

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

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Objectives: 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 HD. Different regimens are recommended in US and EU. We aimed to characterize the pharmacokinetics oseltamivir phosphate (OP) and its active metabolite oseltamivir carboxylate (OC) and propose optimal oseltamivir dosing regimens in this patient population.

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 term that was turned on during HD sessions. Simulations of several dosing regimens (30 mg after every or every other session) and PK bridging (comparison of exposures to that for subjects with normal renal function at recommended doses) were used to select the dosing regimen.

Results: OC clearance in ESRD subjects was very low. For a typical subject, OC apparent clearance was estimated at $CL_M/F=0.189L/hr$ (95% CI: 0.0383-0.484L/hr), while apparent HD clearance was $CL_{HD}/F=7.43L/hr$ (95% CI: 5.74-9.34L/hr). Simulated concentration-time profiles (Figure 1) and bridging indicated the adequate OC exposure following 30 mg dose administered after every HD session. HD had no clinically relevant influence on OP exposure.

Conclusions: 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. If the treatment is initiated between the dialysis sessions, the post-HD session dose should also be administered independently of the treatment initiation time. A 30 mg dose administered after alternate hemodialysis sessions, as currently recommended, is sufficient for prophylaxis.

Figure 1. Conditional Predictions of OC Concentrations Following Administration of 30 mg Oseltamivir after Every HD Session

