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TEACHERS' TOPICS

Role of Protein Binding in Pharmacokinetics

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This article describes the learning resources that are available to pharmacy students during a lecture on the role of protein binding in pharmacokinetics and pharmacodynamics as part of a clinical pharmacokinetics course. The activities are designed to enable students to predict the effects of changes in the blood (or plasma) protein binding of drugs on kinetic parameters and to recommend dosage regimen modifications, if necessary. Using these resources, students realize that the effect of protein-binding alterations on drug clearance and volume of distribution is dependent on the extent of initial extraction ratio and volume of distribution of the drug, respectively. Further, they learn that the interpretation of the total drug concentrations in blood or plasma in relation to the pharmacologic effects requires a clear understanding of the kinetics of the drug and the underlying physiologic changes leading to the altered protein binding.

Keywords: pharmacokinetics, volume of distribution, protein binding, free drug concentration, albumin, α_1-acid glycoprotein

INTRODUCTION

Protein binding is covered in a 75-minute session in the *Clinical Pharmacokinetics* (Pharmacy 2340) course at Texas Tech. The course is offered during the fall semester of the second year of the PharmD program. The details of the educational environment[1] and the format[2] of the course have been published recently. This article describes the learning tools that this instructor uses to facilitate student mastery of the role of protein binding in pharmacokinetics and pharmacodynamics.

General, ability-based outcomes for the session are:

1. Predict the effects of alterations in the blood (or plasma) protein binding of drugs on their kinetic parameters and blood concentration-time courses.
2. Recommend modifications in the dosage regimen based on the protein-binding–induced changes in the kinetic parameters of the drug.

The specific learning objectives of the session are for students to be able to answer the following questions:

1. What are the major plasma proteins? Which type of drugs do they bind to?
2. What are the situations resulting in altered protein binding?
3. What is the relationship between the free (unbound) and total (free plus bound) drug concentrations in blood (or plasma) for linear and non-linear binding?
4. How does a change in the blood (or plasma) protein binding affect the volume of distribution, clearance, and elimination half-life of drugs?
5. How does a change in the blood (or plasma) protein binding affect the steady-state concentration of total and free drug?
6. How does the dosage regimen need to be modified when the blood (or plasma) protein binding of a drug changes?

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SESSION CONTENT

The following material is provided online to students as a reading assignment that must be completed before attending the class session for the discussion of the topic. Additionally, other readings from suggested textbooks serve as optional reading assignments. The equations and a majority of the general concepts presented in the reading handout may be found in most pharmacokinetics textbooks.[3-7]

Total Versus Free (Unbound) Drug Concentrations

In addition to other components, the blood or plasma contains proteins (P) such as albumin and α_1-acid glycoprotein (AAG). Most drugs (D) in plasma are bound to these proteins (DP) to some degree. As shown in Figure 1, the drug-protein interaction is reversible in that the drug-protein complex (DP) can dissociate and release the free drug (D_f).

In practice, what is usually measured as blood or plasma concentration of a drug is the total (bound + free)

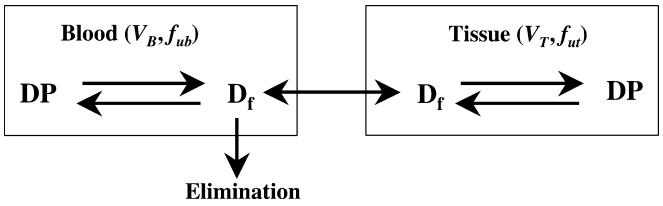

Figure 1. The pharmacokinetic model depicting the equilibrium between the free (D_f) and protein-bound (DP) drug in blood and tissue. The model assumes that only the free drug is subject to elimination and distribution into the tissues (including the site of action).

drug concentration in the sample. However, it is the free drug (D_f) that can pass the cell membranes and reach its site of action; the drug-protein complex (DP) is too large to pass through the membranes (Figure 1). Therefore, the free drug is the moiety responsible for producing the pharmacologic effect. At equilibrium, the percent or fraction of the total drug bound to plasma proteins and red blood cells remains constant for drugs with linear binding. For example, the degree of plasma protein binding of phenytoin in adults is 90% or 0.90 (the percent or fraction unbound is 10% or 0.10). So, if the total plasma concentration of phenytoin is 20 mg/L, the free concentration is 2 mg/L, and the bound concentration is 18 mg/L. This ratio remains constant when the concentration is reduced to 15 mg/L: the free concentration is 1.5 mg/L and the bound concentration is 13.5 mg/L. Therefore, because the change in the free drug concentration (responsible for the pharmacologic effect) is proportional to that for the total drug concentration, a measurement of the total drug concentration in practice can result in a prediction of the desired effects in most cases.

