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Effect of Changes in Plasma Protein Binding on Half-Life of Drugs

Keyphrases □ Pharmacokinetics—effect of changes in plasma protein binding on biological half-life of drugs □ Protein binding—effect of changes in plasma protein binding on biological half-life of drugs □ Half-life—effect of changes in plasma protein binding on biological half-life of drugs

To the Editor:

The binding of drugs to plasma proteins and extravascular tissues affects their distribution, elimination, and overall pharmacological activity. If the extent of such binding is altered by the presence of other drugs or the accumulation of certain endogenous compounds in various disease states, subsequent changes in the pharmacokinetic characteristics of the drug may be anticipated. Gibaldi *et al.* (1) suggested that the biological half-life of a drug bound to plasma proteins and tissues in a drug concentration-independent manner is a function largely of tissue binding but is independent of changes in binding to plasma proteins. However, they pointed out that this phenomenon generally is true only for drugs with apparent distribution volumes substantially larger than the plasma space. These drugs include those that distribute throughout the total body water and, more commonly, those that demonstrate extensive tissue binding as well.

The present discussion focuses on situations where the drug is bound to plasma proteins and the unbound drug is excluded from intracellular fluids. While these conditions may apply to only a few drugs, they can be important. A good example is the antibacterial agent sulfisoxazole. This compound is ~86% bound to plasma proteins after therapeutic doses (2) and is distributed only in extracellular fluids (3, 4). Since the drug does not enter the cells, it exhibits a slightly diminished toxicity while producing higher blood levels at lower doses as compared with sulfanilamide and sulfadiazine, both of which distribute throughout body water. Another example is streptomycin, which is distributed in the extracellular fluids and also is bound to plasma proteins, although to a lesser extent than sulfisoxazole (5).

Based on the physiological approach to drug distribution originally developed by Gillette (6), Øie and Tozer (7) recently proposed the following expression for the apparent volume of distribution, V:

$$V = V_P(1 + R_{E/I}) + f_P V_P(V_E/V_P - R_{E/I}) + \frac{V_T f_P}{f_T} \quad \text{(Eq. 1)}$$

where V_P is the plasma volume; V_E is the extracellular space minus the plasma volume; V_T is the physical volume into which the drug distributes minus the extracellular space; $R_{E/I}$ is the ratio of the amount of protein to which the drug binds in extracellular fluids outside the plasma to that in the plasma; and f_P and f_T are the drug fractions unbound in the spaces V_P and V_T, respectively. Furthermore, by assuming the extracellular fluid volume outside the plasma to be 12 liters and the plasma volume to be 3 liters and by assuming that the total extracellular drug-binding protein is distributed so that $R_{E/I}$ is ~1.4, Eq. 1 can be approximated as:

$$V = 7 + 8f_P + V_T\left(\frac{f_P}{f_T}\right) \quad \text{(Eq. 2)}$$

It then was pointed out (7) that if the distribution of a drug is restricted to the extracellular fluid, its apparent volume of distribution becomes:

$$V = 7 + 8f_P \quad \text{(Eq. 3)}$$

It has been shown (8) that the total clearance, Cl, of a drug whose elimination is linear and not perfusion rate limited in the organ of elimination is directly proportional to its free fraction in plasma, *i.e.*:

$$Cl = f_P Cl^* \quad \text{(Eq. 4)}$$

where Cl^* represents the intrinsic clearance. Moreover, since:

$$Cl = V\beta \quad \text{(Eq. 5)}$$

it follows that:

$$\beta = \frac{f_P Cl^*}{V} \quad \text{(Eq. 6)}$$

where, for a drug obeying two-compartment model kinetics, V is V_{area} and β equals ln 2 divided by the terminal half-life, $t_{1/2}$. Substituting Eq. 3 into Eq. 6 gives:

$$\beta = \frac{f_P Cl^*}{7 + 8f_P} \quad \text{(Eq. 7a)}$$

or:

$$t_{1/2} = \frac{\ln 2(7 + 8f_P)}{f_P Cl^*} \quad \text{(Eq. 7b)}$$

Equation 7*b* describes the effect of plasma protein binding on drug biological half-lives. When the fraction of drug unbound in plasma is changed to f'_P and the new β and $t_{1/2}$ are designated as β' and $t'_{1/2}$, respectively, then:

$$\frac{\beta'}{\beta} = \frac{t_{1/2}}{t'_{1/2}} = \frac{f'_P(7 + 8f_P)}{f_P(7 + 8f'_P)} \quad \text{(Eq. 8)}$$

or:

$$\frac{\beta'}{\beta} = \frac{7f'_P + 8f_P f'_P}{7f_P + 8f_P f'_P} \quad \text{(Eq. 9)}$$

