The Øie-Tozer Model of Drug Distribution and its Suitability for Drugs with Different Pharmacokinetic Behavior

Abstract

Introduction: Drug distribution is a major pharmacokinetic process that affects the time course of drug concentrations in tissues and biological fluids and the resulting pharmacological activities. Drug distribution may follow different pathways and patterns and is governed by the drug's physicochemical properties and the body's physiology. The classical Øie-Tozer model is frequently used for predicting volume of drug distribution and for pharmacokinetic calculations.

Areas covered: Suitability of the Øie-Tozer model for drugs that exhibit different distribution patterns is critically analyzed and illustrated using a pharmacokinetic modeling and simulation approach. It is demonstrated that the major limitation of the Øie-Tozer model stems from its focus on the total drug concentrations and not on the active (unbound) concentrations. Moreover, the Øie-Tozer model may be inappropriate for drugs with non-linear or complex pharmacokinetic behavior, such as biopharmaceuticals, drug conjugates, or for drugs incorporated into drug delivery systems. Distribution mechanisms and alternative distribution models for these drugs are discussed.

Expert opinion: The Øie-Tozer model can serve for predicting unbound volume of drug distribution for 'classical' small molecular weight drugs with linear pharmacokinetics. However, more detailed mechanism-based distribution models should be used in pre-clinical and clinical settings for drugs that exhibit more complex pharmacokinetic behavior.

Keywords: volume of distribution, plasma protein binding, displacement of drug from plasma proteins, pharmacokinetic modeling
1. Introduction

Drug distribution is a major pharmacokinetic process that affects the time course of drug concentrations in tissues and biological fluids following drug administration and the magnitude and duration of pharmacological activities. Drug distribution is a complex process which may follow different pathways and patterns that are dependent on the drug's physicochemical properties and the physiological processes within a specific patient. Individual drug's distribution pattern following systemic administration can range from presence in systemic circulation only (e.g., heparin), up to extensive permeation and binding to major organs and tissues (e.g., amitriptyline). Importance of drug distribution was recognized early during development of quantitative pharmacology, and the concept of volume of distribution, a key pharmacokinetic parameter that relates the total plasma (systemic) drug concentration to its amount in the body, was introduced in 1934 by Dominguez [1], a decade prior to introduction of pharmacokinetics term by Dost in 1953 (for excellent reviews of history of pharmacokinetics see [2, 3]).

Drug distribution patterns and their quantification using volume of drug distribution are among the primary considerations in drug discovery, development, and their clinical use. Numerous studies have accessed the theoretical and applied aspects related to estimation of volume of distribution and its use in pharmacokinetic calculations [4, 5]. The scientific theory of pharmacokinetics and its major concepts were laid out in the second part of the previous century (1960's-1980's) by several research groups [2, 3]. Major contributions to the concept of drug distribution at that period were seminal papers by Wilkinson and Shand [6] and by Gibaldi and McNamara [7] that were based on previous works of Gillette and introduced the following formula for drug distribution [8]:

\[
V_{SS} = V_P + V_T \cdot \frac{f_{up}}{f_{uT}}
\]  

(1)

where \(V_P\) and \(V_T\) are the volumes of plasma and tissues, respectively; and \(f_{up}\) and \(f_{uT}\) are the fractions of drug unbound in the plasma and tissues, respectively. This formula is based on assumption that the value of volume of distribution reflects the relative drug amounts that are present in the plasma vs. tissues. More detailed form of this formula was introduced by Svein Øie and Thomas N. Tozer in 1979 [9] and was termed the Øie-Tozer model of drug distribution. According to this model, volume of drug distribution is calculated as:

\[
V_{SS} = V_P \cdot (1 + R_{E/I}) + V_P \cdot f_{up} \cdot \left(\frac{V_E}{V_P} - R_{E/I}\right) + V_R \cdot \frac{f_{up}}{f_{uT}}
\]  

(2)
where $R_{E/I}$ is the extravascular/intravascular ratio of binding proteins, and $V_P$, $V_E$, and $V_R$ refer to the volumes of plasma, extracellular fluid, and remainder fluid, respectively. Both these equations derive from assumptions that the drug molecules in the body are distributed into kinetic pools that are in equilibrium (2 or 3 pools that correspond to the individual body fluids, Eq. 1 or 2, respectively), and linearity of the underlying pharmacokinetic processes (i.e., lack of saturation of processes of drug transport between the pools, protein binding, and elimination). The scheme of the 3-pool model of drug distribution is shown in Figure 1.

