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Pharmacokinetics and Diffusion into Sputum of Oseltamivir and Oseltamivir Carboxylate in Adults with Cystic Fibrosis▽

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Oseltamivir is a prodrug of oseltamivir carboxylate (OC), a neuraminidase inhibitor used for treatment and prevention of influenza. The pharmacokinetics of these 2 compounds were investigated after a single 75-mg oseltamivir dose in 6 patients with cystic fibrosis (CF). Means ± standard deviations of the area under the curve from time zero to infinity (AUC) were 173 ± 58 μg · h/liter for oseltamivir and 2,256 ± 394 μg · h/liter for OC. The concentrations of OC in sputum 4 to 6 h and 22 to 26 h after the intake ranged from 4.1 to 62.2 μg/liter. The AUC of OC was approximately 30% lower than and significantly different from published values for volunteers. On the basis of the present results and because the anti-A/H1N1 influenza virus efficacy of OC is related to its AUC/50% effective concentration (EC_{50}) ratio, an increase in the oseltamivir unitary dose could be considered for the treatment of influenza in CF patients. This should nevertheless be confirmed by a controlled pharmacokinetic study performed on a larger number of patients.

Patients with cystic fibrosis (CF) have chronic lung disease with bacterial infections of the respiratory tract leading to respiratory insufficiency (21). Viral infections due to influenza virus can also contribute to infectious exacerbations, leading to a decrease in respiratory function (2, 5, 9, 20, 27). Although the first clinical reports on 2009 A/H1N1 influenza virus infection in CF patients mostly described mild illnesses (8, 18), the potential implications for a more virulent A/H1N1 influenza virus pandemic in the future are a real concern for the CF community (18). It has furthermore been suggested that early oseltamivir-based treatment of CF patients presenting with an influenza-like illness favorably influenced the outcome (8). Oseltamivir, one of the drugs currently available for the treatment of infections due to influenza viruses, may therefore be an important tool for the management of influenza in CF patients.

However, the adequate dose of oseltamivir to be administered to CF patients is unknown. CF can indeed be associated with modifications in the pharmacokinetics (PK) of drugs, leading to a lower systemic exposure and to a subsequent need for higher doses in order to achieve concentrations similar to those in non-CF subjects (24, 25).

Despite potential interest in its use in CF patients, the PK of oseltamivir in this population are still unknown. There are nevertheless several aspects suggesting that oseltamivir PK might be altered in patients with CF. First, oseltamivir is a prodrug that is converted to the active compound, oseltamivir carboxylate (OC), via first-pass metabolism by hepatic esterases (6). The production of carboxylate could therefore be modified in CF patients since CF can change drug bioavailability (10, 26). Second, the aqueous distribution volume and renal clearance of drugs are often increased in CF patients (24). This could have consequences for OC, which has a volume of distribution of about 25 liters, corresponding to extracellular body water, and is excreted via the kidneys, with a renal clearance corresponding to 93% of the total clearance (6, 11). Last, the activity of hepatic carboxylesterases, the enzymes responsible for the transformation of oseltamivir to OC, is reduced by interleukin-6, a cytokine whose production is increased in CF patients (3, 30). Therefore, the PK of oseltamivir might be modified by CF, with a risk of underexposure possibly leading to inefficacy.

Since the respiratory tract is the primary site of infection and propagation of the influenza virus, an inadequate concentration of OC at this level might also be deleterious in terms of efficacy and because it could create the conditions required to develop viral resistance. Because of this, concentrations of OC in sputum are also of clinical interest. Considering this potential negative impact, we investigated the pharmacokinetics of oseltamivir and oseltamivir carboxylate in plasma and sputum of patients with CF.

MATERIALS AND METHODS

Patients. Six adult patients previously diagnosed with CF (i.e., with sweat chloride concentrations of ≥60 mmol/liter and 2 CF-causing mutations) were included in the study. Age, body weight (BW), serum creatinine level (SCR), and concomitant treatments were noted. Creatinine clearance (CL_{CR}) was calculated for each patient by the use of the Cockcroft-Gault formula. Pregnant women and transplant patients were excluded from the study.

