Physiologically Based Pharmacokinetic (PBPK) Modeling in Neurotoxicology

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Resent advances in computer technology have introduced a sophisticated capability for computing the biological fate of toxicants in a biological system. This methodology, which has drastically altered risk assessment skill in toxicology, is designed using all the mechanistic information, and all claim better accuracy with extrapolating capability from animal to people than conventional pharmacokinetic methods. Biologically based mathematical models in which the specific mechanistic steps governing tissue disposition (pharmacokinetics) and toxic action (pharmacodynamics) of chemicals are constructed in quantitative terms by a set of equations leading to prediction of the outcome of specific toxicological experiments by computer simulation. Pharmacokinetic and pharmacodynamic models are useful in risk assessment because their mechanistic biological basis permits the high-to-low dose, route to route and interspecies extrapolation of the tissue disposition and toxic action of chemicals.

Currently, no information is available for the ways to assess human risk of organic anionic neurotoxicants. A number of classical neurotoxins are organic acids and the list is continuously growing. It has become clear that individual testing of compounds to determine their health impact on the brain is not possible. Since the versatility of physiologically-based pharmacokinetic (PBPK) model can provide quantitative information on the disposition of chemicals for various administrered doses, exposure routes, and target species of all ages with its extrapolating capability from animal to human, a PBPK dosimetry model could be a valuable tool to predict the specific target tissue dose of organic anions in the central nervous system (CNS) for neurotoxicity risk assessment.

Because of its limited metabolism in animals, 2,4-dichloro-phenoxyacetic acid (2,4-D)

has been chosen as a representative for organic anion for developing PBPK models. Basic PBPK models for the dosimetry of organic acids in the brain were developed and fit to data from rats, rabbits as well as pregnant rabbits for maternal and fetal brains administered a single dose of 2,4-D by IP or IV, respectively.

The PBPK model consisted of arterial and venous compartments together with the adult brain and the rest of the body. The adult brain was further divided into eight subcompartments: hypothalamus, caudate nucleus, brainstem, forebrain, cerebellum, hippocampus, cerebrospinal fluid (CSF), and brain plasma. In the model, chemical uptake by the brain is membrane-limited through the blood-brain barrier with saturable clearance from the celebrospinal fluid into the venous blood by the choroid plexus. The body has both a central and a deep compartment with saturable clearance from the central copmpartment.

In the pregnancy model, the fetus was incorporated into the previous model in which both maternal and fetal compartments were joined through venous equilibrium at the placenta. The fetus consisted of brain tissue, brain plasma, CSF, body, amniotic fluid, and arterial and venous compartments. 2,4-D entered the maternal plasma compartment and diffused through the placenta into the fetal plasma. The pregnancy model was expressed by a flow-limited model at the placenta. The transport of 2,4-D across the maternal and fetal choroidalequithelial cell membranes as well as martenal renal clearance occurred by a saturable mechanism described by Michaelis-Menten kinetics; transport from the plasma into the maternal brain and the fetal brain was incorporated as a membrane-limited process.

The model was used to examine regional brain and plasma concentrations of 2,4-D against time with experimental data from rats or rabbits given 2,4-D. The model adequately simulated the 2-hr time-course of 2,4-D concentrations in both blood and brain regions. Comparison of model simulations and experimental data also indicated that the pregnancy model was sufficiently versatile to represent the 2-hr time-course of 2,4-D concentrations in fetal brain, amniotic fluid, both maternal and fetal plasma, and maternal brain regions. These basic generic PBPK models should prove important for determining the target tissue dose for the whole class of organic acids in the brain.