Equation 2 has been derived by Øie and Tozer based on law of mass action and assumption that unbound drug concentrations in different body fluids are equal. According to this equation, volumes of the individual body fluids and distribution of drug-binding protein/s between these fluids are the major parameters that determine the volume is distribution for an individual drug. For a normal 70-kg man, it is usually assumed that the volumes of plasma, extracellular fluid, and remainder fluid are 3 L, 12 L, and 27 L, respectively. Therefore, Equation 2 helps to interpret the volume of distribution value for individual drug and its relation to the pattern of its penetration and protein binding in the individual body fluids. For instance, the smallest value of volume of distribution for albumin-binding drug is 7 L, reflecting relative concentrations of albumin in the plasma and extravascular fluids ad the volumes of these fluids [9]. For a drug that does not bind proteins, the volume of distribution is a sum of volumes of body fluids to which it penetrates (i.e., 3, 15 and 42 L for a drug that stays in the plasma, distributes to the extracellular fluid, or in the total body water, respectively). From these examples, it can be seen that the Øie-Tozer model made possible physiologically-based interpretation of the observed volumes of drug distribution based on prior knowledge on drug ability to penetrate into different body fluids and on its protein binding properties. Indeed, introduction of the Øie-Tozer model in 1979 has been a major achievement in the field of pharmacokinetics that served and continues to serve generations of researchers and clinicians. Specifically, Øie-Tozer model is frequently used to predict and interpret volume of drug distribution based on in silico, pre-clinical and clinical data, to predict changes in drug distribution in pathological states (e.g., in hypoalbuminemia due to hepatic or renal disease) or due to drug interactions (protein binding displacement), to calculate drug's loading dose, etc.

Since the publication of the Øie-Tozer model many other approaches for interpretation and prediction of volume of drug distribution have been proposed. Majority of these approaches are based on estimation of extent of drug distribution to the body tissues using
physiologically-based pharmacokinetic (PBPK) models [10]. These models are based on analysis of drug properties (lipophilicity, pKa, protein binding, etc.) and tissue properties (composition, perfusion, etc.) that affect drug distribution to the individual tissues. Analysis of drug’s volume of distribution (and other pharmacokinetic parameters) can be done by developing PBPK model that incorporates all the major tissues to which the drug is penetrating. Alternatively, this analysis can be performed using limited set of parameters, such as drug distribution to selected tissues [4, 11], in vitro drug-tissue binding [12, 13], drug interaction with artificial membranes [14], etc. Volume of distribution of a specific drug can be also predicted based on its pharmacokinetic data in other species (allometric scaling) and taking into account parameters that describe drug's molecular properties (molecular descriptors) [15, 16]. For some drugs, presence of non-linear (or unique) drug distribution processes makes analysis of volume of distribution difficult and requires development of 'customized' pharmacokinetic models. For instance, target-mediated drug disposition (TMDD) models [17] can be used for drugs whose pharmacokinetics is substantially governed by extent of binding to the drug target (i.e, specific receptor, enzyme, target tissue, etc., see Section 2.3).

2. Applicability and limitations of the Øie-Tozer model

The 2 or 3-pool models of drug distribution (that will be collectively termed in this review as 'the Øie-Tozer model') are widely used in the scientific community and in the clinics for interpretation of VSS and fAUC values, calculations of drug doses and dose adjustments (e.g., due to drug interactions [18]), predicting volume of drug distribution for new drugs/chemicals [19, 20], inter-species scaling of volume of distribution (e.g., for prediction of human VSS based on animal data [21]), etc. There is no doubt that the Øie-Tozer model can be generally applied for drugs characterized by linear pharmacokinetic behavior and can provide valuable insights on pharmacokinetics of these drugs. Indeed, in a recent study by the Pharmaceutical Research and Manufacturers of America (PhRMA) group, the Øie-Tozer model was found to be superior to many other approaches for the prediction of human volume of distribution at steady state (VSS) [22]. However, application of the Øie-Tozer model can be inappropriate for certain drugs or drug classes due to the following factors: 1) focusing on the total and not unbound drug concentrations in the body fluids, 2) lack of drug distribution equilibrium, 3) non-linearity of drug distribution processes, and 4) masking of drugs' physicochemical properties by the drug delivery system. Effects of these factors on the drug's distribution...
behavior are analyzed in detail in this review and are illustrated using a pharmacokinetic modeling and simulation approach.

2.1 Focus on total vs. unbound drug concentrations in the body fluids

Value of volume of distribution relates the total plasma (systemic) drug concentration to its amount in the body and reflects the relative drug amounts that are present in the plasma vs. tissues at steady state conditions. The value of $V_{SS}$ therefore is dependent on extent of tissue permeation of the drug that derives from kinetics of its permeation vs. kinetics of its elimination (see Figure 1).

