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Windows® based general PBPK/PD modeling software

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Abstract

A physiologically based pharmacokinetic (PBPK) model and program (called PostNatal) was developed which focuses on postnatal growth. Algorithms defining organ/tissue growth curves from birth through adulthood for male and female humans, dogs, rats, and mice are utilized to calculate the appropriate weight and blood flow for the internal organs/tissues. This Windows® based program is actually four linked PBPK models with each PBPK model acting independently or totally integrated with the others through metabolism by first order or Michaelis–Menten kinetics. Data fitting is accomplished by a weighted least square regression algorithm. The model includes linkages for the simulation of pharmacodynamic (PD) effects.
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Keywords: PBPK/PD; Pharmacokinetic model; Pharmacodynamic model; Windows® software; Postnatal growth; Human; Dog; Rat; Mouse

1. Introduction

The concept of physiologically based pharmacokinetic (PBPK) models was introduced by Bischoff and Dedrick over 35 years ago [1–3]. These models are currently used for extrapolating dose and blood/tissue levels from animal data to human for chemical risk assessment [4–6]. As the PBPK models became more complex, sophisticated computer programs such as SimuSolv (Dow Chemical Co., Midland, MI) became the standard platform for simulations [7]. Easterling et al. [8] compared and contrasted SimuSolv and Matlab (The Math Works, Natick, MA) and indicated that each program required familiarity with the specific file structure and some additional programming for specific models. Luecke et al. [9] reported on a generalized PBPK model for pregnancy that did not require additional programming but could be used by supplying appropriate pharmacokinetic parameter estimates for the chemicals of interest. The present work is an extension and generalization of the work by Luecke and co-workers to postnatal development, still with no programming required, but with input/output via a user-friendly Windows® environment.

This software was developed to provide a user-friendly and general model platform to investigate the PBPK and, if appropriate data are available, pharmacodynamics (PD) of a chemical during postnatal development. The familiarity of most users with Windows® menu based systems provides the template (developed on XP, but is compatible with any Windows® based PC) of a user-friendly interface for specification of input data and retrieval of results. Internal algorithms correlate organ/tissue weights and blood flow values based on total body weight. Appropriate physiological parameters throughout postnatal development are based on species, gender, and weight or age. The PBPK simulation may be linked to PD data with one of two general schemes patterned after either a complex model of second order enzyme kinetics or a simpler model of formation and decay of a measurable physiological event. The PD portion is a physiological result, endpoint, or effect that is

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functionally related to one or more of the chemical concentrations in one or more of the tissues. The PD portion is an option, not a necessity, for the PBPK simulation.

In addition to studies of development and growth, this PBPK software has considerable utility in describing complex scenarios of drug metabolism and disposition in juvenile or adult mice, rats, dogs, or humans. The integrated properties of the software permit modeling across species, based on body weight, which make data generated in experimental animals more readily extrapolatable to humans. Similarly, the ability to readily interchange kinetic equations (i.e., first order vs. saturable enzyme kinetics) allows rapid testing of different possible models of metabolism and disposition against the experimental data. The integration of four separate PBPK models, with the possibility of interactions, permits unusual flexibility in the kinds of studies that can be simulated: mixtures of administered compounds via various routes; enterohepatic recirculation; or direct comparisons of different doses or routes of administration in a common simulation.

2. PBPK/PD program details

Four complete PBPK models (Fig. 1) within the program provide the framework for simultaneously simulating a parent compound and three metabolites, four independent compounds, or any intermediate configuration. Each PBPK model represents the dynamic partitioning of a substance into 28 fluids/organs/tissues along with metabolism and elimination via urine, feces, and/or hair (Fig. 2). Matrix style spreadsheet entries are used to specify route(s) of administration, absorption parameters, experimental data, partition coefficients (PCs), reaction rate constants, and to configure graphical or tabular output results. All metabolic pathways and fecal elimination may be described by either Michaelis–Menten or first order kinetics and are dependent on the concentration of