The problem arises, however, when a disease or coadministration of another drug would change the binding equilibrium ratios. For instance, in patients with hypoalbuminemia, the degree of binding of phenytoin to albumin is reduced. Therefore, the free fraction in this case will be higher than normal. Consequently, a total plasma concentration of 20 mg/L, which under normal conditions resulted in a free concentration of 2 mg/L, would now result in a free concentration higher than 2 mg/L for these patients. This, however, will not be apparent by just measuring the total drug. Therefore, it is necessary to understand the effects of changes in the protein binding on various kinetic parameters and the total and free drug concentrations in order to interpret the total plasma or blood concentrations and appropriately adjust the dosage regimen, if necessary.

Additionally, protein binding of some drugs in the blood or plasma may be nonlinear. This means that as the total blood concentrations of the drug increase, the free fraction also increases, resulting in a more than proportional increase in the free drug concentration at higher total drug concentrations. In other words, at higher concentrations, the sites responsible for binding the drug are saturated, therefore, a greater proportion of the drug is in free form. One of the examples of such drugs is disopyramide, which shows higher plasma free fractions at higher therapeutic concentrations. For these drugs, interpretation of the total plasma concentration is extremely difficult. Therefore, experimental measurement of free drug, as opposed to normally measured total drug, may be necessary in these cases.

Major Plasma Proteins

Albumin is the most important plasma protein with a concentration of 3.5 to 5 g/dL (Table 1). Most acidic (anionic) drugs bind to plasma albumin. Some examples include tolbutamide, phenytoin, ibuprofen, naproxen, and warfarin. Albumin is synthesized in the liver. Therefore, the concentrations of albumin may be reduced in liver diseases such as cirrhosis, resulting in changes in the protein binding of the above drugs. Other diseases causing a reduction in the plasma concentrations of albumin include burns, surgery, acute viral hepatitis, renal failure, and malnutrition. On the other hand, an increase in the plasma concentrations of albumin is observed in situations like dehydration and some neurological disorders. However, clinically, occurrence of hypoalbuminemia is much more frequent than hyperalbuminemia.

In addition to the concentration, the affinity of albumin to bind drugs can affect the degree of protein binding of drugs. The affinity of albumin for binding drugs may be decreased by some other drugs or in diseases, resulting in higher free fractions in plasma.[8] Additionally, drugs with higher affinity to albumin may displace drugs with lower affinity from their binding sites. For instance, salicylates are capable of displacing warfarin from the plasma albumin and increasing the free fraction of warfarin.

AAG has a much lower concentration (0.04-0.1 g/dL) than albumin and binds mostly to basic (cationic) and neutral drugs (Table 1). Similar to albumin, AAG is synthesized in the liver. Most drugs that bind to AAG also bind to albumin. Examples of such drugs are propranolol, lidocaine, verapamil, disopyramide, and imipramine. In contrast to albumin, clinical situations resulting in higher concentrations of AAG are more frequent than those resulting in lower concentrations of this binding protein. The plasma concentrations of AAG are increased in trauma injuries, inflammatory diseases, surgery, burns, and acute myocardial infarction. Liver diseases such as cirrhosis would cause a reduction in the plasma concentrations of AAG. Similar to albumin, an apparent decrease

Table 1. Major Drug Binding Proteins in Plasma[4,7]

Protein	MW, g/mole	Normal Concentration g/dL	Normal Concentration μM	Type of Drugs Bound	Example
Albumin	67,000	3.5-5	500-700	acidic, basic	Warfarin
α_1-Acid glycoprotein	42,000	0.04-0.1	9-23	basic, neutral	Propranolol
Lipoproteins	200,000-2,400,000	Varies	Varies	lipophilic basic and neutral	Cyclosporine

in the affinity for binding to AAG can occur when one drug displaces the other from its binding sites.

