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Basic Concepts of Recirculatory Pharmacokinetic Modeling

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Introduction

The science of pharmacokinetic analysis embodies the description of the time-dependant concentration changes of a drug. Pharmacokinetic models may be used to predict the behavior of the drug in individuals, preferably under various circumstances. In the practice of anesthesia pharmacokinetics can be studied on the work floor. Differences in pharmacokinetics between individuals are observed on a daily basis. Factors responsible for the inter-individual variability are being studied extensively and more data become available in time. From these data the significance of demographic factors such as age and gender become increasingly apparent. Other factors like weight or lean body mass may substitute parameters for physiologically based variations in pathways of distribution and elimination. Obesity e.g. may be considered as a disproportionate increase of adipose tissue mass. Peripheral blood flow must increase to supply this extra tissue. As organ-specific blood flow remains equal, cardiac output will increase. The surplus of fatty tissue will act as an extra depot for lipid-soluble drugs like thiopental. As a consequence, peak-concentrations are expected to decrease, whereas the terminal half-life and steady state volume of distribution may increase.[1] Physiological parameters such as cardiac output, flow and tissue distribution have a more direct relationship with pharmacokinetic parameters like distribution volumes and clearances. Inclusion of a parameter like cardiac output into a pharmacokinetic model may improve the accuracy of the model, especially with respect to fast acting drugs like intravenous anesthetics. The influence of changes in cardiac output on the pharmacokinetics of anesthetic agents is under research. The largest impact of a change in the cardiac output on the behavior of drugs can be expected in compounds showing a flow-limited distribution and/or clearance such as thiopental[1], lidocaine[2], alfentanil[3] and propofol.[4] Pulmonary uptake may also be of influence on the early-phase distribution of a substance. These influences will be described in more detail further on in this chapter.

Another factor of influence on drug behavior is the method of administration. A rapid intravenous bolus injection will be best characterized by a set of pharmacokinetic parameters different from parameters derived after a prolonged intravenous infusion, as is used in devices for target controlled infusion (TCI).[5,6] Prolonged infusion of a drug with a rapid clearance and extensive distribution, such as propofol, may be better characterized by a 3-compartment model, whereas for a bolus injection a 2-compartment model may suffice. In a study published by Schnider and colleagues, is shown that propofol concentrations after a bolus injection were not adequately described

by the pharmacokinetics derived from blood samples taken during a propofol infusion in the same patients.[7] The drug concentrations during the first 10 minutes after a bolus injection were significantly biased with an overestimation at minute 2 and 4 followed by a subsequent underestimation of the actual propofol concentration. Selecting the right pharmacokinetic model for the right type of administration and phase of interest (early-phase or steady-state) is important.

Selecting a pharmacokinetic model

A large variety of pharmacokinetic models exists ranging from very abstract to naturalistic.[8] The commonly used models are linear and time-invariant (Figure 1). Empirical models describe the relationship between input, the drug dose, and output, the plasma concentration, in a mathematical form without reference to a physiological or pharmacological explanation. Empirical models treat the human body as a black box. The key to this method is the fitting procedure. Compartmental models are most frequently applied, consisting of 2- or 3-compartments. These compartments may have a physiological (plasma, tissue) basis but are derived purely mathematically.

