deficiency; history of raised intracerebral pressure or clinically significant vertebral joint pathology; major illness in the 30 days before screening or febrile illness in the 14 days prior to CSF sampling; pregnancy or lactation; relevant history of, or positive test for, drugs of abuse or alcohol; infection with hepatitis B or C virus or human immunodeficiency virus; or any other condition or disease rendering the subject unsuitable for the study. Prescription medication was not permitted to be taken within 7 days or six times its elimination half-life ($t_{1/2}$) (whichever was longer) before study drug administration (excluding hormone replacement therapy and oral contraception). Occasional use of acetaminophen/paracetamol (up to 3 g/day) was allowed up to 24 h before dosing and as needed for treatment of side effects related to the CSF sampling procedure. Intravenous caffeine was also permitted for headache prophylaxis or treatment of side effects caused by the CSF sampling procedure.

All subjects underwent a screening period from day −28 to day −2, during which eligibility was assessed and written informed consent was provided. Screening involved a full medical history, a physical examination, an electrocardiogram (ECG), and a lumbar spine X-ray (unless the subject had such an X-ray taken within 1 year of screening). Samples for laboratory safety assessments (including serum biochemistry, hematology, urinalysis, and serology) and drug and alcohol abuse tests were taken after a 4-h fasting period. Female subjects were to undertake pregnancy tests.

Following successful screening, volunteers were admitted to the study unit on day −1 for a baseline safety assessment (recording of vital signs, ECG and laboratory safety assessments, and drug/alcohol abuse and pregnancy tests). On day 1, following an overnight fast, all subjects were catheterized in the lumbar region (for example, L3 to L4) for CSF sampling. This was performed using the dynabridging technique (California Clinical Trials Inc., California), in which the catheter is connected to a peristaltic pump for automatic timed withdrawal of CSF samples (approximately 6 ml per withdrawal). Subjects then received a single oral dose of 150 mg oseltamivir phosphate (F. Hoffmann-La Roche Ltd.), which corresponds to the recommended daily adult treatment dose of 75 mg twice daily. Venous blood samples (2 ml per withdrawal) were taken at the same time as CSF sampling was performed. Blood and CSF samples were taken immediately before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 20, and 24 h after dosing in the manner described above (14 sampling points in total). Subjects were discharged from the unit on day 4 and returned for a follow-up examination on days 10 to 12. Adverse events were recorded from screening until the end of follow-up.

Oseltamivir and OC assay. Blood samples were drawn into EDTA blood collection tubes, and plasma was separated by centrifugation for 10 min at 1,500 × g and 4°C. CSF and plasma samples were stored at −70°C until analysis. Concentrations of oseltamivir and OC in plasma and CSF were measured using a specific and validated high-performance liquid chromatography method coupled with tandem mass spectrometry (Bioanalytical Systems Inc., Kenilworth, United Kingdom; SAP.055) based on a previously published method (35). The CSF samples were analyzed along with human EDTA plasma and human CSF control samples against calibration standards prepared in human EDTA plasma.

Pharmacokinetic analysis. Concentration-versus-time profiles were generated, and the observed maximum concentration (C_{max}) and time to observed maximum concentration (T_{max}) were then determined for oseltamivir and OC in CSF and plasma. Standard noncompartmental methods were employed to characterize pharmacokinetic parameters using WinNonlin software (version 5.2; Pharsight Inc.). The following parameters were calculated where possible: area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-last}) and infinity ($AUC_{0-\infty}$), apparent $t_{1/2}$, and apparent oral clearance (CL/F). AUC values were computed using the linear-trapezoidal rule. $AUC_{0-\infty}$ was estimated using $AUC_{0-last} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration and λ_z is the apparent elimination rate constant determined by log-linear regression of the last four terminal concentration data points fitting with an adjusted residual squared value of ≥0.90. The ratios of CSF/plasma exposure for C_{max} and AUC_{0-last} were also determined for each of the two analytes. In addition, oseltamivir/OC ratios (adjusted for the molecular weight differences) were calculated for C_{max} and AUC_{0-last}, once for the matrix plasma and separately for the matrix CSF.

