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Clinical Pharmacokinetic Applications of Recirculatory Models

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Additional information is available at the end of the chapter

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1. Introduction

In clinical practice, conventional pharmacokinetic analysis usually relies on the use of classic pharmacokinetic procedures, such as compartmental models. The main advantage of these models in clinical practice is their excellent capacity to predict the concentrations of drugs from different doses and administration conditions. Also the relative ease with which they can be optimized using polyexponential analysis. Moreover, this type of model affords information about the fundamental pharmacokinetic parameters of disposition, such as elimination clearance or apparent distribution volumes, which can be correlated with the demographic (age, weight, etc.) or clinical variables (renal function, hepatic function, etc.) that may be altered in disease states. The principal drawback of compartmental models is that they fail to reflect physiological reality, which hinders the interpretation of the biological alterations induced by disease states and the influence of these in pharmacokinetics. Among the physiological variables affected by disease states are regional blood flow, renal and liver extraction, extracellular water volume and membrane permeability, etc., all of which contribute to changes in drug plasma and tissue levels, and in the pharmacological response.

Physiological pharmacokinetics contributes to the interpretation of the influence of physiological and biochemical changes in the pharmacokinetic behavior. For more than a hundred years, the indicator-dilution method was proposed to measure blood flow. Different authors, however, have suggested the possibility of using those methods to measure physiological variables [1]. The indicator-dilution theory, combined with the concept of drug recirculation, permitted the development of the recirculatory models [2].

Recirculatory models are a type of so-called physiologically based pharmacokinetic models (PBPK). Analysis of drug disposition based on blood recirculation incorporates important physiological factors affecting the pharmacokinetics, such as cardiac output. The fundamental

assumption is that there is a circulatory transport function that may be considered as a probability density function of transit times after a first passage through the system. In the recirculatory models, drug disposition is analyzed as the convolution of its circulatory transport function [2]. Clinical application of the recirculatory models in the field of pharmacokinetics was proposed by Weiss [3]. Currently, clinical application of these models is quite varied, especially in the field of anesthesiology [4-6] and contributes to the analysis and interpretation of clinical pharmacokinetic data.

2. Theoretical considerations

Recirculatory models are a type of physiological modelling alternative to classical compartmental modelling and they use physiological concepts such as circulatory transport function, cardiac output, and systemic extraction by elimination organs such as the liver and the kidney. These models arise from the tracer indicator-dilution theory combined with the concept of drug recirculation. This method was developed by Hearing in 1824 to measure the blood flow. In the early 20th century, and after the work of Stewart in 1897 and later Hamilton, it was used to estimate clinical hemodynamic blood flow [7, 8]. Variants of these methods have been used to study the physiology of the circulation and their pathological changes, including cardiac output. A marker such as indocyanine green (ICG) (Stewart-Hamilton method) or thermodilution can be used, by measuring temperature instead of concentration after injecting a saline solution at low temperature [9]. These models assume the existence of circulatory transport functions that may be modelled by empirical functions.

3. Concept of circulatory transport function

The circulatory transport function represents the density function of the transit times of the molecules in the first passage through the system or subsystem. Its profile depends on the injection and sampling sites in the vascular system.

Assuming a stochastic analysis of drug transport through a single-blood perfused organ without recirculation, when one unit of drug is injected as a single pulse a transport function $f(t)$ may be defined [10, 11]. According to the tracer kinetic theory, the circulatory transport function represents the transit time density function of the molecules travelling from the beginning to the end of the organ or system. The central tendency of the transport function is given by the mean transit time and dispersion can be characterized by the variance in transit times [12, 13].

The zero, first, and second moments of the circulatory transport function correspond to the area under the curve (AUC), the mean transit time (MTT), and the variance of transit times (VTT), respectively, and may be calculated as:

$$AUC = \lim_{s \rightarrow 0} f(s) \quad (1)$$

and

$$MTT = \lim_{s \rightarrow 0} -d/ds \ln f(s) \quad (2)$$

and

$$VTT = \lim_{s \rightarrow 0} -d^2/ds^2 \ln f(s) \quad (3)$$

where $f(s)$ represents the function transport expressed in the Laplace domain.