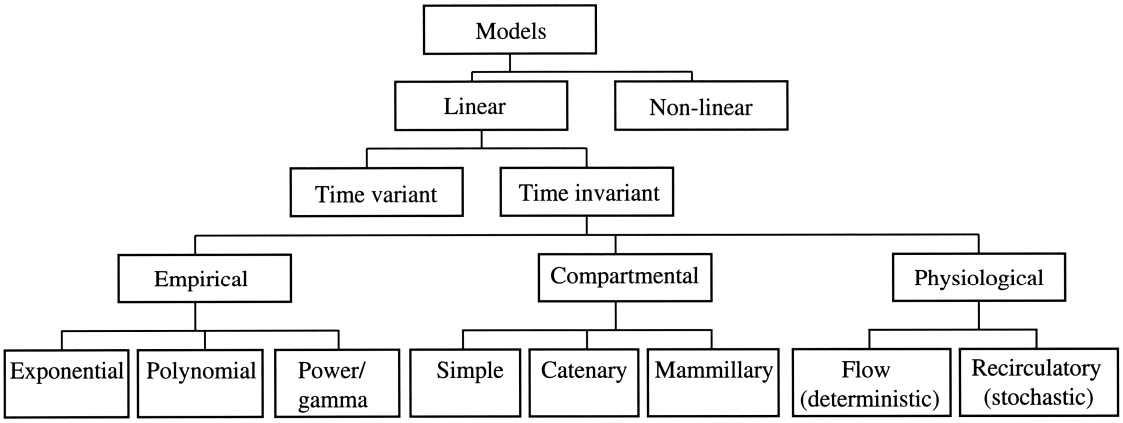

Figure 1 A taxonomy of pharmacokinetic models. Reproduced from J. Kuipers, Pharmacokinetic modelling of anaesthetics: The role of cardiac output. PhD thesis, with permission.

Compartmental models are based on the assumption of instantaneous mixing of the drug after a bolus injection within the central compartment. Distribution and elimination occur solely from the central compartment. Other

compartments serve as “peripheral” compartments, with “slow” equilibration constants, from which the drug is redistributed. By assuming complete initial mixing within the central compartment, which is actually not the case, the compartmental model becomes inaccurate when pulmonary uptake or the process of initial mixing in the first minutes after injection are studied.

The development of recirculatory models

In the process of the pharmacokinetic evaluation of concentration-time data, analysis is frequently performed by fitting data to a 2- or 3-compartment model. However, for some anesthetic agents this may not be the best model suited. More and more drugs are introduced that exhibit a very rapid initial distribution, resulting in the propagation of a clinical effect before complete mixing has occurred. Ignoring the mechanism of initial mixing may lead to significant deviations in the estimation of the volume of the central compartment.[9] Other drugs such as fentanyl, meperidine[10], sufentanil[11], propofol[12,13], ketamine[14] and lidocaine[15,16] are known to undergo substantial pulmonary uptake. Furthermore, in fast acting compounds the distribution appears to be flow dependant.[17] Including a flow parameter such as cardiac output into the model is therefore strongly desired.[1] Taking these factors into consideration, one may suggest that the examination of early phase pharmacokinetics based exclusively on conventional compartment modeling, may be insufficient[18] and provide inaccurate data.

One solution to the issues mentioned is the system dynamics approach as described by van Rossum.[19] This approach provides a different method of modeling by calculation of so-called body transfer functions. The transport function of the body (closed loop) is considered a stochastic process characterized by a density function of total body residence times. The relationship between the body transit time distribution and the body residence distribution is determined by the feedback-loop arrangement, the cardiac output and the extraction ratio. The cardiac output is included as an important hemodynamic variable in this model.[20]

Other models allowing recirculation have been introduced, constructed as catenary compartmental models with different compartments linked in a serial manner. In a study by Avram and colleagues, this model of concurrent disposition of ICG and thiopental allowed to analyze intravascular mixing by computing the recirculation of the intravascular marker ICG, combined with a

peripheral compartment for thiopental.[21] Further development led to recirculatory models using ICG as a marker for the intravascular compartment.[22] Finally, a combination of recirculatory compartments and peripheral slow and fast tissue compartments was developed that made the recirculatory model more physiologically based.[23]

For any drug the complete recirculatory model can be built on the basis of a model for ICG. Since the distribution of ICG is limited to the intravascular space, the ICG model describes the passage through the central and peripheral blood compartments. The central compartments are by definition located between the venous point of injection and the arterial point of sampling. The central intravascular part of the model, representing the flow through the heart and lungs, is best described by two compartments. Hereby, modeling of pulmonary uptake and redistribution is allowed. Since the mean transit time of one compartment is shorter that that of the other compartment, they are identified as the fast central and the slow central compartment. Peripheral compartments are described similarly. The compartments for ICG are considered to represent the effect of dispersion of ICG in the vascular tree. In the model this dispersion is simulated by so-called tanks-in-series, being very small consecutive compartments from which the drug is cleared exponentially. Parallel pathways can differ in the number of tanks in series and the proportion of the blood flow to the respective compartments.

