

P-84

**STEREOSELECTIVE METABOLISM AND INHIBITION OF
LANSOPRAZOLE ENANTIOMERS ON HUMAN LIVER CYPs.**Kyung-Ah Kim, Young-Ran Yoon, and Jae-Gook ShinDepartment of Pharmacology, Inje University College of Medicine, 633-165, Gaegum-dong,
Pusanjin-gu, Pusan 614-735, Korea

E-mail: phshinjg@ijnrc.inje.ac.kr

Stereoselective metabolism and inhibitory potential of lansoprazole enantiomers were evaluated from the incubational studies of human liver microsomes and cDNA-expressed CYP isoforms *in vitro*. The formation of lansoprazole sulfone from both enantiomers appeared to be catalyzed by single and low affinity enzyme. Lansoprazole 5-hydroxylation, however, appeared to be mediated by two kinetically distinct CYP enzymes. The intrinsic clearance of sulfone metabolite and 5-hydroxylansoprazole formation from *S*-enantiomer were 3-fold and 8-fold greater than those from *R*-enantiomer in the microsomal incubations, respectively. The formation rate of 5-hydroxy-lansoprazole from *S*-enantiomer by cDNA-expressed CYP2C19 was three fold less than that from *R*-form, but cDNA-expressed CYP2C9 produced 5-hydroxy metabolite at 3.3-fold greater formation rate at 50 μ M of *S*-enantiomer than of *R*-form. The estimated IC_{50} of *S*-lansoprazole on the inhibition of CYP2C19-catalyzed *S*-mephenytoin (50 μ M) hydroxylation was 22-fold lower than that of *R*-enantiomer ($0.5 \pm 0.3 \mu$ M vs 11.6 ± 2.5 mM). These results suggest that CYP2C9, CYP2C19, and CYP3A4 involve in the stereoselective metabolism of lansoprazole, and lansoprazole inhibits CYP2C19 isoform in a stereoselective manner.