



Role of the *ABCB1* Drug Transporter Polymorphisms in the Pharmacokinetics of Oseltamivir in Humans: a Preliminary Report

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Oseltamivir is a substrate of P-glycoprotein, an efflux drug transporter encoded by *ABCB1*. The objective of this study was to assess the role of *ABCB1* (c.1236C>T, c.2677G>T/A, and c.3435C>T) polymorphisms in the pharmacokinetics of oseltamivir and its active metabolite, oseltamivir carboxylate in humans. Nineteen healthy male subjects were enrolled, and their *ABCB1* polymorphisms were evaluated. After the oral administration of 75 mg oseltamivir, the plasma concentrations of oseltamivir and oseltamivir carboxylate were measured. Pharmacokinetic analysis was carried out. Systemic exposure to oseltamivir and oseltamivir carboxylate was higher in the mutant group than in the wild-type and heterozygous groups. We suggest that *ABCB1* polymorphisms affect the pharmacokinetics of oseltamivir in humans. Further studies in a large population are necessary to validate the results of this preliminary study (Clinical Trial Registration Information [CRIS] registry: <http://cris.nih.gov.kr>, No. KCT0001903).

Keywords: *ABCB1*; P-glycoprotein; Polymorphism; Oseltamivir; Pharmacokinetics

Oseltamivir is a neuraminidase inhibitor that is widely used in prophylaxis and in the treatment of influenza A and B viral infections (1-3). From a pharmacokinetic perspective, oseltamivir is readily absorbed with an oral bioavailability of more than 80%. It is extensively hydrolyzed in the liver to its active metabolite, oseltamivir carboxylate. Oseltamivir carboxylate reaches peak concentrations after 3–4 hours, exceeding the systemic exposure of oseltamivir by > 20-fold. It is eliminated mainly by renal route with an elimination half-life of 6–10 hours (3,4). From a safety perspective, the causal relationships between oseltamivir administration and neuropsychiatric adverse events have been continuously issued up to date, although several studies of neuropsychiatric adverse events with oseltamivir has not established a direct causal relationship (1,2,5-7). The US Food and Drug Administration's adverse events reporting system has warned of high odds ratio scores in oseltamivir-associated neuropsychiatric adverse events such as abnormal behavior (29.35), psychiatric and behavioral symptoms (15.36), delirium (13.50), and hallucinations (12.00) (8).

P-glycoprotein (P-gp) is expressed in the intestinal epithelium, liver, kidney, and blood-brain barrier (BBB) as an efflux transporter by pumping out substrates and resulting in altered substrates' pharmacokinetic characteristics (9,10). A series of preclinical studies were conducted to explore the role of P-gp, which is expressed in the BBB, on the distribution of oseltami-

vir in the brain. In vitro and in vivo studies suggest that oseltamivir might be a substrate of P-gp, encoded by adenosine triphosphate (ATP)-binding cassette subfamily B member 1 (*ABCB1*) gene. By contrast, oseltamivir carboxylate transport by P-gp was negligible in preclinical studies (1,2).

The functional activity of *ABCB1* polymorphisms c.1236C>T, c.2677G>T/A, c.3435C>T, and their substrates' pharmacokinetics have been studied widely, since *ABCB1* polymorphisms are related to dysfunction of P-gp (9-14). In this context, we hypothesized that *ABCB1* polymorphisms might alter systemic exposure to oseltamivir. However, the effect of *ABCB1* polymorphisms on the pharmacokinetics of oseltamivir in humans has not been studied. Therefore, we assessed the potential role of *ABCB1* polymorphisms in altering the pharmacokinetics of oseltamivir.

In total, 19 healthy individuals were enrolled. The study was conducted in accordance with the principles enshrined in the Declaration of Helsinki as well as Good Clinical Practice. All participants were given a 75 mg single oral dose of oseltamivir (Tamiflu®; Roche Korea, Seoul, Korea). Blood samples were collected at scheduled times during the study period: prior to dosing (0 hour), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after drug administration. Blood samples were collected in fluoride-oxalate tubes. Plasma was separated by centrifugation at 1,700 g and 4°C for 15 minutes and stored at -70°C until drug concentration analysis was performed. A blood sample

was drawn from each individual for genetic analysis and stored in ethylenediaminetetraacetic acid (EDTA) at -20°C until DNA extraction was performed.