The relative dispersion of the tracer (RD^2) may be calculated as a normalized variance of the transit times according to the following expression [14]:

$$RD^2 = \frac{VTT}{[MTT]^2} \quad (4)$$

The relative dispersion (RD^2) may be used for the interpretation of the intravascular mixing of markers [14, 15].

According to the linear systems theory, the concentration–time curve at the output of the organ $C(t)$ is the convolution of the input function $f_I(t)$ and the transport function $f(t)$ according to the following expression [11]:

$$C(t) = \int f_I(\tau) f(t - \tau) d\tau \quad (5)$$

In the Laplace domain this equation is expressed as:

$$C(s) = f_I(s) \cdot f(s) \quad (6)$$

Depending on the kind of input used, $f_I(s)$ may take the following expressions:

$$f_I(s) = Dose \quad (7)$$

when the drug is administered as an instantaneous i.v. bolus injection, or

$$f_I(s) = \frac{(Dose / T_{inf})}{s} \cdot (1 - e^{-T_{inf} \cdot s}) \tag{8}$$

when the drug is administered by i.v. infusion with zero-order input, where T_{inf} is the infusion time.

Different approaches to the circulatory transport function, either model-dependent or -independent, have been made [2, 12, 16]. Some empirical approaches to the circulatory transport function of tracers in each subsystem, such as inverse Gaussian, log-normal, Gaussian, or Erlang functions have been proposed, as shown in Table 1 [17-20].

Inverse Gaussian	$f(t) = \sqrt{\frac{MTT}{2\pi RD^2 t^3}} \exp\left\{-\left[\frac{(t - MTT)_+^2}{2RD^2 MTT t}\right]\right\}$
Gaussian	$f(t) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left[\frac{t-t_0}{\sigma}\right]^2}$
Erlang	$f(t) = \frac{k^n t^{n-1}}{\Gamma(n)} e^{-k \cdot t}$
Log-Normal	$f(t) = \frac{1}{\sigma\sqrt{2\pi\sigma \cdot t}} e^{\left(-\frac{1}{2\sigma^2}\left[\ln\frac{t}{\mu} + \frac{\sigma^2}{2}\right]^2\right)}$

MTT: mean transit time, RD^2 : relative dispersion, μ : mean, σ : variance, k : first order rate constant.

Table 1. Empirical equations used for the characterization of the circulatory transport function of tracers in different subsystems.

In addition, mathematical dispersion-convection models using partial differential equations have been proposed. Such models have been used for the modelling and simulation of the circulatory transport function of tracers after a single-pass, depending on the administration/sampling sites [21]. The parameters of the circulatory transport function may be estimated using nonlinear regression procedures.

The circulatory transport function combined with a recirculation model allows predictions to be made about the initial distribution of a drug after its first passage through the systemic circulation and also permits the plasma levels curve after recirculation in the body to be generated.

4. Recirculatory models

From a physiological standpoint, the circulatory system consists of two circuits through which blood flows: pulmonary and systemic. The pulmonary circuit moves the blood to the lungs to

be oxygenated and then returns it to the heart. The systemic circuit moves the blood between the heart and the rest of the organs and tissues of the body.

The body can be considered as a system of parallel compartments perfused with arterial blood, which is recirculated via the venous blood. Each compartment represents organs and tissues such as kidney, liver, muscle, etc., or groups of organs connected in parallel or in series. Blood flow between the compartments goes from the arterial line to the venous line and the recirculation of blood from the venous blood line passes through the heart-lung system as shown in Figure 1. Assuming the body to be a closed-loop system, the drug is injected into the venous system, circulating through the heart and pulmonary circulation, returning to the heart and the arterial system, and finally returning to the venous system.

