PL-6

Pharmacokinetic applications for assessing toxicity and therapeutic efficacy of recent new-drug candidates

Ho-Chul Shin, Hee-Ok Shim, Young-Mi Lee,
Moon-Koo Chung, Jung-Koo Roh
PK/TK Lab, Toxicology Research Center, KRICT, Taejon

Toxicokinetics is emerging as a new and important discipline in new drug discovery, design and development. The present works describe pharmacokinetic application examples, recently carried out in our laboratory, targeting a new herbicide LGC-40863, organophosphorus insecticide KH-502 and new formulated osteoporosis drug ipriflavon (IP). ① Effects of LGC-40863 on dams and embryonic development were examined. Several external anomalies were observed at the lowest dosage level but not at higher dosages. Toxicokinetic studies were performed to clarify whether the fetal anomalies are related to LGC-40863. Overall kinetic data suggested that the fetal anomalies at the lowest dose are not associated with LGC-40863 but are with spontaneously generated. ② *In vivo* metabolism kinetics of KH-502 and its metabolite PTMHP was studied modelling two-compartmental metabolic kinetics. Simultaneous fitting both the parent and metabolite well characterized the plasma elimination kinetics. The elimination rate constant of metabolite PTMHP was much larger than the metabolic rate constant of KH-502. This indicates that PTMHP occurs as a major metabolite in plasma and that the parent compound directly governed elimination rate of PTMHP due to the rapid elimination rate. ③ IP has a extremely poor bioavailability. Absorption kinetics of new formulated IP was compared to that of commercial IP formulates. By spray drying and mixing with PVP, the new IP formulate markedly improved its oral bioavailability, calculating >7 times of AUC and C_{max}.