RESULTS

A total of eight healthy male volunteers (four Caucasian and four Japanese) entered the study. No females were available for enrollment within the study timeframe (approximately 1 month). Demographic baseline characteristics were well balanced between the Caucasian and Japanese groups (Table 1).

TABLE 1. Demographic baseline characteristics by ethnic group and total population

Parameter	Mean (range)		
	Caucasian (n = 4)	Japanese (n = 4)	Total (n = 8)
No. of subjects by gender			
Male	4	4	8
Female	0	0	0
Age (yrs)	29.0 (24–33)	26.8 (24–35)	27.9 (24–35)
Wt (kg)	66.9 (61.2–73.5)	65.6 (57.8–82.6)	66.3 (57.8–82.6)
Ht (cm)	173.3 (169–177)	172.8 (169–176)	173.0 (169–177)
Body mass index (kg/m²)	22.2 (20.7–23.5)	22.1 (18.8–28.9)	22.2 (18.8–28.9)

Assay validation. In both matrices, the calibration curve ranged from lower limits of quantification of 1 ng/ml and 10 ng/ml for oseltamivir and OC, respectively, up to 250 ng/ml for oseltamivir and 10,000 ng/ml for OC. For the analysis in plasma, the interassay precision (coefficient of variation) ranged from 3.8% to 5.4% for oseltamivir and from 2.2% to 9.1% for OC, and the accuracy ranged from 100.0% to 105.7% for oseltamivir and from 97.5% to 99.3% for OC. For the analysis in CSF, the interassay precision ranged from 0.9% to 3.3% for oseltamivir and from 1.6% to 9.1% for OC, and the accuracy ranged from 104.0% to 114.5% for oseltamivir and from 98.2% to 105.8% for OC. No marked inaccuracies were found in the concentration ranges of the plasma and CSF study samples.

Pharmacokinetic analysis. Figure 1 and Fig. 2 show the mean (± standard deviation [SD]) plasma and CSF concentration-time profiles for oseltamivir and OC in plasma and CSF for Japanese and Caucasian subjects and the overall population after a single oral dose of 150 mg oseltamivir phosphate. For both analytes, mean concentrations in CSF were considerably lower than those in plasma. Table 2 and Table 3 summarize the measured and computed pharmacokinetic parameters for oseltamivir and OC in plasma and CSF. Mean (± SD) C_{max} plasma values were 115 (±40.0) ng/ml for oseltamivir and 544 (±92.6) ng/ml for OC. The corresponding median (range) T_{max} values were 1.0 (0.5 to 4.0) h and 5.0 (4.0 to 6.0) h for oseltamivir and OC postdosing, respectively. In CSF, mean (± SD) C_{max} values for oseltamivir and OC were 2.4 (±0.9) ng/ml and 19.0 (±14.9) ng/ml, respectively; these were measured at median (range) T_{max} values of 3.5 (1.0 to 5.0) h and 8.0 (6.0 to 12.0) h postdosing.

Oseltamivir concentrations were quantifiable for up to 12 h postdosing in plasma and 9 h in CSF. OC concentrations were detected for up to 24 h in plasma and for up to 12 h in CSF in all but one Caucasian subject. This subject displayed the highest CSF concentrations for OC with a C_{max} value of 45.9 ng/ml at 7 h postdosing, but the oseltamivir concentrations in CSF were not remarkably high compared to those for the remaining subjects. This subject was also shown to have blood contamination of the CSF up to 5 h postdosing, and OC persisted in the subject's CSF samples until 24 h after drug administration. In a different Caucasian subject, OC concentrations were not detected in CSF at any time point, while oseltamivir concen-