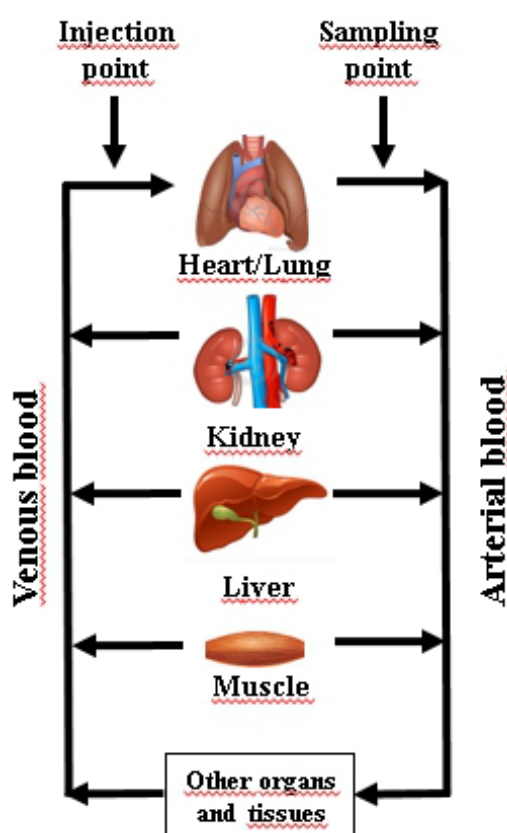


Figure 1. Scheme of the circulatory system and the recirculation of blood. The tracer is administered by bolus intravenous injection and the sampling is made at the arterial line.

Depending on the injection and sampling points, the space covered by the drug in its first passage through the systemic circulation can be variable, conditioning the profile of the circulation transport function. Considering the circulatory system as a linear one, and from a mathematical point of view, the recirculatory process is considered to be the convolution of the circulatory transport function in the different subsystems [2].

Different kinds of pharmacokinetic recirculatory models with experimental and clinical applications have been proposed. For the development and validation of recirculatory models

many types of markers have been used. Indocyanine green (ICG) is frequently used as a marker of the vascular space; inulin is a marker of extracellular fluid, and antipyrine is used as a marker of the total body water [14].

From experiments using ICG in sheep, a recirculatory model based on the estimation of a body transport function was proposed. The tracer was injected into the right atrium of the heart and the dilution curve of ICG was measured using a catheter in the aorta. The model considers the body transport function to be composed of two different subfunctions associated with two parallel functional compartments of the body: namely, a fast compartment with a low transit time value and a slow compartment with a higher transit time [19].

From a physiological interpretation, a minimal recirculatory model including pulmonary and systemic circulation, as shown in Figure 2, has been proposed [15, 22, 23].

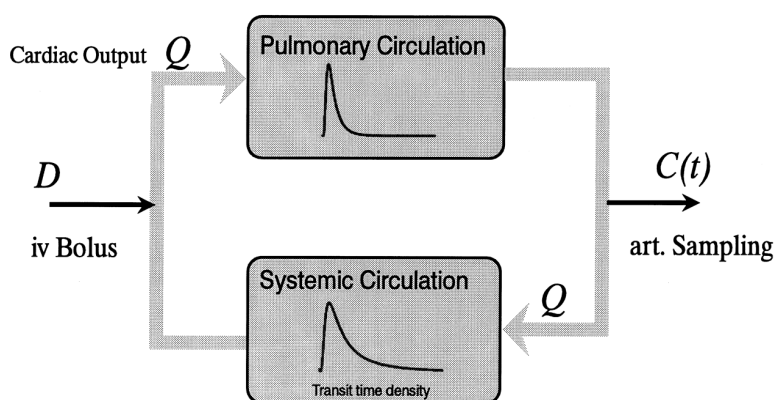


Figure 2. Minimal recirculatory model based on pulmonary and systemic circulation. Reproduced with permission from Elsevier [22].

In this model, the basic equation for the arterial concentration–time curve for infinite cycles in a closed loop system for a vascular space marker such as ICG after a standard input may be expressed in the Laplace domain by the following equation:

$$C_p(s) = (f_I(s) / CO_p) \frac{f_p(s)}{1 - (1 - E) \cdot f_s(s) \cdot f_p(s)} \quad (9)$$

$f_p(s)$ and $f_s(s)$ represent the Laplace transform of the pulmonary and systemic circulation transport functions, respectively; E is the systemic extraction by elimination of the drug; CO_p is the plasma cardiac output; and $f_I(s)$ represents the Laplace transform of the input function of the drug in the body. The plasma concentration–time curve, $C_p(t)$, is finally obtained as the inverse Laplace transformation:

$$C_p(t) = L^{-1}(C_p(s)) \quad (10)$$

A more complex recirculatory model was developed to characterize the disposition of drugs having a wide tissue distribution with potential clinical applications. In addition to circulatory transport functions in the different subsystems, the model considers the processes of tissue distribution.

