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Amino acid prodrug of quinidine: An approach to circumvent P-glycoprotein mediated cellular efflux

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This research is directed to investigate the effect of large neutral amino acid modification in overcoming P-gp mediated cellular efflux of quinidine. L-isoleucine ester prodrug of quinidine (Ile-quinidine) was synthesized in our laboratory. [14C]-Erythromycin was selected as a model substrate to study interaction of quinidine and Ile-quinidine with P-gp. Transport studies were conducted to delineate translocation kinetics of quinidine and Ile-quinidine in MDCK-MDR1 cells. [14C]-Erythromycinuptake was enhanced significantly in the presence of quinidine (25 and 50μM). However,[14C]-Erythromycin uptake remained fairly constant in presence of Ile-quinidine (25 μM). Apparent A-B and B-A permeabilities of quinidine observed in MDCK-MDR1 cells were $1.6 \pm 0.2 \times 10^{-6}$ and $7.0 \pm 0.4 \times 10^{-6}$cm/s, a 4.4-fold difference. Apparent permeabilities of Ile-quinidine observed in A-B and B-A transport study were $4.3 \pm 0.9 \times 10^{-6}$ and $5.5 \pm 0.4 \times 10^{-6}$ cm/s, a 1.3-fold difference. Importantly, A-B transport of Ile-quinidine did not change dramatically in the presence of cyclosporine and GF 120918. Based on these results, it was apparent that quinidine displayed higher substrate affinity towards P-gp relative to Ile-quinidine. Chemical or enzymatic hydrolysis of Ile-quinidine resulted in regeneration of low quantities of quinidine during transport studies. In conclusion, chemical modification of quinidine with neutral amino acids results in circumvention of P-gp mediated drug efflux. Hence, amino acid modified prodrugs might be a viable strategy for improving drug accumulation in P-gp over expressing ocular tissues..

Biography

Mitesh Patel is currently pursuing Ph.D. from University of Missouri-Kansas City, Missouri. He is working on transporter targeted drug delivery, transport and pharmacokinetics. His area of research focuses on amino acid and peptide derivatization of drugs to improve cellular permeability in P-gp and MRPs over expressing tissues. He currently has seven research manuscripts, seven book chapters and has presented more than fifteen posters in national and regional meetings.

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