Population Pharmacokinetics (PPK) and Optimal Dosing of Oseltamivir in Patients with End Stage Renal Disease (ESRD) on Hemodialysis

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BACKGROUND

Oseltamivir (Tamiflu®) is an ethyl ester pro-drug that is rapidly absorbed after oral administration and metabolized in the liver to form oseltamivir carboxylate (OC), a potent, stable and selective inhibitor of influenza A and B neuraminidase (NA) enzymes. OC is excreted by the kidney via glomerular filtration and active tubular secretion through the organic anion transport system. ESRD patients are at increased risk of influenza and its complications. There is no consensus on dosing of oseltamivir for treatment and prophylaxis of influenza in ESRD patients on hemodialysis (HD). Different regimens are recommended in US and EU.

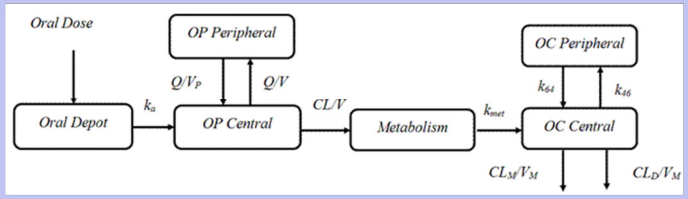
OBJECTIVES

- To characterize the pharmacokinetics (PK) of oseltamivir (OP) and its active metabolite oseltamivir carboxylate (OC) in ESRD patients on HD;
- To propose oseltamivir dosing regimens for treatment and prophylaxis of influenza in ESRD patients on HD.

METHODS

Rich PK data of 24 subjects with ESRD on hemodialysis administered oral oseltamivir 30 mg or 75 mg doses were described by a 5-compartment PPK model. Two compartments with first-order absorption described OP, two compartments described OC, and one compartment described OP to OC metabolism. HD clearance was described by an additional clearance term that was turned on during HD sessions.

Figure 1: Schematic representation of the oseltamivir population PK model



The population PK analysis was conducted via nonlinear mixed-effects modeling, using NONMEM software, version 7.2.0 (ICON Development Solutions). The first-order conditional estimation method with the interaction option (FOCEI) was employed for all model runs.

The extensive model evaluation was performed using diagnostic plots and various visual predictive check (VPC) procedures.

Simulations of several dosing regimens (30 mg after every or every other session) and PK bridging (comparison of exposures with exposures of subjects with normal renal function at recommended doses) were used to select the dosing regimen.

RESULTS

The data set contained 210 and 645 quantifiable plasma samples of OP and OC, respectively, from 24 subjects (Figure 2).

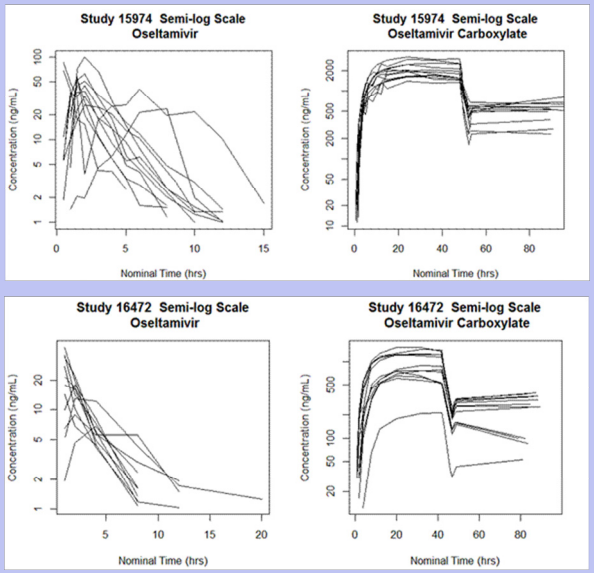
Elimination of oseltamivir was mostly completed before start of dialysis. Therefore, the effect of dialysis on oseltamivir PK parameters cannot be evaluated from the available data. As oseltamivir renal clearance is negligible, ESRD and dialysis are not expected to affect oseltamivir concentrations.

The model with the one-compartment OC part described the data well except the rebound of concentrations after the end of the dialysis. A two compartment OC model explained the rebound by OC re-distribution from the peripheral to central compartment.

REFERENCES

[1] Richard Robson, Adrian Buttimore, Kelvin Lynn, Mike Brewster and Penelope Ward, The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis, Nephrol Dial Transplant (2006) 21: 2556–2562.

Figure 2: Observed data (top: 75 mg oral dose; bottom: 30 mg oral dose).