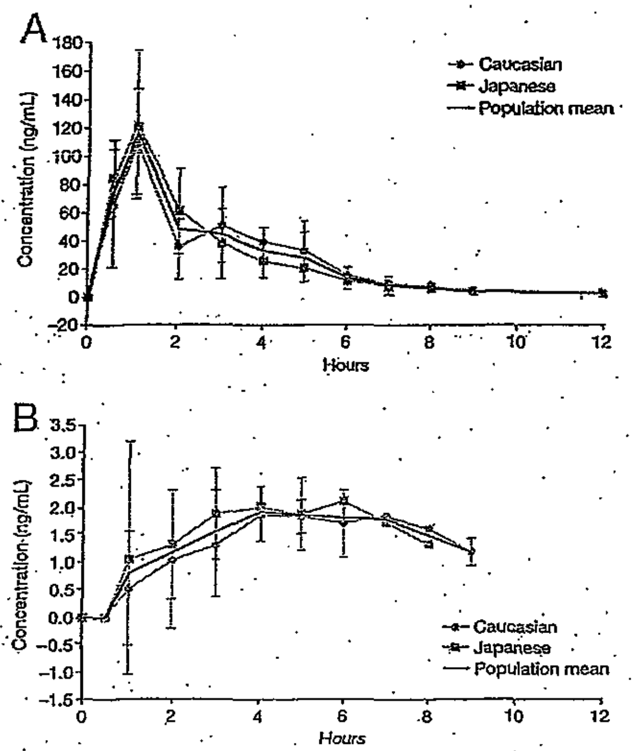

FIG. 1. (A) Mean (± SD) concentration-time profile for oseltamivir in plasma after a single oral dose of 150 mg oseltamivir phosphate in Caucasian (n = 4) and Japanese (n = 4) subjects and the overall population (n = 8). (B) Mean (± SD) concentration-time profile for oseltamivir in CSF after a single oral dose of 150 mg oseltamivir phosphate in Caucasian (n = 4) and Japanese (n = 4) subjects and the overall population (n = 8).

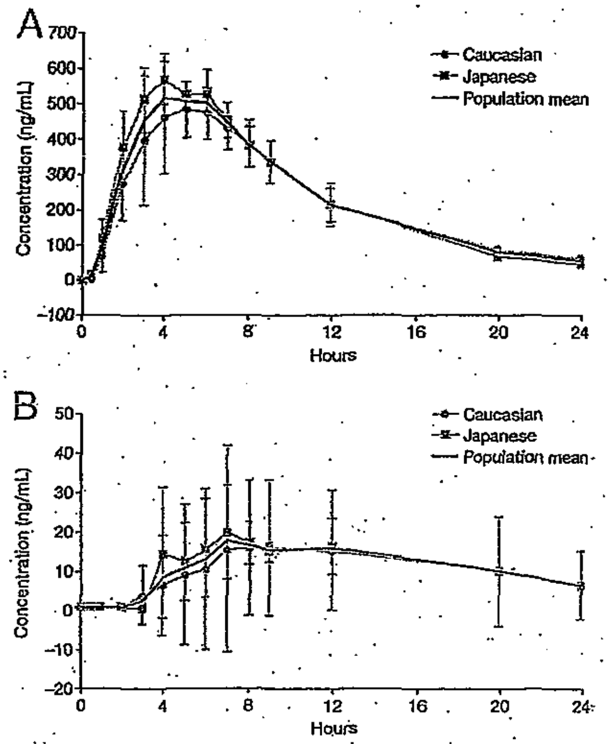

FIG. 2. (A) Mean (± SD) concentration-time profile for OC in plasma after a single oral dose of 150 mg oseltamivir phosphate in Caucasian (n = 4) and Japanese (n = 4) subjects and the overall population (n = 8). (B) Mean (± SD) concentration-time profile for OC in CSF after a single oral dose of 150 mg oseltamivir phosphate in Caucasian (n = 4) and Japanese (n = 4) subjects and the overall population (n = 8).

trations were measurable until 6 h postdosing. In this subject, values for OC in CSF of zero were assigned for C_{max}, AUC_{0-last}, and the respective CSF/plasma ratios, and these values were included in the respective summary statistics. The intersubject pharmacokinetic variabilities (SDs) for the parameters C_{max} and AUC_{0-last} in plasma in relation to the sample mean (percent coefficient of variation) were approximately 34% and 17% for oseltamivir and OC, respectively. This is consistent with previous experience with the drug (Roche data on file). The corresponding intersubject variabilities for C_{max} and AUC_{0-last} in CSF were higher for oseltamivir (36% for C_{max} and 48% for AUC_{0-last}) and OC (78% for C_{max} and 129% for AUC_{0-last}), the latter two percentages reflecting the most extreme C_{max} values measured for OC (0 ng/ml and 45.9 ng/ml).

