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

Liliane Gschwind, Victoria Rollason, Youssef Daali, Pascal Bonnabry, Pierre Dayer, Jules Desmeules

Division of clinical pharmacology and toxicology, Geneva University Hospitals and School of pharmaceutical sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

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 cyclosporine 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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Contact: Liliane.Gschwind@hcuge.ch