

구연 7

Pharmacokinetics of Hm30181A, a Novel P-gp Inhibitor, after Single Oral Administration in Healthy Male Subjects

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HM30181A is a novel P-glycoprotein (P-gp) inhibitor that enhanced the oral bioavailability and cytotoxicity of various anticancer agents in preclinical studies. The objective of this study was to investigate the pharmacokinetic profiles of HM30181A after single oral administration in healthy male subjects. A dose block-randomized, double-blind, placebo-controlled, dose-escalation study was performed in 180, 360, 600, and 900 mg dose groups with 10 subjects (including 2 placebo subjects) per group. Serial blood samples were collected up to 120 h after drug administration and were analyzed for HM30181A and its metabolites by liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were calculated by noncompartmental methods. Time to peak concentration (T_{max}) of HM30181A was delayed with increase in dose. The mean AUC_{last} were 169.9, 292.9, 380.7, and 548.7 ug*h/L, C_{max} were 2.4, 4.0, 5.2, and 6.6 ug/L and terminal elimination half-lives were 114.8, 169.3, 75.7, and 122.8 hours in HM30181A 180, 360, 600, and 900 mg dose groups, respectively. Pharmacokinetics of HM30181A showed a less than linear increase in C_{max} and AUC_{last} with increasing doses, with considerable intersubject variation. Metabolic ratios of the AUC_{last} of major metabolite M1 to that of HM30181A after HM30181A 180, 360, 600, and 900 mg administration were 0.053, 0.063, 0.100, and 0.067. This study provided data describing the pharmacokinetic characteristics of HM30181A in humans. These results may provide clues for HM30181A regimens in further studies involving combinations with P-gp substrates, including anticancer drugs.