In the overall population, the mean (± SD) C_{max} CSF/plasma ratios (in %) for oseltamivir and OC were 2.1% (±0.5%) and 3.5% (±2.9%), respectively (Tables 2 and 3). For both oseltamivir and OC, the concentration-versus-time profiles in plasma were sufficient to estimate $AUC_{0-\infty}$ and $t_{1/2}$ and to derive the apparent oral plasma clearance for oseltamivir. For both analytes, plasma AUC_{0-last} covered more than 90% of plasma $AUC_{0-\infty}$. The mean plasma $t_{1/2}$ of OC was triple that of oseltamivir (5.4 h versus 1.8 h), and the mean plasma CL/F for oseltamivir was 502 liters/h. In contrast to the pharmacokinetic plasma data, the CSF concentration-versus-time profiles did not allow a reliable assessment of $AUC_{0-\infty}$ for either analyte; hence, only AUC_{0-last} values are reported for CSF. The mean (± SD) AUC_{0-last} CSF/plasma ratios for the total population for oseltamivir and OC were 2.4% (±1.1%) and 2.9% (±4.1%), respectively. The individual AUC_{0-last} values in CSF covered a time period between 2 and 9 h for oseltamivir and 12 or 24 h for OC and the individual AUC_{0-last} values in plasma covered between 9 and 12 h for oseltamivir and 12 and 24 h for OC. If approximate free plasma concentrations (58% for oseltamivir and 95% for OC [Roche data on file]) were used to calculate the respective CSF/plasma ratios, these figures would double for oseltamivir (that is, to approximately 5%) but would remain similar for OC. In the subject with blood-contaminated CSF, in whom higher OC CSF concentrations were observed, the resulting CSF/plasma ratios based on total concentrations for OC were 9.5% (C_{max}) and 11.7% (AUC) (these values would be only slightly higher if free concentrations were considered). In the overall population, the mean (± SD) C_{max} oseltamivir (prodrug)/OC (active metabolite) ratios (adjusted for the molecular weight differences) were 18.8% (±4.1%) and 12.4% (±5.1%) in plasma and CSF, respectively. The AUC_{0-last} oseltamivir/OC molar ratios were 5.1% (±0.9%) and 9.4% (±8.8%) in plasma and CSF, respectively.

This study was not empowered to identify differences be-

TABLE 2. Summary of the pharmacokinetic parameters of oseltamivir in plasma and CSF by ethnic group and total population[a]

Group (n)	C_{max} (ng/ml)		T_{max} (h)		C_{last} (ng/ml)		T_{last} (h)		AUC_{0-last} (h · ng/ml)		$t_{1/2}$ (h)		$AUC_{0-\infty}$ (h · ng/ml)		CL/F (liters/h)		CSF/plasma ratio (%)	
	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	C_{max}	AUC_{0-last}
Caucasian (4)	100 ± 39.6	2.1 ± 0.5	2.0 (0.5–4.0)	4.0 (2.0–5.0)	1.9 ± 0.5	1.3 ± 0.3	12.0 (9.0–12.0)	7.5 (5.0–9.0)	299 ± 62.8	9.4 ± 4.6	1.8 ± 0.2	NC[b]	304 ± 64.0	NC	512 ± 118	NC	2.3 ± 0.5	3.0 ± 1.0
Japanese (4)	130 ± 39.8	2.6 ± 1.3	1.0 (0.5–1.0)	3.0 (1.0–5.0)	2.3 ± 0.9	1.4 ± 0.3	9.0 (9.0–12.0)	4.0 (2.0–8.0)	317 ± 92.3	5.9 ± 4.0	1.7 ± 0.4	NC	323 ± 93.6	NC	492 ± 126	NC	1.9 ± 0.5	1.7 ± 0.8
Total (8)	115 ± 40.0	2.4 ± 0.9	1.0 (0.5–4.0)	3.5 (1.0–4.0)	2.1 ± 0.7	1.4 ± 0.3	10.5 (9.0–12.0)	5.5 (2.0–9.0)	308 ± 73.7	7.6 ± 4.4	1.8 ± 0.3	NC	313 ± 74.9	NC	502 ± 113	NC	2.1 ± 0.5	2.4 ± 1.1

