate Penetration into the CNS

Data on CNS penetration in humans are very limited. A recent exploratory study in healthy volunteers (four each of Caucasian and Japanese origin) measured 24-hour cerebrospinal fluid (CSF) and plasma PK profiles of oseltamivir and oseltamivir carboxylate after a single 150-mg dose of oseltamivir. CSF penetration was very limited – mean CSF : plasma ratios in all patients were 2.11%

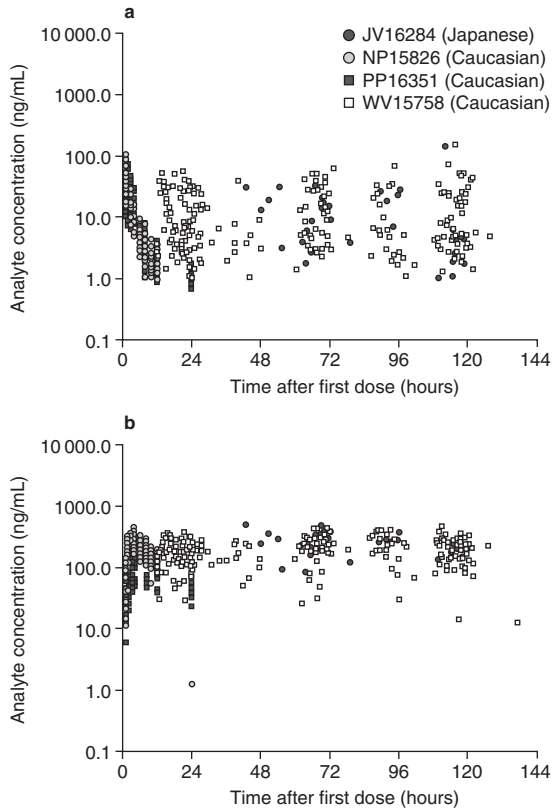

Fig. 2. Plasma concentrations of (**a**) oseltamivir and (**b**) oseltamivir carboxylate in Caucasian and Japanese children using sparse sampling of data pooled from four separate studies. Data are normalized to a dose of 2 mg/kg.[19]

(± standard deviation [SD] 0.52%) for oseltamivir and 3.47% (±2.94%) for oseltamivir carboxylate (based on maximum concentration [C_{max}] values); the respective ratios based on AUC_{last} were 2.35% (±1.09%) and 2.93% (±4.06%).[20]

Quantitative whole-body autoradiography in ferrets and rats after oral doses of radiolabelled oseltamivir showed limited distribution of drug to the brain.[5,16] More specifically, brain concentrations of drug-related radioactive material were generally lower than 20% of those in plasma. After oral treatment, brain : plasma AUC ratios in rats were approximately 0.15 for oseltamivir and 0.01 for oseltamivir carboxylate.[5] These data are consistent with the low CNS exposure of oseltamivir and oseltamivir carboxylate described in humans.

6.3 Regulation of Oseltamivir Levels in the CNS

The low CNS exposure to oseltamivir and oseltamivir carboxylate can be understood by their physicochemical and PK properties. Because oseltamivir is more lipophilic than oseltamivir carboxylate, it is more likely to cross the blood-brain barrier (BBB) by passive transport, whereas oseltamivir carboxylate penetration into the CNS seems to be very limited.[5]

Several systems are known to actively transport drugs out of the CNS, for example, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and human multi-drug resistance protein 2 (MRP2).[21] Oseltamivir is a good substrate for the P-gp system, but not for BCRP and MRP2.[5] Organic anion transporter 1 (OAT1), for which oseltamivir carboxylate is a weak substrate,[5] and the homologous transporter OAT3[22] are expressed in the BBB and could theoretically transport oseltamivir carboxylate out of the brain. However, no evidence for a relevant contribution of such active transport has yet been reported. As oseltamivir is a good substrate for P-gp, impairment or inhibition of this transport system is likely to increase the brain : plasma concentration ratio. The brain : plasma concentration ratio of oseltamivir in P-gp knock-out mice was recently reported to be five to six times that in wild-type mice,[23] but an increase of this magnitude is thought to be of limited clinical relevance.