Let's consider effect of changes in drug distribution pattern on volume of distribution and the shape of the concentration vs. time curves for a drug that rapidly equilibrates between plasma and highly-perfused tissues. Kinetically, molecules of such drug will form four different pools/compartments: unbound and protein-bound drug in the plasma, and unbound and protein-bound drug in the highly-perfused tissues. For such drug we expect faster tissue distribution kinetics as compared to elimination, and very rapid equilibrium of drug-protein association/dissociation kinetics [23]. No true distribution steady state will be obtained following intravenous administration of such drug (see Figure 2), due to gradual permeation of the drug to the tissues (e.g., extracellular and intracellular fluids) following each dosing. For such drug, partial displacement from plasma proteins, e.g. due to drug interaction, will induce drug redistribution from the plasma to the tissues, leading to increased $f_{up}/f_{uT}$ ratio and increased volume of distribution. These changes in drug distribution will change the shape of plasma concentration vs. time curve: shortened terminal half-life, and decreased AUC (area under the drug plasma concentrations vs. time curve) values (see $V$ and $C_P$ curves on Figure 2).

These changes of drug distribution and increased volume of distribution are consistent with the Øie-Tozer model [9, 24, 25]. However, the observed changes in the total plasma concentrations do not reflect the changes in the unbound drug concentrations (see $C_{Pu}$ curve on Figure 2A). It can be seen that decreased plasma protein binding increases the fluctuations of the unbound plasma concentrations (higher $C_{u_{max}}$ and lower $C_{u_{min}}$), while the average unbound plasma drug concentrations (and unbound AUC values) remain unchanged. This outcome is consistent with analysis of consequences of drug displacement from plasma proteins by Benet and Hoener [18] that predicted lack of change in unbound AUC values for intravenously-administered drug with low extraction ratio, like diazepam that was used to generate Figures 2-4 in this manuscript. Only in small number of cases (e.g., for intravenously
administered high extraction ratio drug), drug displacement from protein binding is expected to increase unbound AUC values and may require dose reduction [18].

For majority of drugs, pharmacological effects are governed by unbound (and not total) drug concentrations in the plasma or within the target organ/tissue [26-29]. Therefore, for drugs with direct pharmacokinetic-pharmacodynamic (PK-PD) relationship [30, 31] (e.g., majority of anesthetic, diuretic, anti-arrhythmic agents, etc.) the time course of drug effects is expected to follow the unbound drug plasma concentrations (see Figure 2A) and displacement from plasma proteins will increase fluctuations of drug's pharmacological activity. The overall pharmacological activity of the drug in this case may decrease as a function of PK (e.g., reduction of unbound AUC values, see above), or PK-PD factors (e.g., drug efficiency at different concentrations, development of tolerance, etc. [32]). On the other hand, drug displacement from plasma proteins is expected to have limited effect on the pharmacological activities of drugs with indirect PK-PD relationship [30, 31] (e.g., anti-diabetic, lipid-lowering, antacidic, agents, etc.) which are less sensitive to fluctuations in the unbound drug plasma concentrations.

In general, focusing on the total and not unbound plasma concentrations using the Øie-Tozer model is a major pitfall that apparently originates from lack of ability to measure unbound (active) drug concentrations at the time that the major concepts of pharmacokinetics were established. Even nowadays, despite general availability of methods for measurement of unbound drug concentrations [33, 34], total plasma (or serum) drug concentrations are measured and reported in majority of studies and clinical analyses. This practice hampers understanding of the drugs' pharmacokinetics and PK-PD relationships (see below) and can lead to improper dose adjustment during therapeutic drug monitoring [34].

Due to these considerations, it is preferable to use analytical techniques to quantify both unbound and total drug concentrations, and to report and analyze unbound volumes of distribution (see figure 2B and Table 1) in pharmacokinetic studies [23]. Indeed, importance of unbound volume of distribution was recognized in several studies that analyzed relationships between drug physico-chemical parameters, protein binding, and tissue permeability/perfusion and unbound volume of distribution [4, 29, 35, 36]. The following equations can be applied for calculation of unbound volumes of distribution for drugs distributed in the body into 2 (plasma and tissues) or 3 (plasma, extracellular, and intracellular fluids) kinetic pools are:
\[ V_{SSU} = \frac{V_P}{f_{uP}} + \frac{V_T}{f_{uT}} \] (3)

\[ V_{SSU} = \frac{V_P}{f_{uP}} + \frac{V_{EX}}{f_{uEX}} + \frac{V_{IN}}{f_{uIN}} \] (4)

It can be seen that these equations are extensions of Eq. 1 and 2 that provide alternative interpretation of the Øie-Tozer model. The changes in values of unbound volume of drug distribution calculated using these equations reflect the changes in the time course of unbound plasma drug concentrations, e.g., increased \( C_{Pu} \) fluctuations due to reduced plasma protein binding, increased tissue penetration or tissue binding (see Table 1). The values of \( f_{uT} \) (or \( f_{uEX} \) and \( f_{uIN} \)) for the individual drugs can be estimated from \textit{in vivo} preclinical data, or based on drug physicochemical properties (e.g., lipophilicity and ionization) [22].