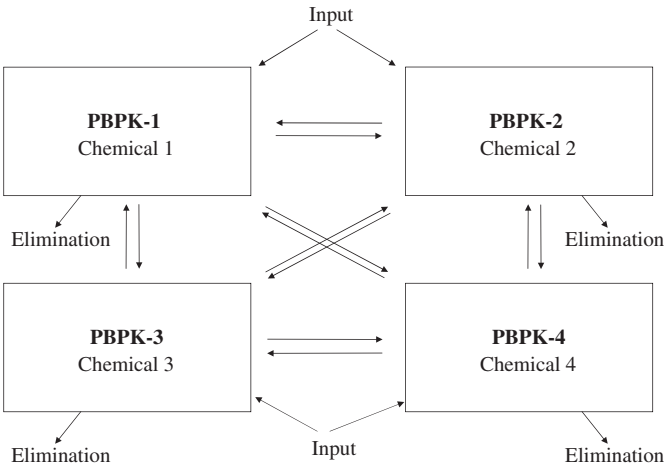

Fig. 1. The generalized block diagram of the interactions of the four PBPK model in the PostNatal program. Each of the PBPK models is comprised of 28 fluids/organs/tissues as illustrated in Fig. 2.

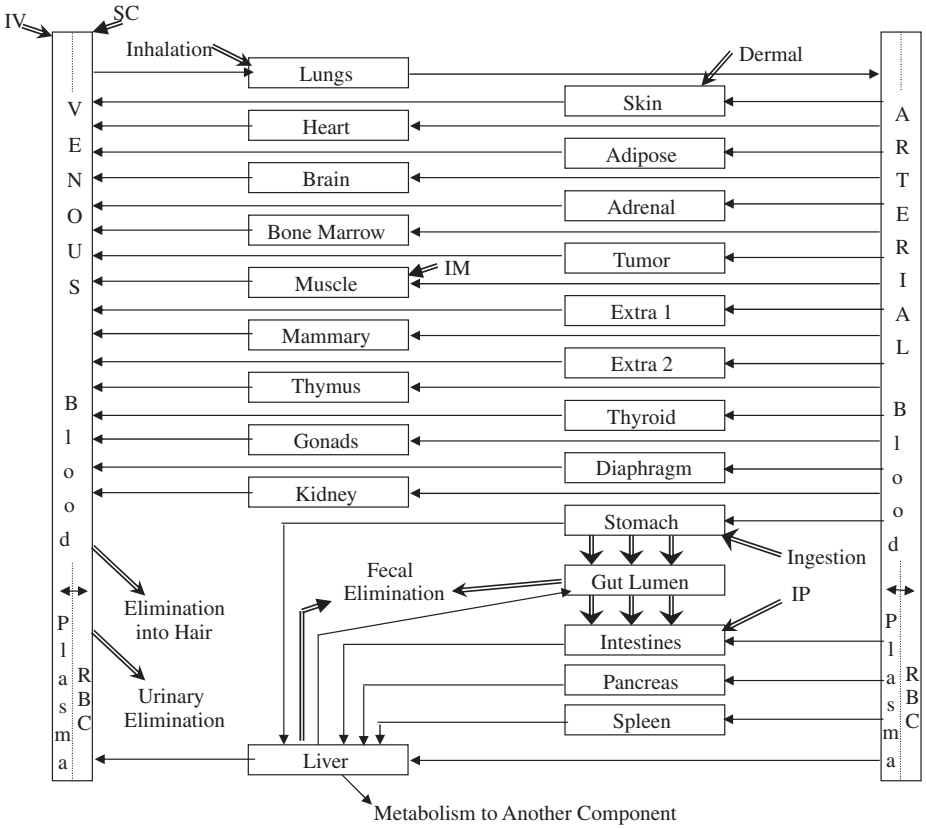

Fig. 2. The detailed schematic diagram of one of the four PBPK models in Fig. 1.