Another possible source of increased oseltamivir carboxylate exposure in the brain is the intracranial cleavage of oseltamivir to oseltamivir carboxylate. In rat and human brains, only low levels of messenger RNA expression of the carboxylesterases HCE1, HCE2 and HCE3 were detected, suggesting that conversion of oseltamivir to oseltamivir carboxylate in the brain is unlikely to be significant.[5] In addition, the capacity to convert oseltamivir to oseltamivir carboxylate was shown to be very low in studies on rat and human brain homogenates (S9 fractions).[5]

Generally, the mechanisms regulating the distribution of oseltamivir and oseltamivir carboxylate in the CNS seem to be complex, but clinical and nonclinical data suggest a limited CNS exposure for both compounds.

7. Pharmacodynamic Profile in CNS

7.1 Safety Pharmacology

An extensive safety pharmacology programme was performed in adult mice and rats to establish the CNS safety profile of oseltamivir. Single oral doses as high as 1000 mg/kg were administered to normal healthy mice and rats. In an Irwin test,[24] a systematic observational method was used to evaluate whether oseltamivir has overt effects on general behaviour and physiology. There were no behavioural or physiological changes on any of the 42 parameters tested.[5] This was also confirmed in a quantitative assessment addressing spontaneous locomotor activity. Oseltamivir did not exert significant effects on locomotion in mice, whereas diazepam, which was used as a positive control substance, produced its well characterized decrease in locomotor activity.

In a specially designed, safety pharmacology investigation in 7-day-old juvenile rats,[5] the effects of oseltamivir on behaviour were assessed. In this study, there were either no effects on behaviour or effects at very high plasma exposure levels considered related to non-specific general toxicity. Brain

levels of oseltamivir as compared with plasma were only 2- to 3-fold higher in 7-day-old rats compared with adult rats, and consistent with recalculated values from a previous study in juvenile rats,[5] and with a published study in juvenile mice.[22] In all cases, the brain levels were well below those in plasma.

Further studies in adult mice and rats investigated pro- and anti-convulsant activity, effects on hexobarbital-induced sleeping time and effects on nociception, respiration and body temperature. No modulation of any of these parameters was observed, whatever the dose level tested. In these safety pharmacology studies, the highest oral dose of oseltamivir tested, 763 mg/kg, produced mean C_{max} values for oseltamivir and oseltamivir carboxylate at least 100 times higher than the effective clinical dose[5] without producing significant behavioural effects in rodents.

7.2 Neuraminidase Inhibition

As human and influenza virus neuraminidases show significant differences, including binding specificity,[25,26] the probability of oseltamivir carboxylate binding to the human enzyme is low. Although oseltamivir carboxylate is a highly potent inhibitor of viral neuraminidases, with Ki values in the low nanomolar range (0.2–1.7 nM),[27] no inhibitory activity was observed in mammalian neuraminidases (human liver, mouse liver and mouse uterus) at concentrations up to 1 mM, over 500 times the mean C_{max} of oseltamivir carboxylate at steady state from a 75-mg twice-daily dose.[5] As at least two human neuraminidases (NEU1 and NEU4) are expressed in both liver and brain,[28,29] it seems unlikely that oseltamivir carboxylate would inhibit brain-derived neuraminidases at therapeutic concentrations. In order to fully exclude inhibition of human host neuraminidases by oseltamivir or oseltamivir carboxylate, all four human neuraminidases expressed in recombinant systems, as well as neuraminidase activity in extracts of non-human primate (*Macaca fascicularis*) and rat brains, were tested for an inhibitory activity of oseltamivir and oseltamivir carboxylate. At concentrations of up to 1 mM, representing concentrations of >100 000-(oseltamivir) and >10 000-fold (oseltamivir carboxylate) the extrapolated CNS concentrations achieved with standard oseltamivir dosing, neither oseltamivir nor oseltamivir carboxylate produced a significant inhibition of human recombinant or tissue-derived neuraminidases;[5] a recent study by Hata et al.[30] fully confirms the lack of any inhibitory activity of oseltamivir carboxylate at or below a concentration of 1 nM. These data demonstrate that oseltamivir has no significant inhibitory activity on human host neuraminidases at therapeutically relevant concentrations and that a potential interaction between oseltamivir and human host neuraminidases is thus very unlikely to be a mechanism for producing or exacerbating NPAEs in humans.

