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Poster presentation

Viciriviroc, A Novel CCR5 Inhibitor, is NOT A p-glycoprotein Substrate In Vitro

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The CCR5 chemokine receptor is a promising target for antiretroviral therapy because of its role as a coreceptor for HIV entry and propagation of infection. Viciriviroc, a small molecule CCR5 inhibitor being studied in clinical trials, is well absorbed in rats and monkeys; in vitro studies were performed with caco-2 cells to determine its bi-directional permeability and potential as a p-glycoprotein (pGp) efflux substrate.

Caco-2 cells (passage 60 to 61) were grown for 3 weeks to confluency and the integrity of the monolayer was confirmed by TEER measurements in the presence of viciriviroc (50 to 400 mM). For bi-directional permeability studies, viciriviroc was placed on either the apical (A) or basolateral (B) compartment at a concentration of 40 mM and permeability (n = 3) was determined over 2 hrs with an LC/MS/MS assay. Total recovery exceeded 85% in all studies. The passive permeability (A to B) performance of the caco-2 cell monolayers were confirmed with atenolol (Pc = 3 ± 1.7 nm/s) and pindolol (Pc = 200 ± 9 nm/s). Functional expression of pGp was confirmed with the standard pGp substrate digoxin (bi-directional efflux ratios: 4- to 10-fold).

Viciriviroc showed high A to B permeability (Pc = 400 ± 4 nm/s) consistent with its high in vivo oral absorption. The bi-directional efflux ratio of viciriviroc was only 0.6 indicating that it is not a pGp substrate in vitro. These data suggested that pGp is unlikely to affect the oral absorption of viciriviroc and that co-administration of viciriviroc with a pGp inhibitor is unlikely to cause significant drug-drug interactions.