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Physiology-based approach to modeling of dialysis

Physiologically based pharmacokinetic models attempt to utilize basic physiological, biochemical, biophysical, and physicochemical information to describe the distribution, disposition, conversion, and elimination of a given substance. More specifically, such models require information about organ volumes, physiological blood flow rates, solute generation rates, enzymatic reactions, as well as information on thermodynamic characteristics such as solubilities, dissociation constants, partition coefficients, diffusivities, and membrane permeabilities. Teorell was among the first to present a physiologically based pharmacokinetic model more than 70 years ago [1].

The distribution volume, the number of compartments, and the exchange of solute between compartments are important components of a kinetic model. Models for hemodialysis are characteristic for assuming a change in compartment volume because of ultrafiltration. On the other hand, rate constants describing the exchange between compartments, the generation and the elimination of solute are generally assumed as constant.

Parameters of physiologically based models have an important meaning. For example, transport within and between compartments is described by convection and diffusion through the cardiovascular system. Two limiting cases of transport may be distinguished: Flow-limited transport for solutes with high diffusivity and membrane permeability such as urea, and diffusion-limited transport for solutes with low membrane permeability such as creatinine. Notice that transport of solutes between organs is determined by convection irrespective of solute diffusivity. The importance of organ perfusion for solute kinetics in hemodialysis was first recognized by Dedrick [2]. Thus, even if diffusion across cell membranes is almost instantaneous for substances such as urea, the equilibration throughout the whole body during the typical post-dialysis urea rebound takes about 30 min because of differences in regional perfusion [3]. Surprisingly, a similar time course is observed for other solutes such as creatinine which, unlike urea, have much reduced membrane permeability. The kinetics for both urea and creatinine (and possibly other solutes) can be described by a unified model combining flow-limited transport between organs and diffusion-limited transport within organs [4]. The assumption of constant exchange rates between compartments must be questioned when hemodialysis and ultrafiltration-induced changes in blood volume are known to affect cardiovascular control and regional blood flow distribution [5, 6].

Indicator dilution has a long tradition in physiology to model characteristics of solute transport and to identify important model parameters inaccessible to direct measurement [7, 8]. In hemodialysis, the focus of indicator dilution is on measuring blood flows such as access blood flow and cardiac output, and distribution volumes such as central blood volume and lung water [9, 10]. A variant of indicator dilution is the modeling of ultrafiltration-induced changes in blood volume and vascular refilling in the microcirculation for the purpose of understanding fluid balance during hemodialysis [11, 12].

Physiologic models are more complex and require more data that usually cannot be obtained in the single experiment. It is often impossible to analyze various tissues relating to specific compartments, especially in man, and one has to rely on in-vitro or animal data. In addition to data acquisition problems, the models are often composed of complex sets of nonlinear differential equations that must be solved numerically. Also, the expansion of compartments has been criticized as an addition of arbitrary parameters to artificially improve the model fit whereas in reality each additional compartment represents a constraint that can be checked against real data should they become available [13].

Physiologically based kinetic models can be used to identify meaningful physiological parameters inaccessible to direct measurements such as volumes, flows, and permeabilities. Unlike statistical models extrapolation of mechanistic models outside the range of data is possible with some confidence. In hemodialysis this is important when scaling the treatment with regard to treatment duration, treatment frequency, and body size [14, 15].

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