The basic form of this model includes the pulmonary and systemic circulations. Pulmonary circulation is characterized by an empirical transit time density function $f_p(s)$ and systemic circulation $f_s(s)$ is based on an axially distributed capillary-tissue exchange model with vascular and extravascular distribution volumes. Distribution parameters such as the tissue distribution volume (V_T), the permeability-surface product (PS), and diffusional transport into the tissue space using an equilibration time parameter (ds) may be characterized with this model. Flow-limited distribution kinetics of drugs such as antipyrine or diffusion-limited distribution kinetics of substances such as inulin may be modelled [24]. In the advanced version of the model, the systemic organs are grouped into two subsystems, non-fat tissues and fat tissues [23].

Recirculatory models incorporating dispersion concepts or models based on the fractal geometry of the vascular tree and the hydrodynamics of the blood flow have also been proposed. The spatiotemporal kinetics of tracers is described using partial differential equations incorporating dispersion and convection processes [21, 25, 26].

As an alternative, a pharmacokinetic recirculatory model based on the analysis of arterial and mixed venous data was proposed and applied successfully to characterize the pharmacokinetics of ICG, antipyrine and lidocaine. ICG and antipyrine have been used as markers of the vascular space and total body water, respectively. This model is based on catenary compartmental models linked in series [27-30].

As an alternative to the classical two-compartment mammillary model, a two-compartment recirculatory model has been proposed to characterize drug disposition [31]. In this model, the central compartment is defined by the lungs and the peripheral compartment by the rest of the body, without the lungs. The mass balance between compartments depends on the distribution volumes of both compartments, cardiac output, and the arterial (C_A) and venous plasma concentrations (C_V) [31].

This model has been used to fit the data set of arterial thiopental concentrations in sheep. They are considered to be the sum of two components: the first-pass arterial concentrations and the recirculated concentrations. A dynamic component can easily be added to the model by introducing a target organ for which there is a defined target organ concentration-effect relationship. This design has been applied also for propofol [32]. Despite its simplicity, this model highlights the fact that slowing the bolus injection rate of a fixed dose can lead to significantly lower peak arterial concentrations. Also an inverse relationship was found between these concentrations and cardiac output [31]. More complex recirculatory models to characterize the disposition of drugs in specific tissues such as the brain have been proposed [33].

An important aspect of recirculatory models is that they are able to fit the data from arterial and venous blood samples obtained simultaneously. It is common in pharmacokinetic studies of anesthetics to include early arterial samples but for convenience later samples are taken from a vein. Although these venous drug concentrations are assumed to differ non-significantly from simultaneously sampled arterial concentrations, this is not always true, as found in a phase I study for remimazolam. [34]. In this study, the data on each subject included early arterial, late venous points, and samples from both at some middle points. Two population pharmacokinetic models were applied to the plasma levels: a conventional mammillary model with 3 or 4 compartments and a recirculation model. The compartmental models that assume that the drug is distributed instantaneously throughout the central compartment are only valid with compounds whose distribution and clearance kinetics are relatively slow compared with the blood flow. This was not the case of remimazolam, which showed significantly higher venous concentrations than arterial ones (ratio >1, 44) [34]. Only a recirculatory pharmacokinetic model including both venous and arterial compartments, a cardiac blood/pulmonary compartment for the dose and clearance from the peripheral compartment was able to fit the data. Three- and four-compartment mammillary models gave much poorer fits [34].

A more complex, six-compartment hybrid physiological model was used to define propofol kinetics and dynamics [35]. The model includes a description of initial bolus kinetics, lung kinetics and cardiac output, along with the effects of propofol-induced changes in cerebral blood flow and a combined description of systemic kinetics as two tissue pools. It was able to simulate the complex effects of circulatory changes on the pharmacokinetics and pharmacodynamics of propofol in sheep as well as in humans [32, 33]. With this model it was shown that increased cardiac output resulted in decreased duration of anesthesia, whereas increased cerebral blood flow increased the depth (but not the duration) of anesthesia [36]. This was attributed to the influence of cardiac output on tissue distribution. On the basis of this evidence, it has been speculated that a reduction in cardiac output caused by co-administration of drugs such as midazolam and fentanyl to anxious patients, might be part of the mechanism by which these drugs reduce the required induction dose of propofol [37]. When applied to define propofol kinetics in a standard patient, the model was consistent with the clinical data and was able to predict other data not used in its development [33].