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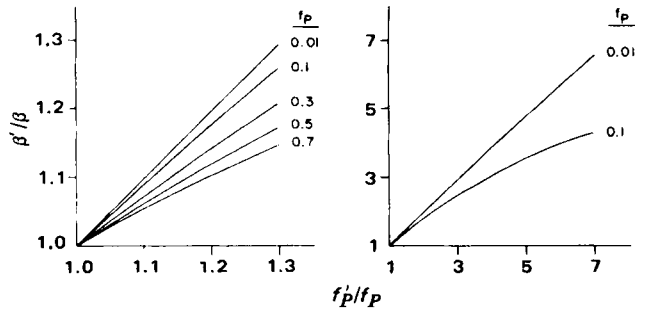

Figure 1—*Relationship between β'/β and f'_P/f_P for drugs with varying degrees of plasma protein binding.*

For the case where the binding of a drug is decreased (*i.e.*, $f'_P > f_P$), it is clear from Eq. 9 that β'/β (or $t_{1/2}/t'_{1/2}$) is smaller than f'_P/f_P but approaches f'_P/f_P as f_P approaches zero or as f'_P approaches f_P. These latter conditions apply to drugs that normally are bound to a large extent or to situations where the decrease in binding is slight.

To illustrate the relationship between relative changes in the drug half-life and plasma protein binding, Fig. 1 was constructed based on Eq. 9 using different f_P values.

From Fig. 1, it is obvious that the relationship between β'/β and f'_P/f_P is almost linear, especially when the change in f_P is relatively small. For drugs that are predominantly plasma protein bound (*e.g.*, $f_P = 0.01$), the slope of the plot is approximately one, indicating that $t_{1/2}$ is inversely proportional to f_P. Although this simple, inverse proportionality vanishes with less extensively bound drugs, the almost linear relationship between β'/β and f'_P/f_P offers a means of rapid estimation of half-life changes as a result of altered plasma protein binding.

When the percentage change in f_P is relatively large, a more rapid loss of linearity in the curves is observed with increasing f_P. Fortunately, for drugs that initially are predominantly unbound, such large percentage increases in f_P are not possible. Furthermore, the β or half-life values of these drugs are relatively insensitive to changes in binding (Fig. 1), and adjustments in the dosage regimen to correct for binding changes may not be necessary.

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BOOKS

REVIEWS

Foundations of Molecular Pharmacology, Vol. 1: Medicinal and Pharmaceutical Chemistry. By J. B. STENLAKE. The Athlone Press, University of London, Four Gower St., London WC1, England. 1979. 936 pp. 15 × 23 cm. Price $90.00.

It is easy to be enthusiastic about this well-crafted and scholarly book. The author skillfully leads us through a treatment of principles of organic chemistry applied to pharmaceutical agents. The organizational approach and its careful implementation consistently afford interesting reading.

The book is organized similar to an organic chemistry text. The medicinal agents are organized into 23 chapters by their organic chemical class; such groups as the alkanes, alkenes, benzenoid aromatic hydrocarbons, alkynes, and monohydric alcohols are included. Each chapter discusses the organic chemistry of the particular chemical class. The discussions generally are clear and succinct. The immediate pharmaceutical significance of the particular chemical property is illustrated by one or more examples from the pharmaceutical sciences. For example, following an explanation for the acidic nature of the acetylenic hydrogen atom, it is noted that the formation of a silver acetylide by the addition of silver nitrate is used as a test for identity and is the basis for the assay of some acetylenic pharmaceutical products such as ethclorvynol. Also, after a discussion of hydride reduction of aldehydes and ketones by lithium aluminum hydride and sodium borohydride, there ensues an account of the enzymatic reduction of these functional groups involving hydride donation from NADPH.

Almost all of the transitions from the general organic chemical discussion to the pharmaceutical application are made easily. Additionally, the particular pharmaceutical example usually is appropriate. One effect of this approach is to make the point repeatedly, without ever explicitly stating so, that knowledge of fundamental chemical properties is mandatory for an understanding of pharmaceutical procedures and pharmacological activities.

This reviewer has two minor criticisms relative to the author's pharmaceutical examples. There are several occasions when more appropriate pharmaceutical examples could have been presented. Also, the examples chosen could have been treated more in proportion to their importance. The following are instances in which these criticisms apply.

1. The decarboxylation of salicylic acid on bromination is discussed, but the decarboxylation of *p*-aminosalicylic acid in an acidic aqueous medium is not mentioned.
2. The structures of the amino acids GABA and taurine are given, but only GABA is cited as being an important transmitter.
3. Carbonic anhydrase-inhibiting sulfonamides are treated in detail, but benzothiazides are treated briefly.
4. The importance of ylids in synthesis is not developed.

However, these criticisms are minor, especially considering the great range of the book and the usually impressive appropriateness of the examples.

Medicinal and pharmaceutical chemists and many others in the pharmaceutical sciences should find this book to be an interesting and thought-provoking source of information. Additionally, teachers of medicinal and pharmaceutical chemistry may find that the volume is useful as a supplemental reference for both graduate and undergraduate students. Where the curriculum allows room for a course based on a format similar to that of the book (chemical class → chemical properties → pharmaceutical application), the book can serve as a textbook, although the cost is high.

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