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TABLE 1. Characteristics of the patients[a]

Patient	Age (yr)	BW (kg)	Sex	SCR (μM)	CL_{CR} (ml/min)	Combined drugs
1	20	56.7	M	57	147.6	Salbutamol, fluticasone, salmeterol, ergocalciferol, vitamin E, colistin, pancreatic enzymes, omeprazole
2	17	47	M	61	117.1	Terbutaline, metoclopramide, ergocalciferol, tobramycin, omeprazole, vitamin E, vitamin K, pancreatic enzymes
3	28	48	F	55	102.3	Pancreatic enzymes, insulin, cetirizine, paroxetine, omeprazole
4	33	58	M	75	102.6	Salbutamol, terbutaline, fluticasone, salmeterol, pancreatic enzymes, azithromycin, ceftazidime, netilmicin, ursodesoxycholic acid
5	34	49	F	NA	NA	Fluticasone, salmeterol, salbutamol, azithromycin, ceftazidime, netilmicin
6	33	51	F	69	83.6	Salmeterol, ursodesoxycholic acid, heparin, vitamin E, repaglinide, insulin, aztreonam, acyclovir, netilmicin
Mean ± SD	27.7 ± 7.1	51.6 ± 4.7		63.4 ± 8.4	110.6 ± 23.8	

[a] M, male; F, female; NA, not available.

The protocol was approved by local ethics committee, and all patients signed an individual informed consent before inclusion in the study.

Collection of samples. Under observation, patients received a single 75-mg dose of oseltamivir in its capsule form at time zero. For each patient, 1 ml of whole blood was drawn in fluoride oxalate tubes at times zero (i.e., predose) and 0.5, 1, 2, 4, 6, 8, 12, 24, 30, and 36 h after oseltamivir intake. Samples were centrifuged within 30 min following collection, and the plasma was then separated and aliquoted into 2 polypropylene tubes that were stored at −70°C until analysis.

Two samples of sputum were also obtained from each subject by expectoration with the help of a physiotherapist. The first one was collected at between 2 and 4 h (H2-H4) after oseltamivir intake, and the second one was collected at between 22 and 26 h (H22-H26) after the intake. Sputum samples were diluted to one-half with a solution of acetylcysteine (10% in water; Digest-Eur). A study of oseltamivir stability in sputum performed in our laboratory evidenced that oseltamivir is stable in diluted sputum for at least 1 h at ambient temperature and that no degradation occurs when diluted sputum is frozen at −70°C. So, sputum samples had to be processed and frozen at −70°C within 1 h after collection. The samples were stored under these conditions until analysis.

Drug assay. Samples were analyzed by the use of a liquid chromatography combined with tandem mass spectrometry method. Sputum samples were analyzed as described for plasma samples, and calibration curves as well as quality controls were performed with plasma. Briefly, 100 μl of internal standard (deuterated oseltamivir and OC) were added to 100 μl of each sample. Samples were then precipitated by 500 μl of acetonitrile. The supernatants were evaporated under a stream of nitrogen, and the dry residues were reconstituted with 500 μl of water. Five microliters was injected into the chromatographic system. The chromatographic column was an Atlantis T3 column (2.1 by 100 mm; particle size, 3 μm; Waters). The mobile phase consisted of a mixture of water plus 0.05% of formic acid (solvent A) and methanol plus 0.05% formic acid (solvent B). The initial conditions were 75% solvent A and 25% solvent B for the first 2 min. The proportion was progressively changed to attain 20% solvent A and 80% solvent B at 7 min. Then, the mobile phase was returned to its initial condition for 3 min. These chromatographic conditions allowed ion suppression due to endogenous compounds in plasma and sputum to be avoided. The *m/z* transitions followed were 313.2 to 165.85 for oseltamivir, 316.2 to 168.85 for deuterated oseltamivir, 285.6 to 137.81 for OC, and 288.6 to 140.81 for deuterated OC. The limit of quantification (LOQ) was 1.5 μg/liter for oseltamivir and OC. The intra- and interday precisions and accuracies were lower than 15% over the linear calibration range of the method (1.5 to 150 μg/liter for oseltamivir, 1.5 to 300 μg/liter for OC). The use of deuterated analogs of oseltamivir and oseltamivir carboxylate as internal standards permitted any matrix-related change in the recovery of the 2 compounds from plasma and sputum to be avoided. Consequently, calibration standards and quality controls made in plasma could be used for the quantification of the compounds in sputum. The calculated concentrations in sputum were corrected for the dilution with acetylcysteine.

Pharmacokinetic analysis. Pharmacokinetic parameters were calculated by classical noncompartmental analysis using WinNonLin software (version 6.1; Pharsight Corp., Mountain View, CA). The following parameters were calculated for each patient and each compound: maximal concentration (C_{max}), area under the curve from time zero to infinity (AUC), terminal half-life ($t_{1/2}$), apparent clearance (CL/*F*), and weight-normalized apparent clearance (CL/BW). The dose of OC was derived from the oseltamivir dose using the molecular weights of oseltamivir and OC and assuming a transformation recovery of 100%. AUC was used to facilitate the comparison with literature data, as it can be directly compared to the steady-state area under the curve between 2 drug intakes.