7.3 Interactions with Other CNS Molecules and Receptors

Possible effects of oseltamivir and oseltamivir carboxylate on host molecular targets could provide the basis for potential pharmacological activity in the CNS. Interactions with 155 known molecular targets, including several targets that could potentially underlie mechanisms for triggering or exacerbating NPAEs, such as dopamine and serotonin receptors and transporters, as well as ionotropic and metabotropic glutamate receptors, were examined using *in vitro* radioligand binding and functional assays. Oseltamivir and oseltamivir carboxylate were found to have no relevant pharmacological activity on any of the targets tested; the highest concentration tested (30 μM is approximately 100 and 30 times, respectively, the oseltamivir phosphate and oseltamivir carboxylate plasma C_{max} values achieved from the 75-mg twice-daily clinical dose, and >4000- and >300-fold the extrapolated oseltamivir and oseltamivir carboxylate CNS concentrations achieved with standard oseltamivir dosing.[5]

8. Genetic Differences

8.1 Interference with Hydrolysis of Oseltamivir: Modelling Studies

Hydrolysis *in vitro* of oseltamivir to the active form, oseltamivir carboxylate, seems to depend mainly on HCE1, and recombinant HCE1, but not HCE2, has been shown to hydrolyse oseltamivir.[31] These authors also described several naturally occurring HCE1 polymorphic variants with different *in vitro* hydrolysis rates to the wild-type enzyme – HCE1 S58N was slightly faster, and HCE1 C70F and HCE1 R128H markedly slower. HCE1 C70F was expressed at a much lower level than the other variants.[31] Genetic variation in the *HCE1* and *HCE2* genes has also been reported by other groups.[32,33] HCE1 appears to be encoded by two distinct genes that may have arisen from a duplication event.[33,34] The clinical relevance of these genetic data, however, is unclear – the allele frequencies of several HCE polymorphisms are unknown, and the organization of the HCE1 locus complicates the prediction of enzyme activity *in vivo* based on genotype alone.[33] There are no clinical data yet on how HCE1 polymorphisms affect the PK of oseltamivir and oseltamivir carboxylate in humans.

If metabolism of oseltamivir to oseltamivir carboxylate was completely blocked, the resultant increase in oseltamivir levels could theoretically be responsible for adverse safety findings. This possibility has been investigated using population PK modelling to simulate complete inhibition of oseltamivir hydrolysis and estimate the maximum possible resulting oseltamivir exposure. A population PK model for oseltamivir and oseltamivir carboxylate was built using data from five healthy volunteer studies, using non-linear mixed-effect modelling (NONMEM version VI). Using Berkeley Madonna (version 8.3.9), 100 individuals were simulated with both normal and completely inhibited oseltamivir hydrolysis after oral doses of 75 mg twice daily. Basing the simulations on normal metabolism (hydrolysis) of oseltamivir to oseltamivir carboxylate as estimated by the population PK model (metabolic clearance of 96.5 L/h), the mean assumed steady state C_{max} value was 39.9 ng/mL. Assuming complete inhibition of oseltamivir to oseltamivir carboxylate conversion (metabolic clearance of 0 L/h), the simulations produced a mean steady-state C_{max} value for oseltamivir of 555 ng/mL, 14 times higher than those simulated under the normal metabolism scenario.[5] Even still, this exposure is lower than the mean C_{max} in six subjects who received a single dose of oseltamivir 1000 mg and who experienced no NPAEs.[5] Although the mean oseltamivir C_{max} in 99 volunteers who received oseltamivir 450 mg twice daily for 5 days was only 352 ng/mL, some individuals had C_{max} values higher than the 555 ng/mL mean value simulated in the no-metabolism scenario, but again, without provoking any NPAEs.[5] Collectively, these data suggest that HCE polymorphisms are unlikely to provide a plausible explanation for the observed NPAEs.

8.2 Renal Excretion of Oseltamivir Carboxylate

Once formed in the body, oseltamivir carboxylate is not further metabolized, and besides glomerular filtration, is eliminated primarily via tubular secretion in the kidney,[16] principally by the action of the active transport system OAT1 mentioned previously.[35] Although gene polymorphisms of *OAT1* have been found, allele frequencies and levels of variability are low.[36] Coding region variants of *OAT1* do not seem to contribute substantially to inter-individual differences in renal clearance of oseltamivir,[36,37] which is consistent with the similarity in PK profiles of Japanese and Caucasian populations.[18] Moreover, inhibition of OAT1 and OAT3 activity by probenecid in healthy volunteers, resulting in a 2- and 2.5-fold increase in oseltamivir carboxylate C_{max} and exposure, respectively, did not elicit NPAEs in a clinical trial setting.[5,35] Therefore, polymorphisms of the *OAT1* gene affecting excretion of oseltamivir carboxylate are unlikely to contribute to the reported NPAEs.