For the test drug peripheral tissue compartments are added to the ICG model. These tissue compartments are similar to the compartments of other catenary models. The tissue compartments are coupled to the peripheral vascular compartments such that the slow vascular compartment is coupled to the slow tissue compartment. If the drug undergoes significant pulmonary uptake a pulmonary tissue compartment may be added[21] (see figure 2).

Recirculatory modeling in practice

Recirculatory models for different compounds such as thiopental[21], halothane[24], alfentanil[3,25], propofol[12], and rocuronium[26] have been described. As a marker for the intravascular compartment ICG was used. To adequately measure the recirculation of ICG the sampling frequency must be high; the process of initial mixing is complete within 5 minutes. The quality of model fitting is therefore highly dependent on the amount of blood samples taken within the first minutes after the bolus dose administration. From these samples the first-pass

concentration curve of ICG can be determined, described by two parallel pathways consisting of Erlang functions, represented by a number of tanks in series. A representation of such a model is depicted in figure 2.

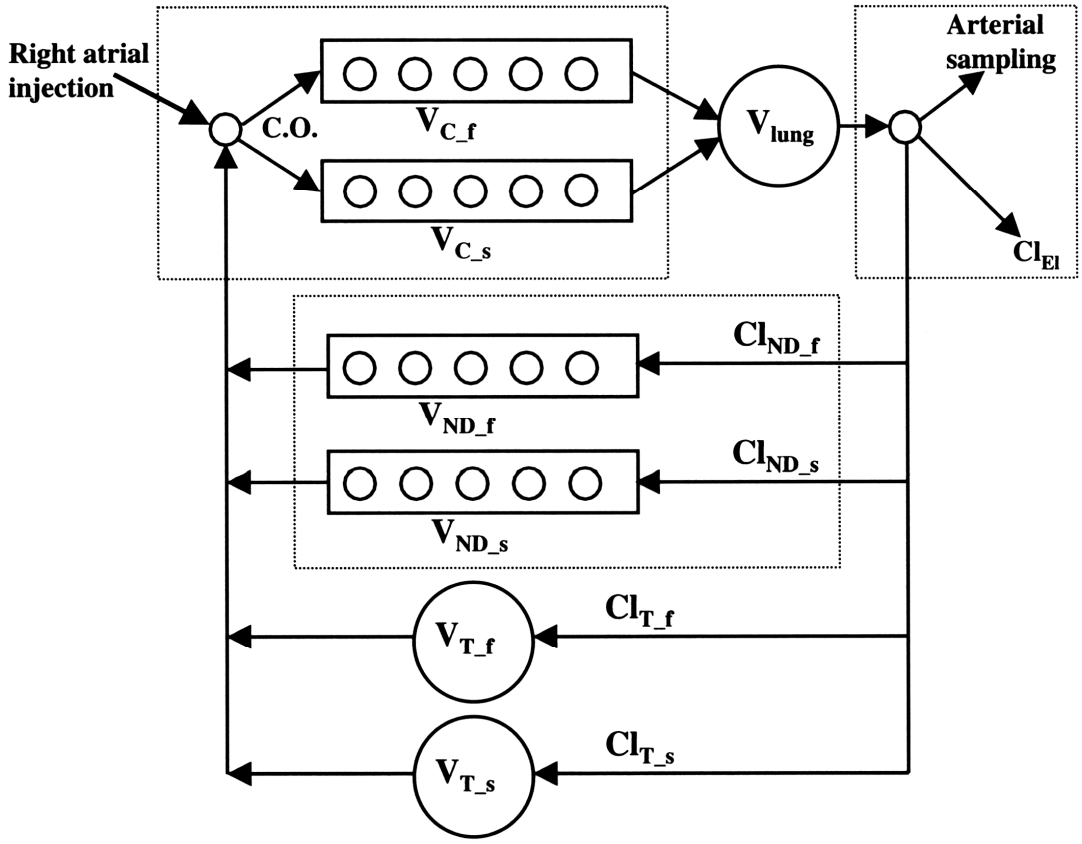

Figure 2. Recirculatory pharmacokinetic model used for analysis of indocyanine green and simultaneously injected drug (modified from Krejcie et al.[23]). The parts in the dashed boxes represent the recirculatory model for indocyanine green, the intravascular part of the model. These intravascular compartments are represented by a rectangle with five compartments, but the actual number of compartments may vary and has no physiological background. The intravascular model consists of a central part, receiving all of the cardiac output, divided in a slow (V_{C_s}) and a fast (V_{C_f}) central compartment and a peripheral part, divided in a slow (V_{ND_s}) and a fast (V_{ND_s}) peripheral compartment. The simultaneously injected drug distributes into organs and therefore, 3 tissue compartments are added to the intravascular indocyanine green model; the lung compartment (V_{lung}), a slow (V_{T_s}) and a fast (V_{T_f}) peripheral tissue compartment. The sum of the peripheral clearances equals the cardiac output. Reproduced from J. Kuipers, Pharmacokinetic modelling of anaesthetics; The role of cardiac output. PhD thesis, with permission.