The means of the values of AUC, CL/*F*, and $t_{1/2}$ for the six patients were compared to the means of the values published for healthy volunteers. The bilateral statistical test was based on log-transformed values, with an alpha risk of 5%.

RESULTS

Six patients, three men and three women aged 17 to 34 years, were included in the study. Serum creatinine was measured in five patients; the remaining one had had a normal creatinine level and a similar clinical status 6 months before the study. The patient demographic characteristics are presented in Table 1. Pharmacokinetic parameters for oseltamivir and OC in plasma are displayed in Table 2. One patient (pa-

TABLE 2. Individual pharmacokinetic parameters[a]

Patient	Oseltamivir						Oseltamivir carboxylate						
	C_{max} (μg/liter)	T_{max} (h)	AUC (μg · h/liter)	CL/*F* (liter/h)	V/*F* (liters)	$t_{1/2}$ (h)	C_{max} (μg/liter)	T_{max} (h)	C_{24} (μg/liter)	AUC (μg · h/liter)	CL/*F* (liter/h)	V/*F* (liter)	$t_{1/2}$ (h)
1	121	1.00	288	260	339	1.19	176	4	19.62	2,430	28.1	315	7.78
2	27.7	2.25	139	539	951	2.05	166	6	19.92	2,106	32.4	271	5.80
3	39.6	1	146	514	780	1.03	174	4	9.43	1,850	36.9	343	6.44
4	48.3	0.5	150	499	539	0.96	132	6	26.88	1,928	35.4	355	6.96
5	50.4	2.33	175	429	390	0.53	231	6	36.87	2,926	23.3	257	7.65
6	51.3	2	139	539	537	0.91	261	4	10.7	2,296	29.7	197	4.59
Mean ± SD	56.4 ± 32.9	1.51 ± 0.77	173 ± 58	461 ± 106	589 ± 234	1.22 ± 0.50	190 ± 47	5 ± 1	20.52 ± 10.34	2,256 ± 394	30.9 ± 5.0	290 ± 60	6.54 ± 1.21

[a] T_{max}, time to maximal plasma concentration; C_{24}, concentration observed 24 h after the intake; *V/F*, apparent distribution volume.

TABLE 3. Concentration of oseltamivir carboxylate in respiratory secretions

Patient	OC concn (μg/liter) at:	
	H2-H4	H22-H26
1	10.3	10.8
2	12.1	10.2
3	15.0	4.1
4	11.4	8.80
5	26.0	62.2
6	29.9	32.8
Mean ± SD	17.5 ± 8.4	21.5 ± 22.3

tient 1) had an oseltamivir exposure about twice as high as the five other patients. This difference was, however, not confirmed for OC. Another patient (patient 5) had a slow and delayed absorption compared to the five other subjects. The ranges of apparent clearance of oseltamivir and OC were 260 to 539 liters/h and 23.3 to 36.9 liters/h, respectively. Elimination half-lives were between 0.53 and 2.5 h for oseltamivir and between 4.59 and 7.78 h for OC. The level of OC remained above the LOQ during all sampling periods, with concentrations at 36 h postdose ranging from 3.45 to 13.3 μg/liter. Oseltamivir carboxylate was quantifiable in all sputum samples, and its concentrations in these respiratory secretions are given in Table 3. Oseltamivir was detectable in only 2 sputum samples, corresponding to the H2-H4 sampling times. The measured oseltamivir concentrations in these 2 samples were 2.88 and 1.57 μg/liter. Mean ± standard deviation (SD) ratios of the OC concentration in sputum to that in plasma were 12.8% ± 4.4% at H2-H4 and 111% ± 112% at H22-H26.