Recently, three pharmacokinetic compartmental models and one recirculatory model (Upton model) have been compared to simulate the time course of propofol plasma concentrations. Published C_p data from studies of both manual (bolus and short infusion) and computer-controlled (TCI) propofol dosing schemes were used. The performance indices of the models during the first 5 min after a bolus injection revealed a clear overprediction for all three compartmental models after 1 min. The Upton model only performed reasonably well after 120 s. For short infusions, the recirculatory model did not provide accurate prediction of C_p before 1 min and after the termination of drug administration. This was attributed to the fact that the lag time was modeled from centrally administered propofol while in the datasets used the drug was administered peripherally. However, the authors concluded that more studies were required to assess the validity of the Upton model predictions for the first minute [138]. Although the Upton recirculatory model did not show any clear advantage in the fitting of the

datasets employed, the authors pointed out its inherent interest since it should be able to predict the effect of common hemodynamic disturbances such as congestive heart failure, severe blood loss, dehydration, and other high and low cardiac output states on propofol pharmacokinetics, as previously reported for animal studies. However, this remains to be studied.

Krejcie and Avram [29] developed a recirculatory pharmacokinetic model using antipyrine as a surrogate for lipophilic drugs such as thiopental to study factors affecting the initial disposition of drugs with a rapid onset of effect. This model was used to study antipyrine disposition in dogs with altered cardiac output and blood flow distribution [4, 9, 39, 40]. They found that not only cardiac output but also its peripheral distribution affects the early history of antipyrine concentrations after rapid intravenous administration [41].

This model was also applied in a study that simulated the usefulness of a recirculatory model compared with a three-compartment mammillary pharmacokinetic model, to design an adequate target-controlled drug infusion. They found that the fitting of the data was indistinguishable for both types of models. However, the mammillary model overestimated not only V_c but also V_F and CL_F (volumes and clearance for rapid-equilibrating tissues), which could lead to concentrations higher than the target concentrations. The use of a reasonable estimate of V_c as the sum of V_c and V_{ND} (non-distributive distribution volume) from the recirculatory model was recommended. Accordingly, it was proposed that better estimates of V_c can be obtained from studies in which the drug of interest is administered in a short-term intravenous infusion in order to avoid many of the mistaken assumptions made when fitting data obtained after rapid intravenous drug administration [42].

The most realistic application of the recirculatory models involves frequent data collection after drug injection, including first-pass and recirculation peaks. This information allows the physiological changes induced by disease states that may affect the pharmacokinetic behavior of drugs and their influence on the pharmacological response to be interpreted.

Recirculatory models have some pitfalls for their practical clinical application such as:

1. Their greater numerical and computational complexity in comparison with classic models, since they often have to work with mathematical functions in the Laplace domain.
2. The complexity involved in performing experiments with plasma indicator dilution curves in humans, especially in clinical practice.
3. The difficulty inherent to estimating cardiac output or regional blood flows in patients.
4. The need to have a sufficiently large number of experimental data, which is also a limitation in clinical practice.
5. Greater computational difficulties, because conventional pharmacokinetic software is not appropriate for this type of model and it is necessary to use specific software based on the numeric inversion of the Laplace transform such as Scientist [43], FILT [44], or MAPLE [45] among others.

5. Recirculatory models and disease states

Recirculatory models are a relatively unexplored alternative to classic pharmacokinetic analysis. Although there have been instances of their use in clinical practice, especially in the field of anesthesiology [4-6], their application in the analysis and interpretation of the physiological changes induced by disease states and their influence on pharmacokinetics is infrequent. The main advantage of recirculatory models as compared with classic models such as compartmental ones lies in their greater physiological basis in the sense that they handle parameters, such as cardiac output, that are directly related to the physiology of the body and the changes that may occur to it in disease states or clinical situations deriving from the diagnosis or treatment of the patient.

