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

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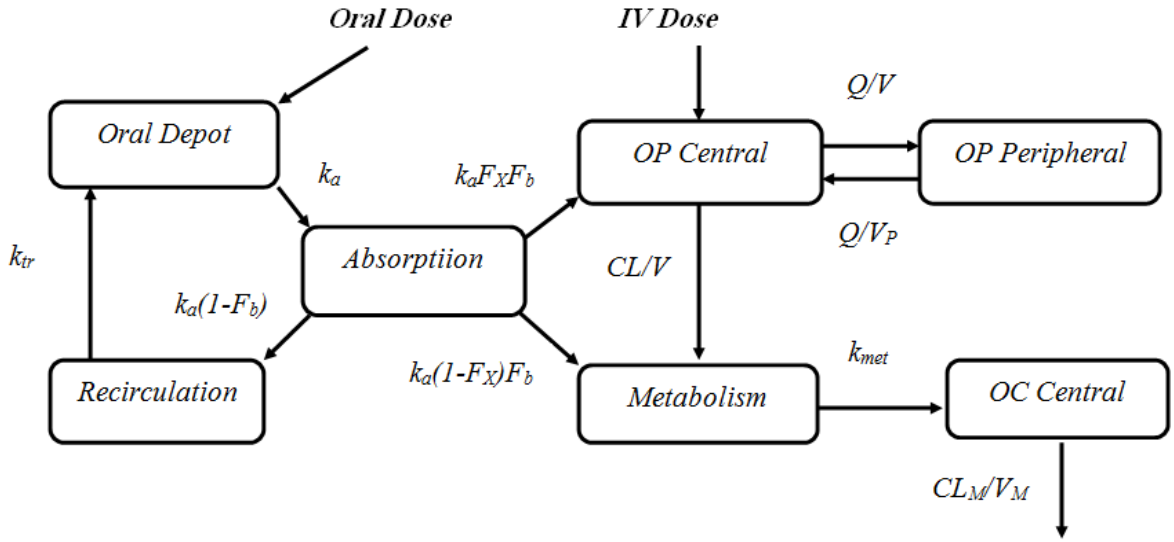
Objectives: To characterize the pharmacokinetics of oseltamivir phosphate (OP) and its active metabolite oseltamivir carboxylate (OC) and propose oseltamivir IV dosing regimens for treatment of influenza in patients with normal renal function and with various degrees of renal impairment.

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. Simulations and PK bridging were used to recommend the IV dosing regimens.

Results: Renal function had a major effect on OC clearance (CL_M) and exposure. CL_M for subjects with mild, moderate, and severe renal impatient was, respectively, 18%, 51%, and 84% lower than for subjects with normal renal function. Simulations indicated that 75 mg IV BID dose administered to subjects with normal renal function or subjects with mild renal impairment, 30 mg IV BID dose administered to subjects with moderate renal impairment, and 30 mg IV QD dose administered to subjects with severe renal impairment provides OC C_{min} coverage and exposures that are comparable to that of 75 mg BID oral dose administered to subjects with normal renal function.

Conclusions: Similar 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.

Figure 1. Diagram and Parameters of the Population PK Model for Oseltamivir



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		