2.2 Lack of distribution equilibrium

Drugs that distribute extensively into peripheral organs and tissues can exhibit two- or multi-exponential pharmacokinetic behavior. Following intravenous bolus administration, significant amounts of these drugs reach peripheral compartment during the initial distribution phase, and slow return to the central compartment limits the speed of drug elimination form the body during the elimination phase (see Figures 1 and 3A). For such drugs, volume of distribution changes with time as a function of tissue penetration and binding of the drug [37, 38]. In this case the volume of distribution is initially low (\( V_1 \) – volume of the central compartment), increases to the higher value (\( V_{SS} \) – steady-state volume) when the steady-state is achieved, and reaches the maximum value (\( V_\beta \) - terminal volume of distribution) during the elimination phase (linear terminal phase) (see Figure 3B and Table 2).

In this state of constant lack of equilibrium, there is significant drug redistribution between the central and peripheral compartments (please notice the log scale of Y axis on Figure 3B) during the time course of drug treatment. Thus, \( V_{SS} \) values calculated using the Øie-Tozer model represent the average volume of distribution, but do not account for the fluctuations of the drug plasma concentrations and volume of distribution during the distribution vs. elimination phases (see Figure 3B). Extent of these fluctuations can be dependent not only on the pathways of drug distribution, but also on the pathways of drug clearance, e.g., in case of drug degradation in peripheral compartment/s (see Table 2). The Øie-Tozer model (and the 'classical' pharmacokinetic models) assumes drug clearance from
the central compartment only (usually by the liver and the kidneys), but this assumption can be inappropriate for certain classes of drugs, especially for the biopharmaceuticals (e.g., therapeutic peptides, antibodies, nucleic acids, etc.) that can be efficiently degraded in all tissues and body fluids [39, 40]. Development of specialized, non-mamillary pharmacokinetic models that include multiple elimination processes is required for analysis of time-dependent pharmacokinetics and patterns of volume of distribution change for these drugs.

Uncorrelated changes in total and free drug plasma concentration (see Chapter 2.1) are characteristic also for drugs that exhibit two- or multi-exponential pharmacokinetic behavior. Partial displacement of drug from plasma proteins leads to reduced total plasma concentrations and increased volume of distribution (see \(C_p\) and \(V\) curves on Figure 3), but can have very limited effect on the time course of unbound plasma concentrations and unbound volume of distribution (see \(C_{pu}\) and \(V_U\) curves on Figure 3) due to the 'buffering' effect of the peripheral compartment/s that can accept the displaced drug. The curves presented on Figure 3 are based on pharmacokinetic data of diazepam [23], but lack of pronounced changes in unbound plasma concentrations upon changes in plasma protein binding is expected for other drugs that exhibit two- or multi-exponential pharmacokinetic behavior (e.g., barbiturates, benzodiazepines, tricyclic antidepressants, etc. [35]). For such drugs, analysis of \(V_{SS}\) values using the Øie-Tozer model can be inappropriate and unbound volumes of distribution should be preferably used for the purpose of pharmacokinetic analysis and calculations.

2.3 Non-linear drug distribution

One of the basic assumptions of the Øie-Tozer model is linearity (lack of saturation) of all drug distribution and elimination processes. Although it is characteristic for some clinically-important drugs (e.g., phenytoin, theophylline, etc.), non-linear elimination is generally attributed to time- or concentration-dependent changes in drug's clearance and is not discussed in this review that is focused on processes of drug distribution. Several possible reasons for non-linear distribution in the clinically-used concentrations range [41-43] are presented in Table 2. Non-linear drug distribution can originate from saturable drug binding in the tissues (drugs claimed to exhibit these phenomena include paclitaxel [44], aminoglycosides [45], phenytoin [46], ouabain [47], etc.), or saturable transporter-mediated drug transport [21]. In addition, volume of distribution can vary in drug concentration-dependent manner due to drug-drug interactions for transporter-mediated transport that have been recently reviewed by Grover and Benet [48]. The authors concluded that location of the
interaction is the primary factor that determines its magnitude: liver usually contributes more than the kidneys, while interactions at other locations, such as the blood-brain barrier, usually have limited effect on volume of drug distribution. Concentration-dependent drug distribution can also originate from non-linear plasma protein binding (e.g., due to self-induction of drug-protein binding due to two-step mechanism of drug protein binding with binding at the first site leading to activation of the second binding site, as suggested recently for propofol, indomethacin, lidocaine and other drugs by Berezhkovskiy [49]) that can lead to significant, clinically-relevant changes in plasma drug protein binding in patients with decreased plasma protein concentrations (e.g., due to uremia, hepatic diseases, epilepsy, etc.). It should be noted that the Øie-Tozer model can be applied for analysis of drug distribution in conditions of constant magnitude of non-linear process, i.e., steady-state conditions with constant extent of saturable tissue or protein binding, drug-drug interactions for transporter-mediated transport, etc. However, application of the Øie-Tozer model in conditions of lack of drug distribution equilibrium is inappropriate.

