Population Pharmacokinetics (PPK) and Optimal Dosing of Oseltamivir Administered IV and Orally to Healthy Subjects and Subjects with Renal Impairment

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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. While conversion to OC in the liver is rapid, release of OC from the hepatocyte is the rate-limiting step. Data from two studies that evaluated oseltamivir pharmacokinetics (PK) following oseltamivir i.v. administration to healthy volunteers and patients with normal and impaired renal function were available. There were too few subjects with severe renal impairment in the i.v. studies to reliably estimate the impact of severe renal impairment on OC pharmacokinetics. Therefore, following completion of the analysis of the i.v. studies, data from eight studies with oral oseltamivir administration that included patients with renal impairment were added to confirm the influence of renal impairment on OC pharmacokinetics.

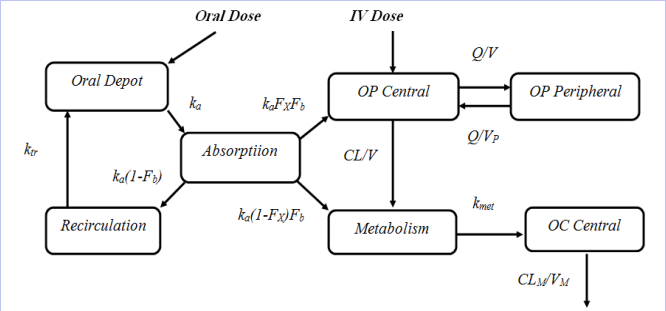
OBJECTIVES

- To characterize the pharmacokinetics of oseltamivir phosphate (OP) and its active metabolite OC following IV and oral administration in patients with normal renal function and with various degrees of renal impairment;
- To propose oseltamivir IV dosing regimens for treatment of influenza in patients with normal renal function and with various degrees of renal impairment.

METHODS

Initially, data of 149 subjects with normal renal function and mild to severe renal impairment administered 40 to 200 mg oseltamivir IV were described by a 4-compartment model. Two compartments described OP, one compartment described OC, and one compartment described OP to OC metabolism (Figure 1). Then, data of 128 subjects administered 20 to 1000 mg oseltamivir orally were added. The absorption model consisted of absorption and recirculation compartments with the direct (via first-pass) and indirect (via oseltamivir) input in the OC compartment.

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.

To assess optimal doses of oseltamivir in subjects with different degrees of renal impairment, for various dosing regimens OP and OC concentrations were simulated over time. Metrics of steady-state exposure (C_{max}, C_{min} and AUC) were computed. Values of creatinine clearance for simulations were sampled from the uniform random distribution restricted to the range from 10 to 150 mL/min. The distributions of simulated exposures were compared with historical exposures following oral administration in adults. Doses were selected to match the exposure in adults with normal renal function administered 75 mg BID regimen.

RESULTS

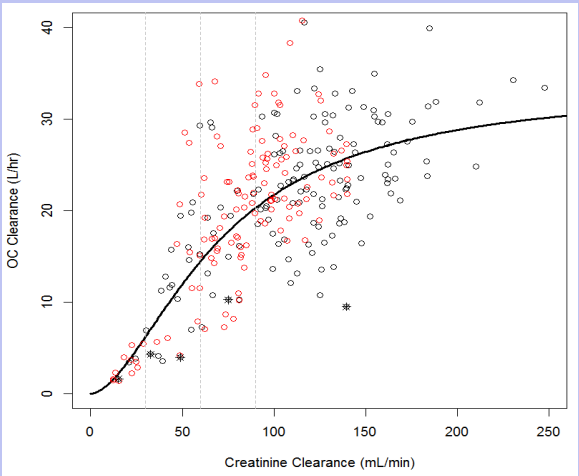
The i.v. data contributed 1,597 and 1,873 plasma concentrations of OP and OC, respectively, from 149 subjects. The oral data added 1,957 and 2,418 concentrations from 128 subjects. Although all renal impairment groups were represented in both datasets, there were only 4 subjects with severe renal impairment in the i.v. dataset. The oral data added 11 subjects with severe renal impairment. The addition of the oral dataset to the i.v. dataset also significantly increased the number of subjects in the other renal impairment groups.