Lipoproteins, which consist of very low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins, are synthesized in the liver and intestinal mucosa, and their normal plasma concentrations are variable (<0.5 g/dL; Table 1). Usually, basic and neutral drugs with a high degree of lipophilicity are substantially bound to lipoproteins. The concentrations of lipoproteins change in a variety of diseases such as renal failure, diabetes mellitus, hyperlipoproteinemia, and alcoholism. Examples of drugs significantly binding to lipoproteins are cyclosporine,[9] tacrolimus,[10] and propofol.[11]

Blood Versus Plasma

The pharmacokinetic parameters of drugs are usually estimated after measurement of drugs in plasma rather than whole blood. However, the relationships between major pharmacokinetic parameters (such as volume of distribution or clearance) and their physiological determinants (such as perfusion or protein binding) are based on the value of these parameters in blood. If the blood: plasma concentration ratio of a drug is equal to 1, the kinetic parameters obtained using the plasma and blood will be identical. Additionally, for drugs with a blood to plasma ratio different than 1, the plasma concentrations may be easily converted to the respective blood values if the blood to plasma ratio is known. Unfortunately, most reports in the literature use blood and plasma kinetic values interchangeably, even if it is not shown that the blood to plasma ratio is equal to 1. In the following section, we will base our discussion on blood data and provide alternative relationships, if they exist, for the plasma data. For simplicity, when literature examples are used to demonstrate concepts, we assume a blood to plasma ratio of 1.

How Does Protein Binding Affect Major Pharmacokinetic Parameters?

Volume of distribution. The volume of distribution at steady state (V_{SS}) may be defined by the following equation[3]:

$$V_{SS} = V_B + \left(\frac{f_{ub}}{f_{ut}}\right) V_T \qquad (1)$$

where V_B and V_T are the volume of blood and tissue (extravascular space), and f_{ub} and f_{ut} are the unbound fractions in the blood and tissue, respectively. V_B is ~0.07 L/kg or 5 L/70 kg. V_T is the real extravascular volume in which the drug is distributed. For lipophilic (non-polar) drugs, V_T (~0.6 L/kg) is the total body water minus the blood water volume, because these drugs distribute to both the extracellular and intracellular spaces. The value of V_T for hydrophilic (polar) drugs that do not penetrate intracellular space is the volume of extracellular water minus the plasma water volume (~0.13 L/kg).[5]

As mentioned above, the concentrations of drugs are mostly measured in plasma (instead of whole blood), and free fractions are also estimated in plasma (f_{up}). However, if the blood:plasma concentration ratio of the drug is known, f_{ub} may be easily estimated from f_{up} and blood to plasma ratio as demonstrated below:

$$f_{ub} = \frac{f_{up}}{B:P} \qquad (2)$$

In the absence of blood to plasma ratio, another parameter, V_{SS} based on the plasma data (V'_{SS}), may be estimated using the following equation:

$$V'_{SS} = V_P + \left(\frac{f_{up}}{f_{ut}}\right) V'_T \qquad (3)$$

where V'_{SS} is a proportionality constant relating the amount of drug in the body to the plasma concentrations (as opposed to blood concentration for V_{SS}). V'_T is different from V_T in that it also contains the volume of red blood cells in addition to the extravascular space.[3] For drugs that are restricted to plasma (such as macromolecules), V_P is equal to the volume of plasma (~3 L/70 kg). However, because plasma proteins such as albumin enter slowly into the interstitial fluid, at equilibrium V_P may be larger than the volume of plasma (~7 L/70 kg or 0.10 L/kg) for small molecule drugs.[4]

As one may recognize from the above equations, V_{SS} may differ significantly from V'_{SS}. However, most investigators use these 2 terms interchangeably, which is correct only if the blood to plasma ratio is equal to unity.

Conceptually, these equations predict a larger V_{SS} (or V'_{SS}) if f_{ub} (or f_{up}) is increased and a lower V_{SS} (or V'_{SS}) if f_{ut} is increased. This is understandable because a higher free fraction in blood/plasma results in a movement of the

free drug from blood/plasma to the tissues and an increase in the distribution of the drug. On the other hand, a higher free fraction in the tissue would result in a movement of the drug from the tissue to blood/plasma and a reduction in the volume of distribution. The magnitude of the increases or decreases in V_{SS} (or V'_{SS}), however, depends on the original V_{SS} (or V'_{SS}).

