Determination of the inhibitory potencies of p-glycoprotein inhibitors by transcellular permeability of Caco-2 cells

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Purpose: P-glycoprotein (P-gp, MDR1, ABCB1) is a multidrug efflux transporter that has a defined role in the absorption and disposition of many substrate drugs. P-gp inhibition has been proposed for use as an adjuvant therapy to treat diseases that involve drug transporter mediated resistance and to boost the oral bioavailability of a substrate drug. Also, it may be possible to use P-gp inhibitors as PET tracers to study P-gp distribution and function in vivo. However, PET tracers require a high affinity to their target. This present study was performed to rank various first, second and third generation P-gp inhibitors according to their potency in order to inform selection of appropriate inhibitors for further in-vivo/in-vitro experiments.

Methods: A Caco-2 cell monolayer transport model was employed [1] and the apparent permeability (Papp) of the prototypic P-gp substrate digoxin (1μM) and imatinib (1μM) was determined in the basal to apical (B-A) and the apical to basal direction (A-B). The efflux ratio was calculated by the Papp_{B-A} divided by the Papp_{A-B}. The IC_{50} values were determined for the P-gp inhibitors by measuring the basolateral to apical transport of digoxin or imatinib. Results are expressed as the mean IC_{50} (±SD) from at least three experiments, using seven different concentrations of each inhibitor.

Results: The efflux ratio of digoxin was 7.6 with Papp_{B-A} of 11.9x10^{-6} cm.s^{-1} and Papp_{A-B} of 1.6x10^{-6} cm.s^{-1}. The efflux ratio of imatinib was 4.4 with Papp_{B-A} of 27.6 x10^{-6} cm.s^{-1} and Papp_{A-B} of 6.3 x10^{-6} cm.s^{-1}. This confirmed that digoxin and imatinib were suitable P-gp substrates in this transport system. Rank order of potency of P-gp inhibitors (low to high) was as follows for inhibition of digoxin transport: verapamil 4.3μM (± 0.02μM) < dipyridamole 2.4μM (± 0.64μM) < cyclosporine A 2.3μM (± 0.42μM) < laniquidar 443nM (± 47.5nM) < PSC-833 91nM (± 24nM) < elacridar 15.6nM (± 5.5nM) < tariquidar 12.9nM (± 1.7nM). The potency of tariquidar inhibition on imatinib transport was 14.5nM (± 10nM).

Conclusions: Tariquidar and elacridar were the most potent inhibitors of P-gp studied and tariquidar inhibition potency was not substrate dependent. These inhibitors now warrant further investigation into their therapeutic potential and use as in-vivo probes.

Elsby, R., et al., Validation and application of Caco-2 assays for the in vitro evaluation of development candidate drugs as substrates or inhibitors of P-glycoprotein to support regulatory submissions. Xenobiotica, 2008. 38(7-8): p. 1140-64.