[a] Values are arithmetic means (± SDs) apart from T_{max} and T_{last}, which are medians (range). Values are reported with three significant figures and/or a maximum of one decimal place.
[b] NC, not calculated.

tween ethnic groups. Nevertheless, no gross differences for any pharmacokinetic parameters were observed for either oseltamivir or OC between the Caucasian and Japanese subjects (Fig. 1 and 2).

Safety. A total of 20 adverse events were reported during the study, all of which were mild to moderate in intensity and resolved without sequelae (Table 4). All but two events were unrelated to the study medication; one chest pain with a remote relationship to oseltamivir and one headache with a possible relationship to oseltamivir. In general, headache, back pain, and post-lumbar-puncture syndrome occurred due to the lumbar puncture procedure. Caffeine and paracetamol were administered to treat these conditions. No deaths, serious adverse events, or withdrawals after drug administration occurred during the study, and there were no clinically relevant changes in vital signs, ECG, or laboratory parameters at follow-up.

DISCUSSION

In the current exploratory study, we evaluated the pharmacokinetics of oseltamivir and OC in the CSF and plasma of healthy Japanese and Caucasian adult volunteers to further our understanding of the CNS penetration of these entities. Concentrations of oseltamivir and OC in CSF were low (mean C_{max}, 2.4 ng/ml for oseltamivir and 19.0 ng/ml for OC in CSF), and maximum concentrations were 2.1% and 3.5% of those attained in plasma, respectively (mean C_{max}, 115 ng/ml for oseltamivir and 544 ng/ml for OC in plasma). Overall exposure was also low in CSF compared with plasma (mean AUC CSF/plasma ratios of 2.4% for oseltamivir and 2.9% for OC). Collectively, these findings demonstrate that the CNS penetration of oseltamivir and OC is low in healthy individuals. The relative C_{max} and AUC_{0-last} oseltamivir/OC ratios in plasma reported in this study are consistent with data from previous studies with healthy volunteers (Roche data on file).

These findings are consistent with two case reports describing CNS penetration in influenza virus-infected individuals (5, 31). These cases comprise examination of the CSF of a 10-year-old male with influenza B virus-associated encephalitis (31) and a postmortem examination of several brain regions from a 13-year-old Japanese male with influenza who had taken a single dose of oseltamivir and subsequently fell to his death from a building (5). In both of these cases, no or low concentrations of oseltamivir or OC were detected in CSF or human brain homogenates (5, 31). Preclinical studies involving rats and ferrets also show uniformly low brain penetration following administration of oseltamivir phosphate (Roche data on file). For oseltamivir, brain exposure in rats after intravenous administration was approximately 20% of plasma values, whereas for OC it was approximately 3%. It should also be noted that these studies employed whole-brain homogenates and that concentrations in tissue may have been overestimated due to confounding by blood vessel content, especially in cases with high plasma-to-brain ratios (Roche data on file). Recent studies in mice showed that access to the CNS by oseltamivir was also restricted by P-glycoprotein (P-gp); it should be noted that in the absence of P-gp in knockout mice, the brain/plasma ratio was still low (around 0.35) (20, 25). The limited access of

OC to brain is thought to be due to its low lipophilicity leading to low passive diffusion across the blood-brain barrier (BBB).