The parameters derived from this model can now be combined with peripheral compartments to represent distribution and elimination as described above. Constructing such a model is possible using the SAAM II program (SAAM institute, University of Washington, Seattle, USA). It consists of a numerical mode and compartmental mode. The latter allows for the construction of a model on a canvas where the program attaches the formulas. The solver function of the program computes the parameters in an iterative way with fixed or relative weights (SAAM II manual). The statistics performed on the parameters are calculation of the standard deviation, fractional standard deviation and representation of a correlation matrix, covariance matrix or the residual sum of squares, including the Akaike criterion. Other statistical tests described are the one sample runs test to check for random scatter around the fit. The group of Krejcie uses the IDENT2 program to check for identifiability and estimability of the parameters.[27]

Results

As an example of differences in pharmacokinetic outcome using conventional 2-compartment modeling compared to recirculatory modeling, a short representation will be given of the results from a study performed by Kuipers and colleagues regarding the pharmacokinetics of rocuronium in patients.[26] In this study a recirculatory model has been used based on arterial ICG concentrations collected with a rapid sampling device. In addition, cardiac output was determined by dividing the dose of ICG by the area under the first-pass ICG concentration-time curve. Rocuronium had been selected as a model drug because of its fast onset of action. The effect of rocuronium could be quantified easily and reliably and be expected to be linked to cardiac output based on its dependency on the blood flow through the muscles. In addition, the effect measurements were included in a PK-PD model to determine the k_{e0} of rocuronium using compartmental modeling parameters and recirculatory modeling parameters. The recirculatory model, used to analyze indocyanine green and rocuronium pharmacokinetics and the rocuronium pharmaco-dynamics, was built like the model in figure 2, with the exclusion of the lung compartment and with the addition of an effect compartment placed after the arterial sampling site. The effect compartment was not included in the recirculatory system. The sum of the clearances through the parallel fast and slow non-distributive circuits for ICG equals the cardiac output. Rocuronium data were evaluated by addition of a fast and slow peripheral distributive compartment to the ICG model. The ratio between fast and slow peripheral

clearances was set equal for ICG and rocuronium, but the absolute values were allowed to differ. The pharmacokinetic data could well be fitted using recirculatory pharmacokinetics, whereas the two-compartment model showed large uncertainty regarding the drug behavior in the first minutes. A pharmacokinetic-pharmacodynamic analysis could be done using recirculatory pharmacokinetics as well. Some of the parameters determined by the recirculatory model and the two-compartment model can be seen in table 1.

