A Semi-mechanistic Pharmacokinetic-Enzyme Turnover Model for Dichloroacetic Acid Auto-inhibition in Rats

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Objective: Dichloroacetic acid (DCA) is a pyruvate dehydrogenase kinase (PDK) inhibitor that has been used to treat congenital or acquired lactic acidosis in children and is currently in early phase clinical trials for cancer treatment. DCA was found to inhibit its own metabolism by irreversibly inactivating glutathione transferase zeta (GSTZ1-1), resulting in non-linear kinetics and abnormally high accumulation ratio after repeated dosing. The aim of this analysis was to develop a semi-mechanistic pharmacokinetic-enzyme turnover model for DCA to characterize the unusual nonlinear pharmacokinetic of DCA observed in rats.

Methods: 20 rats received oral doses of 50 mg/kg DCA once daily for one or two days. Blood samples were collected 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post dose. Population pharmacokinetic analysis was performed in NONMEM 7.3 to characterize the observed plasma concentration-time profiles of DCA in rats. A one compartment disposition model combined with an enzyme turnover model was used to describe the dramatic reduction in clearance after repeated DCA dosing. To account for the double peaks observed in DCA absorption phase possibly caused by gastrointestinal region-dependent absorption, a sequential first order absorption model was implemented.

Results: The intrinsic DCA hepatic clearance decreased from 1.26L/h after first dose to 0.017L/h dose after second dose. The rate constant for DCA induced GSTZ1-1 inactivation (0.85 /h) is 97 times that of the rate constant for GSTZ1-1 natural degradation (0.00875 /h). The DCA concentration that corresponds to 50% of maximum enzyme inhibition (EC50) is 3.44 mg/L. 98.7% of the total clearance is inhibited by DCA according to model estimates. The remaining clearance that is unaffected by DCA indicated alternative metabolic pathways for DCA apart from GSTZ1-1 mediated metabolism.

Conclusions: The proposed semi-mechanistic pharmacokinetic-enzyme turnover model was able to capture DCA auto-inhibition, gastrointestinal region-dependent absorption, and time dependent change in bioavailability in rats. The constructed PK-enzyme turnover model, when scaled up to human, could be used to predict the accumulation of DCA after repeated oral dosing, guide selection of dosing regimens in clinical studies, and facilitate clinical development of DCA.