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Drug-Drug Plasma Protein Binding Interactions of Ivacaftor

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Abstract : Ivacaftor is a novel CF trans-membrane conductance regulator (CFTR) potentiator that improves the pulmonary function for cystic fibrosis patients bearing a G551D CFTR-protein mutation. Because ivacaftor is highly bound (>97%) to plasma proteins, there is the strong possibility that co-administered CF drugs that compete for the same plasma protein binding sites and impact the free drug concentration. This in turn could lead to drastic changes in the in vivo efficacy of ivacaftor and therapeutic outcomes. This study compares the binding affinity of ivacaftor and co-administered CF drugs for human serum albumin (HSA) and α1-acid glycoprotein (AGP) using surface plasmon resonance and fluorimetric binding assays that measure the displacement of site selective probes. Due to their high plasma protein binding affinities, drug-drug interactions between ivacaftor are to be expected with ducosate, montelukast, ibuprofen, dicloxacillin, omeprazole and loratadine. The significance of these drug-drug interactions is interpreted in terms of the pharmacodynamic/pharmacokinetic parameters and molecular docking simulations. The translational outcomes of the data are presented as recommendations for a staggered treatment regimen for future clinical trials which aims to maximize the effective free drug concentration and clinical efficacy of ivacaftor.

Keywords : human α-1-acid glycoprotein, binding affinity, human serum albumin, ivacaftor, cystic fibrosis
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