At one extreme, a drug with a very low V_{SS} (or V'_{SS}) will have a V_{SS} (or V'_{SS}) almost equal to V_B (or V_P), meaning that the drug does not distribute much into the tissues. For these drugs, the above equations may be simplified as:

$$V_{SS} \approx V_B \tag{4}$$

$$V'_{SS} \approx V_P \tag{5}$$

Therefore, changes in the blood/plasma or tissue binding (f_{ub}/f_{up} or f_{ut}) would not significantly affect the V_{SS} (or V'_{SS}) of these drugs. Examples of such drugs are chlorpropamide (V'_{SS} of 0.097 L/kg), tolbutamide (V'_{SS} of ~0.1 L/kg), and dicloxacillin (V'_{SS} of 0.086 L/kg).[12]

At the other extreme, for drugs with very large V_{SS} (or V'_{SS}), the value of V_B (or V_P) is relatively insignificant, and the above equation may be rewritten as:

$$V_{SS} \approx \left(\frac{f_{ub}}{f_{ut}}\right) V_T \tag{6}$$

$$V'_{SS} \approx \left(\frac{f_{up}}{f_{ut}}\right) V'_T \tag{7}$$

Therefore, changes in the values of f_{ub}/f_{up} or f_{ut} would affect the value of V_{SS} (or V'_{SS}) almost proportionally. Examples of such drugs are propranolol (V_{SS} of 4.3 L/kg) and amitriptyline (V_{SS} of 15 L/kg).[12] Most drugs, however, fall in between these 2 categories; thus, their V_{SS} is affected to some degree (less than proportional) by changes in f_{ub} and/or f_{ut}. In conclusion, the effect of changes in f_{ub} or f_{ut} on V_{SS} depends on the initial extent of the distribution of the drug.

Clearance. Based on the well-stirred model of hepatic metabolism, the hepatic clearance (Cl_h) is related to hepatic extraction ratio (E) and its components f_{ub}, intrinsic clearance of the free drug (Cl'_{int}), and liver blood flow (Q) according to the following equation:[4]

$$Cl_h = Q \cdot E = Q\frac{f_{ub} \cdot Cl'_{\text{int}}}{Q + f_{ub} \cdot Cl'_{\text{int}}} \tag{8}$$

According to the above equation, drugs with a high E (close to 1) have a high clearance close to the hepatic blood flow, whereas drugs with a low E (E close to zero) have a low Cl significantly less than the hepatic blood flow. For these 2 extreme cases of very low and very high E (or Cl) drugs, the above equation may be simplified:

$$Cl \approx f_{ub} \cdot Cl'_{\text{int}}, \text{ for low E or low Cl} \tag{9}$$

$$Cl \approx Q, \text{ for high E or high Cl} \tag{10}$$

Therefore, a change in f_{ub} for the low E (or low Cl) drugs would directly affect their Cl_h. Examples of drugs with low E (or low Cl) are phenytoin, diazepam, warfarin, and valproic acid. On the other hand, a change in the f_{ub} of high E (high Cl) drugs would not have any effect on their Cl. Examples of high E (high Cl) drugs are tricyclic antidepressants, verapamil, and propranolol.

In contrast to all or none effects for high and low Cl drugs, a change in the f_{ub} of a drug with an intermediate Cl or E would have some effect on its clearance. However, the change in clearance will not be proportional to the change in f_{ub}.

The effect of f_{ub} on the renal clearance of drugs is also similar to those explained for hepatic clearance in that the drugs with low renal E are affected most and those with high renal E are affected least by changes in f_{ub}. Examples of high and low renal E drugs are penicillins and gentamicin, respectively.

In conclusion, the effect of changes in f_{ub} of drugs on their clearance is dependent on the initial clearance or E of the drug.

Half-life. The elimination half-life is not an independent parameter and only reflects the magnitude of distribution and elimination.[1] The half-life is dependent on both V and Cl as defined below:

$$t_{1/2} = \frac{0.693V}{Cl} \tag{11}$$

Therefore, the effect of changes in f_{ub} of drugs on their half-life is dependent on the changes in V and/or Cl induced by the alterations in protein binding.

The Case for Four Extreme Scenarios

As examples of the effects of protein binding on the kinetics and dosage requirement of drugs, let us consider the following four scenarios.