A special case of non-linear drug distribution is saturable drug binding to its target [50]. For most drugs, only small fraction of the drug is bound to its pharmacological target (e.g., specific receptor) at the therapeutic concentrations and binding of the drug to its target has no significant effect on the drug's pharmacokinetics. On the other hand, many biopharmaceuticals (e.g., therapeutic proteins, peptides, etc.) are characterized by extensive and high affinity binding to their targets which significantly affects the shape of their concentration vs. time curves. Specifically, antibody therapeutics undergo uptake by target cells and by the cells that express neonatal Fc receptor (FcRn) [39, 40, 51], and their concentrations (in the plasma, tissues, and at the site of action) vary in a concentration-dependent manner. While FcRn-mediated binding of antibodies can be reversible, binding to the target cells (for instance, specific and high-affinity interaction of anti-cancer antibodies with cell surface receptors on tumor cells) is usually irreversible and is followed by local degradation of the tumor-bound antibody (hopefully accompanied by the lysis of the tumor cell) Thus, distribution and elimination processes coincide in irreversible drug-target binding, resulting in non-linear changes of volume of drug distribution and clearance. The Øie-Tozer model does not account for existence of these concentration-dependent processes that govern pharmacokinetics of biopharmaceuticals and may give erroneous predictions regarding their volume of distribution and dosing. More detailed, mechanistically-based models that account for non-linear processes of drug-target binding, such as target-mediated drug disposition (TMDD) models [17], should be used for pharmacokinetic analysis and calculations for these
drugs. Indeed, in addition to the regular processes of drug distribution and elimination (e.g., according to the classical compartmental PK models), TMDD models can account for rates of formation and elimination of drug targets and drug-target complexes and can appropriately describe non-linear pharmacokinetic behavior. Biopharmaceuticals and other drugs that are characterized by target-mediated drug disposition are characterized by profound concentration-dependent distribution/elimination processes and complex changes of volume of distribution that limit application of this parameter in pharmacokinetic calculations. Therefore, TMDD models are usually applied to analyze and predict the time course of plasma drug concentrations, to estimate the time course of target-occupancy, and to study its pharmacodynamic implications by linking TMDD models to appropriate PK/PD model [17].

2.4 Masking of drugs' physicochemical properties by drug delivery system

Increasing amount of therapeutic agents are used nowadays in form of complex drug delivery systems, such as liposomes, nanoparticles, drug-polymer conjugates, dendrimers, etc. Processes that govern distribution of these delivery systems are complex, and are distinct from the 'simple' permeability and protein binding pathways that are assumed by the Øie-Tozer model. Encapsulation of drug into specific delivery system efficiently masks its physicochemical properties and significantly alters its disposition. For instance, drug-loaded liposomes and nanoparticles can be endocytosed by the cells of the mononuclear phagocyte system (formerly termed reticuloendothelial system) in a size/shape/charge-dependent manner [52, 53]. In cancer patients, these delivery systems can accumulate within tumor tissue due to 'leakiness' of the tumor capillaries that leads to enhanced permeability and retention (EPR) effect [54]. These factors significantly affect the tissue distribution of drug encapsulated in the drug delivery system and are distinct from the diffusion and permeability pathways that govern distribution of the free drug.

Encapsulated drug is usually not active, and should eventually be released from the drug delivery system in order to exert its pharmacological activity. Therefore, accumulation of encapsulated drug in the specific tissue does not necessarily indicate enhanced pharmacological activity at this location. When the drug is released from the delivery system, e.g., due to drug diffusion or following destabilization of the delivery system, the free drug becomes subject to the 'regular' factors that govern drug distribution. For instance, free drug that is a substrate for the P-glycoprotein (but not the drug encapsulated in the drug delivery system) will undergo active efflux from the tumor cells.
It can be seen that following administration of drug that is encapsulated into drug delivery system, it can exist in the body in several forms, each one of which is subject to different distribution/elimination processes. As a result, assumption that volume of drug distribution is governed primarily by permeability of the drug to the body fluids and its protein binding in these fluids is not valid and precludes use of the Øie-Tozer model for analysis of drug distribution. Following administration of a drug encapsulated into drug delivery system, drug disposition is not constant and cannot be described by a single volume of distribution parameter. Pharmacokinetics of drugs incorporated in delivery systems can be described using sophisticated distribution mechanism-based pharmacokinetic models, such as physiologically-based PK (PBPK) models [10, 55] that can incorporate processes of tissue diffusion and drug release from the delivery system [56, 57].