Many pathophysiological situations or disease states affect one or several parameters included in the recirculatory model equations such as cardiac output (CO_p), regional blood flows (Q_T), tissue distribution volumes (V_T), tissue (E_T) and systemic (E_S) extraction. As a consequence, recirculatory model equations are very useful for simulating the influence of these variables in the plasma or serum levels of drugs.

Within the context of distribution and elimination kinetics, distribution (Cl_D) and systemic elimination (Cl_s) clearances may be considered on the basis of the following equations:

$$Cl_D = CO_p \cdot E_T \quad (11)$$

$$Cl_s = CO_p \cdot E_S \quad (12)$$

5.1. Drug distribution

Tissue distribution is affected by tissue extraction, which reflects the overall contribution of the different organs and tissues to the distribution of the drug. The tissue extraction coefficient, E_T , depends on factors such as regional blood flow, membrane permeability, and tissue binding. Overall tissue extraction may be related to extraction by a specific tissue (E_{ST}), according to the following expressions:

$$E_T = E_{ST} \cdot \frac{Q_T}{CO_p} \quad (13)$$

and

$$E_{ST} = \frac{E_T \cdot CO_p}{Q_T} = \frac{Cl_D}{Q_T} \quad (14)$$

where Q_T represents the plasma perfusion to a specific tissue.

According to equations 13 and 14, changes in extraction by a specific tissue (E_{ST}) due to alterations in regional perfusion, tissue permeability, or tissue binding induced by disease states will be reflected in the overall tissue extraction (E_T) and, consequently, in the distribution clearance (CL_D) of drugs.

In drugs with flow-limited distribution, the distribution clearance to specific tissues is equal to the regional blood flow. In this situation, the overall tissue extraction of equation 13 reflects the fraction of the plasma cardiac output that contributes to the tissue distribution of the drug.

Tissue blood flow is dependent on cardiac output, which can be modified in different disease states or in response to certain drugs. Cardiac output is moderately reduced with age and in the presence of cardiovascular diseases such as congestive heart failure, hypertension, and others. Some drugs may increase or reduce the cardiac output. For example, all anesthetics decrease cardiac output and distribution clearance [46].

The effect of reduced distribution clearance is to reduce the initial plasma concentrations after drug administration. This is particularly important in drugs with rapid onset such as anesthetics [47]. Recirculatory models may help to evaluate the initial distribution and pharmacodynamic response of this type of drugs.

Anesthetists frequently rely on drugs administered by intravenous bolus, whose effects start in 1–2 min. Thus, the first few minutes are particularly relevant in monitoring drug and side effects. It seems clear that the so-called front-end kinetics plays a large part in determining the rate and extent of drug distribution to the site of drug effect and that it is the early distribution kinetics that should be characterized most accurately [37].

Standard compartment mammillary models assume that a drug is mixed instantaneous and completely in the central compartment. This implies that for bolus administration the predicted plasma concentrations at time zero are the highest, whereas in reality they are zero. These models ignore the complexity of the early distribution processes, which depend on cardiac output and its distribution, tissue perfusion and affinity for a drug, and the relative concentrations of the drug in blood and tissues. Thus, they overestimate the actual initial distribution volume, which, along with the dose, determine early drug concentrations and the intensity of the drug effect. Accordingly, despite their widespread use to describe drug disposition they have some limitations when applied to the rapid administration of anesthetic drugs, particularly those with a rapid onset of effect [37].

Recirculatory pharmacokinetic models retain the relative simplicity (compared with physiological models) of mammillary models but incorporate descriptions of key physiologic processes that have been recognized as important determinants of IV anesthetic disposition [48]. The inclusion of pulmonary drug uptake, cardiac output, and its regional disposition enables recirculatory models to identify the pharmacokinetic basis of interindividual differences in response to IV anesthetics attributable to age, disease, or drug-induced physiological disturbances. They can also be used to design target-controlled drug infusions (which do not result in early drug concentrations in excess of the target be-

cause of overestimation of the initial distribution volume) and to estimate pharmacodynamic parameters with greater precision [47].