8.3 Effect of Active Transport Processes for Oseltamivir and Oseltamivir Carboxylate in the CNS

As mentioned in section 6.3, except for P-gp, no other active transport systems have been identified that regulate export of oseltamivir from the CNS. As no relevant active transport of oseltamivir carboxylate through the BBB has yet been described, the very limited CNS exposure to oseltamivir carboxylate is thought to be due to passive transport.

P-gp is encoded by multidrug resistance gene 1 (*MDR1*), for which many polymorphisms in humans have been reported, with a range of allele frequencies across different populations.[38,39] However, although *MDR1* genotypic variants are reported to influence the PK and pharmacodynamics of various drugs, clinical studies in which MDR1 substrates were given to individuals with known *MDR1* genetic variants have proved inconclusive and sometimes contradictory,[39] and variants were not substantially different to the wild-type when tested *in vitro*.[40] As mentioned in section 6.3, complete inhibition of P-gp function in humans would be expected to have little effect on the safety of oseltamivir, based on the extent of changes seen in gene knock-out studies in animals, and genetic variability in *MDR1* function is therefore unlikely to result in adverse effects.

Anion transporters such as OAT1, OAT3 and OATP1A2 also contribute to regulation of the BBB.[41] It seems unlikely, however, that pharmacogenetic variations of these transporters could be associated with NPAEs – inhibition of OAT activity by probenecid did not elicit NPAEs, as described in the preceding section. Moreover, the clinical relevance of polymorphisms in these genes has not been firmly established despite intensive investigative efforts, suggesting that the pharmacological effect of potentially functional polymorphisms in these genes is likely to be modest.[36,37,42-44]

Despite the continuing accumulation of data on polymorphisms of genes suspected to contribute to maintenance of the BBB with respect to oseltamivir and oseltamivir carboxylate, there is no evidence that they result in a clinically relevant mechanism for producing adverse effects.

9. Conclusions

The existing and new data reviewed in this article provide some answers to the questions posed at the start of this assessment made by Roche. In patients with influenza taking oseltamivir, the most frequent NPAEs are in the categories of abnormal behaviour and delusions and perceptual disturbances. Most of the spontaneously reported NPAEs resolved, but very occasionally resulted in injury, in some cases with a fatal outcome. The majority of NPAEs have been reported in Japan, mostly in children, and more frequently in males than females, but in the context of the number of prescriptions issued for oseltamivir, the crude reporting rate shows NPAEs to be uncommon events. As the timing of most events is within the first 2 days of oseltamivir treatment, coinciding with the onset of other influenza symptoms such as fever and malaise, it is difficult to distinguish the effect of the treatment from those of the disease. In prospective clinical studies, no evidence was found for a higher incidence of NPAEs in patients who receive oseltamivir than in those who received placebo, and results of retrospective observational studies of two large US claims databases indicate that the risk of NPAEs in oseltamivir-treated patients is no higher than in patients receiving no antiviral treatment. This evidence strongly supports that the events are more likely to be caused by the disease itself rather than by oseltamivir, which is consistent with the UK GPRD medical records analysis showing that the risk of NPAEs in influenza patients is significantly higher than in the general population.

Human and animal studies show that CNS concentrations of oseltamivir and its active metabolite oseltamivir carboxylate are low relative to plasma concentrations, and that conversion of oseltamivir to oseltamivir carboxylate in the brain is very low; indeed oseltamivir appears to be actively exported from the CNS. Exposure to oseltamivir and oseltamivir carboxylate in the CNS does not result in any relevant pharmacodynamic effects, and no genetic differences between Japanese and Caucasian patients have been found that might result in differences in the concentration, metabolism or activity of

oseltamivir and oseltamivir carboxylate in the CNS. A range of clinical and animal studies have not suggested any plausible mechanisms by which oseltamivir could cause NPAEs.

The available data do not indicate that the incidence of NPAEs in patients with influenza receiving oseltamivir is higher than in those not receiving it, and do not suggest any mechanism by which oseltamivir could cause such events.

Acknowledgements

All of the investigations described in this article were supported by Roche. All authors are current employees of Roche, and Stephen Toovey, Eric Prinssen, Bharat Thakrar, Regina Dutkowski, Gerhard Hoffmann, Alexander Breidenbach, Susan Sacks, Jonathan Solsky and David Reddy have stock ownership options in the company.

All authors contributed to the design, conduct, collection, analysis and interpretation of at least one of the investigations described in this article. All authors participated in the preparation, review and approval of this article. Editorial support for the development of this article was provided by Scott Malkin, a medical writer at Gardiner-Caldwell Communications, Macclesfield, UK, funding for which was provided by Roche.