It is recognized that, due to the short time period in which quantifiable concentrations in CSF could be measured, there was a potential for underestimation of CSF AUC_{0-last} values. This could also have led to underestimation of the calculated AUC_{0-last} CSF/plasma ratios. However, it is reassuring that even when a "worst-case scenario" was applied, with the last measurable CSF concentration for each subject extrapolated to the plasma time to last measurable concentration (T_{last}), the AUC_{0-last} values in CSF for the total population for oseltamivir and OC were 14.0 (±3.6) h · ng/ml and 291 (±204) h · ng/ml, respectively. The values remained of the same magnitude as those of the AUC_{0-last} values estimated using the actual CSF T_{last} values, which were 7.6 (±4.4) h · ng/ml for oseltamivir and 151 (±202) h · ng/ml for OC. The corresponding mean (± SD) AUC_{0-last} (CSF)/AUC_{0-last} (plasma) ratios for the total population were still very low when this conservative approach was employed: 4.6% (±1.0%) for oseltamivir and 5.2% (±3.9%) for OC.

No females were available for enrollment within the restraints imposed by the study timelines. This was not expected to affect the outcome of the study, as previous investigations within the wider oseltamivir clinical program have indicated no significant gender differences in the pharmacokinetics of either oseltamivir or OC (Roche data on file).

In the overall study population, oseltamivir was detectable in the CSF for a median duration of 5.5 h and in OC for a median duration of 12.0 h. In one subject, whose first six CSF samples were contaminated with blood, OC persisted in the CSF for 24.0 h. While oseltamivir is a P-gp substrate and is eliminated from the CNS by this transporter, it has been speculated that active efflux of OC from the brain at the BBB may occur via organic anion transporter 3 (OAT3) (25), which is a homologue of OAT1, the mediator of renal tubular secretion of OC (11). OAT3 is expressed at the BBB and actively eliminates organic anions from the brain (15, 16).

Within the limitations of the study design (i.e., exploratory nature and limited sample size), no gross differences in the CSF or plasma pharmacokinetics of oseltamivir or OC were observed between the Caucasian and Japanese subjects. This is consistent with published findings showing no discernible differences in the overall pharmacokinetic profiles of oseltamivir in plasma between Japanese and Caucasian adults (28) and children (7). It has been suggested that genetic variations may contribute to the higher incidence of CNS events reported in certain ethnic groups. For example, Shi et al. postulated that variations in the human carboxylesterases hCES1 and hCES2 could lead to decreased conversion and therefore higher-than-expected systemic concentrations of oseltamivir (30). Utilizing a population pharmacokinetic model, simulations of oseltamivir 75-mg twice-daily dosing without oseltamivir conversion to OC gave steady-state C_{max} values that were around 14-fold higher than those achieved when the metabolic pathway was intact (Roche data on file). Nevertheless, these estimated values were approximately 1.4-fold lower than those observed in a clinical trial of six subjects who received 1,000-mg doses, in which no neuropsychiatric adverse events of note were seen (Roche data on file). Genetic variants of OAT1 (which mediates renal secretion of OC) (1, 4, 19) and P-gp (which controls

TABLE 3. Summary of the pharmacokinetic parameters of OC in plasma and CSF by ethnic group and total population[a]

Group (n)	C_{max} (ng/ml)		T_{max} (h)		C_{last} (ng/ml)		T_{last} (h)		AUC_{0-last} (h · ng/ml)		$t_{1/2}$ (h)		$AUC_{0-\infty}$ (h · ng/ml)		CSF/plasma ratio (%)	
	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	Plasma	CSF	C_{max}	AUC_{0-last}
Caucasian[b] (4)	507 ± 117	17.7 ± 19.7	5.5 (4.0–6.0)	8.0 (7.0–12.0)	56.4 ± 9.8	12.0 ± 1.3	24.0 (24.0–24.0)	12.0 (12.0–24.0)	5,380 ± 1,180	185 ± 297	5.9 ± 0.4	NC[c]	5,860 ± 1,210	NC	3.5 ± 4.2	3.6 ± 6.0
Japanese (4)	581 ± 50.5	20.4 ± 11.3	4.5 (4.0–6.0)	7.5 (6.0–12.0)	44.0 ± 19.4	16.3 ± 7.3	24.0 (24.0–24.0)	12.0 (12.0–12.0)	5,700 ± 826	129 ± 67.6	5.0 ± 0.9	NC	6,030 ± 1,000	NC	3.5 ± 1.7	2.3 ± 1.1
Total (8)	544 ± 92.6	19.0 ± 14.9	5.0 (4.0–6.0)	8.0 (6.0–12.0)	50.2 ± 15.7	14.5 ± 5.7	24.0 (24.0–24.0)	12.0 (12.0–24.0)	5,540 ± 957	157 ± 202	5.4 ± 0.8	NC	5,950 ± 1,030	NC	3.5 ± 2.9	2.9 ± 4.1

