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TUTORIAL

Physiological spaces and multicompartmental pharmacokinetic models

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The idea of body compartments has its origins in physiology and antedates their use in both physiologically-based predictive pharmacokinetic models and in the simpler compartmental models used to analyze pharmacokinetic data. Whereas physiologically-based pharmacokinetics has evolved to use increasingly sophisticated organ-based models, most compartmental models for data analysis are used without regard for their underlying physiological basis. However, detailed analysis of inulin and urea kinetics has offered some understanding of the physiological basis underlying some three-compartment pharmacokinetic models. In addition, these simple models have yielded new insight into physiological phenomena.

Initial Characterization of Physiological Fluid Spaces

In the mid-nineteenth century long-standing empirical interest in bodily fluids was brought into sharper focus by Claude Bernard[1] who wrote that modern scientific or experimental medicine is based on knowledge of the composition and influence of the "milieu intérieur". At that time, initial measurements of total body water could be obtained by desiccation of cadavers[2] and blood volume was estimated from the volume of exsanguinated blood collected from two criminals who were executed by guillotine.[3]

In the twentieth century various substances were introduced as indicators to measure physiological space volumes using the dilution principle. In 1915, Keith et al.,[4] used intravenous injections of phenol red to estimate plasma volume from the early distribution kinetics of this dye, then calculated blood volume from the hematocrit. In 1940, Painter[5] used urea and sulfanilamide distribution volumes to estimate total body water in dogs and confirmed the accuracy of her results by desiccation. Measurement of the extracellular fluid volume has been more challenging and a number of different markers have been used, including electrolytes such as sulfate and bromide and the carbohydrate nonelectrolytes mannitol and inulin.[2] More recent studies have employed radioisotopes or stable isotope labeled compounds to provide more accurate estimates of distribution volumes of naturally occurring compounds that had been identified as physiological space markers. For example, both deuterium oxide[6] and carbon-14 labeled urea[7] have been used to measure total body water.

These early studies did not extend their analysis to a multicompartmental analysis of the distribution kinetics of the marker compounds. However, in 1949, Gaudino[8] administered inulin to healthy subjects and obtained plasma level vs. time curves that he manually fitted to a two-compartment model. As a result, interstitial fluid has been assumed to be kinetically homogenous in its equilibration with intravascular space, leading to the conventional three-compartment catenary model of body fluid spaces shown in Figure 1A.

Evolution of Multicompartmental Pharmacokinetic Models

Teorell has been credited with being the father of both multicompartment and physiologically-based models.[9] In the first of two companion publications, he solved the differential equations for a two-compartment model in which the central compartment corresponded to intravascular space and the peripheral compartment represented the aggregate of perfused tissues.[10] Renal, hepatic, and pulmonary elimination routes were modeled as occurring from the central compartment. In the 1960's the development of appropriate chemical assays [11] and general availability of digital computer methods[12] facilitated kinetic analysis of both endogenous compounds and pharmaceuticals. In most cases, multicompartmental models used for routine analysis of pharmacokinetic data were based on curve fitting without regard for their underlying physiological

basis. Non-compartmental pharmacokinetic models also were introduced by Oppenheimer et al.,[13] and became increasingly popular.

Another important development was the introduction of more sophisticated multicompartment physiologically-based models. In a landmark study, Price[14] modeled thiopental pharmacokinetics with a four-compartment model in which drug distributed rapidly from the intravascular space to visceral organs and more slowly to muscle and fat. The model incorporated published values for tissue mass, blood flow, and thiopental blood/tissue partition ratio but made the assumption that thiopental was not metabolized or excreted during the study period. Price then implemented this model on a digital computer to compare its predictions with actual measurement of thiopental in tissue obtained during surgical operations on human subjects who had received an intravenous thiopental dose. In order to resolve questions regarding the relative importance of thiopental distribution and elimination, Bischoff and Dedrick[15] used a chemical engineering approach in which the intravascular compartment of their model was connected with a series of compartments representing visceral, poorly perfused lean tissue, and adipose tissue. This model also incorporated existing values for tissue partitioning and blood flow, as well as compound elimination rate. The authors found a close agreement between their a priori predictions and previously published experimental results. In a labor-intensive study, Benowitz et al.,[16] compared lidocaine plasma-concentration vs. time data obtained in monkeys after both bolus injection and prolonged infusion with those simulated from a seven-compartment anatomically-based prediction model that incorporated lidocaine binding to erythrocytes, organ blood flows, and plasma/organ tissue partition ratios.

