

Optimization of a Bioanalytical Method for Ondansetron in Multiple Rodent Tissues for Physiologically-Based Pharmacokinetic Study

Celine Park, Manting Chiang, Leonid Kagan
Rutgers, The State University of New Jersey

Plasma is often used as a surrogate to reflect therapeutic drug concentrations, but it is not always accurate. Physiologically-based pharmacokinetic (PBPK) models and simulations are important because they accurately describe drug concentrations at the tissue level and may help to establish concentration-effect and concentration-toxicity relationships. A PBPK study usually requires sacrificing animals at specific time points following drug administration and collection of all tissues. To provide accurate quantitative concentration measurements, bioanalytical methods must be developed, optimized, and validated to support the PBPK study. During the PBPK study, ondansetron was administered to rats as a 10 mg/kg IV bolus via the jugular vein. Animals were sacrificed at 10, 15, 30, 60, 90, 120, and 150 minutes, and CSF, brain, spinal cord, heart, lungs, liver, kidneys, spleen, GI, skin, fat, and muscle were collected. Tissues were homogenized according to the optimized protocol using Next Advance bullet blender and various homogenizing beads. Homogenates were used for tissue extraction to quantify the concentration of ondansetron in tissue via the High-Pressure Liquid Chromatography (HPLC) machine. Brain, spinal cord, and fat were able to be homogenized by dense beads made of zirconium oxide. Heart, lungs, liver, and kidneys required higher speed and longer time using rough steel "UFO" beads to cut through tough tissues. Muscle and skin required hand-held homogenizer, with temperature changes to avoid unwanted tissue degradation. In summary, bioanalytical method optimization was a critical step in producing reliable data and it required technical expertise to navigate the tissue homogenization experiment, to support the PBPK study.

