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Plasma Binding and Limitation of Drug Access to Site of Action

The measurement of blood or plasma drug concentration is now a therapeutic tool that is widely applied in clinical practice, especially in the intensive care unit. However, total drug in plasma exists in two forms: that which is bound to plasma proteins and other plasma constituents (the most important of which are albumin and α_1-acid glycoprotein [AAG]) and that which is free or unbound. Pharmacokinetic dogma states that the extent of protein binding is an important determinant of drug distribution and elimination since it is the free or unbound fraction of drug in plasma that readily diffuses across biologic membranes, such as the placenta and blood–brain barrier, and thus is available for distribution outside the plasma space.[1] Therefore, the greater the degree of protein binding, the lesser is the drug available to leave the plasma space and hence the smaller is the volume of distribution. A reduced volume of distribution would be expected to give rise to an increased total drug concentration since the same amount of drug is being distributed into a smaller "bucket" or compartment.

Although the effects of drug binding on pharmacokinetics have been extensively investigated, whether changes in drug binding result in altered pharmacodynamic effect is a relatively unexplored area, mainly because it is so difficult to design and conduct meaningful studies. A few interesting clinical studies have suggested that the concentration of free or unbound drug may correlate with clinical effect better than does the total drug concentration,[2,3] but there are indeed few definitive studies in the area of free drug concentration–effect relationships. It is in part for this reason that free drug concentration measurement as a monitor of drug toxicity is not routine in clinical practice.

The relationship between pharmacodynamic effect and plasma binding of drugs that cross the blood–brain barrier to enter the central nervous system is complex. It has long been recognized that drug binding to plasma proteins limits the passage of drug across the blood–brain barrier and that it is only the unbound free fraction that is available for transport across the blood–brain barrier into the tissues of the central nervous system—the "free drug" hypothesis. However, in the 1980s, this hypothesis was challenged by a number of investigators who studied drug uptake into the brain[4–7] and liver[8–10] and suggested that certain plasma proteins might be involved in an active transport process beyond the passive transport of unbound moiety along a concentration gradient—*i.e.*, *in vivo* enhanced dissociation. For example, although the similarity of cerebrospinal fluid (CSF) concentration of diazepam to that of unbound drug in plasma[11–13] would support conventional theory, brain diazepam uptake measured by the technique of tissue sampling following single carotid artery injection of diazepam yielded data that suggested that the brain extraction was greater than predicted.[14] Similar findings have been reported for other drugs, including propranolol,[15] lidocaine,[15] and bupivacaine.[16] However, later direct studies of the transport of diazepam across the blood–brain barrier under conditions of true equilibrium failed to provide support for enhanced dissociation *in vivo*.[17]

Thus, there is controversy: first, does the plasma-protein–mediated transport of drug and hormones exist as a specific mechanism to enhance dissociation from their plasma binding proteins and so to facilitate drug tissue uptake? and second, if the enhanced *in vivo* dissociation hypothesis is correct, does it invalidate the "free drug"

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hypothesis? Clearly there was a need for an *in vivo* study to evaluate the effect of protein binding on drug uptake by the central nervous system in a whole laboratory animal, and the work by Marathe *et al.*[18] in this issue of ANESTHESIOLOGY addresses this point.

To test the hypothesis that lidocaine entry into the central nervous system is predicated by free drug concentration rather than total concentration, the effect of serum protein binding on lidocaine distribution into brain and CSF was investigated by Marathe and co-workers[18] in dogs following intravenous lidocaine administration. Protein binding was manipulated by rifampin pretreatment, which produced a 4-fold increase in AAG, a major binding protein for lidocaine. Hence, rifampin administration led to a decrease in lidocaine free fraction and a decrease in free lidocaine concentration, but an increase in total lidocaine concentration in plasma, probably secondary to the decreased volume of distribution that resulted from increased plasma binding. Importantly, equilibration of lidocaine between serum and brain tissue or CSF was reached 10 min after lidocaine administration, and there was a significant correlation between brain-to-serum or CSF-to-serum ratios and serum free fractions, indicating that the free fraction of lidocaine is an important determinant of lidocaine entry into brain and CSF. Thus, Marathe *et al.*'s study[18] confirms the long-held theory that free drug concentrations in plasma govern tissue concentrations. How then does this finding help the anesthesiologist understand drug action in patients?

