일반연제 2

Lansoprazole Activation of CYP2C9-Catalyzed Metabolism: Evidence for Stereoselective/Substrate-Specific Activation and a Two-Site Model

Kwang-Hyeon Liu, Min-Jung Kim, In-June Cha, Jae-Gook Shin

Department of Pharmacology and Pharmacogenomics Research Center,
Inje University College of Medicine, Busan, Korea

In the previous study we reported that *R*-lansoprazole activate CYP2C9-catalyzed tolbutamide 4-methylhydroxylation. To further explore the activation of CYP2C9-mediated metabolism by lansoprazole, we evaluated the stereospecific activation for different CYP2C9 substrates using human liver microsomes *in vitro*. For the CYP2C9-catalyzed tolbutamide 4-methylhydroxylation and phenytoin 4-hydroxylation, only *R*-lansoprazole showed stereospecific activation (140% and 550% of control, respectively) whereas *S*- lansoprazole showed inhibition (IC_{50} 54.0 μM) and no effect, respectively. Additionally, hydroxylansoprazole formation was measured from incubations containing phenytoin, exhibiting a kinetic profile that was minimally affected by the presence of phenytoin. Racemic lansoprazole and its enantiomers inhibited CYP2C9-catalyzed warfarin 7-hydroxylation (IC_{50}s 59.4~71.8 μM). For the CYP2C9-catalyzed diclofenac 4-hydroxylation, only *S*-lansoprazole showed stereospecific inhibition (IC_{50} 80.6 μM) whereas racemic lansoprazole and *R*-lansoprazole didn't show inhibition or activation. Overall, these results suggest that *R*-lansoprazole activates CYP2C9-mediated metabolism in a substrate-specific manner by binding within the active site and causing positive cooperativity, thus lending further support to a two-site binding model of CYP2C9-mediated metabolism.