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EVALUATION OF P-GLYCOPROTEIN-MEDIATED TRANSPORT OF ESTER PRODRUGS AND EXPRESSION OF ESTERASES IN LLC-GA5-COL300 CELLS

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ABSTRACT

Prodrugs introduced ester linkage improve oral bioavailability due to increasing hydrophobicity. However, ester modification possibly alters an affinity for P-glycoprotein (P-gp), an efflux transporter, which could lead to failure of prodrug approach. In this study, we evaluated P-gp-mediated transport of two model prodrugs using cell monolayers of LLC-PK1 and LLC-GA5-COL300 that expresses human P-gp. We selected fexofenadine (FXD), a P-gp substrate, and fluphenazine (FPZ), a P-gp inhibitor but a poor substrate, as a model active drug.

Ethyl-FXD, a prodrug of FXD, was equally permeated in both cells, but it inhibited transport of taxol, a P-gp substrate. As shown in Fig. 1, the modification of carboxyl group in FXD leads to the conversion from P-gp substrate to inhibitor. In contrast, caproyl-FPZ, a prodrug of FPZ, was transported by P-gp. FPZ converted from P-gp inhibitor to substrate by esterification of hydroxyl group in FPZ molecule. Consequently, it is found that hydroxyl and carboxyl groups are important for the molecular recognition by P-gp. Prodrug approach is successful for FXD, but inappropriate for FPZ. Furthermore, we found the abundant induction of carboxylesterase in LLC-GA5-COL300 by the expression of human P-gp in LLC-PK1 cell. Long-term culture with colchicine to maintain expression of P-gp partially participated in the induction of carboxylesterase. This might cause erroneous results due to hydrolysis of prodrugs during transport.

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