5.2. Drug elimination

As mentioned earlier, systemic elimination is influenced by systemic extraction, which reflects the overall contribution of the different elimination routes to the extraction of the drug. Systemic extraction is related to hepatic (E_H) and/or renal extraction (E_R) according to the following expressions:

$$E_S = E_H \cdot \frac{Q_H}{CO_p} \quad (15)$$

and

$$E_S = E_R \cdot \frac{Q_R}{CO_p} \quad (16)$$

Thus:

$$E_H = \frac{E_S \cdot CO_p}{Q_H} = \frac{Cl_S}{Q_H} \quad (17)$$

$$E_R = \frac{E_S \cdot CO_p}{Q_R} = \frac{Cl_S}{Q_R} \quad (18)$$

where Q_H and Q_R represent the hepatic and renal plasma flows, respectively. According to equations 15 to 18, changes in hepatic or renal extraction induced by disease states will be reflected in the systemic extraction and systemic clearance of the drug.

The hepatic extraction of a drug may depend on changes in hepatic blood flow, protein binding, or intrinsic clearance. All these factors may be altered in different disease states. In this sense, hepatic blood flow may be altered in patients with congestive heart failure or in patients with hepatic disease [49-53]. Protein binding and intrinsic clearance may also be affected in patients with liver disease [52, 54, 55].

The renal extraction of a drug may depend on changes in renal blood flow, glomerular filtration, protein binding or intrinsic clearance by tubular excretion, etc. These factors may also be affected in several disease states. Renal blood flow and the glomerular filtration rate are altered in patients with congestive heart failure [53] or hemorrhagic shock. Protein binding may be affected in different clinical situations, such as hepatic or renal failure [56]. Intrinsic clearance by tubular secretion is altered in different renal pathologies.

5.3. Clinical applications

Recirculatory models usually use the plasma cardiac output of the patient, the parameters of the circulatory transport functions, and the systemic extraction coefficient as fundamental parameters as an alternative to classical elimination and distribution parameters. This offers a potential advantage over classic compartmental models since the model estimates the components of the elimination and distribution clearances separately; that is, cardiac output and systemic extraction. In clinical practice, the most suitable way of working with this model would be to estimate the plasma cardiac output of the patient by a thermodilution technique [57] and then introduce the estimated values into the function of the model in order to optimize the other pharmacokinetic parameters later by nonlinear regression. However, in most studies addressing clinical pharmacokinetics the cardiac output of the patient is not measured, such that a reference value must be assumed or optimized by nonlinear regression as a parameter of the model.

The modifications in systemic and distribution clearances induced by changes in plasma cardiac output or in the systemic and tissue extraction coefficients may affect plasma levels and the pharmacological response in different ways during the initial distribution of the drug or after a recirculation process.

Modifications in cardiac output may be responsible for changes in the elimination of drugs in different disease states, these not being accompanied by changes in the functionality of organs of elimination, such as the kidney or the liver. Thus, in situations such as congestive heart failure, hemorrhagic shock, or hypermetabolic states, alterations in the cardiac output or regional blood flow of patients that lead to a decrease or an increase in the drug elimination clearance may occur, with no modifications to the intrinsic elimination capacity of the liver or kidney. Additionally, changes in cardiac output may also account for variations in the distribution clearance of drugs when tissue blood flows are modified, as previously reported [58], where a correlation between the intercompartmental clearance of alfentanil and the measured cardiac output of the patient was found.

One of the advantages of recirculatory models is that they allow simultaneous evaluation of the changes occurring in the distribution and elimination of drugs as a result of changes in cardiac output.

Among other factors, the systemic extraction coefficient is related to the functional status of the organs of elimination, that is, the liver or kidney. The changes in the functionality of eliminating organs as a consequence of a given pathology will be reflected in the systemic extraction coefficient. Thus, modifications in the intrinsic metabolic clearance of a liver marker with low hepatic extraction, such as antipyrine, in hepatic diseases [59, 60] will be reflected in a reduction in the systemic extraction coefficient of the model, which in turn explains the reduction in metabolic clearance. Additionally, the reduction in renal functionality in patients with nephropathies will in turn be reflected in the systemic extraction coefficients of drugs that are eliminated through the kidney, such as the aminoglycoside antibiotics [60]. Moreover, changes in the regional blood flow of the liver or kidney and in drug protein binding induced by disease states may be reflected in the systemic extraction coefficient. Finally, changes in the

tissue extraction coefficient of a drug in different types of patients reflect changes in the physiological factors that control tissue distribution, such as regional blood flow, membrane and cell permeability, or tissue binding, as a result of disease states.