The plasma concentrations of oseltamivir and oseltamivir carboxylate were analyzed by validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method after protein precipitation with acetonitrile. In brief, plasma samples (0.1 mL) were spiked with an internal standard (10 μL of oseltamivir- d_3 300 ng/mL, and 10 μL of oseltamivir- d_3 carboxylate 4 $\mu\text{g}/\text{mL}$), and 500 μL of methanol. After vigorous vortex mixing, 100 μL of deionized water was added to the 100 μL of supernatant. A 3 μL aliquot of this solution was injected into the LC (Shimadzu Prominence LC; Shimadzu Co., Kyoto, Japan) and

detected by an MS/MS (API5000; AB SCIEX, Foster city, CA, USA) system. Chromatographic separation of the compound was conducted using a T3 column (1.8 μm , 2.1 \times 50 mm) with a mobile phase consisting of acetonitrile including 0.1% formic acid. The mass spectrometer with an electrospray source was run in the positive mode and m/z was 313.25 \rightarrow 225.1 for oseltamivir, 316.25 \rightarrow 228.1 for oseltamivir- d_3 , 285.25 \rightarrow 197.1 for oseltamivir carboxylate, and 288.25 \rightarrow 200 for oseltamivir- d_3 carboxylate. The lower limits of quantification for oseltamivir and oseltamivir carboxylate were 1 ng/mL and 10 ng/mL. Linearity calibration curves were established within the ranges of 1–200 ng/mL for oseltamivir and 10–2,000 ng/mL for oseltamivir carboxylate (coefficients of determination: $r^2 \geq 0.9950$). The respective accuracy