The PK parameters obtained for the six patients were compared to the values published for healthy volunteers (Tables 4 and 5). When the study performed in volunteers was conducted on several days, the PK parameters obtained at steady state were used for comparison (7, 19, 22). The average changes in oseltamivir CL/*F*, AUC, and $t_{1/2}$ in the CF patients compared to healthy volunteers were −16.7, +34.2, and −23.3%, respectively. The average changes in OC CL/*F*, AUC, and $t_{1/2}$ in CF patients compared to healthy volunteers were +37.5, −25.2, and +4.3%, respectively. However, mean oseltamivir CL/*F* and AUC (461 liters/h for CL/*F* and 173 μg · h/liter for AUC) were not statistically different from the mean values in healthy subjects (i.e., 608 liters/h for CL/*F* and 133 μg · h/liter for AUC), with *P* values being greater than 0.05 and 0.1, respectively. A finding opposite this is that the mean values of CL/*F* and AUC for OC in CF patients (30.9 liters/h for CL/*F* and 2,256 μg · h/liter for AUC) were statistically significantly different from the mean values in healthy subjects (i.e., 22.4 liters/h for CL/*F* and 3,381 μg · h/liter for AUC), with *P* values being <0.01 and <0.002, respectively. In addition, the mean oseltamivir $t_{1/2}$ in CF patients (1.22 h) was statistically significantly different ($P < 0.02$) from the mean value in healthy volunteers (2.05 h), whereas the mean OC $t_{1/2}$ in CF patients (6.54 h) was not different ($P > 0.2$) from the mean value in healthy subjects (7.03 h).

DISCUSSION

Because of their preexisting respiratory disease and chronic bacterial infection, CF patients are expected to be particularly vulnerable to influenza. Oseltamivir, the benefit of which in treatment of H1N1 influenza virus infection was recently suggested (13), could be a valuable option for the treatment and the prevention of influenza in these patients. It is therefore important to know the pharmacokinetics of oseltamivir and, more particularly, those of OC in this population. This is, to our knowledge, the first report on OC pharmacokinetics in patients with CF.

By comparing our present results with data available for healthy subjects (Tables 4 and 5), the PK of the prodrug seem to be unchanged, despite a statistically significant decrease in $t_{1/2}$, whereas the OC AUC is reduced by about 25 to 30% in CF patients. This result concerning OC is consistent with previous findings for aminoglycosides or beta-lactam antibiotics (14, 16). Such a consistency could be anticipated. Indeed, aminoglycosides, beta-lactams, and OC are hydrophilic drugs characterized by low protein binding and a distribution volume corresponding to extracellular water and are mainly excreted via the kidney without any metabolic transformation. Since CF is associated with an increase in the glomerular filtration rate

TABLE 4. Pharmacokinetic parameters of oseltamivir: present results and comparison with published data[a]

Study or reference	CL/*F*		*V*/*F*		AUC[b]		$t_{1/2}$ (h)	
	Mean (liters/h)	Δ%	Mean (liters)	Δ%	Mean (μg-h/liter)	Δ%	Mean	Δ%
Present study	461 (9.07[c])		589 (11.7[d])		173		1.22	
28	8.29[c]	+5	11.0[d]	+6	NA		1.01	+21
7	550	−16	1,720	−66	152	+14	2.21	−45
19	529	−13	NA		156	+12	2.2	−45
23	642	−28	NA		141	+23	2.30	−47
1	653	−29	1,350	−56	119	+46	1.45	−16
4	600[e]	−23	NA		125	+39	1.33	−8
22	735[e]	−37	NA		102	+71	1.91	−36
15	547[e]	−16	NA		137	+27	2.94	−58

[a] NA, not available; *V*/*F*, apparent distribution volume; *V*/BW, weight-normalized distribution volume; AUC, area under the curve from time zero to infinity for single-dose studies or between two doses at steady state for repeated-dose studies; Δ%, relative change (in percent) compared to the results of the cited study.
[b] Normalized for a 75-mg dose.
[c] The values are CL/BW (in liters/h/kg).
[d] The values are *V*/BW (in liters/kg).
[e] Derived from AUC and dose.

TABLE 5. Pharmacokinetic parameters of oseltamivir carboxylate: present results and comparison with published data[a]

Study or reference	CL/*F*		*V*/*F*		AUC[b]		$t_{1/2}$	
	Mean (liters/h)	Δ%	Mean (liters)	Δ%	Mean (μg · h/liter)	Δ%	Mean (h)	Δ%
Present study	30.9 (0.60[c])		290 (5.61[d])		2,256		6.54	
28	0.42[c]	+43	3.31[d]	+69	NA		5.08	+28
7	24.2	+28	153	+89	3,220	−30	7.44	−12
19	20.7	+49	NA		3,450	−35	6.0	+9
23	21.2	+46	NA		3,310	−32	6.60	−1
1	24.8	+25	213	+36	3,176	−29	6.40	+2
4	23.1	+34	NA		2,950	−24	6.56	0
22	30.1	+3	NA		2,270	−1	9.67	−32
15	12.9	+135	NA		5,290	−57	7.0	−6
12	15.4	+100	NA		4,875	−54	8.60	−24