Drugs with high clearance and large volume of distribution. Because the clearance of these drugs is mostly controlled by the blood flow (Cl = Q), a change in f_{ub} is not expected to affect the clearance of these drugs. On the other hand, the V_{SS} of large volume drugs are almost proportional to the free fraction of the drug in blood ($V_{SS} \approx [(f_{ub}/f_{ut}) \times V_T]$). Therefore, an increase in the blood free fraction, for example, would result in an almost proportional increase in the V_{SS} of these drugs.

Consequently, the half-life will be prolonged proportionally. Because the clearance does not change ($\leftrightarrow$), the total average steady state concentration (C^{∞}_{ave}) after intravenous administration remains the same ($\leftrightarrow$):

$$\leftrightarrow C^{\infty}_{ave} = \frac{Dose/\tau}{\leftrightarrow Cl} \qquad (12)$$

Consequently, based on the total concentrations, one may assume that no adjustment in dosing rate is necessary. However, because the free fraction of the drug in blood is increased ($\uparrow$), the average steady state concentration of the free drug ($C^{\infty}_{ave,free}$) will be increased ($\uparrow$), which may result in toxicity or adverse effects despite apparently "normal" total blood values.

$$\uparrow C^{\infty}_{ave,free} = C^{\infty}_{ave} \leftrightarrow \times \uparrow f_{ub} \qquad (13)$$

For these drugs, therefore, a change in the free fraction in blood may require adjustment of the dosing rate (in this case, a reduction).

An example of such drugs is propranolol with V_{SS} of 4.3 L/kg, Cl of 16 mL/min/kg, and f_{up} of 0.13, respectively.[12] Patients with acute myocardial infarction have higher AAG concentrations in plasma.[13] Therefore, the free fraction of propranolol in plasma of these patients decreases.[13] Because of its high E, however, the clearance and consequently the steady state total concentration of intravenous propranolol are not expected to change in these patients. On the other hand, the lower free fraction is anticipated to cause a reduction in the free concentrations and pharmacologic effects of the drug in patients with acute myocardial infarction. Indeed, higher than normal dosing rates of propranolol may be required in patients with established infarction.[5]

Drugs with low clearance and small volume of distribution. For drugs with low clearance and small volume of distribution, clearance is proportional to the free blood fraction ($Cl \approx f_{ub} \times Cl'_{int}$). Therefore, a change in the free fraction is almost proportionally reflected in the clearance of the drug. On the other hand, the V_{SS} of these drugs is not sensitive to changes in the free fractions ($V_{SS} \approx V_B$). Consequently, the half-life will increase if f_{ub} is decreased (Cl is decreased), and it will decrease if f_{ub} is increased (Cl is increased). A change in clearance would result in an inverse change in the total average steady state concentration. However, this change is not expected to affect the pharmacologic effects of the drug because the free average steady state concentration is expected to remain the same. Therefore, the dosing rate generally does not have to be changed for these drugs.

An example of such drugs is warfarin with V'_{SS} of 0.14 L/kg, clearance of 0.045 mL/min/kg, and f_{up} of 0.01.[12] Trichloroacetic acid, a metabolite of chloral hydrate, is known to displace warfarin from its binding site in plasma, thereby increasing its f_{up}.[14] Consequently, the clearance of warfarin increases almost proportionally to the increase in f_{up}, and its half-life decreases. At equilibrium, the total average steady state concentration of warfarin in this interaction decreases, whereas the free concentration remains the same. Therefore, in the long term, the pharmacologic effect remains the same and no dosage adjustment is necessary.[14] However, because warfarin has a narrow therapeutic range, the initial increase in f_{up} before equilibrium (reduction of total plasma concentrations) may result in a significant increase in the free drug concentration and pharmacologic effect. Therefore, a temporary reduction in dosing rate may be necessary.

Drugs with low clearance and large volume of distribution. Both the clearance and V_{SS} of drugs with low clearance and large volume of distribution are very sensitive to the changes in f_{ub}. However, the half-life remains almost constant because the effects of changes in the clearance and V_{SS} on the half-life are cancelled out. Similar to the above case, the change in the clearance results in a change in the total drug concentration. However, the average free drug concentration remains the same. Therefore, there is no need for an adjustment in the dosing rate.