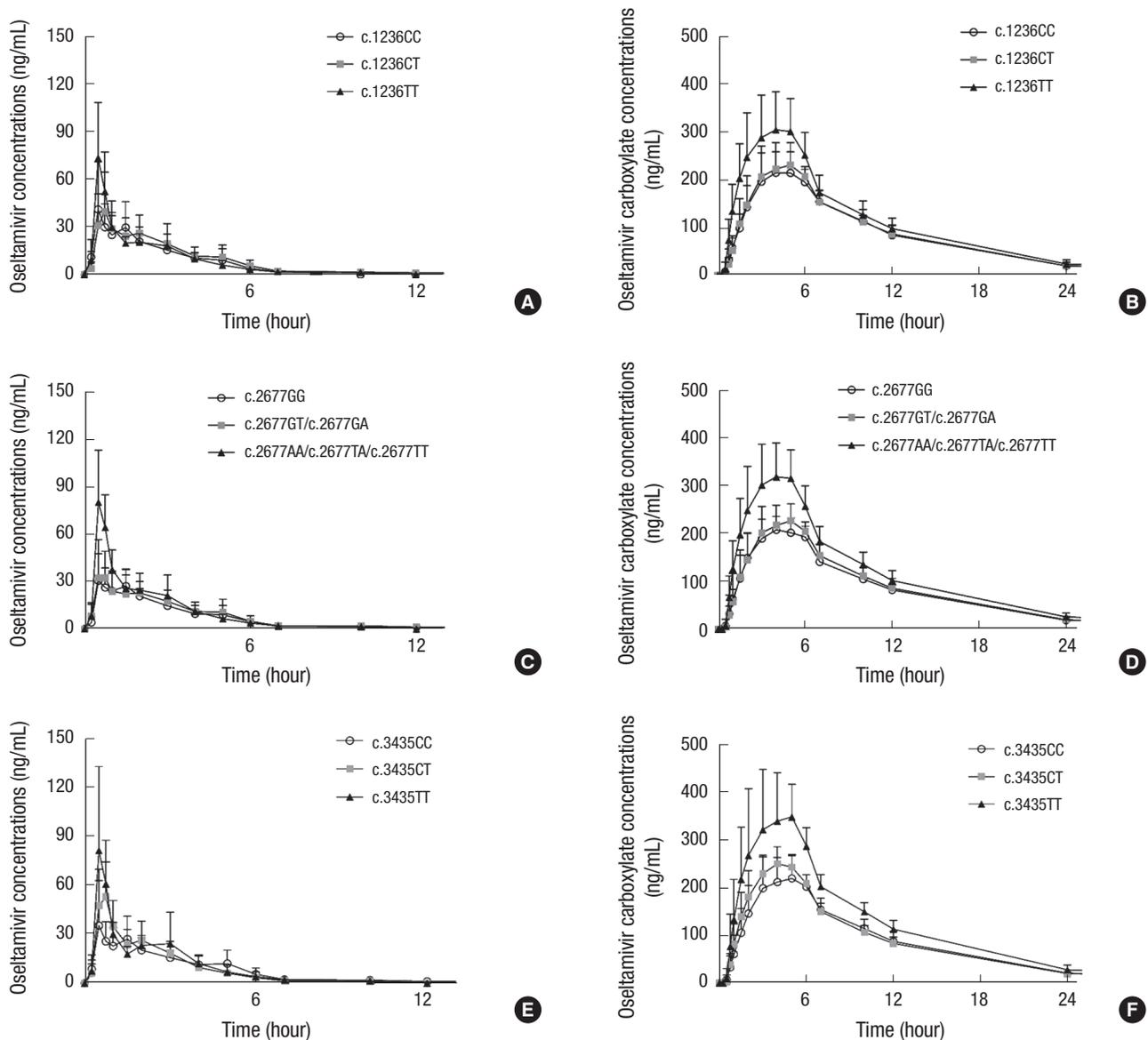


Fig. 1. Mean (\pm SD) plasma concentration profiles of oseltamivir and oseltamivir carboxylate according to *ABCB1* c.1236C>T (A, B), c.2677G>T/A (C, D), and c.3435C>T (E, F) polymorphisms.

SD = standard deviation, *ABCB1* = ATP-binding cassette subfamily B member 1.

levels of oseltamivir and oseltamivir carboxylate ranged from 84.1%–121.4% and 91.4%–114.4%. The respective precision levels of oseltamivir and oseltamivir carboxylate, expressed as coefficients of variation, were 4.4% and 2.6%.

DNA was extracted using standard methods (QIAamp DNA Blood Mini Kit; Qiagen, Hilden, Germany). *ABCB1* polymorphisms c.1236C>T, c.2677G>T/A, and c.3435C>T were genotyped in all subjects by pyrosequencing methods using a Pyrosequencer (Biotage, Uppsala, Sweden), as referenced from a previous study (13). The validity of method was confirmed by direct sequencing.

The pharmacokinetic variables of oseltamivir were estimated by non-compartmental methods using Phoenix[®] version 6.4 (Certara USA Inc., St. Louis, MO, USA). The peak drug concentrations (C_{max}) and the time to reach C_{max} (T_{max}) were obtained. The area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_{inf}) was calculated using the formula:

$$AUC_{inf} = AUC_{last} + C_t/k_e$$

C_t is the final recorded plasma concentration, k_e is the elimination rate constant as determined by the linear regression of the log-linear part of the plasma concentration-time curve, and AUC_{last} is the AUC from time zero to the final measurable time, derived using the linear trapezoidal rule from 0 to 24 hours for oseltamivir and 0 to 48 hours for oseltamivir carboxylate. The elimination half-life ($t_{1/2}$) was calculated as $0.693/k_e$.

Statistical comparisons of pharmacokinetic variables were performed using the Kruskal-Wallis tests, followed by the Mann-Whitney U-test involving post hoc comparisons with a Bonferroni correction. Differences were considered statistically significant when the P value was below 0.05 for the Kruskal-Wallis test and the P value was below 0.017 for the Mann-Whitney U-test involving post hoc comparisons with a Bonferroni correction.

The data were analyzed using IBM SPSS 19.0 for Windows (IBM Corp., Chicago, IL, USA).

The mean oseltamivir and oseltamivir carboxylate plasma concentration profiles for each group are illustrated in Fig. 1. Systemic exposure to oseltamivir and oseltamivir carboxylate was higher in the mutant group than in the wild-type and heterozygous variant groups. For oseltamivir, C_{max} and AUC_{inf} measured in *ABCB1* c.2677G>T/A mutant group were 88%–92% and 26%–36% higher than that measured in the wild-type and heterozygous groups ($P = 0.030$ and $P = 0.034$, respectively). For oseltamivir carboxylate, C_{max} and AUC_{inf} measured in *ABCB1* c.1236C>T mutant group were 31%–41% and 27%–30% higher than that measured in the wild-type and heterozygous groups ($P = 0.040$ and $P = 0.052$, respectively). With regard to *ABCB1* c.2677G>T/A polymorphism, C_{max} and AUC_{inf} measured in mutant group were 37%–58% and 34%–41% higher than that measured in the wild-type and heterozygous groups ($P = 0.002$ and $P = 0.009$, respectively). In terms of *ABCB1* c.3435C>T polymorphism, C_{max} and AUC_{inf} measured in mutant group were 40%–59% and 40%–46% higher than that measured in the wild-type and heterozygous groups ($P = 0.021$ and $P = 0.034$, respectively) (Tables 1-3). No serious adverse events were observed in the current study.

