Abstract

Physiologically based pharmacokinetic (PBPK) models, also known as recirculation models, consist of a series of tissue and organ blocks linked together by blood circulation, mimicking the anatomical structure of mammalian body. Each tissue is divided into vascular, interstitial, and intracellular sub-compartments. Linear system analysis (LSA)-recirculation models differ from the classical PBPK model in that they characterize each organ or tissue with a unit impulse response in the framework of input output convolution relationship rather than systems of differential equations. Target mediated disposition (TMD) is a phenomenon where drug disposition is influenced by capacity-limited binding to a target, resulting in dose-dependent events, such as a decrease in drug clearance with increasing dose level. Erythropoiesis stimulating agents such as recombinant human erythropoietin (EPO) and Continuous Erythropoietin Receptor Activator (C.E.R.A.) exhibit TMD where their disposition and anti-anemic activity are mediated by their interaction with EPO receptor (EPOR).

The objectives of this work were: 1) to develop a minimal, receptor-based LSA recirculation model, 2) to apply the developed model in analyzing the effect of bone marrow (BM) ablation on C.E.R.A. elimination kinetics, and comparing EPO and C.E.R.A. interaction with EPOR *in vivo*, 3) to investigate the efficiency of the experimental design used to achieve the previous objective for estimation of the

developed model parameters, and 4) To identify the physiological conditions at which TMD-compartmental models approximate TMD-recirculation models.

A literature review of LSA- recirculation models is provided in Chapter 2. In Chapter 3, receptor-based, LSA-recirculation model was mathematically formulated, and applied to analyze C.E.R.A. pharmacokinetics studied in adult sheep with normal and ablated BM using a tracer interaction method (TIM). In Chapter 4, the model developed in Chapter 3 was further applied to analyze EPO and C.E.R.A. TIM data collected in adult sheep. A comprehensive, sensitivity analysis was performed in Chapter 5. In Chapter 6, statistical moments of linearized receptor-based compartmental and recirculation models were computed; and simulation of plasma drug concentrations, and receptor profiles in both structures were presented.

The developed model, together with the TIM, was able to quantitatively assess the interaction of C.E.R.A. with hematopoietic and non-hematopoietic EPOR population and provide a mechanism based explanation for C.E.R.A.'s slower elimination and greater erythropoietic activity *in vivo* compared to EPO, despite its lower affinity to EPOR. The TIM detected a saturable interaction between C.E.R.A. and non-hematopoietic EPOR which contradicts the behavior of EPO. The TIM experimental setting is adequate for estimation of the developed model parameters. TMD-recirculation models reduce to TMD-compartmental models

under conditions of well-perfused target tissue, comparable drug initial distribution volume and target tissue extracellular volume, negligible non-receptor mediated clearance, and rapid equilibrium between venous and arterial blood drug concentrations, small extracellular volume, reduced cardiac output, low receptor pool concentration, and high drug-receptor equilibrium dissociation constant.