3. Conclusion
The Øie-Tozer model is frequently used to describe drug distribution. However, as shown in this review, application of the Øie-Tozer model can be inappropriate if it is used to interpret total (and not unbound) plasma concentrations, or for drugs with complex or non-linear distribution behavior. This factor can be crucial for analysis and prediction of time course of active drug concentrations (unbound drug concentrations at the site of action) that determine the time course of drug effects based on the pharmacokinetic-pharmacodynamic correlation (PK-PD correlation) [58, 59].

Distribution of small molecular weight drugs that are characterized by linear pharmacokinetics (with one-, two- or multi-exponential pharmacokinetic behavior) is usually consistent with the Øie-Tozer model. For these drugs, the shapes of total and unbound plasma drug concentration vs. time curves are similar (i.e., extent of fluctuations, the terminal half-life, etc., see solid lines on Figures 2A and 3A) and it is possible to correlate the extent of pharmacological effects to either unbound or total plasma drug concentrations. This PK-PD correlation will be appropriate for pharmacological effects that are governed by unbound plasma drug concentrations (for drugs acting in highly-perfused tissues, or if drug concentrations at the site of action are in rapid equilibrium with unbound drug in the plasma). However, these correlations will be inappropriate for drugs acting in slowly-perfused tissues, or in case of pathophysiological states or drug interactions that lead to altered drug protein binding (see Figures 2A and 3A). In these cases, use of the Øie-Tozer model for analysis of total, and not unbound, plasma drug concentrations may lead to erroneous conclusions and predictions of drugs' pharmacological effects.
If site of drug action is located in the peripheral compartment (for drugs with two- or multi-exponential pharmacokinetic behavior), PK-PD correlation should be based on the tissue drug concentrations (unbound or total), and not on plasma concentrations. In this case, use of the Øie-Tozer model is inappropriate, and physiologically-based PK (PBPK) models [10, 55] can be used instead to predict the time course of drug concentrations in the specific organ or tissue (e.g., see adipose and brain concentrations vs. time curves at Figure 4A). Detailed PBPK models that include numerous organs and tissues may not be required, as it was shown that for many drugs majority of the organs can be 'lumped' together to 2 or 3 compartments with distinct shapes of drug concentration vs. time curves [35, 60]. This is indeed true for diazepam that is acting in the brain, as can be seen from similar shape of its brain and plasma (unbound and total) drug concentration vs. time curves (see Figure 4A).

For drugs that are characterized by concentration- or time-dependent pharmacokinetic behavior, such as drugs with saturable binding to plasma proteins or tissue components, biopharmaceuticals, drug conjugates, or drugs incorporated into drug delivery systems, use of the Øie-Tozer model is usually not appropriate. Sophisticated pharmacokinetic models, such as TMDD models or PBPK models that that incorporate saturable distribution processes, are required to describe disposition of such drugs. It should be noted that certain small molecular weight drugs can exhibit complex pharmacokinetic behavior that requires use of specialized pharmacokinetic models, e.g., angiotensin-converting enzyme inhibitors (ACEI) and warfarin that are characterized by target-mediated drug disposition [17].

4. Expert opinion
The Øie-Tozer model is a valuable tool for analysis of drug distribution that describes relationship between volume of distribution, drug permeability of the drug to the body fluids and its protein binding in these fluids. This model is widely used to understand how physicochemical properties of the drug molecule affect its pharmacokinetic behavior, to analyze and predict volume of drug distribution values, and for pharmacokinetic calculations in pre-clinical and clinical settings. However, modern drug therapy is characterized by gradual shift from the 'classical' small molecular weight drugs to biopharmaceuticals, drug conjugates and drug delivery systems. Due to this shift, and because of the more detailed understanding of complex drug distribution pathways, simplistic approaches for studying drug pharmacokinetics, such as the Øie-Tozer model, are gradually replaced with more complex, detailed, mechanistically-based approaches that take into account the time course of unbound drug concentrations at the site of action and the resulting pharmacological effects.
For small molecular weight drugs characterized by linear pharmacokinetic behavior, drug distribution can usually be adequately described by the 'classical' compartmental models or by simplified 'lumped' PBPK models, and the Øie-Tozer model can be generally used to analyze drug distribution and to estimate volume of distribution. Such estimation, however, will be correct in distributional steady-state (e.g., for long-term administration of the drug by intravenous infusion), or in conditions with low fluctuations in plasma and tissue drug concentrations (e.g., prolonged extravascular drug input as controlled release formulations, transdermal patches, etc.). Any condition that prevents achievement of steady state, such as bolus drug administration and drug redistribution between body tissues, will lead to changes in the value of volume of distribution. Magnitude of these changes, and extent of deviation of volume of distribution from the value predicted by the Øie-Tozer model, will be affected by the drug dose (increased for higher doses), route of administration (higher for IV bolus vs. extravascular dosing), pattern and kinetics of drug distribution (e.g., higher for drug that do not permeate into peripheral tissues), and kinetics of drug elimination (e.g., higher for drug with short elimination half-life).