In this study, we provide evidence of a partial contribution of *ABCB1* polymorphisms to the pharmacokinetics of oseltamivir in humans. We found that the systemic exposure to oseltamivir and oseltamivir carboxylate was increased in the mutant group compared to other groups.

The increased systemic exposure to oseltamivir in the mutant group may relate to the findings that oseltamivir is a substrate of P-gp (1,2) and that *ABCB1* polymorphisms are associated with lower intestinal P-gp expression and function (12,13), which results in elevated blood concentration of its substrates. Namely,

Table 1. Pharmacokinetic parameters of oseltamivir and oseltamivir carboxylate in individuals with *ABCB1* (c.1236CC, c.1236CT, and c.1236TT) polymorphisms after oral administration of 75 mg oseltamivir

Parameter	Wild-type	Heterozygous variant	Mutant	P value*	P value [†]		
	c.1236CC (n = 5)	c.1236CT (n = 8)	c.1236TT (n = 6)		A vs. B	B vs. C	A vs. C
Oseltamivir							
$t_{1/2}$, hr	0.93 ± 0.26	1.77 ± 1.12	1.25 ± 0.58	0.453	0.222	0.573	0.792
T_{max} , hr	0.500 (0.5–0.75)	1.125 (0.5–5.0)	0.500 (0.5–0.75)	0.008	0.019	0.013	0.931
C_{max} , ng/mL	49.2 ± 21.7	48.4 ± 18.8	74.9 ± 33.0	0.155	0.943	0.081	0.177
AUC_{inf} , ng·h/mL	102.9 ± 30.6	117.9 ± 18.3	112.3 ± 21.5	0.397	0.284	0.491	0.429
Oseltamivir carboxylate							
$t_{1/2}$, hr	5.66 ± 0.87	5.67 ± 0.63	5.84 ± 0.86	0.984	1.000	0.950	0.931
T_{max} , hr	5.0 (4.0–6.0)	4.0 (3.0–5.0)	5.0 (3.0–5.0)	0.195	0.127	0.662	0.247
C_{max} , ng/mL	226.1 ± 53.9	243.6 ± 26.1	318.1 ± 82.3	0.040	0.435	0.029	0.052
AUC_{inf} , ng·h/mL	2,385.8 ± 491.5	2,438.6 ± 179.6	3,094.9 ± 592.0	0.052	0.435	0.029	0.082

Data are expressed as mean values ± SD, T_{max} as median (minimum–maximum).

ABCB1 = ATP-binding cassette subfamily B member 1, $t_{1/2}$ = half-life, T_{max} = time to C_{max} , C_{max} = peak plasma concentration, AUC_{inf} = area under plasma concentration-time curve from 0 to infinity.

* P values were calculated using the Kruskal-Wallis tests, boldface indicates statistical significance, $P < 0.050$; [†] P values were calculated using the Mann-Whitney U-test with a Bonferroni correction, boldface indicates statistical significance, $P < 0.017$.

Table 2. Pharmacokinetic parameters of oseltamivir and oseltamivir carboxylate in individuals with *ABCB1* (c.2677GG, c.2677GT/c.2677GA, and c.2677AA/c.2677TA/c.2677TT) polymorphisms after oral administration of 75 mg oseltamivir