Diazepam is an example for this group. Diazepam has a V'_{SS} of 1.1 L/kg, clearance of 0.38 mL/min/kg, and f_{up} of 0.013.[12] Situations resulting in an increase in f_{up} of the drug (eg, hypoalbuminemia) are expected to increase both the V'_{SS} and clearance of the drug (with no significant change in half-life). However, no change in the pharmacologic effect is expected.

Drugs with high clearance and small volume of distribution. A change in blood protein binding is not expected to substantially affect the clearance, V_{SS}, or half-life of these drugs. Therefore, the total blood concentrations are expected to remain the same in the presence of altered protein binding. However, the free drug concentrations will change proportional to the changes in the free fraction in blood. Therefore, the dosing rate of these drugs needs to be altered despite a "normal" blood concentration of the total drug.

Penicillins belong to this category of drugs. Salicylates increase the free fraction of penicillins without causing any change in their clearance or total concentration.[15] Although the plasma concentration of the free drug increases in these situations, in practice, no dosage adjustment is carried out. This is because of the high therapeutic index and relative safety of these drugs.

Summary of Pharmacokinetic Changes

Table 2 demonstrates the effects of changes in the binding of drugs in blood on various pharmacokinetic parameters, blood concentrations of the free and total drug, and the need for an adjustment in the dosing rate of drug. As demonstrated in the Table, a change in the binding of drugs in blood does not generally require an alteration in the dosing rate for low clearance drugs. In contrast, alterations in protein binding require dosage adjustment in the case of highly cleared drugs. Pharmacokinetic-based design of dosage regimens (dose and dosage interval) and its adjustment in the presence of alterations in the pharmacokinetic parameters[16] are the subject of a separate topic in this course.

Implications of Protein Binding in Therapeutic Drug Monitoring

An example of applying the above concepts in a clinical setting is the reduction in the plasma protein binding of phenytoin in the presence of renal disease. The f_{up} of phenytoin is around 0.1.[12] The therapeutic range of the total drug in plasma is between 10 mg/L to 20 mg/L, resulting in an estimated free concentration range of 1-2 mg/L. Let us assume that with the administration of a daily dose of 400 mg phenytoin, the average steady state plasma concentration of the total drug is 15 mg/L. This means that the free drug concentration is 1.5 (15×0.1) mg/L. In renal failure, the f_{up} of phenytoin is increased by a factor of 2 to 3.[17] Let us assume that the f_{up} in renal failure is 0.2. Phenytoin is a drug with a very low clearance. Therefore, a twofold increase in the f_{up} of the drug would result in an almost proportional increase in its plasma Cl. Consequently, the average concentration of the total drug at steady state would decrease by a factor of 2 to a value of 7.5 mg/L. This concentration may be regarded as subtherapeutic because the normal range is within 10-20 mg/L. However, a more careful examination of the data indicates that the concentration of the free drug (responsible for the pharmacologic effect) in the renal failure patient ($7.5 \times 0.2 = 1.5$ mg/L) is the same as that in the normal patient ($15 \times 0.1 = 1.5$ mg/L). Therefore, despite lower total concentrations of phenytoin, no adjustment in the dosing rate of the drug is necessary. However, the maximum and minimum concentrations (and fluctuation between them) are affected by the changes in the half-life. Therefore, if the half-life is significantly decreased, the fluctuation may be outside the therapeutic range (despite the acceptable average concentration). Consequently, dose and dosage intervals may need adjustments (lower doses given more frequently). In this particular case, normally no adjustment is needed in renal disease. This is because an increase in f_{up} is also expected to almost proportionally increase the V_{SS} of phenytoin, which is relatively large (~50 L). Therefore, a simultaneous increase in Cl and V is expected to result in minimal changes in the half-life.

For drugs substantially bound to plasma albumin, such as phenytoin, the total plasma concentrations in hypoalbuminemic patients may be adjusted based on the degree of decrease in the albumin level, before making a therapeutic judgment. The adjusted plasma concentration ($C_{Adjusted}$) may be obtained from the observed plasma concentration of the drug ($C_{Observed}$), free fraction of the drug in subjects with normal albumin levels (f_{up}) and the protein (albumin) concentrations in normal subjects (P_{Normal}) and the hypoalbuminemic patient ($P_{Hypoalbumin}$):[6]

$$C_{Adjusted} = \frac{C_{Observed}}{\left[(1 - f_{up}) \times \frac{P_{Hypoalbumin}}{P_{Normal}}\right] + f_{up}} \qquad (14)$$