The parameter estimates are presented in Table 1. OC was very low. The estimate of the dialysis clearance was in an agreement with the literature results [1].

VPC plots (below) indicated a good agreement of the observed and simulated data.

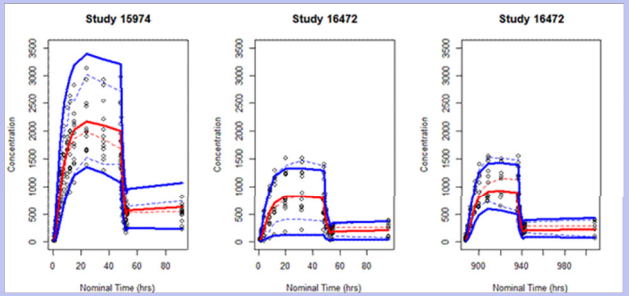
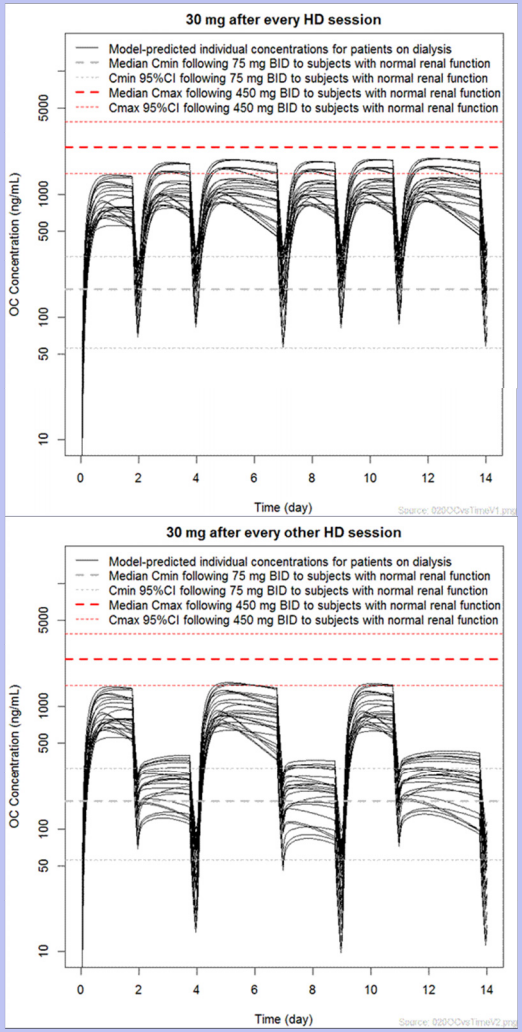


Table 1: Parameter estimates and bootstrap confidence intervals of the PPK model

Parameter	Estimate	95%CI	Variability	Shrinkage
k_a (hr^{-1})	2.94	21.32-21.0	CV=116% (70.2-247)%	25.9%
CL/F (L/hr)	385	294-457		
V/F (L)	1650	1110-2530	CV=59.4% (40.0-75.2)%	9.0%
Q/F (L/hr)	126	75.8-324		
V_P/F (L)	4950	2100-107000		
CL_M/F (L/hr)	0.189	0.0383-0.484	CV=68.1% (50.5-209)%	7.1%
CL_D/F (L/hr)	7.43	5.74-9.34	CV=25.9% (17.6-31.5)%	7.4%
V_M/F (L)	16.1	11.1-20	CV=27.2% (19.3-31.8)%	1.6%
k_{46} (hr^{-1})	0.213	0.131-0.453		
k_{64} (hr^{-1})	0.512	0.366-0.849		
k_{met} (hr^{-1})	0.218	0.17-0.302		
$\sigma_{OP\text{-}prop}$	CV=84.4%	64.7-101 %		1.4%
$\sigma_{OC\text{-}10}$	CV=130 %	103-262%		6.9%
$\sigma_{OC\text{-}inf}$	CV=7.4%	3.4 - 8.9 %		

Figure 3: Conditional Predictions of Oseltamivir Carboxylate Concentrations Following Administration of 30 mg Oseltamivir



CONCLUSIONS

- The results of the analysis support a regimen of 30 mg oseltamivir administered after each dialysis session for treatment of influenza in subjects with ESRD on hemodialysis. The previously recommended dose of 30 mg after alternate sessions would provide sub-therapeutic C_{min} coverage.
- A 30 mg dose administered after alternate hemodialysis sessions, as currently recommended, is sufficient for prophylaxis.
- If the treatment is initiated between the dialysis sessions, the post-HD session dose should be administered independently of the treatment initiation time.
- Dialysis had no clinically relevant influence on oseltamivir exposure.