Parameters	Wild-type	Heterozygous variant	Mutant	<i>P</i> value*	<i>P</i> value†		
	c.2677GG (n = 4)	c.2677GT/c.2677GA (n = 9)	c.2677AA/c.2677TA/c.2677TT (n = 6)		A vs. B	B vs. C	A vs. C
Oseltamivir							
<i>t</i> _{1/2} , hr	1.52 ± 1.18	1.17 ± 0.67	1.62 ± 0.95	0.676	1.000	0.388	0.762
<i>T</i> _{max} , hr	0.625 (0.5–1.5)	0.750 (0.5–5.0)	0.500 (0.5–0.75)	0.481	0.710	0.328	0.610
<i>C</i> _{max} , ng/mL	43.8 ± 14.9	44.8 ± 11.6	84.0 ± 29.9	0.030	0.825	0.018	0.038
<i>AUC</i> _{inf} , ng-h/mL	97.6 ± 23.5	105.1 ± 15.9	132.4 ± 18.2	0.034	0.604	0.026	0.038
Oseltamivir carboxylate							
<i>t</i> _{1/2} , hr	5.62 ± 0.82	5.62 ± 0.76	5.94 ± 0.73	0.789	0.940	0.456	1.000
<i>T</i> _{max} , hr	4.5 (4.0–5.0)	5.0 (3.0–6.0)	4.5 (3.0–5.0)	0.961	1.000	0.864	0.914
<i>C</i> _{max} , ng/mL	209.1 ± 30.2	240.8 ± 27.5	330.6 ± 72.2	0.002	0.076	0.001	0.010
<i>AUC</i> _{inf} , ng-h/mL	2,271.3 ± 331.9	2,403.3 ± 194.7	3,215.4 ± 482.9	0.009	0.414	0.005	0.019

Data are expressed as mean values ± SD, *T*_{max} as median (minimum–maximum).

ABCB1 = ATP-binding cassette subfamily B member 1, *t*_{1/2} = half-life, *T*_{max} = time to *C*_{max}, *C*_{max} = peak plasma concentration, *AUC*_{inf} = area under plasma concentration-time curve from 0 to infinity.

**P* values were calculated using the Kruskal-Wallis tests, boldface indicates statistical significance, *P* < 0.050; †*P* values were calculated using the Mann-Whitney U-test with a Bonferroni correction, boldface indicates statistical significance, *P* < 0.017.

Table 3. Pharmacokinetic parameters of oseltamivir and oseltamivir carboxylate in individuals with *ABCB1* (c.3435CC, c.3435CT, and c.3435TT) and polymorphisms after oral administration of 75 mg oseltamivir

Parameters	Wild-type	Heterozygous variant	Mutant	<i>P</i> value*	<i>P</i> value†		
	c.3435CC (n = 9)	c.3435CT (n = 7)	c.3435TT (n = 3)		A vs. B	B vs. C	A vs. C
Oseltamivir							
<i>t</i> _{1/2} , hr	1.38 ± 0.98	1.34 ± 0.82	1.48 ± 0.82	0.844	0.606	0.833	0.864
<i>T</i> _{max} , hr	0.50 (0.5–5.0)	0.75 (0.5–2.0)	0.50 (0.5–0.75)	0.761	1.000	0.517	0.600
<i>C</i> _{max} , ng/mL	44.7 ± 19.4	61.2 ± 15.7	84.0 ± 47.2	0.066	0.042	0.517	0.145
<i>AUC</i> _{inf} , ng-h/mL	106.0 ± 26.1	113.2 ± 18.4	128.2 ± 15.5	0.274	0.470	0.267	0.209
Oseltamivir carboxylate							
<i>t</i> _{1/2} , hr	5.70 ± 0.67	5.73 ± 0.90	5.78 ± 0.80	0.986	1.000	1.000	0.864
<i>T</i> _{max} , hr	5.0 (3.0–6.0)	4.0 (3.0–5.0)	5.0 (3.0–5.0)	0.401	0.210	0.667	0.727
<i>C</i> _{max} , ng/mL	230.1 ± 42.5	260.2 ± 29.2	365.0 ± 94.3	0.021	0.142	0.033	0.018
<i>AUC</i> _{inf} , ng-h/mL	2,428.3 ± 377.3	2,513.5 ± 303.9	3,519.4 ± 390.6	0.034	0.681	0.017	0.018

Data are expressed as mean values ± SD, *T*_{max} as median (minimum–maximum).

ABCB1 = ATP-binding cassette subfamily B member 1, *t*_{1/2} = half-life, *T*_{max} = time to *C*_{max}, *C*_{max} = peak plasma concentration, *AUC*_{inf} = area under plasma concentration-time curve from 0 to infinity.