[a] NA, not available; *V*/*F*, apparent distribution volume; *V*/BW, weight-normalized distribution volume; AUC, area under the curve from time zero to infinity for single-dose studies or between two doses at steady state for repeated-dose studies; Δ%, relative change (in percent) compared to the results of the cited study.
[b] Normalized for a 75-mg dose.
[c] The values are CL/BW (in liters/h/kg).
[d] The values are *V*/BW (in liters/kg).

and in the lean body weight/total body weight ratio, which corresponds to an increase in the proportion of extracellular water volume, hydrophilic drugs are expected to have their distribution volume and systemic clearance increased in patients with CF (24). Interestingly, the elimination half-life of OC was consistent with previous data, which might suggest a proportional increase in its distribution volume and in its clearance. Comparison of OC apparent distribution volumes in our six patients with the few values available in healthy subjects seems to confirm this hypothesis. Furthermore, since the AUC of oseltamivir is at least equal to historical data, it is unlikely that the decrease in OC AUC can be explained by a reduced absorption of oseltamivir. Besides, the nonsignificant change in oseltamivir AUC in CF patients compared to that in healthy subjects does not support a decrease in the production of OC secondary to a decrease in the activity of hepatic esterases, despite the existence of a possible biological rationale for such a phenomenon in CF patients (3, 30). In addition, one could also highlight the increase in inflammatory cytokine production in CF patients that has been described at the pulmonary level, so the possible influence of the pulmonary inflammatory status on the activity of hepatic esterases is uncertain. However, it must be acknowledged that, despite its lack of statistical significance, a mean 34% increase in the oseltamivir AUC was observed in our patients compared to reference values in healthy volunteers (Table 4). So, it is possible that the low number of subjects included in the present study penalized the statistical power of the analysis.

The conflicting results between an unchanged AUC for oseltamivir and a decreased AUC for OC are indeed quite surprising. However, oseltamivir and OC do not have the same physicochemical properties, with OC being much more polar, with a log*P* (where *P* is the octanol-water partition coefficient) value of −2.1 for OC versus a log*P* value of 0.36 for oseltamivir (13). Thus, one can imagine that OC is more sensitive to the modifications in the proportion of extracellular water and in the renal excretion that occur in CF.

The potential consequences of this decrease in OC AUC are unclear since no concentration threshold value for efficacy has been determined to date. It can nevertheless be noted that both plasma and sputum concentrations of OC were several times higher than its reported concentration inhibiting 50% of neuraminidase activity (IC_{50}) against various subtypes of influenza viruses (0.2 to 0.6 μg/liter for H1N1, 2 μg/liter for H5N1) (6). A finding opposite this is that oseltamivir was not quantifiable in most sputum samples. Assuming that oseltamivir has a sputum-to-plasma ratio similar to that of OC, it is very likely the LOQ of our analytical method (i.e., 1.5 μg/liter) was too high to allow its quantification. The concentration of OC in the respiratory secretions is of clinical relevance, since the respiratory tract is the primary site of infection and propagation of the virus. However, although these data about the diffusion of OC in sputum are encouraging, an *in vitro* hollow-fiber infection model has previously evidenced that the ratio of the AUC/concentration reducing the number of PFU by 50% (the 50% effective concentration [EC_{50}]) is the variable correlated with anti-influenza virus A efficacy, with EC_{50}s against the viral strains used ranging from 2 to 29 μg/liter. Besides, the *in vitro* model has shown that the slope of the exposure/response curve was weak, so the concentrations providing the maximal efficacy are several times higher than the EC_{50} (about 25 times the EC_{50}) (17), which would be far above the concentrations of OC in sputum that were observed in the present study. As it is unclear whether these EC_{50}s are relevant *in vivo*, a prospective efficacy study performed in CF patients is therefore warranted to determine the adequate dosage regimen of oseltamivir. Without such data and because of its good safety profile and the linearity of its pharmacokinetics (6, 29), an increase in oseltamivir dose of 35 to 40% should be considered in CF patients in order to balance the 25 to 30% decrease in OC AUC. Consequently, for CF patients with body weights of >40 kg, oseltamivir doses of 100 mg once a day and 100 mg twice daily could be used for prevention and treatment of influenza, respectively. However, because of the low number of subjects and the lack of a control arm, this result needs to be further validated with a higher number of patients by controlled PK studies.

In conclusion, the present study, which was performed with a limited number of noninfected CF patients, suggested the use of a unitary dose greater than the currently recommended 75-mg dose. The appropriate dosing regimen should neverthe-

less be confirmed with a larger panel of CF patients with influenza virus infection.

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