Substituting for P_{Normal} (4.4 g/dL) and f_{up} (0.1 for phenytoin), the following equation may be used for

Table 2. Summary of Changes in the Pharmacokinetic Parameters and Steady-State Blood Concentrations of the Free and Total Drug and the Need For Dosing Rate Adjustment in the Presence of Altered Free Fraction in Blood*

Drug	f_{ub}	V_{SS}	Cl	$t_{1/2}$	$C_{SS,TOTAL}$	$C_{SS,FREE}$	Dosing Rate
High Cl-High V	↑	↑	↔	↑	↔	↑	↓
	↓	↓	↔	↓	↔	↓	↑
Low Cl-Low V	↑	↔	↑	↓	↓	↔	↔
	↓	↔	↓	↑	↑	↔	↔
Low Cl-High V	↑	↑	↑	↔	↓	↔	↔
	↓	↓	↓	↔	↑	↔	↔
High Cl-Low V	↑	↔	↔	↔	↔	↑	↓
	↓	↔	↔	↔	↔	↓	↑

*f_{ub}: free fraction in blood; V_{SS}: volume of distribution at steady state; Cl: clearance; $t_{1/2}$: elimination half-life; $C_{SS,TOTAL}$: steady-state concentration of total drug; $C_{SS,FREE}$: steady-state concentration of free drug

phenytoin:

$$C_{Adjusted} = \frac{C_{Observed}}{\left[0.9 \times \frac{P_{Hypoalbumin}}{4.4}\right] + 0.1} \qquad (15)$$

Example. A patient with an albumin level of 2 g/dL has an average plasma phenytoin concentration of 6 mg/L. Not considering the patient's low albumin level, one might conclude that the phenytoin concentration in this patient is subtherapeutic. However, calculation of adjusted concentration shows a value of 11.8 mg/L, which is within the therapeutic range:

$$C_{Adjusted} = \frac{6\,\text{mg/L}}{\left[0.9 \times \frac{2\,\text{g/dL}}{4.4\,\text{g/dL}}\right] + 0.1} = 11.8\,\text{mg/L} \qquad (16)$$

The adjusted concentration of 11.8 mg/L means that an observed concentration of 6 mg/L in this hypoalbuminemic patient is equivalent to a concentration of 11.8 mg/L in a patient with normal albumin concentration (in terms of free drug concentration and pharmacologic effect).

PRACTICE PROBLEM, QUIZ, AND ASSIGNMENT

In addition to the reading handout discussed above, the students are given a practice problem (Appendix 1) ahead of the scheduled session. Students are expected to work on the problem before attending the class, consulting the reading note. After a brief introduction of the topic by the instructor, most of the class time is devoted to both students and the instructor discussing the solution to the practice problem.

During the last 10 minutes of the 75-minute session, students take an online quiz[18] consisting of questions related to the topic of protein binding covered during the session. Finally, students are required to submit an individualized, online assignment[19] by the end of the day the session is held.

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Appendix 1. Practice Problem

Tolbutamide is a weakly acidic drug that is almost completely eliminated by hepatic metabolism. The drug has a volume of distribution (V) of 0.10 L/kg, clearance (Cl) of 0.24 mL/min/kg, and an unbound fraction (plasma; f_{up}) of 0.04 in healthy volunteers. In patients with acute viral hepatitis, the f_{up} of tolbutamide increases.

1. What is the main plasma protein responsible for binding to tolbutamide? What are the disease states/drugs that affect the extent and/or affinity of binding of this protein to drugs like tolbutamide?
2. How is the binding of a weakly basic or neutral drug different from that of tolbutamide?
3. How would you characterize tolbutamide in terms of its extent of Cl and V?
4. Predict the changes in the kinetic parameters (Cl, V, $t_{1/2}$) of tolbutamide in acute viral hepatitis.
5. Predict the changes in the average steady-state concentration of tolbutamide (both total and free drug) as a result of the disease.
6. How should the dosage regimen be different, if any, in patients with acute viral hepatitis compared with patients without this disease?

Instructions: For simplicity, assume a blood:plasma ratio of 1 and a twofold increase in f_{up} in acute viral hepatitis. Also, please use an average blood flow of 1500 mL/min in a 70-kg subject for your calculations.