These changes in the value of volume of distribution reflect fluctuations in the drug concentrations in plasma vs. tissues, and may be correlated with changes in drug's pharmacological activities (e.g., for drugs with direct PK-PD relationship). However, use of the Øie-Tozer model for prediction of time course of pharmacological effects is hampered by its focus on steady-state (and not lack of drug distribution equilibrium) conditions and on total (and not unbound) plasma drug concentrations. A modified version of the Øie-Tozer model for calculation of unbound volume of drug distribution ($V_U$) is preferred in case of fluctuations in the drug concentrations in plasma vs. tissues for the purpose for pharmacokinetic analysis and calculations. This is because $V_U$ reflects the time course of unbound drug plasma concentrations and accounts for changes in drug protein binding and drug redistribution due to two- or multi-compartmental pharmacokinetic behavior.

Both total and unbound volumes of distribution can change due to time- or concentration-dependent pharmacokinetics, for example for drugs with saturable protein or tissue binding, or due to drug-drug interactions for transporter-mediated drug transport. The Øie-Tozer model can be useful in case that the above-mentioned factors result in achievement of a new stable condition with altered drug distribution, e.g., with stable extent of protein binding or transporter saturation during constant IV infusion or constant extravascular drug input to the body. However, fluctuations in extent of non-linear process will lead to complex
patterns of change in volume of distribution that will deviate from the predictions of the Øie-Tozer model.

For drugs characterized by complex pharmacokinetic behavior such as biopharmaceuticals, drug conjugates, and drugs incorporated into drug delivery systems, disposition significantly deviates from the classical mamillary pharmacokinetic models and can't be explained by the 2- or 3-pool models (see Figure 1). Use of the Øie-Tozer model for these drugs is usually not appropriate, and drug disposition should be analyzed using sophisticated physiologically-based pharmacokinetic models, such as TMDD models or PBPK models, that reflect major processes that govern drug pharmacokinetics.

Shift from the 'classical' small molecular weight drugs to more sophisticated drugs is accompanied by trend for individualization of drug therapy and adjustment of dosage regimen for specific patient based on gender, health status, pharmacogene tic data, and other factors. Simple tools and models, such as the Øie-Tozer model, can serve for crude analysis of drug disposition and pharmacokinetic behavior, but predictions based on these tools can systematically deviate from the real values of volume of drug distribution. More precise mechanism-based tools and models should be applied in pre-clinical and clinical studies in order to attain optimized drug treatment for the individual patients.
**Article highlights box**

- Volume of distribution is a key pharmacokinetic parameter that relates the total plasma (systemic) drug concentration to its amount in the body.
- The Øie-Tozer model is frequently used for understanding the patterns of drug distribution and for calculation of drug doses in pre-clinical and clinical settings.
- The major limitation of the Øie-Tozer model stems from its focus on the total drug concentrations in the body fluids, which may be unrepresentative of the active (unbound) drug concentrations.
- The Øie-Tozer model is usually not appropriate for drugs characterized by complex pharmacokinetic behavior, such as biopharmaceuticals, drug conjugates, or drugs incorporated into drug delivery systems.
- Use of more detailed mechanism-based models of drug distribution, such as physiologically-based pharmacokinetic (PBPK) models or target-mediated drug disposition (TMDD) models, is recommended for drug development and for optimizing drug therapy.
Table 1. Properties of the total and unbound volumes of distribution

<table>
<thead>
<tr>
<th>Properties</th>
<th>Total volume of distribution (V&lt;sub&gt;ss&lt;/sub&gt;)</th>
<th>Unbound volume of distribution (V&lt;sub&gt;ss U&lt;/sub&gt;)</th>
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<tbody>
<tr>
<td>correlates the total body drug amount to:</td>
<td>the total plasma drug concentrations (protein-bound + unbound)</td>
<td>unbound plasma drug concentrations</td>
</tr>
<tr>
<td>value reflects:</td>
<td>extent of drug accumulation in tissue vs. plasma</td>
<td>extent of drug plasma binding, tissue penetration, and binding to the tissue</td>
</tr>
<tr>
<td>partial displacement of drug from plasma proteins leads to:</td>
<td>for drugs that distribute in plasma only: no change of V&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>for all drugs: decrease of V&lt;sub&gt;ss U&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>for drugs that distribute in plasma and into tissues: increase of V&lt;sub&gt;ss&lt;/sub&gt;</td>
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Table 2. Factors that may lead to change of volumes of drug distribution during the time course of drug treatment