[a] Values are arithmetic means (± SDs) apart from T_{max} and T_{last}, which are medians (ranges). Values are reported with three significant figures and/or a maximum of one decimal place.

[b] For one Caucasian subject, all CSF metabolite concentrations were below quantifiable limits and were interpreted as 0 ng/ml; pharmacokinetic parameters for OC in CSF were not calculated, but C_{max} and AUC_{0-last} values of 0 were included in the respective summary statistics for these parameters and were used to calculate the respective CSF/plasma ratios of 0.

[c] NC, not calculated.

TABLE 4. Subjects reporting adverse events by ethnic group and total population

Ethnic group (n)	All body system disorders		No. of subjects with:						
	No. of subjects with ≥1 AE[a]	Total no. of AEs	Nervous system disorders	Gastrointestinal disorders		Musculoskeletal and connective tissue disorders		Injury, poisoning, and procedural complications	Eye disorders
			Headache	Nausea	Vomiting	Back pain	Musculoskeletal stiffness	Post-lumbar-puncture syndrome	Photophobia
Caucasian (4)	2	6	2	1	0	1	1	1	0
Japanese (4)	4	14	4	3	1	2	0	2	1
Total (8)	6	20	6	4	1	3	1	3	1

[a] AE, adverse event.

BBB penetration of oseltamivir) (13, 27) do occur, but alterations to their function as a result have not been demonstrated.

Given the low CSF concentrations observed in subjects in the current study, the potential for oseltamivir and OC to induce or exacerbate CNS dysfunction appears low. Ose et al. have suggested that OC could act on human neuraminidase enzymes (sialidases) in the brain and disrupt the mitochondrial apoptotic pathway in neuronal cell death (25). However, in vitro data suggest that neither oseltamivir nor OC inhibits any of the four human neuraminidases at concentrations of up to 1 mM (32). Furthermore, investigation of 155 different molecular drug targets, covering a broad range of receptors, enzymes, and ion channels, many of which are relevant to the CNS, did not produce any relevant findings, indicating a lack of mechanism for neuropsychiatric adverse events with oseltamivir or OC (18). Clinical data also support the lack of an association between oseltamivir and CNS adverse events in young individuals with influenza. In two Japanese case series, the onset of abnormal or delirious behavior was found to occur both before and after the initiation of oseltamivir therapy (8, 23), suggesting no temporal association between the two events. Epidemiological studies also demonstrate that the incidence of neuropsychiatric adverse events is similar between patients with influenza who receive oseltamivir and those who receive no antiviral (2, 34).

Oseltamivir was well tolerated in this study, with the majority of adverse events related to the continuous indwelling lumbar catheterization lumbar puncture technique used to obtain CSF samples. Methods involving continuous collection of CSF for 12 to 36 h, with up to two sampling periods separated by a 7- to 14-day recovery period, are used in experimental medicine and proof-of-principle studies. They can establish pharmacokinetic-pharmacodynamic models (hence "dynabridging") and downstream (proteomic) effects of drug administration. Continuous indwelling lumbar catheterization has been performed in over 450 healthy volunteers and patients at California Clinical Trials, from 1997 to the present (3). There have been no serious adverse events from these procedures, and the rate of adverse events has been no different from that for single lumbar punctures (14).

This study supports the idea that the CNS penetration of oseltamivir and OC is low in healthy Japanese and Caucasian individuals. Preclinical and clinical data support the idea that oseltamivir and OC have a limited potential to induce or exacerbate CNS adverse events in individuals with influenza. A disease- rather than drug-related effect appears likely.

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