Role of P-glycoprotein in the uptake/efflux transport of oral vitamin K antagonists and rivaroxaban through the Caco-2 cell model

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Vitamin K antagonists (VKAs) are prescribed worldwide and remain the oral anticoagulant of choice. These drugs are characterized by a narrow therapeutic index and a large inter- and intra-individual variability. P-glycoprotein could contribute to this variability. The aim of this study was to investigate the involvement of P-gp in the transport of acenocoumarol, phenprocoumon and warfarin using an in vitro Caco-2 cell monolayer model. These results were compared with those obtained with rivaroxaban, a new oral anticoagulant known to be a P-gp substrate. The transport of these four drugs was assessed at pH conditions 6.8/7.4 in the presence or absence of the P-gp inhibitor ciclosporine A (10 μM) and the more potent and specific P-gp inhibitor valspodar (5 μM). Analytical quantification was performed by LC/MS. With an efflux ratio of 1.7 and a significant decrease in the efflux (Papp B-A), in the presence of P-gp inhibitors at a concentration of 50 μM, acenocoumarol can be considered as a weak P-gp substrate. Concerning phenprocoumon, the results suggest that this molecule is a poor P-gp substrate. The P-gp inhibitors did not affect significantly the transport of warfarin. The efflux of rivaroxaban was strongly inhibited by the two P-gp inhibitors. In conclusion, none of the three VKAs tested are strong P-gp substrates. However, acenocoumarol can be considered as a weak P-gp substrate and phenprocoumon as a poor P-gp substrate.

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