The close correspondence in these studies between observed and predicted plasma concentration values provided a major impetus for the further development and refinement of physiologically-based pharmacokinetic models which are now widely used in both drug development[17] and regulatory evaluation.[18] However, because of the number of parameters included in these models, they are intended for predicting rather than analyzing pharmacokinetic data.

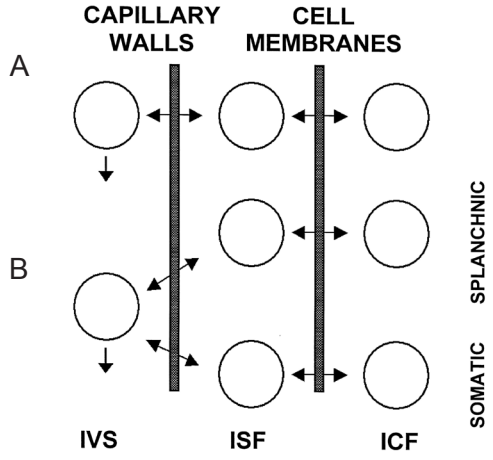

Figure 1. The conventional model of physiological body fluid spaces is shown in Panel A. The current model shown in Panel B is based on evidence that the interstitial fluid space is kinetically heterogeneous with transfer occurring more rapidly across splanchnic than somatic capillaries. In most cases physiological spaces have been measured by injecting marker compounds into the intravascular space. Their elimination is also assumed to occur from this compartment. IVS = intravascular space, ISF = interstitial fluid space, ICF = intracellular fluid space.

Multicompartmental Models of Physiologic Spaces

Retrospective inspection of the figure presented by Gaudino[8] indicates systematic errors in curve fitting that suggest that there are at least two kinetically distinct interstitial fluid compartments. This was confirmed by Henthorn et al.,[19] who demonstrated that two peripheral compartments were needed to model the distribution of inulin and gallamine from the intravascular space to the interstitial fluid. Previously, Sherwin et al.,[20] had demonstrated that a three-compartment model was also needed to model the heterogeneous rate of insulin distribution within extracellular fluid. Glucose was infused during the study to maintain plasma glucose concentrations at a constant level. Because the time course of the glucose infusion rate paralleled the distribution of insulin to the slowly equilibrating peripheral compartment, they concluded that this compartment was largely composed of skeletal muscle. The more rapidly equilibrating compartment was thought to consist of the heart and splanchnic organs. Parenthetically, this is one of the few examples in which the locus of drug action has been shown to correspond to a major drug distribution compartment.

Isotopically-labeled urea has been used to demonstrate that, after rapid intravenous injection, urea also distributes from a central compartment corresponding to intravascular space to two kinetically distinct peripheral compartments.[21] So transcapillary exchange can be identified as the rate-limiting step in the distribution of both inulin and urea, leading to the revised schema of physiological body spaces shown in Figure 1B. The kinetic heterogeneity of transcapillary exchange demonstrated by these studies presumably reflects the fact that the fenestrated capillaries of splanchnic vasculature allows more rapid transit of polar compounds than is possible through the intercapillary junctions of continuous somatic capillaries.[22]

When both inulin and urea kinetics were studied simultaneously in dogs, blood flows (Q) and permeability coefficient-surface area products (P·S) could be estimated from the intercompartmental clearances (CL_I) linking their transfer between the intravascular space and the two peripheral interstitial fluid compartments.[21] These estimates were calculated from a rearrangement of the following permeability-flow equation that

was used by Renkin[23] to analyze solute transfer across single capillaries.

$$CL_I = Q\,(1 - e^{-P \cdot S/Q}) \quad (1)$$

Separate equations for inulin and urea transfer were solved simultaneously after making the assumption that the ratio of the P·S values for inulin and urea was the same as the ratio of their free water diffusion coefficients. Using this approach, the sum of the blood flows estimated for the two interstitial compartments was found to average 97% of cardiac output measured by indicator dilution. Similar results were obtained subsequently when inulin and urea kinetics were analyzed simultaneously in healthy human subjects.[24]

Physiological Insights Gained from Detailed Analysis of Simple Compartmental Models