The final covariate i.v. model included the effect of creatinine clearance (CL_{CR}) on CL, CL_M and k_{met}, and the effect of age >80 years old on CL_M. The main effect, influence of CL_{CR} on CL_M, was implemented as the Hill function of CL_{CR} :

$$CL_M = \frac{CL_{M-EMAX} CL_{CR}^{CLM-Hill}}{CL_{M-EC50}^{CLM-Hill} + CL_{CR}^{CLM-Hill}}$$

Figure 2: Dependence of CL_M on creatinine clearance

Line: model predictions; circles: conditional estimates of the model;
black: IV administration; red: oral administration; stars: age > 80 years.

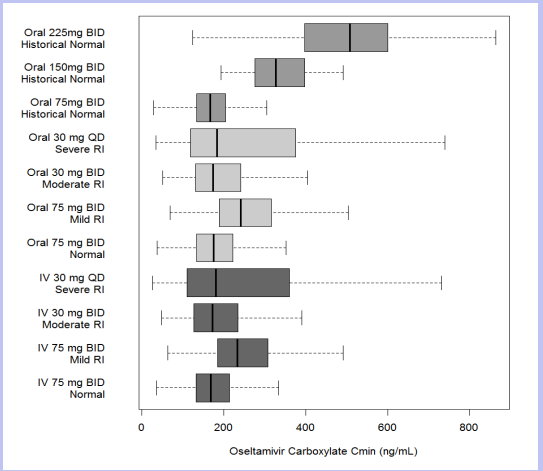


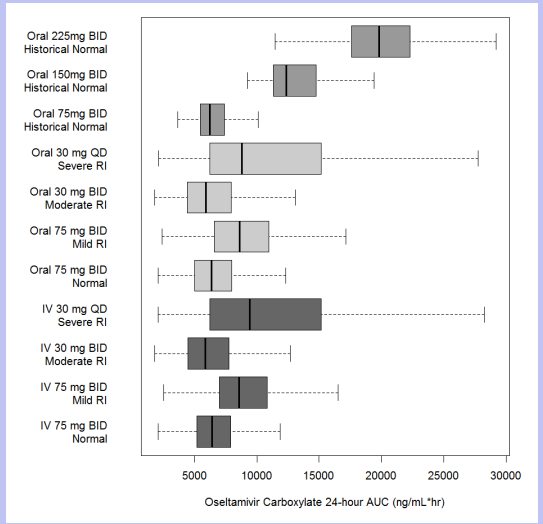
The parameter estimates are presented in Table 1.

Table 1: Parameter estimates of the oseltamivir population PK model

Parameter	Estimate	95%CI	Variability	Shrinkage
CL (L/hr)	184	173 - 195	CV=24.2%	6.1%
Γ	0.236	0.16 - 0.313	$CL_{OP}=CL\cdot(CL_{CR}/100)^{\gamma}$	
V (L)	25.0	20.4 - 29.5		
Q (L/hr)	92.5	85.6 - 99.3		
V_P (L)	122	115 - 129		
V_M (L)	8.91	8.55 - 9.27		
k_{met}	0.0998	0.0954 - 0.104	CV=27.5%	6.3%
$CL_{M\text{-}Emax}$ (L/hr)	33.5	28.3 - 38.8	CV=35.0%	1.2%
β	1.73	1.43 - 2.03	$CL_{OC}= CL_{M\text{-}Emax}(CL_{CR}/100)^{\beta}/[(CL_{M\text{-}EC50}/100)^{\beta}+(CL_{CR}/100)^{\beta}]$	
$CL_{M\text{-}EC50}$	70.4	54.7 - 86		
$CL_{M\text{-}AGE>80}$	0.506	0.302 - 0.71		
$k_{met\text{-}CRCL}$	0.107	0.0349 - 0.18		
k_a (1/hr)	1.63	1.47 - 1.78	CV=44.2%	35.9%
F_X	0.282	0.264 - 0.301		
k_{tr2}	0.0399	0.0359 - 0.0439		
F_b	0.874	0.868 - 0.879		

Figure 3: Comparison of predicted steady-state OC C_{min} and AUC with historical oral data for adult patients with normal renal function (RI)





CONCLUSIONS

Similarly to oral dosing, IV dosing regimens of 75 mg BID, 75 mg BID, 30 mg BID, and 30 mg QD can be recommended for treatment of influenza in subjects with normal renal function, mild, moderate, and severe renal impairment, respectively.

REFERENCES

[1] Rayner CR, Chanu P, Gieschke R, Boak LM, Jonsson EN (2008) Population pharmacokinetics of oseltamivir when coadministered with probenecid. J Clin Pharmacol 48(8):935–947

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