Mechanism-based PK-PD model for Brain Dopamine Responses by Methylphenidate in Rats

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Objectives: To develop a mechanism-based PK-PD model for the change of extracellular dopamine levels in brain after an administration of methylphenidate (MPH) to rats.

Methods: In vitro functional inhibition of MPH on dopamine transporter (DAT) was investigated using Neurotransmitter Transporter Uptake Assay Kit (Molecular devices), and the association and dissociation rate constants (kon, koff) of MPH were calculated by analyzing uptake rate for fluorescent substrates in the presence or absence of MPH. After a single intraperitoneal administration of MPH at 1-6 mg/kg to Wistar rats, plasma and CSF concentrations of MPH were measured by UPLC-MS/MS, and extracellular dopamine levels at nucleus accumbens (NAc) were monitored with microdialysis and HPLC-ECD. The mechanism-based PK-PD model consisted of: (i) 2-compartment model for plasma concentration; (ii) a compartment for CSF concentration attached to the plasma compartment; (iii) a component for DAT occupancy of MPH calculated with CSF concentration, kon and koff; (iv) a model incorporating dopamine biosynthesis, release from synapse, reuptake via DAT into synapse and elimination from synapse. All parameters were estimated by Phoenix WinNonlin.

Results: Kon and koff for MPH could be calculated by the mathematical model which was based on in vitro assay mechanism. After an administration to rats, MPH was rapidly absorbed and eliminated with biphasic profile in plasma, and CSF-to-plasma ratio was 1.25 (on average). In addition, extracellular dopamine levels in NAc increased in a dose-dependent manner. The PK-PD model also described the in vivo observations well. The hill coefficient, which means the degree of interaction between DAT occupancy and dopamine reuptake, was calculated to be 0.578, suggesting that extracellular dopamine levels in brain would be increased non-linearly for increasing of DAT occupancy.

Conclusions: We successfully developed the PK-PD model to describe the dopamine profiles in brain after MPH administration in rats. This model would be useful to understand the pharmacological effects for DAT.