References

1. US FDA. Meeting of the FDA Pediatric Advisory Committee, 16 November 2006 [online]. Available from URL: http://www.fda.gov/OHRMS/DOCKETS/ac/oc06.htm [Accessed 2008 Jul 3]
2. US FDA. Memorandum: Department of Health and Human Services Public Health Service FDA Centre for Drug Evaluation and Research: post-marketing adverse events reports review of central nervous system/psychiatric disorders associated with the use of Tamiflu, September 2006 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_09_01_Tamiflu%20AE%20Review%202006%20Redacted_D060309_092.pdf [Accessed 2008 Jun 30]
3. US FDA. Meeting of the FDA Pediatric Advisory Committee, 27 November 2007 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4325t1_transcript.pdf [Accessed 2008 Jul 3]
4. Fujita T, Mori M, Okumura A, et al. Epidemiologic survey of influenza-associated complications: II. A statistical analysis of symptoms and signs, and medication. J Japan Ped Soc 2007; 111 (12): 2 [online]. Available from URL: http://www.jpeds.or.jp/english/journal/111-12e.html [Accessed 2008 Oct 31]
5. Data on file, Roche, 2008
6. Chung BH, Tsang AM, Wong VC. Neurologic complications in children hospitalized with influenza: comparison between USA and Hong Kong. J Pediatr 2007; 151 (5): e17-8
7. WHO. Suicide Prevention (SUPRE): suicide statistics, last updated 2007 [online]. Available from URL: http://www.who.int/mental_health/prevention/suicide/country_reports/en/index.html [Accessed 2007 Nov 18]
8. Wilcox M, Zhu S. Oseltamivir therapy appears not to affect the incidence of neuropsychiatric adverse events in influenza patients [abstract]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007 Sep 17-20; Chicago (IL)
9. Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. MedGenMed 2007; 9 (4): 23
10. Robinson D, Schultz E, Brown P, et al. Updating the Read codes: user-interactive maintenance of a dynamical clinical vocabulary. J Am Med Inform Assoc 1997; 4: 465-72
11. Okumura A, Kubota T, Kato T, et al. Oseltamivir and delirious behavior in children with influenza [letter]. Pediatr Infect Dis J 2006; 25 (6): 572
12. Goshima N, Nakano T, Nagao M, et al. Clinical study of abnormal behaviour during influenza [in Japanese]. Infect Immun Child 2006; 18 (371): 376
13. Wang YH, Huang YC, Chang LY, et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. J Microbiol Immunol Infect 2003; 36 (2): 111-6
14. Lin CH, Huang YC, Chiu CH, et al. Neurologic manifestations in children with influenza B virus infection. Pediatr Infect Dis J 2006; 25 (11): 1081-3
15. Huang YC, Lin TY, Wu SL, et al. Influenza A-associated central nervous system dysfunction in children presenting as transient visual hallucination. Pediatr Infect Dis J 2003; 22 (4): 366-8
16. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. Clin Pharmacokinet 1999; 37 (6): 471-84
17. Doucette KE, Aoki FY. Oseltamivir: a clinical and pharmacological perspective. Expert Opin Pharmacother 2001; 2 (10): 1671-83
18. Schentag JJ, Hill G, Chu T, et al. Similarity in pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian subjects. J Clin Pharmacol 2007; 47 (6): 689-96
19. Gieschke R, Dutkowski R, Smith J, et al. Similarity in the pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian children. Options for the Control of Influenza VI; 2007 Jun 17-23; Toronto (ON)
20. Jhee SS, Yen M, Ereshefsky L, et al. Low penetration of oseltamivir and its carboxylate into cerebrospinal fluid in healthy Japanese and Caucasian volunteers. Antimicrob Agents Chemother 2008; 52: 3687-93
21. Loscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. NeuroRx 2005; 2 (1): 86-98
22. Ose A, Kusuhara H, Yamatsugu K, et al. P-glycoprotein restricts the penetration of oseltamivir across the blood-brain barrier. Drug Metab Dispos 2008; 36 (2): 427-34
23. Morimoto K, Nakakariya M, Shirasaka Y, et al. Oseltamivir (Tamiflu) efflux transport at the blood-brain barrier via P-glycoprotein. Drug Metab Dispos 2008; 36 (1): 6-9
24. Irwin S. Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. Psychopharmacologia 1968; 13 (3): 222-57
25. Chavas LM, Tringali C, Fusi P, et al. Crystal structure of the human cytosolic sialidase Neu2: evidence for the dynamic nature of substrate recognition. J Biol Chem 2005; 280 (1): 469-75