Although in Marathe *et al.*'s study[18] rifampin was used to alter AAG concentrations, there are numerous pathophysiologic states which are associated with alterations in the concentrations of the plasma proteins to which drugs are bound. Albumin concentrations are decreased in a variety of clinical situations, such as renal disease, hepatic disease, cardiac failure, malignancy, and the postoperative period, whereas AAG (an acute-phase reactant protein) concentrations are increased in infection, myocardial infarction, trauma, chronic pain, and the postoperative period.[1] AAG concentrations are increased in the postoperative period, and it is interesting that plasma bupivacaine concentrations that might be expected to cause central nervous system toxicity have been observed during prolonged epidural infusions without such signs.* It has been suggested that postoperative increases in AAG concentrations after trauma and surgery increase bupivacaine binding, thereby reducing free (putatively active) concentrations. Lidocaine binding after cardiac surgery also increases, coinciding with an increase in plasma AAG concentration.[19] In contrast, patients with a greater than normal unbound fraction of drug may show signs of pharmacologic activity or toxicity at lower than expected total drug concentrations. When phenytoin is used as an anticonvulsant drug in patients with renal failure, the free fraction is increased sometimes even in the presence of normal albumin concentrations. This means that because of the higher free concentrations of phenytoin, suppression of seizure activity occurs at lower total drug concentrations, and even more importantly, toxicity occurs at a total concentration that in normal healthy subjects would be within the normal therapeutic range.[20]

These considerations apply not only to drug penetration across the blood–brain barrier, but also to drug penetration across other membranes, such as the placenta. Once equilibrium is achieved, the free drug concentrations will be equal on both sides of the placenta, and total concentrations will depend on the degree of protein binding. In the example shown in figure 1, consider a drug 90% bound on one side of the membrane where the total concentration is 100 ng/ml. One can thus calculate that the free concentration will 10 ng/ml. Once equilibrium has been achieved, the free concentration on both sides of the membrane will be equal. If protein binding on the other side of the membrane is only 10%, then the total concentration will be only 11 ng/ml. Although the total concentrations are 9-fold higher on one side of the membrane than on the other, since free concentrations are the same, the predicted pharmacologic effects may be similar in mother and baby. It is therefore important to consider protein binding when comparing maternal–fetal drug ratios.

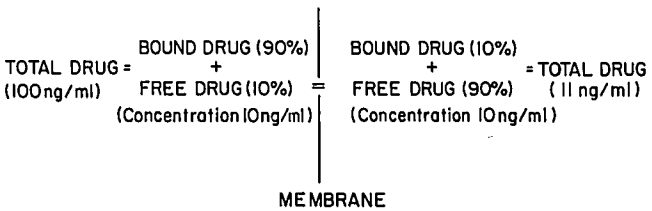

FIG. 1. Disposition at equilibrium of a drug across a membrane when it is 90% bound in plasma on one side of the membrane and 10% bound in plasma on the other side of the membrane. Free concentrations on either side of the membrane will be equal. If, however, the drug is 90% bound on one side of the membrane where its concentration is 100 ng/ml, the free concentration will equal 10 ng/ml. Since this is the concentration that will equilibrate across the membrane, it will be equal on both sides of the membrane. On the other side of the membrane where the drug is only 10% bound, however, the total concentration will equal 11 ng/ml, giving a total concentration ratio of 9:1 across the membrane. (Reproduced by permission from Wood AJJ: Drug disposition and pharmacokinetics, Drugs and Anesthesia: Pharmacology for Anesthesiologists. Edited by Wood M, Wood AJJ. 2nd edition. Baltimore, Williams and Wilkins, 1990, p 14.)

* Denson DD, Myers JA, Hartrick CT, Pither CP, Coyle DE, Raj PP: The relationship between free bupivacaine concentration and central nervous system toxicity (abstract). ANESTHESIOLOGY 61:A211, 1984.

Many drugs have been found to have decreased binding in the neonate as compared to the mother, and these include local anesthetics used by the anesthesiologist. The plasma binding of bupivacaine is higher in maternal blood than in neonatal blood due to lower AAG concentrations in the neonate, and at delivery, following continuous epidural anesthesia with bupivacaine, the total umbilical venous plasma concentration of bupivacaine is lower than the total maternal venous plasma concentration, but the concentration of free or unbound bupivacaine in umbilical venous and maternal venous plasma at delivery is the same.[21] Thus, differences in protein binding of drugs in maternal and fetal plasma may determine differences in total drug concentration on each side of the placenta, although the free concentrations are in fact equal. With the proviso that neonatal "sensitivity" to local anesthetics is similar to that of the mother, the pharmacologic effect should be similar in mother and fetus despite the disparity in total drug concentrations.

In summary, Marathe and co-workers[18] have demonstrated the effect of serum protein binding of lidocaine on entry into the brain and CSF and have confirmed that the free or unbound fraction of lidocaine is indeed an important factor underlying drug transfer. Although there is a close relationship between plasma total concentration and drug effect, for drugs that are highly protein-bound, the effect (subtherapeutic, therapeutic, or toxic) may depend on the free concentration, so that an intelligent understanding of the factors influencing drug binding and hence drug passage across membranes to site of action may be critical to the understanding of drug concentration–effect relationships.

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