<table>
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<tr>
<th>Factor</th>
<th>Effect on drug’s PK</th>
<th>pattern of V and V&lt;sub&gt;U&lt;/sub&gt; changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow equilibrium between drug pools (e.g., in plasma and tissues)</td>
<td>redistribution between compartments</td>
<td>time-dependent</td>
</tr>
<tr>
<td>drug clearance in peripheral tissues and organs</td>
<td>redistribution between compartments</td>
<td>time-dependent</td>
</tr>
<tr>
<td>plasma protein binding saturation/displacement</td>
<td>increased tissue permeation and elimination</td>
<td>concentration-dependent</td>
</tr>
<tr>
<td>saturation of drug transporters in non-eliminating organs and tissues or drug-drug interactions for transporter-mediated drug transport</td>
<td>altered tissue permeation and elimination</td>
<td>concentration-dependent</td>
</tr>
<tr>
<td>pharmacokinetics governed by binding to the drug target</td>
<td>altered tissue binding and elimination</td>
<td>concentration-dependent</td>
</tr>
</tbody>
</table>
Figure captions:

Figure 1. Major processes of drug distribution according to the Øie-Tozer model.

Figure 2. Effect of reduced plasma protein drug binding on time course of total and unbound plasma concentrations for a drug that distributes in plasma and into tissues and exhibits monoexponential pharmacokinetic behavior. This simulation represents pharmacokinetics of diazepam-like drug with reduced tissue penetration according to the 3-compartmental model, with individual compartments corresponding to unbound drug in the plasma, protein-bound drug in the plasma, and drug in the tissues (both unbound and protein-bound). The values of pharmacokinetic parameters that were used in the simulation: Dose - 10 mg IV bolus every 6 hr, \( V_1 \) – 10.24 L, \( k_{i0} \) – 8.68 h\(^{-1}\), \( k_{i2} \) – 4.41 h\(^{-1}\), \( k_{21} \) – 0.324 h\(^{-1}\), \( k_a \) (association with plasma proteins) – 1.35 \( 10^7 \) or 0.675 \( 10^7 \) M\(^{-1}\)h\(^{-1}\) (prior to or after the 18-hr time point, respectively), \( k_d \) (dissociation from plasma proteins) – 797 h\(^{-1}\) (for explanations see [23]). Dotted lines show the time course of drug concentrations for unchanged plasma protein drug binding.

Figure 3. Effect of reduced plasma protein drug binding on time course of total and unbound plasma concentrations and volumes of distribution for a drug that exhibits biexponential pharmacokinetic behavior. This simulation is based on pharmacokinetic data of diazepam according to the 3-compartmental model, with individual compartments corresponding to unbound drug in the plasma, protein-bound drug in the plasma, and drug in the tissues (both unbound and protein-bound). The values of pharmacokinetic parameters that were used in the simulation: Dose - 10 mg IV bolus every 6 hr, \( V_1 \) – 10.24 L, \( k_{i0} \) – 8.68 h\(^{-1}\), \( k_{i2} \) – 22.04 h\(^{-1}\), \( k_{21} \) – 0.324 h\(^{-1}\), \( k_a \) (association with plasma proteins) – 1.35 \( 10^7 \) or 0.675 \( 10^7 \) M\(^{-1}\)h\(^{-1}\) (prior to or after the 18-hr time point, respectively), \( k_d \) (dissociation from plasma proteins) – 797 h\(^{-1}\) (for explanations see [23]). Dotted lines show the time course of drug concentrations and volumes of distribution for unchanged plasma protein drug binding.

Figure 4. Time course of total and unbound plasma drug concentrations and volumes of distribution according to physiologically-based pharmacokinetic model. This simulation is based on PBPK model of diazepam adapted from [61]. Concentration vs. time curves for selected organs are showed, along with the plasma drug concentrations, for the sake of simplicity.
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Figure 1.

![Diagram of drug distribution](image)

- **plasma**
  - protein-bound drug
  - very rapid
  - Unbound drug
  - rapid vs. slow
  - elimination

- **extracellular**
  - protein-bound drug
  - rapid vs. slow
  - Unbound drug

- **intracellular**
  - protein-bound drug
  - rapid vs. slow
  - Unbound drug

Figure 2.

**A.**

![Graph of drug concentration](image)

- Drug conc., μM
  - 0.001 to 10
  - Reduced plasma protein binding

**B.**

![Graph of volume of distribution](image)

- Volume of distribution, L
  - 1 to 1000
  - Reduced plasma protein binding

**Time, hr**
Figure 3.

A. 

Drug conc., μM

B. 

Volume of distribution, L

Time, hr

reduced plasma protein binding
Figure 4.

A. 

Drug conc., μM

- adipose
- Cp
- brain
- Cp_u

Volume of distribution, L

B. 

Time, hr