**P* values were calculated using the Kruskal-Wallis tests, boldface indicates statistical significance, *P* < 0.050; †*P* values were calculated using the Mann-Whitney U-test with a Bonferroni correction.

we suggest that dysfunction of intestinal P-gp in the mutant group play a role in the increased absorption of oseltamivir since oseltamivir extensively metabolized to oseltamivir carboxylate, and there is minimal renal excretion of unchanged oseltamivir (< 5%) (4).

Notably, increased systemic exposure to oseltamivir carboxylate in the mutant group was also observed despite evidence from preclinical studies, which showed that BBB transfer of oseltamivir carboxylate was not influenced by P-gp, indicating that oseltamivir carboxylate is not a substrate of P-gp (1,2). A plausible explanation for this contradictory result is that the differences in oseltamivir exposure between the mutant group and the other two groups was expected to be manifested in oseltamivir carboxylate exposure differences. This assumption is based on the facts that absorbed oseltamivir is extensively bio-trans-

formed to oseltamivir carboxylate and that the *AUC*_{inf} of oseltamivir carboxylate is much greater (> 20-fold) than that of oseltamivir (3).

The increased systemic exposure to oseltamivir and oseltamivir carboxylate in the mutant group compared to other groups could be important to the safety profiles of oseltamivir. Recently, Morimoto et al. (15) and Nakamura et al. (16) reported that the partial contributions of enhanced serum or plasma concentrations of oseltamivir carboxylate on the neuropsychiatric adverse events that occurred after oseltamivir administration in influenza patients. In addition, a clinical study was conducted to explore the role of *ABCB1* polymorphisms on the incidence of neuropsychiatric adverse events in influenza-infected children treated with oseltamivir. An increased incidence of neuropsychiatric adverse events was reported in *ABCB1* c.2677G>T/

A-c.3435C>T diplotype mutant group compared to wild-type and heterozygous variant groups ($P = 0.149$) (17). Oseltamivir dosages of up to 675 mg were well-tolerated in healthy subjects without drug-related neuropsychiatric adverse events (18). Considering the high safety margin of oseltamivir in clinical studies, there is no need for dose adjustment to avoid unexpected adverse events related to increased oseltamivir or oseltamivir carboxylate exposure according to the *ABCB1* polymorphisms. However, we cannot exclude the possibility that increased systemic exposure to oseltamivir in the *ABCB1* mutant group is one of the factors causing the modified distribution of oseltamivir in the brain that leads to neuropsychiatric adverse events occurring in some people following oseltamivir intake. Particularly in the light of the findings from a clinical study that indicate C_{max} cerebrospinal fluid (CSF)/plasma ratios of 2.1% for oseltamivir and 3.5% for oseltamivir carboxylate, AUC CSF/plasma ratios of 2.4% for oseltamivir and 2.9% for oseltamivir carboxylate (19).

This study has some limitations. Firstly, this study was conducted in a small population. Although differences in the systemic exposure to oseltamivir and oseltamivir carboxylate between groups were statistically significant, each group consisted of less than 10 individuals. Secondly, this study was conducted in healthy subjects. However, pharmacokinetic values have been shown to be similar in healthy subjects and influenza patients, encouraging speculation that similar results can be expected in influenza patients (3). Thirdly, this was a single-dose study. However, the pharmacokinetic values were comparable after single-dose and multiple-dose (twice-daily for 7 days) administration of oseltamivir (50–100 mg), except for the accumulation index of oseltamivir carboxylate, which ranged from 1.57 to 1.74, indicating that oseltamivir carboxylate was accumulated after multiple-dose administration of oseltamivir (20). Therefore, the pharmacokinetic variations of oseltamivir carboxylate between the *ABCB1* mutant group and the other groups observed in this study would be much greater in clinical settings, in which multiple-dose (twice-daily dose of 75 mg for 5 days) administration of oseltamivir is prescribed.

Our findings suggest that *ABCB1* polymorphisms are factors influencing the pharmacokinetics of oseltamivir in the body. Further studies in a large population are necessary to confirm the results of this preliminary study.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Korea University Anam Hospital, Korea University College of Medicine (IRB No. ED15060). Informed consent was submitted by all subjects when they were enrolled. The Clinical Research Information Service (CRIS, <http://cris.nih.go.kr>) identifier is KCT0001903.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Cha YJ. Data curation: Cha YJ. Formal analysis: Cha YJ. Investigation: Cha YJ. Writing - original draft: Cha YJ. Writing - review & editing: Ghim JL.

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