Table 1 Pharmacokinetic and pharmacokinetic-dynamic parameters of rocuronium determined by a recirculatory model and 2-compartment model (mean and SD). For abbreviations see legend of figure 2. The unit of k_{e0} is (min^{-1}), of EC_{50} is ($\mu g.L^{-1}$)

	V_C	V_{ss}	V_T	Cl_{EL}	V_1	V_2	Cl_{12}	K_{e0}	EC_{50}
Recirculatory									
Mean	1.52	17.29	14.77	0.45				0.129	876
SD	0.40	4.82	4.85	0.11				0.036	118
2-compartment									
Mean		10.50		0.50	6.76	3.73	0.43	0.239	684
SD		3.54		0.14	1.69	1.98	0.20	0.104	97

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The results showed correlation between cardiac output and the central volume of ICG and rocuronium. The clearances correlated significantly with cardiac output as well. The values of k_{e0} and EC_{50} obtained with the compartmental model were significantly different from the values estimated with the recirculatory model. The k_{e0} determined using the compartmental model was nearly double and the EC_{50} approximately 22% lower compared to those determined on the basis of the recirculatory approach. The k_{e0} of rocuronium showed correlation with cardiac output, although the correlation estimated from the recirculatory model was much stronger. This could well be explained by the difference in accuracy of fitting in the first minutes. It is known that by selecting a model, i.e. a 2- or 3-compartment model, the initial drug concentration may be either seriously underestimated or overestimated. In contrast, the recirculatory model was capable of accurately describing the front-end kinetics.[28] The correlation between cardiac output and effect site-equilibration time could be observed clinically as well. The patient with the lowest cardiac

output (2.4 $L.min^{-1}$) showed 90% twitch depression after 2.5 minutes, whereas the patient with the highest cardiac output (5.0 $L.min^{-1}$) needed only 1.5 minutes for near-complete relaxation. In the context of a rapid sequence induction, this means that not only the dose of muscle relaxant, but also the physiological status of the patient needs consideration. This supports the need for more accurate characterization of pharmacokinetic and pharmacodynamic parameters in the early phase when using fast-acting agents.

Conclusion

With the introduction of an increasing number of compounds exhibiting a rapid, flow dependant distribution and a rapid onset of effect before complete mixing, it becomes increasingly important to look at alternatives in pharmacokinetic modeling. At present, the most frequently used approach is the conventional 2- or 3- compartment model. This model is based on the assumption of complete mixing in the central compartment upon bolus-injection of the compound. In this model recirculation, flow-dependant distribution or pulmonary uptake are not taken into account. The introduction of recirculatory modeling as described by Krejcie et al.[23] provides a tool to model data in these situations. Disadvantages of recirculatory modeling are innate to the small time frame in which the processes take place. First of all, it is necessary to administer a marker for the intravascular space (ICG) in combination with the compound of interest. Secondly, in order to have sufficient data to model the first-pass circulation of ICG, the sampling frequency must be high; every few seconds. Besides the practical implications of this methodology, it implies that the quality of the fit is highly dependant on the number of data points within the first 3 minutes. Accurate modeling of early-phase pharmacokinetics is very important, since the better the understanding of the behavior of a drug in a "standard" situation (read "healthy subject"), the easier to predict the outcome when parameters change. Extending the knowledge in this field may lead to a better prediction of drug behavior in e.g. elderly patients or in patients with an altered cardiovascular state. The development of techniques to measure cardiac output in a non- or minimal invasive way, preferably on a beat-to-beat basis, may lead to fine-tuning of the pharmacokinetics of intravenous anesthetics on a patient-basis. In addition, it has also been shown that recirculatory modeling can be used in pharmacokinetic-pharmacodynamic modeling. This may lead to differences in the estimation of k_{e0} and EC_{50} compared to conventional approaches, as has been shown in the paragraph above.

In conclusion, recirculatory modeling may produce a more accurate prediction of actual blood and tissue drug concentrations, especially for rapid acting agents during rapid changes in concentration.

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