Pk/PD Study Using PET Biomarker

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During development of an antipsychotic drug, it is difficult to define a clinically relevant dosage range from early studies involving healthy volunteers, due to the fact that most healthy volunteers do not tolerate higher doses that would be effective for schizophrenic patients, and also because there are not many well-defined pharmacodynamic biomarkers. Therefore, PK-PD modeling combined with functional imaging methodology such as positron emission tomography (PET) may be a very useful tool in clinical development of antipsychotics, especially in suggesting initial doses for further clinical studies.

YKP1358 is a novel dopamine (D2) and serotonin (5-HT2A) antagonist that in preclinical studies fits the general profile of an atypical antipsychotic. We conducted a study with YKP1358 in healthy volunteers using Positron Emission Tomography (PET), to measure the D2 receptor occupancy (RO) of YKP1358, and to characterize its relationship to plasma drug concentrations. Furthermore, this data was used for the design optimization of the next step in drug development, a patient study, utilizing clinical trial simulations.

A single oral dose, parallel group, dose-escalation (100 mg, 200 mg, and 250 mg) study was performed in 10 healthy male subjects. The D2 RO of striatum was measured with the PET radiotracer [11C]raclopride before dosing, and also at 2, 5, and 10 hours after YKP1358 administration. Serial blood samples were taken for measurement of plasma YKP1358 concentrations.

D2 RO by YKP1358 was 53~83% at 2 hours post-dose, and then decreased afterwards, ranging 40~64% at 5 hours and 20~51% at 10 hours. The dose-plasma concentration relationship exhibited large variability, but there was a good relationship between plasma concentrations and D2 RO that was well predicted by a sigmoid Emax model using non-linear mixed effects modeling. Clinical trial simulation results indicated that effective doses in patients would be greater than 250 mg twice a day.

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Dr. Yu is currently an Assistant Professor of Clinical Pharmacology at the College of Medicine, Seoul National University (SNU), and is also affiliated to the Clinical Trial Center of Seoul National University Hospital (SNUH).

After graduating from the College of Medicine, SNU, he has taken an internship at SNUH, and went on to be trained in the clinical pharmacology residency program there. He has received his Ph.D. from this university in 2000, and has been involved in many clinical pharmacology study projects during and since training.

He is interested in various fields related to early phase clinical trials and pharmacogenomic research.

Educational Background

Seoul National University College of Medicine, Seoul, Korea : M.D. (1996)
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Professional Background

1996～1997	Internship, Seoul National University Hospital (SNUH)
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