OMEPRAZOLE DISPOSITION IN EXTENSIVE AND POOR METABOLIZERS OF *S*-MEPHENYTOIN HYDROXYLATION.

Dong-Ryul Sohn,[1] Sang-Goo Shin,[2] Kan Chiba[3] and Takashi Ishizaki[3]
[1]Dept of Pharmacology, Coll Med, Gyeongsang Natl Univ, Chinju 660-280, [2]Clinical Pharmacology Unit, Seoul Natl Univ Hospital, Seoul 110-460, Korea and [3]Division of Clinical Pharmacology, Clinical Research Institute, Natl Med Center, Tokyo 162, Japan

To determine whether the metabolism of omeprazole would be influenced by the genetically determined *S*-mephenytoin hydroxylation phenotype status, we studied the pharmacokinetics of omeprazole and its two primary metabolites in plasma (hydroxyomeprazole and omeprazole sulfone) and the excretion profile of its principal metabolite in urine (hydroxyomeprazole) in eight extensive (EMs) and eight poor metabolizers (PMs) recruited from previous population study. Each subject received an oral dose of 20 mg of omeprazole, and blood and urine samples were collected up to 24 hr postdose. Omeprazole and its metabolites were measured by high-performance liquid chromatography with ultarviolet detection. The mean omeprazole area under the concentration-time curve (AUC), elimination half-life ($t_{1/2}$) and apparent oral clearance (CL_o) were significantly ($p < 0.001$) greater, longer and lower, respectively, in the PMs than in the EMs. The mean peak concentration (C_{max}) and AUC of hydroxyomeprazole were significantly ($p < 0.001$) less in the PMs than in the EMs. The mean C_{max}, AUC of omeprazole sulfone were greater ($p < 0.001$) and $t_{1/2}$ was longer ($p < 0.001$) in the PMs than in the EMs. The mean cumulative urinary excretion of hydroxyomeprazole up to 24 hr postdose was significantly ($p < 0.001$) less in the PMs than in the EMs. In addition, the $\log_{10}$ 4-hydroxymephenytoin excreted in urine correlated significantly ($p < 0.01$) with CL_o of omeprazole and $t_{1/2}$ of omeprazole, hydroxyomeprazole and omeprazole sulfone. The results indicate that the hydroxylation pathway of omeprazole is impaired and the sulfone in plasma is cumulated in the PMs of *S*-mephenytoinb hydroxylation. Thus, the metabolic disposition of omeprazole is under a pharmacogenetic control of *S*-mephenytoin hydroxylase in Korean subjects.