The central compartment of most pharmacokinetic models is rarely identified as intravascular space unless the drug is administered fairly rapidly by the intravenous route and several blood samples are obtained in the first 30 minutes after administration. Central compartment volumes obtained by measuring plasma concentrations also need to be corrected for drug partitioning into erythrocytes before comparisons are made with expected values for intravascular space. Plasma protein binding should also be measured to correct total distribution volume estimates, unless calculations are based on measured unbound drug concentrations. Drugs that are very tightly bound to plasma proteins (e.g. thyroxine) can be expected to have total apparent distribution volumes approximating extracellular fluid space when calculated from total (bound + unbound) plasma concentrations.[25]

Novel insight into the mechanism of theophylline transcapillary exchange was provided in a pharmacokinetic study in which theophylline was administered intravenously to dogs, simultaneously with inulin and urea as reference compounds.[26] The distribution of all three compounds was analyzed with three-compartment mammillary models similar to that shown in Figure 1B. After correction for erythrocyte partitioning, the central compartment volume calculated for theophylline corresponded to the intravascular space estimates calculated for inulin and urea. Unexpectedly, the theophylline intercompartmental clearances representing theophylline distribution to the peripheral compartments were similar to the corresponding compartmental blood flows estimated from Equation 1 on the basis of the inulin and urea intercompartmental clearances. Even though theophylline is polar and has a higher molecular weight and slower diffusion constant than urea, its transit from the intravascular space was faster than that of urea. This suggests that diffusion of theophylline across capillaries is carrier mediated. From the clinical standpoint, it is likely that this rapid rate of transcapillary exchange contributes to the high frequency of sometimes fatal adverse reactions that have been reported when theophylline is administered to patients by rapid intravenous injection rather than by infusion over at least 20 minutes.[27]

Even when simple compartmental pharmacokinetic models are used, the goal should be to incorporate all possible sources of data in the model. Studies of drug kinetics during hemodialysis have been particularly derelict in this regard, particularly with respect to measuring and including the amount of drug actually removed by dialysis.[28] In an instructive study of the effect of hemodialysis on the pharmacokinetics of N-acetyl procainamide, drug concentrations both entering and leaving the dialysis cartridge were incorporated in the analysis together with the amount of drug recovered in the dialysis bath fluid.[29] A three-compartment model was used to analyze drug distribution and elimination, starting in the pre-dialysis period and continuing during and for three hours after hemodialysis. As in previous studies with this drug, the volume of the central compartment corresponded to expected values for intravascular space. But an unexpected and novel finding was that the intercompartmental clearance linking this compartment to the slowly equilibrating peripheral compartment was reduced by an average of 77% during hemodialysis and returned only partially to predialysis values for at least three hours after hemodialysis was completed. In order to elucidate the mechanism responsible for this finding, inulin and urea kinetics were studied simultaneously before and during hemodialysis of dogs with intact kidneys.[30] Similar decreases in the slow intercompartmental clearances of inulin and urea were observed. When analyzed by Equation 1, these were found to result from a 90% average reduction in blood flow to this compartment. Blood flow to the more rapidly equilibrating splanchnic compartment and the permeability coefficient-surface area products for both peripheral compartments remained unchanged. Subsequent investigations suggest that these changes represent a physiological response to the perceived volume stress that is associated with hemodialysis and that alterations in the mediation of this decrease in blood flow to tissues in the slowly equilibrating compartment may be responsible for the skeletal muscle cramps that some hemodialysis patients experience.[31]

Most data-driven pharmacokinetic studies do not provide novel physiological insight. However, these two examples demonstrate their theoretical potential and emphasize the value of incorporating relevant in vitro results and available experimental measurements in the conduct and analysis of these studies.

Choice of Modeling Approach

By their very nature, all models represent an oversimplification of underlying physiological reality.[12] So the proper choice of model, and even of modeling approach, depends of its intended purpose of use. For example, even most multicompartment pharmacokinetic models assume instantaneous distribution of intravenously administered compounds within the intravascular space. However, analysis of the distribution and effect kinetics of intravenously administered anesthetic agents often requires

specific characterization of the time course of intravascular mixing. For that purpose, a compartmental modeling approach, such as that developed by Henthorn et al.,[32] is required that is more detailed than that used in most pharmacokinetic models. On the other hand, physiologically-based models are appropriate for a priori pharmacokinetic predictions and non-compartmental models are generally acceptable for studies conducted during the process of routine drug development.

Conflict of interest

The author has no conflict of interest.

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