26. Magesh S, Suzuki T, Miyagi T, et al. Homology modeling of human sialidase enzymes NEU1, NEU3 and NEU4 based on the crystal structure of NEU2: hints for the design of selective NEU3 inhibitors. J Mol Graph Model 2006; 25 (2): 196-207

27. Mendel DB, Tai CY, Escarpe PA, et al. Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS 4071 protects mice and ferrets against influenza infection. Antimicrob Agents Chemother 1998; 42 (3): 640-6

28. Monti E, Preti A, Venerando B, et al. Recent development in mammalian sialidase molecular biology. Neurochem Res 2002; 27 (7-8): 649-63

29. Yamaguchi K, Hata K, Koseki K, et al. Evidence for mitochondrial localization of a novel human sialidase (NEU4). Biochem J 2005; 390 (Pt 1): 85-93

30. Hata K, Koseki K, Yamaguchi S, et al. Limited inhibitory effects of oseltamivir and zanamivir on human sialidases. Antimicrob Agents Chemother 2008; 52: 3484-91

31. Shi D, Yang J, Yang D, et al. Anti-influenza prodrug oseltamivir is activated by carboxylesterase human carboxylesterase 1, and the activation is inhibited by antiplatelet agent clopidogrel. J Pharmacol Exp Ther 2006; 319 (3): 1477-84

32. Charasson V, Bellott R, Meynard D, et al. Pharmacogenetics of human carboxylesterase 2, an enzyme involved in the activation of irinotecan into SN-38. Clin Pharmacol Ther 2004; 76 (6): 528-35

33. Tanimoto K, Kaneyasu M, Shimokuni T, et al. Human carboxylesterase 1A2 expressed from carboxylesterase 1A1 and 1A2 genes is a potent predictor of CPT-11 cytotoxicity in vitro. Pharmacogenet Genomics 2007; 17 (1): 1-10

34. Hosokawa M, Furihata T, Yaginuma Y, et al. Structural organization and characterization of the regulatory element of the human carboxylesterase (CES1A1 and CES1A2) genes. Drug Metab Pharmacokinet 2008; 23 (1): 73-84

35. Hill G, Cihlar T, Oo C, et al. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metab Dispos 2002; 30 (1): 13-9

36. Fujita T, Brown C, Carlson EJ, et al. Functional analysis of polymorphisms in the organic anion transporter, SLC22A6 (OAT1). Pharmacogenet Genomics 2005; 15 (4): 201-9

37. Bleasby K, Hall LA, Perry JL, et al. Functional consequences of single nucleotide polymorphisms in the human organic anion transporter hOAT1 (SLC22A6). J Pharmacol Exp Ther 2005; 314 (2): 923-31

38. Kroetz DL, Pauli-Magnus C, Hodges LM, et al. Sequence diversity and haplotype structure in the human ABCB1 (MDR1, multidrug resistance transporter) gene. Pharmacogenetics 2003; 13 (8): 481-94

39. Sakurai A, Tamura A, Onishi Y, et al. Genetic polymorphisms of ATP-binding cassette transporters ABCB1 and ABCG2: therapeutic implications. Expert Opin Pharmacother 2005; 6 (14): 2455-73

40. Ishikawa T, Hirano H, Onishi Y, et al. Functional evaluation of ABCB1 (P-glycoprotein) polymorphisms: high-speed screening and structure-activity relationship analyses. Drug Metab Pharmacokinet 2004; 19 (1): 1-14

41. Kusuhara H, Sugiyama Y. Active efflux across the blood-brain barrier: role of the solute carrier family. NeuroRx 2005; 2 (1): 73-85

42. Marzolini C, Tirona RG, Kim RB. Pharmacogenomics of the OATP and OAT families. Pharmacogenomics 2004; 5 (3): 273-82

43. Nishizato Y, Ieiri I, Suzuki H, et al. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics. Clin Pharmacol Ther 2003; 73 (6): 554-65

44. Lee W, Glaeser H, Smith LH, et al. Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. J Biol Chem 2005; 280 (10): 9610-7

Correspondence: Dr *Stephen Toovey*, Burggartenstrasse 32, CH-4103 Bottmingen, Switzerland.
E-mail: malaria@sunrise.ch