Table 2 shows some disease states that can modify the cardiac output of the patient or in the tissue and systemic extraction or in the distribution volumes of the drug. Thus, in patients with chronic renal failure a reduction occurs in the systemic clearance of drugs that are wholly or partially eliminated through the kidney, such as the aminoglycoside antibiotics. This decrease in clearance is brought about by a decrease in renal functionality, reflected in a decrease in the systemic extraction coefficient. However, there are other disease states in which a reduction or an increase occurs in the systemic clearance of drugs due to a reduction or an increase in plasma cardiac output, as happens in patients with congestive heart failure or in patients with a hypermetabolic condition, respectively.

Disease state	Drug	CO_p	E_s	E_T	Cl_s	Cl_D	V_p	V_T	Ref
ESRD*	Aminoglycosides	\leftrightarrow	\downarrow	?	\downarrow	?	\uparrow	\uparrow	[61]
									[62]
									[63]
Obesity	Thiopental	\uparrow	\uparrow	\leftrightarrow	\uparrow	\uparrow	\uparrow	\uparrow	[6]
									[64]
									[65]
CHF**	Lidocaine	\downarrow	\leftrightarrow	\leftrightarrow	\downarrow	\downarrow	\downarrow	\leftrightarrow	[66]
Hypermetabolic syndrome	Aminoglycosides	\uparrow	\leftrightarrow	?	\uparrow	\uparrow	\uparrow	\uparrow	[67]
Aging	Thiopental	\downarrow	\leftrightarrow	\leftrightarrow	\downarrow	\downarrow	\uparrow	\uparrow	[65]

ESRD* End-Stage Renal Disease
CHF** Congestive Heart Failure

Table 2. Disease states with possible influence on the parameters of the recirculatory model for different drugs.

Recirculatory models allow pathophysiological changes related to liver disease to be assessed. The reduction in the area under the curve of the transport function of ICG after the first recirculation reflects the increase in cardiac output characteristic of these patients. After successive recirculations, the change in slope of the ICG profile can reflect changes in the elimination clearance [68].

Another clinical application of recirculatory models is the optimization of pharmacokinetic/pharmacodynamic (PK/PD) models for the characterization of the rapid response of rocuronium in humans using a recirculatory model coupled to an effect compartment [5]. When compared with a conventional model, the authors found a significant difference between the k_{e0} and CE_{50} calculated with either model. They also demonstrated a significant correlation between CO and k_{e0} for both types of models, which was much stronger with the recirculatory

one. These findings have certain clinical implications since it can be expected that patients with a lower CO will require a longer time for the effect to be reached [5]. Recently, a population analysis used for fitting the data of rocuronium in patients to a circulatory model has provided insight into the role of vascular mixing and interstitial diffusion. The results suggest that rocuronium is distributed in the interstitial space by passive diffusion where it undergoes diffusion-limited distribution. The body distribution depends on cardiac output and on the apparent permeability surface area product [0.6 l/min). It has also been concluded that the heterogeneity of the blood transit time through the systemic circulation decreases and cardiopulmonary volume increases, respectively, with cardiac output [69].

The observed effect of β -adrenergic blockers such as propranolol on the disposition of markers such as ICG and antipyrine using a recirculatory model demonstrates that propranolol decreases cardiac output at the expense of the non-splanchnic intravascular circuit. This phenomenon may explain the need for decreased intravenous anesthetic doses in the presence of β -adrenergic blockade with important clinical implications [18, 70].

6. Conclusion

Recirculatory models are a type of physiologically based pharmacokinetic model (PBPK) that offer an alternative to the classic compartmental models and other models in the pharmacokinetic analysis of clinical data.

Although given its complexity the clinical use of these models is limited, they have important advantages in that they are able to characterize the first passage of the drug in the systemic circulation and evaluate changes in cardiac output or regional blood flow and its impact on distribution and elimination clearances induced by disease states. These models are also able to assess changes in the pharmacokinetics associated with concomitant use of other drugs and can be used to perform pharmacokinetic/pharmacodynamic studies (PK/PD). Anesthetics constitute one of the pharmacological groups where this type of model has great clinical interest.

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